CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214755Orig1s007

Trade Name:	LUMRYZ
Generic or Proper Name:	(sodium oxybate)
Sponsor:	Avadel CNS Pharmaceuticals LLC
Approval Date:	September 26, 2024
Indication:	LUMRYZ is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy

CENTER FOR DRUG EVALUATION AND RESEARCH

214755Orig1s007

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 214755/S-007

SUPPLEMENT APPROVAL

Avadel CNS Pharmaceuticals, LLC
C/O ProPharma Group
Attention: Marla E. Scarola
Senior VP, Regulatory Process Management
1129 Twentieth St. NW, Suite 600
Washington, DC 20036

Dear Marla Scarola:

Please refer to your supplemental new drug application (sNDA) dated and received December 7, 2023, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lumryz (sodium oxybate) for extended-release oral suspension.

This Prior Approval sNDA provides for the inclusion of a starter pack and proposed modifications to the approved Lumryz risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry, *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on September 6, 2024 as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry, *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214755/S-00407**." Approval of this submission by FDA is not required before the labeling is used.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Lumryz was originally approved on May 1, 2023, and the most recent REMS modification was approved on October 31, 2023. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS consists of updating the Prescription Form to include the starter pack as a prescribing option. Your proposed modified REMS, submitted on December 7, 2023, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on May 1, 2023.

There are no changes to the REMS assessment plan as described in our October 31, 2023, letter.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

1. An evaluation of how the benefit-risk profile will or will not change with the new indication.

2. A determination of the implications of a change in the benefit-risk profile for the current REMS.

3. *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

4. *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

5. *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

6. *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous

REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 214755 REMS ASSESSMENT METHODOLOGY**
> **(**insert concise description of content in bold capital letters, e.g.,
> **ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

> **NDA 214755 REMS ASSESSMENT**
>
> *or*
>
> **NEW SUPPLEMENT FOR NDA 214755/S-000**
> **CHANGES BEING EFFECTED IN 30 DAYS**
> **PROPOSED MINOR REMS MODIFICATION**
>
> *or*
>
> **NEW SUPPLEMENT FOR NDA 214755/S-000**
> **PRIOR APPROVAL SUPPLEMENT**
> **PROPOSED MAJOR REMS MODIFICATION**
>
> *or*
>
> **NEW SUPPLEMENT FOR NDA 214755/S-000**
> **PRIOR APPROVAL SUPPLEMENT**

PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 214755/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 214755

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry, *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry, *Providing Regulatory Submissions in Electronic and Non-*

Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Shin-Ye (Sandy) Chang, Senior Regulatory Project Manager at shinye.chang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and Container Labeling
- REMS

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

/s/

TIFFANY R FARCHIONE
09/26/2024 02:39:22 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s007

LABELING

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)

INDICATIONS AND USAGE

LUMRYZ is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy (1).

DOSAGE AND ADMINISTRATION

Dosing Information
- 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).

Important Administration Information
- Prepare the dose of LUMRYZ prior to bedtime; suspend dose in approximately ⅓ cup of water in the mixing cup provided (2.2).
- Allow 2 hours after eating before dosing (2.2).
- Take LUMRYZ while in bed and lie down after dosing (2.2).

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 (incidence ≥ 5% and greater than placebo) reported for any dose of LUMRYZ were nausea, dizziness, enuresis, headache, and vomiting (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Avadel CNS Pharmaceuticals, LLC 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: 9/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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 adults with narcolepsy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dosage 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 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 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.

2.3 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.

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.

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.

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.

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 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 the 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.

LUMRYZ was studied in one placebo-controlled trial (Study 1) *[see Clinical Studies (14)]* 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 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.

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

Safety and effectiveness of LUMRYZ in pediatric patients have not been established.

Juvenile Animal Toxicity Data

In a study in which sodium oxybate (0, 100, 300, or 900 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 21 through 90), mortality was observed at the two highest doses tested. Deaths occurred during the first week of dosing and were associated with clinical signs (including decreased activity and respiratory rate) consistent with the pharmacological effects of the drug. Reduced body weight gain in males and females and delayed sexual maturation in males were observed at the highest dose tested.

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

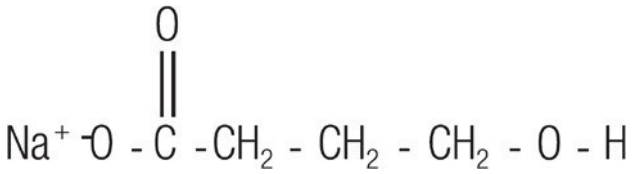
General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation 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

Absorption

Following oral administration of LUMRYZ, the peak plasma concentrations (C_{max}) following administration of one 6 g dose was 66 mcg/mL, and the time to peak plasma concentration (T_{max}) was 1.5 hours. Following oral administration of LUMRYZ, the plasma levels of GHB increased dose-proportionally for C_{max} and more than dose-proportionally for AUC (respectively 2.0-fold and 2.3-fold increases as total daily dose is doubled from 4.5 g to 9 g).

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 (2.2)]*.

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 (2.2)].*

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.

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

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	-	-

Dose	Treatment Group (N)	Change from Baseline*	Difference from Placebo [95% CI]	p-value
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

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 6). Dose packets contain a single dose of LUMRYZ provided in 4.5 g, 6 g, 7.5 g, or 9 g doses.

Table 6: 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. Dose packets contain a single dose of LUMRYZ provided in 4.5 g, 6 g, or 7.5 g doses (see Table 7).

Table 7: 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 to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Central Nervous System Depression

Inform patients 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 to inform their healthcare providers of all the medications they take *[see Warnings and Precautions (5.1)]*.

Abuse and Misuse

Inform patients 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 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 with the telephone number and website for information on how to obtain the product.

Alcohol or Sedative Hypnotics

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

Sedation

Inform patients 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 that they should remain in bed following ingestion of their dose *[see Dosage and Administration (2.2)]*.

Food Effects on LUMRYZ

Inform patients that LUMRYZ should be taken at least 2 hours after eating.

Respiratory Depression and Sleep-Disordered Breathing

Inform patients 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 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 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 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 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)]*.

Distributed By:

Avadel CNS Pharmaceuticals, LLC
Chesterfield, MO

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 to treat the following symptoms in adults with 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.

Do not take LUMRYZ if you:

- 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:

- have a history of drug abuse.
- have short periods of not breathing while sleeping (sleep apnea).
- have trouble breathing or have lung problems. You may have a higher chance of having serious breathing problems when taking LUMRYZ.
- have or had depression or have tried to harm yourself. You 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.
- 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 will take LUMRYZ or breastfeed.

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

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

How should I take LUMRYZ?

- Read the **Instructions for Use** at the end of this Medication Guide for detailed instructions on how to take LUMRYZ.
- Take LUMRYZ exactly as your doctor tells you to take it.
- LUMRYZ is taken by mouth 1 time at bedtime.
- Wait at least 2 hours after eating before taking LUMYRZ.
- After mixing LUMRYZ, take it within 30 minutes. Do not mix LUMRYZ with hot water.
- Take LUMRYZ at bedtime while you are in bed and lie down immediately. You 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 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 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 have symptoms of mental health problems, or a change in weight or appetite.

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

The most common side effects of LUMRYZ in adults include:

- nausea
- dizziness
- bedwetting
- headache
- vomiting

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 in the original packet prior to mixing with water. After mixing with water, store LUMRYZ in the mixing cup provided in each kit.
- Store LUMRYZ at room temperature between 68°F to 77°F (20°C to 25°C).
- 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.

LUMRYZ comes in a child-resistant package. **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.

Distributed By:

Avadel CNS Pharmaceuticals, LLC Chesterfield, MO 63005

For more information, go to www.LUMRYZREMS.com or call the LUMRYZ REMS at 1-877-453-1029.

This Medication Guide has been approved by the U.S. Food and Drug Administration Approved: 5/2023

Instructions for Use

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

Avadel

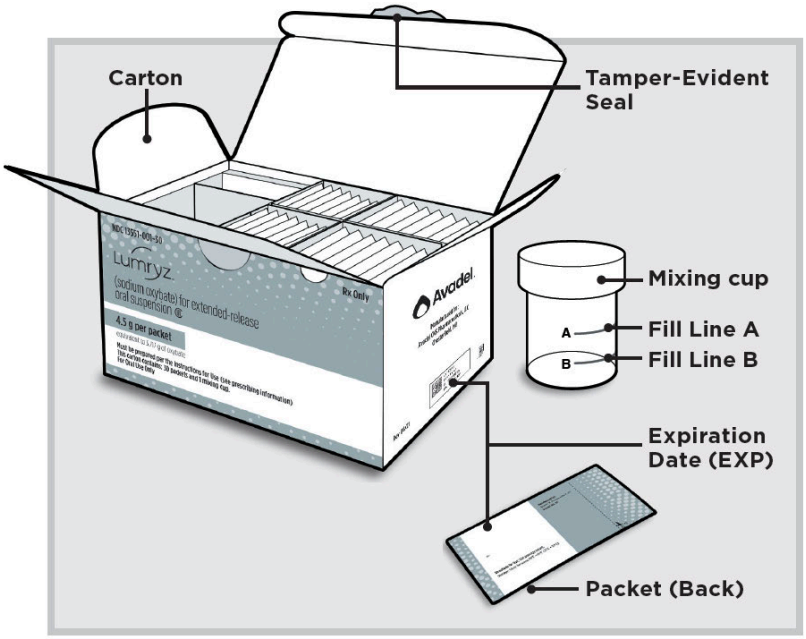
This Instructions for Use contains information on how to take LUMRYZ. Read this Instructions for Use before taking LUMRYZ and each time you get a refill. There may be new information.

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

Important information when taking LUMRYZ

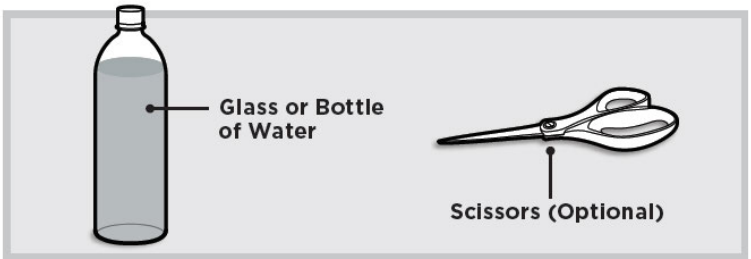
- Take 1 packet of LUMRYZ each day at bedtime.
- Avoid getting out of your bed after taking LUMRYZ. Some people fall asleep within 5 minutes of taking LUMRYZ and most will fall asleep within 15 minutes. The time it takes you to fall asleep might be different from night to night.
- Medicines that cause 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.
- Mix and take LUMRYZ within 30 minutes. If not taken 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 and all medicines out of the reach of children.
- Store LUMRYZ at room temperature, between 68°F to 77°F (20°C to 25°C).
- Store LUMRYZ in a clean and dry place.

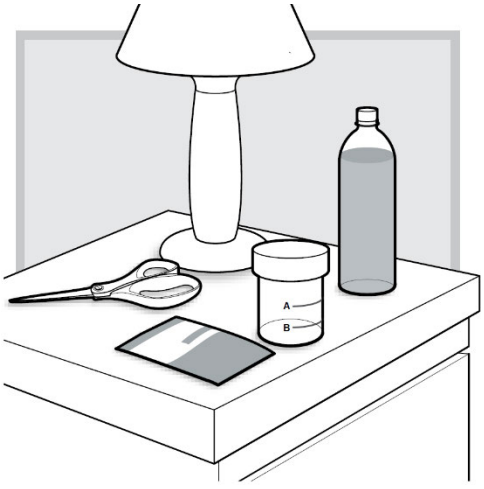
Before using LUMRYZ

- 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.



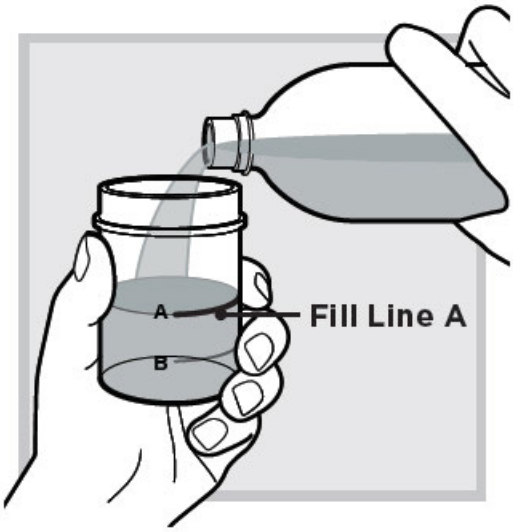
Gather the following supplies and place them on a flat surface at your bedside:

- 1 bottle or glass of water (1/3 cup). Do not use hot water.
- 1 LUMRYZ packet
- 1 clean mixing cup. - The cap is not child resistant.
- 1 pair of scissors (optional)

Mix the LUMRYZ solution at your bedside

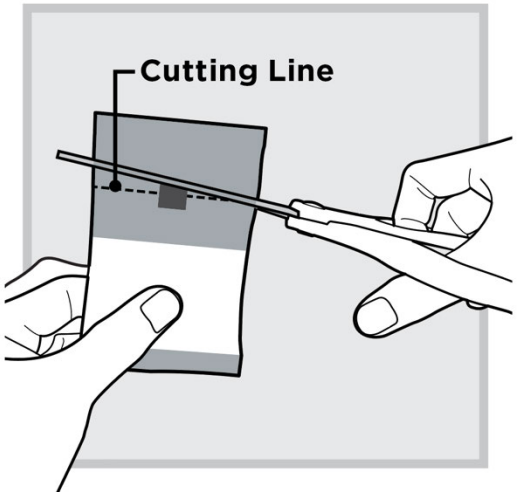
1.) At your bedside, open the mixing cup by twisting the cap to the left (counter-clockwise) to remove it.

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:

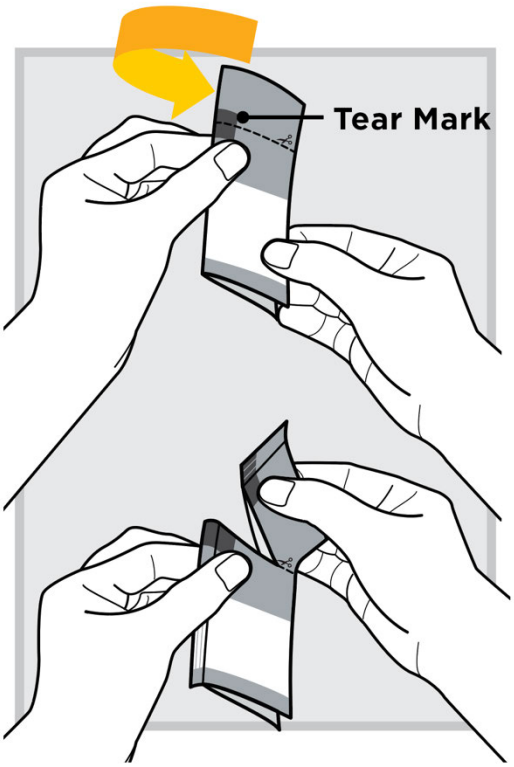
Use scissors to cut open the packet along the **Cutting Line**, located on the back of the packet.



-or-

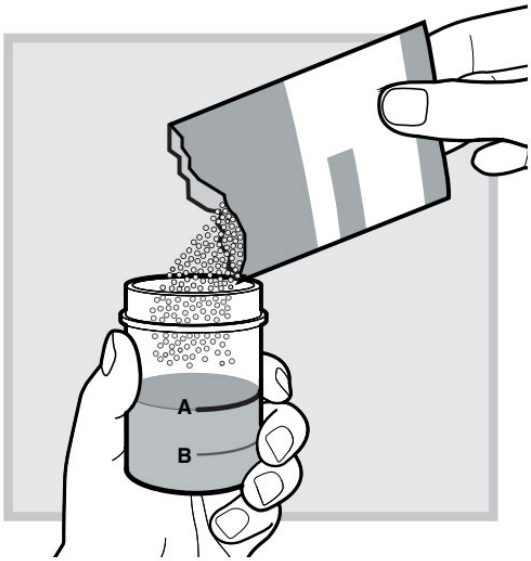
Fold the packet in half at the gray **Tear Mark** located on the back of the packet.

Tear the packet open with your hands.

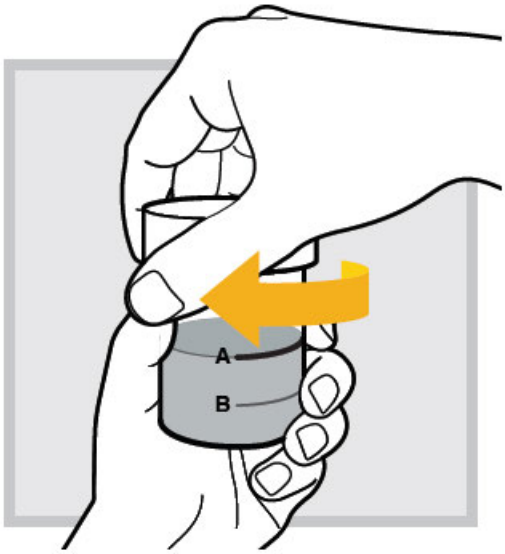


4.) Pour the entire content from the packet into the water-filled mixing cup.

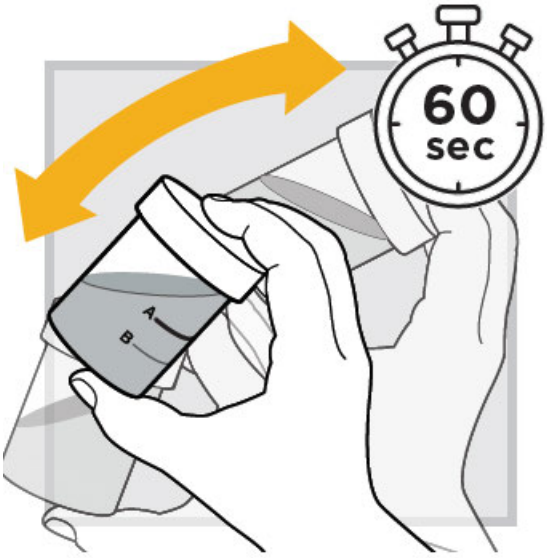
Make sure there is no powder left in the packet.



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

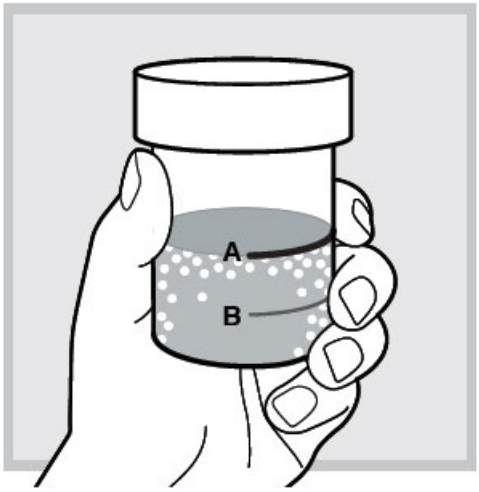


6.) Mix the water and powder solution by shaking the closed mixing cup well for at least **60 seconds (1 minute)**.



7.) Make sure the solution is mixed thoroughly.

The mixed solution will appear slightly milky with some lumps.



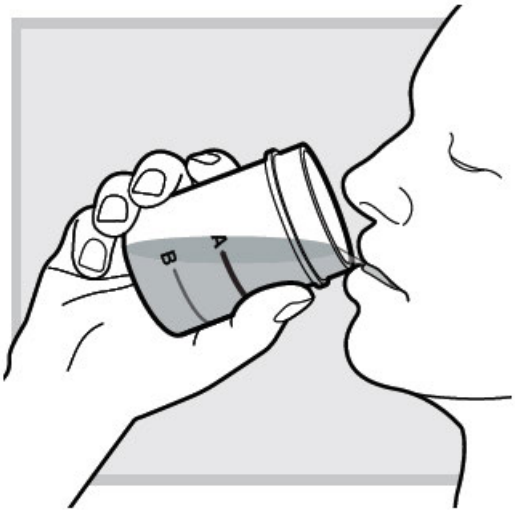
The mixing cup cap is not child resistant. If the mixed solution is not drank immediately, then do not remove the cap, and keep out of reach of children.

Take the LUMRYZ solution at your bedside

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

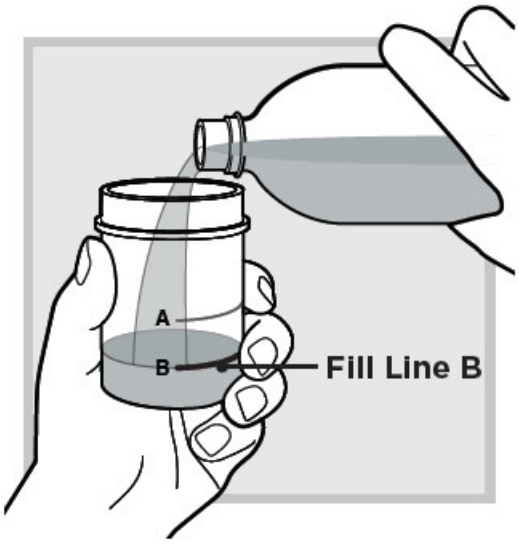
9.) While sitting in bed drink the mixed solution within **30 minutes** of mixing.

Make sure to drink all the mixed solution in the mixing cup.

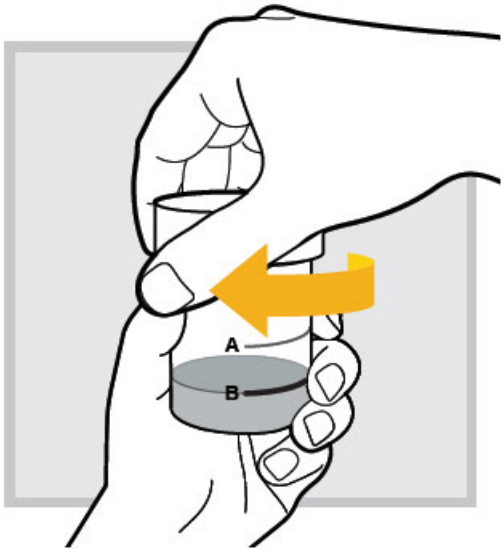


10.) Immediately refill your mixing cup with water up to **Fill Line B** (lower line) to mix in any medicine left in the mixing cup.

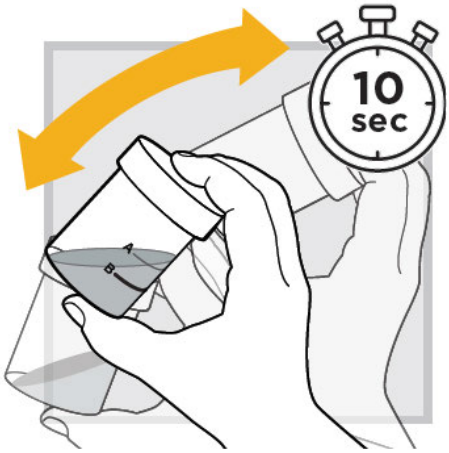
Do not open another packet of LUMRYZ. Take only 1 packet each day at bedtime.



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



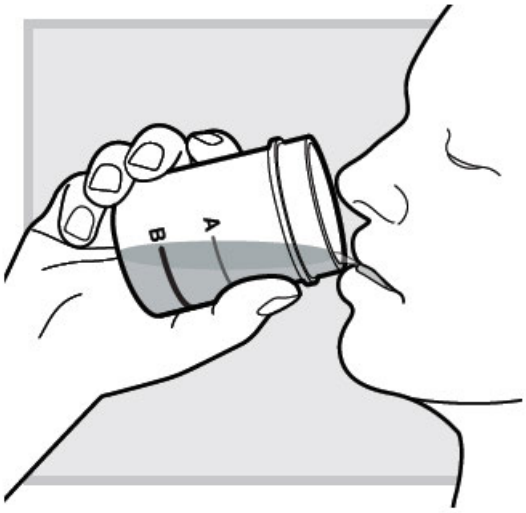
12.) Shake well again for **10 seconds**.



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

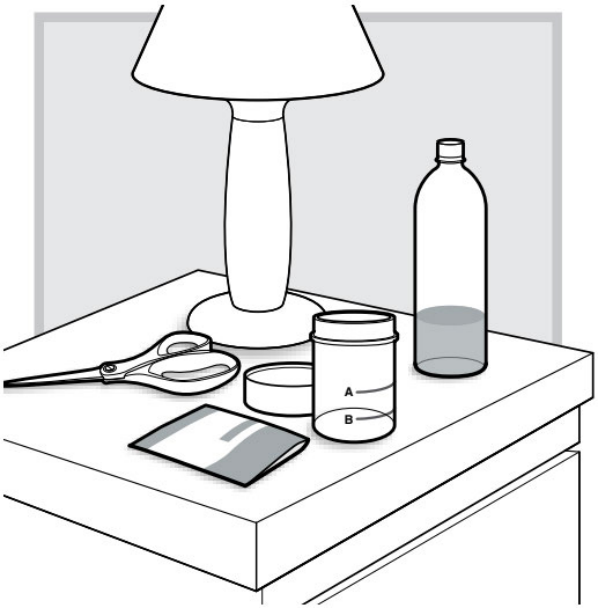
14.) Drink the mixed solution immediately after mixing.

Make sure to drink all the mixed solution in the mixing cup.



15.) Leave the empty mixing cup at your bedside and immediately lie down to go to sleep.

Avoid getting out of your bed after taking your dose.

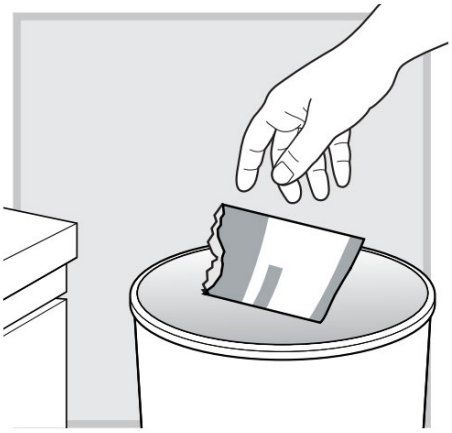


Continue to Step 16

How do I throw away (dispose of) LUMRYZ?

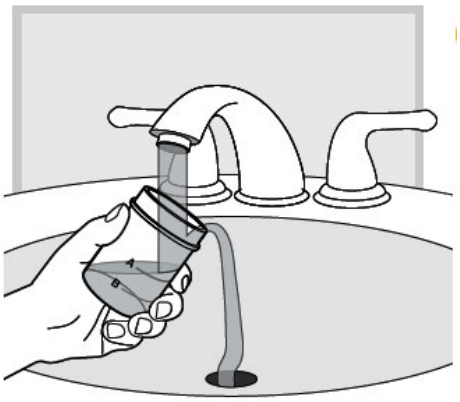
16.) The next day, place the empty LUMRYZ packet in the trash.

If any LUMRYZ remains in the packet, rinse it down the sink prior to disposal.



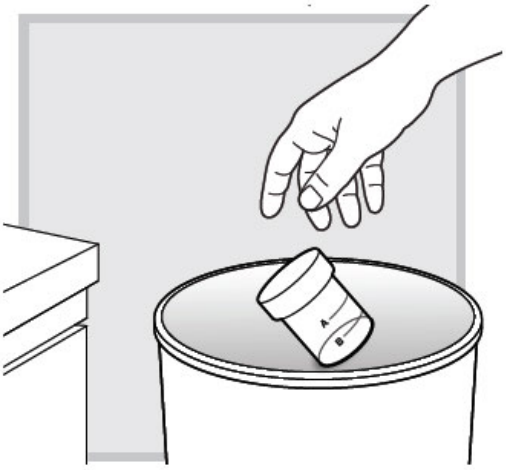
17.) Empty any unused LUMRYZ down the sink drain the next day.

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



After you finish all of the packets in your LUMRYZ carton

After you have finished your 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:
Avadel CNS Pharmaceuticals, LLC
Chesterfield, MO 63005 USA

For more information on LUMRYZ,
visit **www.lumryz.com** or call
888-8AVADEL (888-828-2335).

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

Manufactured for:
Avadel CNS Pharmaceuticals, LLC
Chesterfield, MO 63005 USA

Avadel™

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Revised: 09-2024

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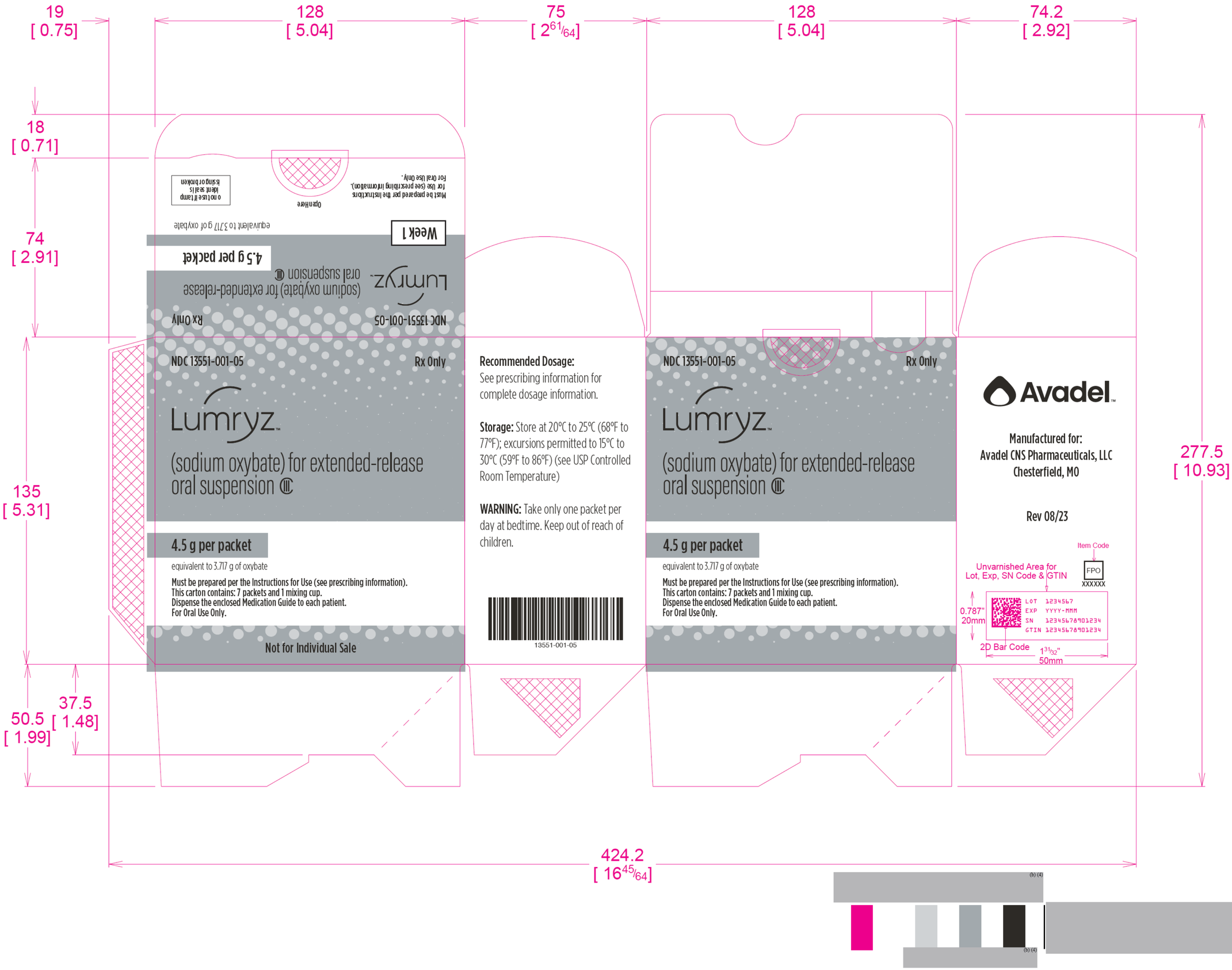

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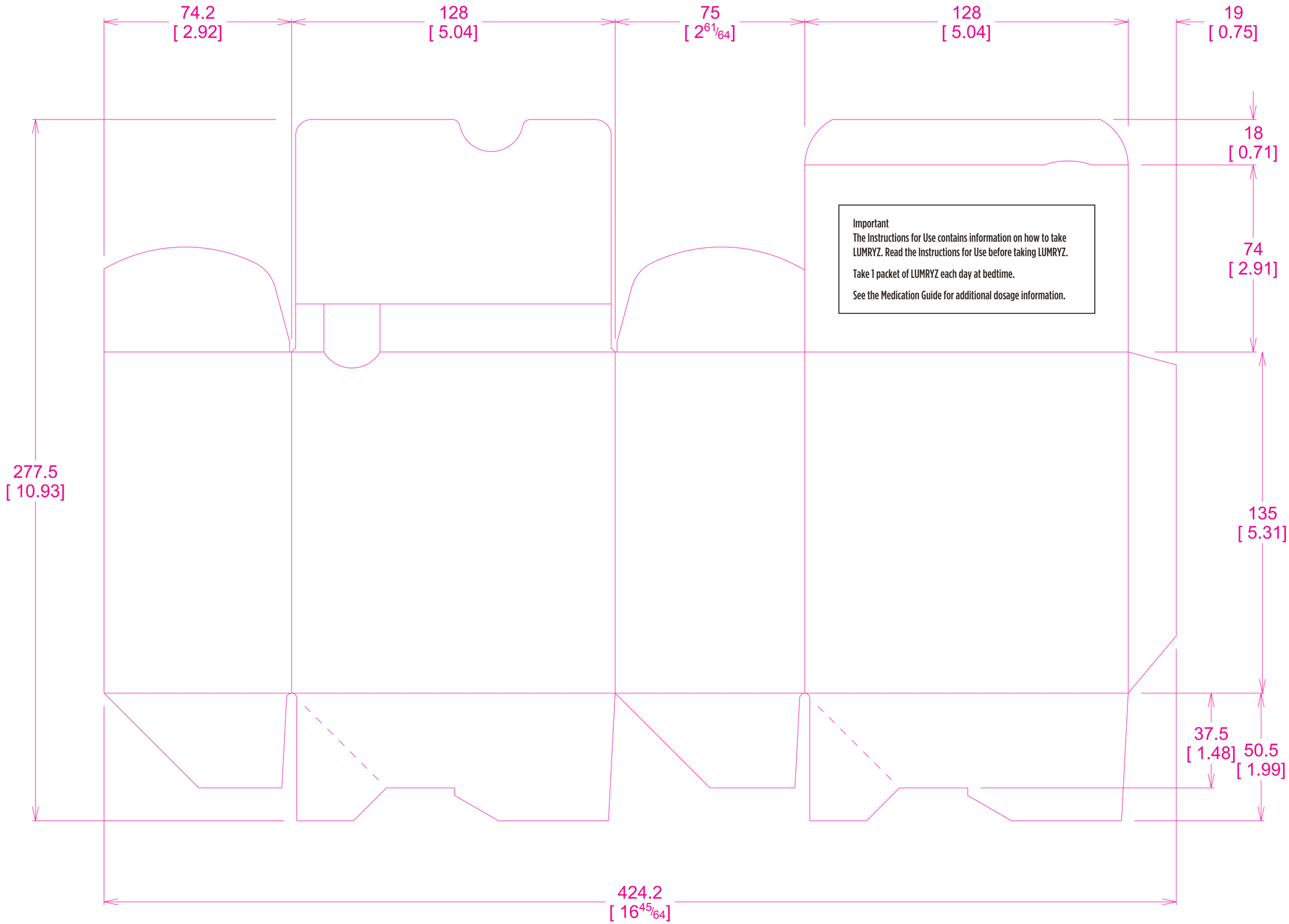

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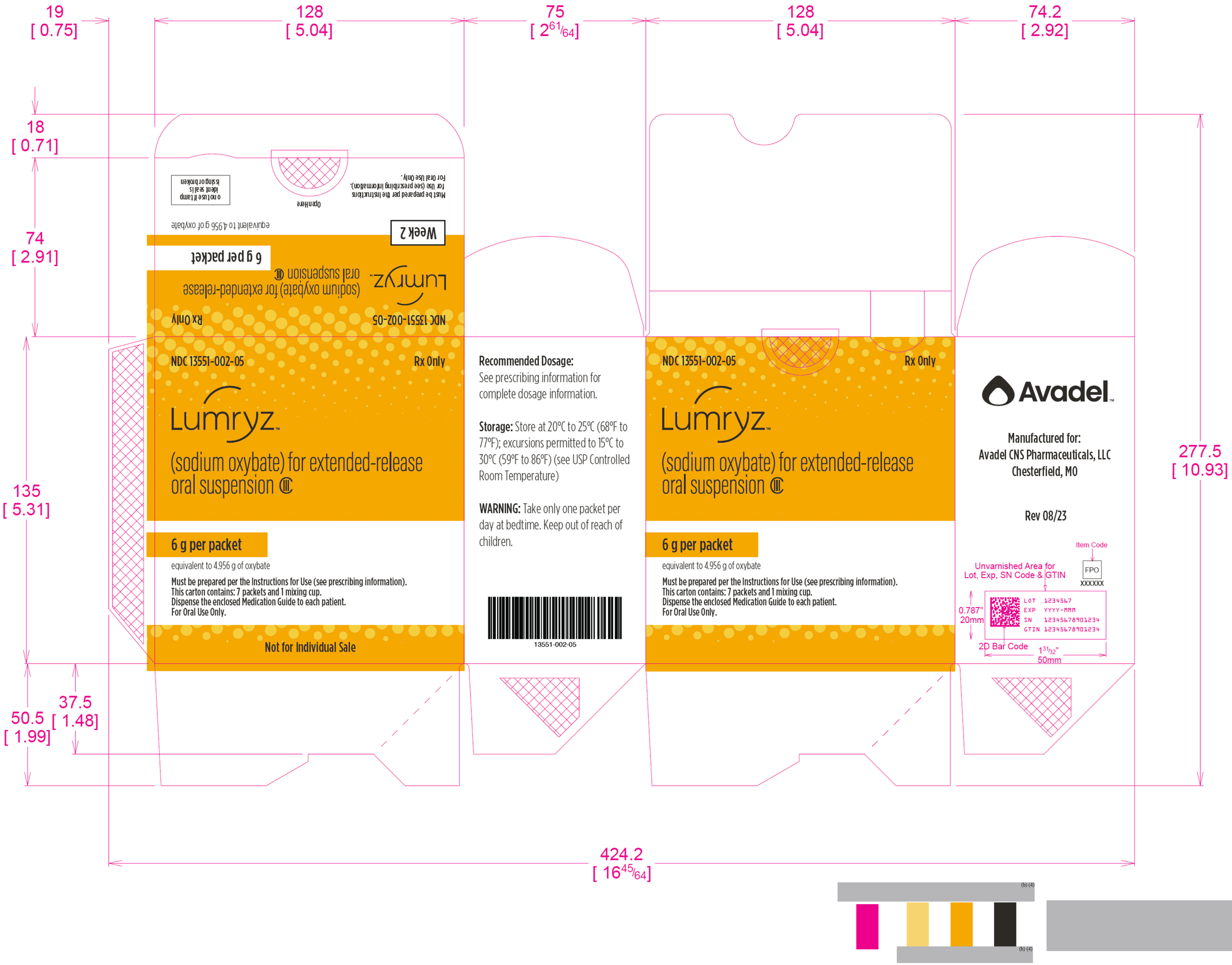

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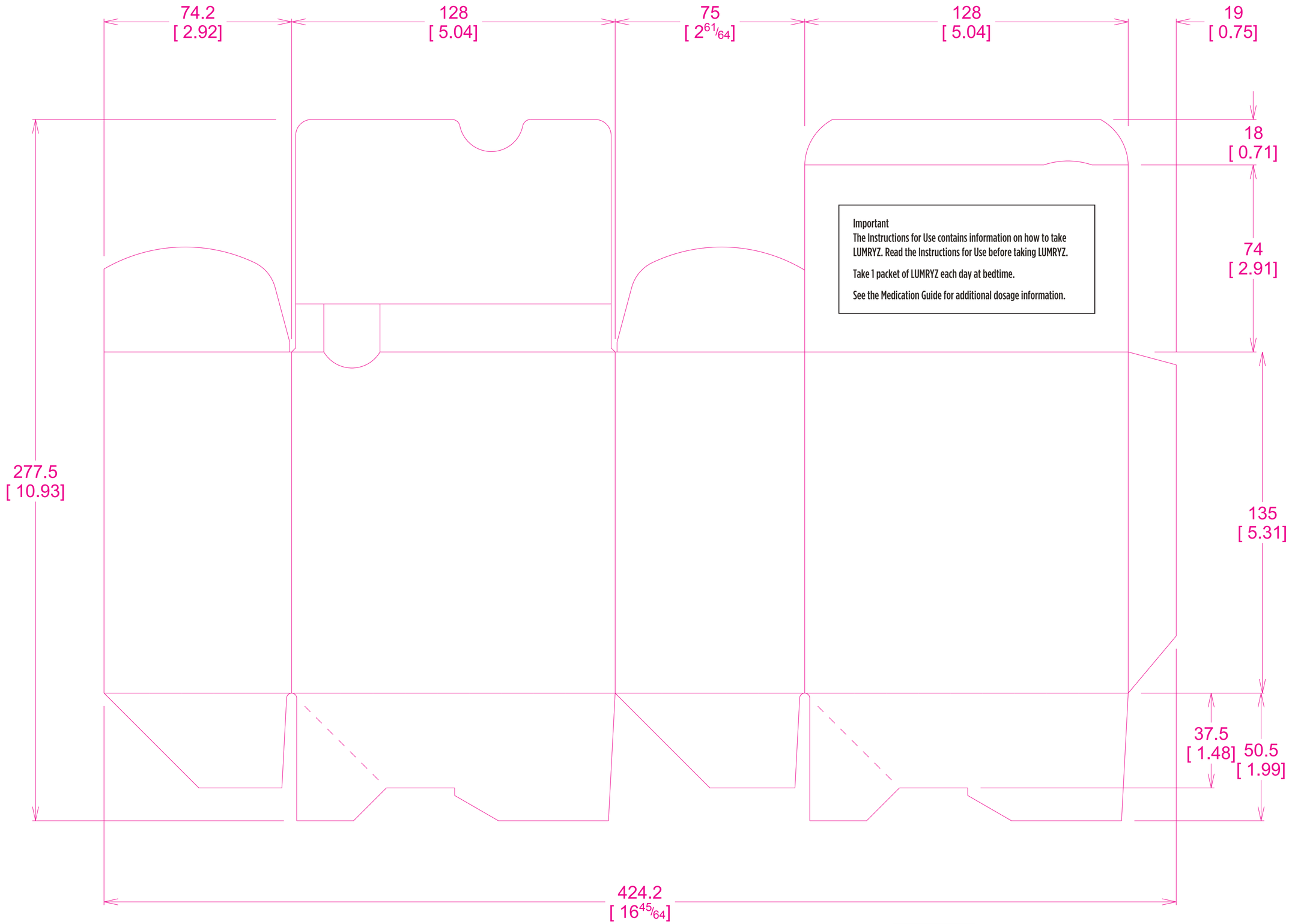

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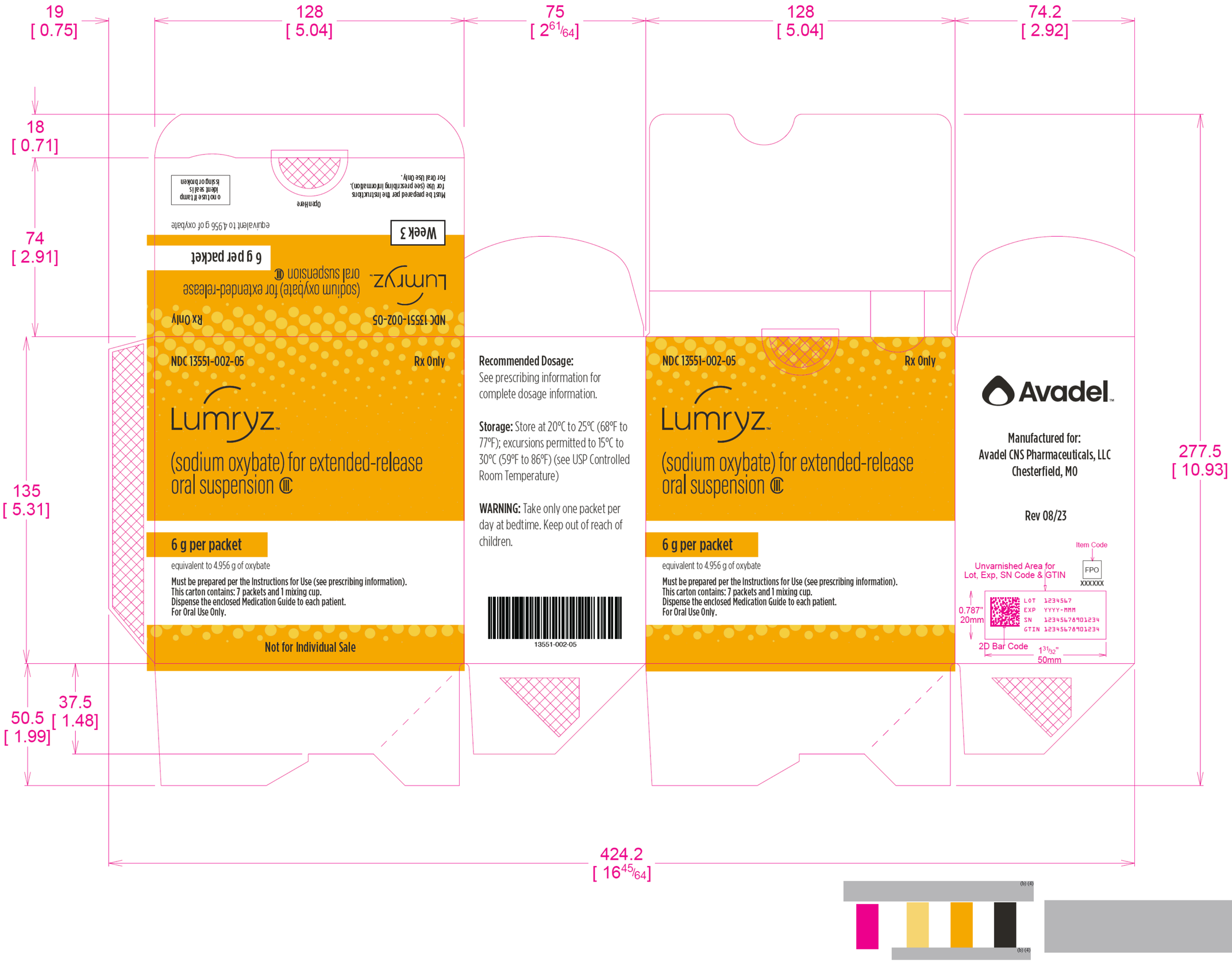

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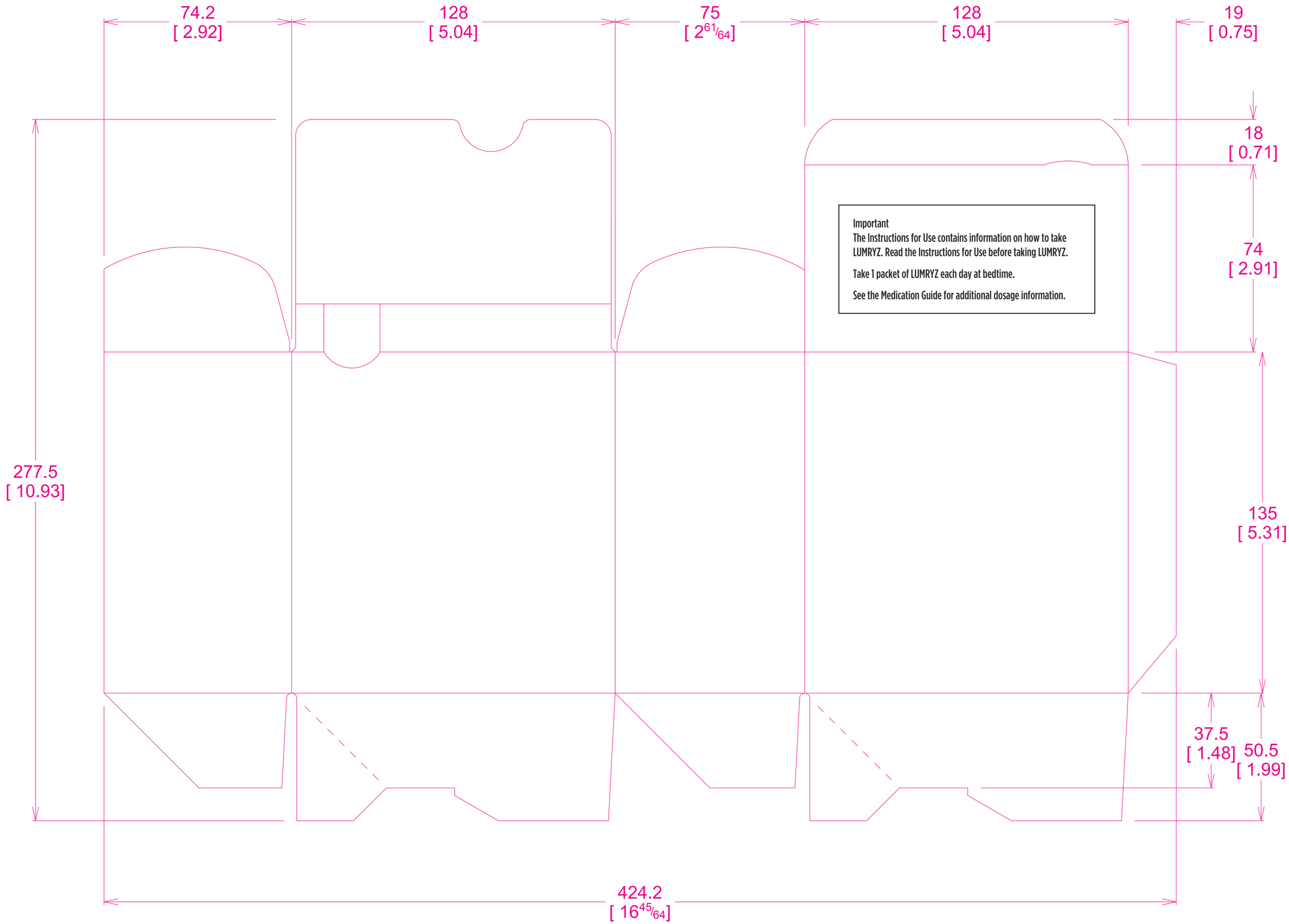

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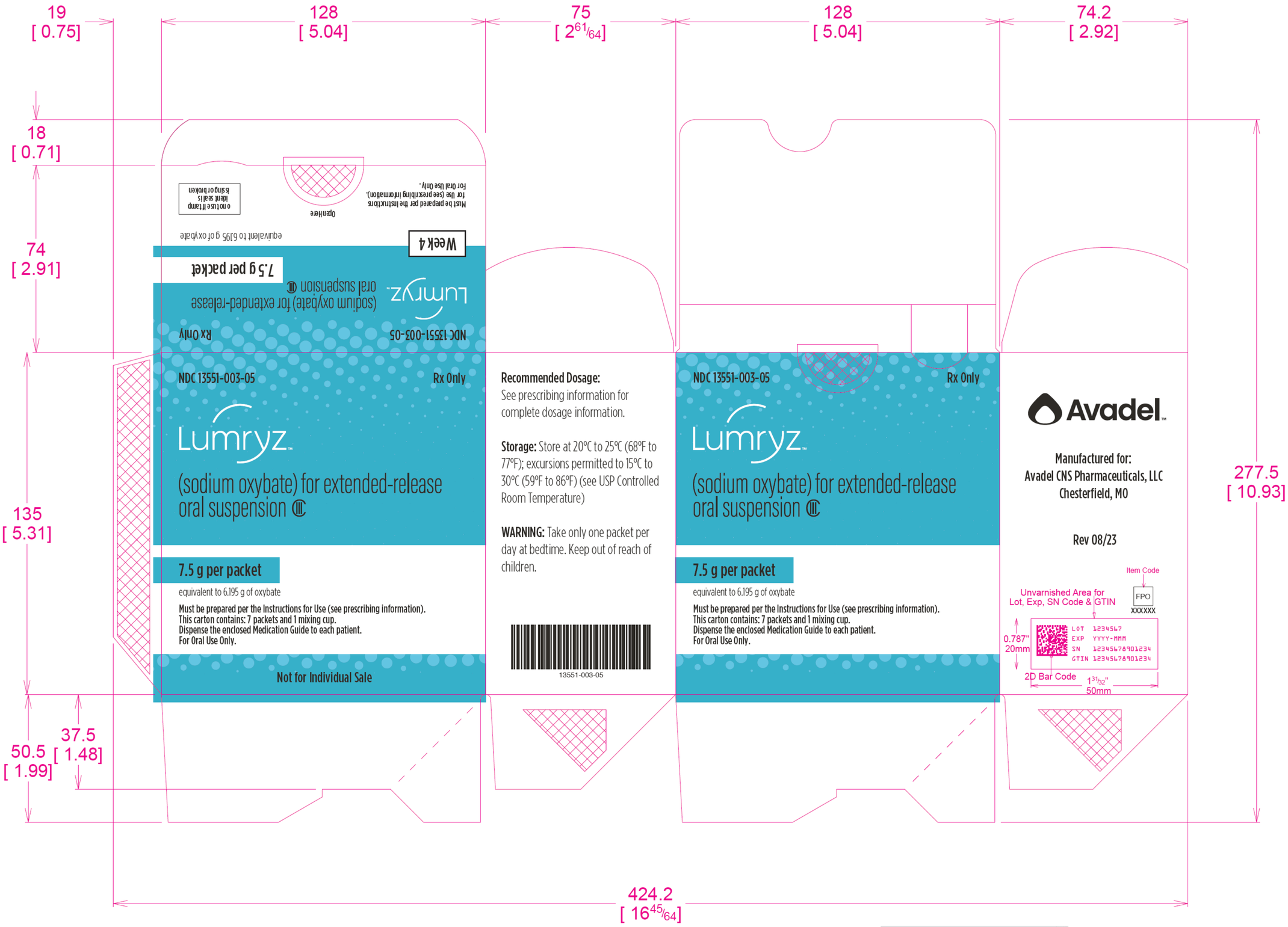

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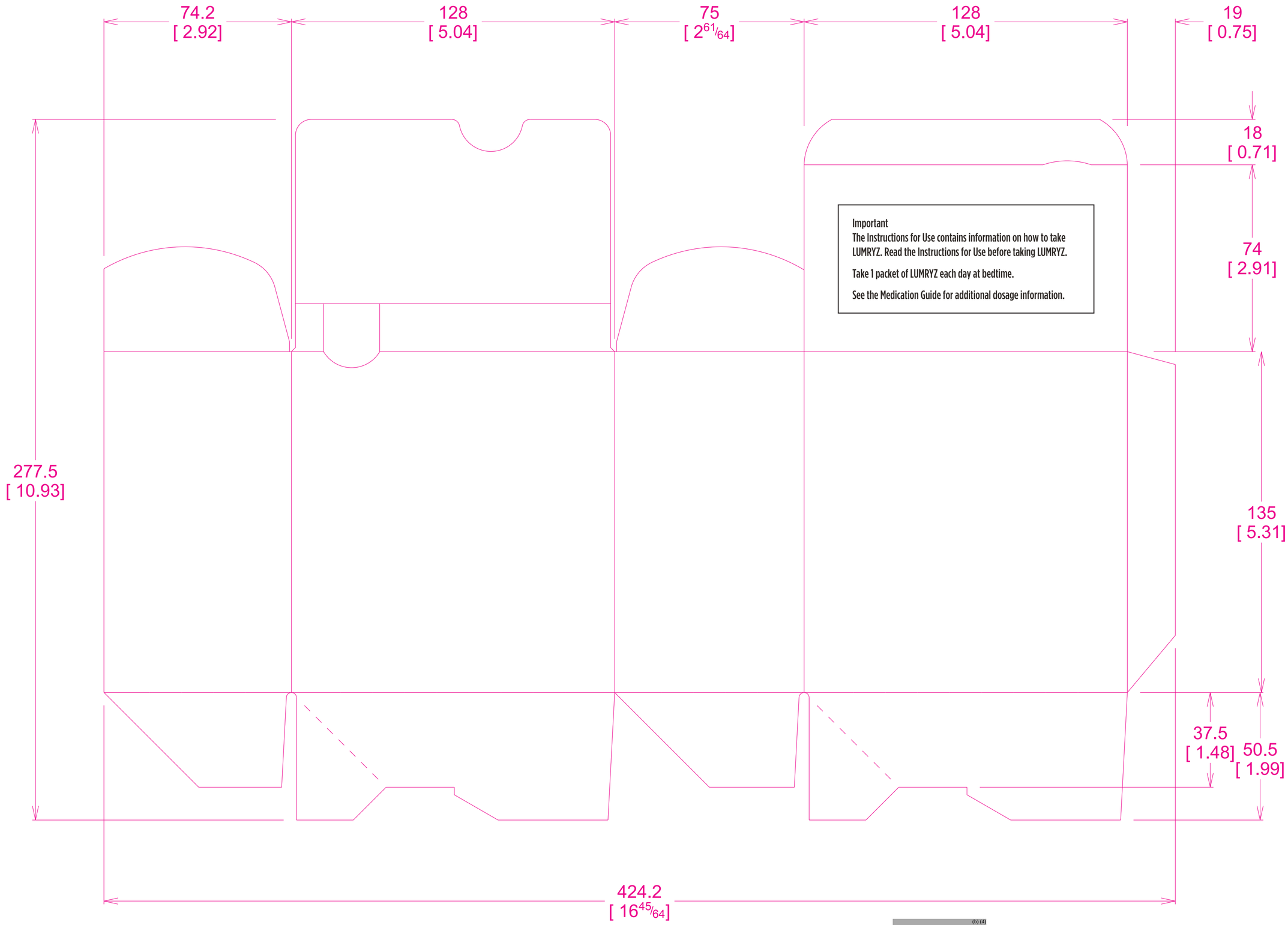

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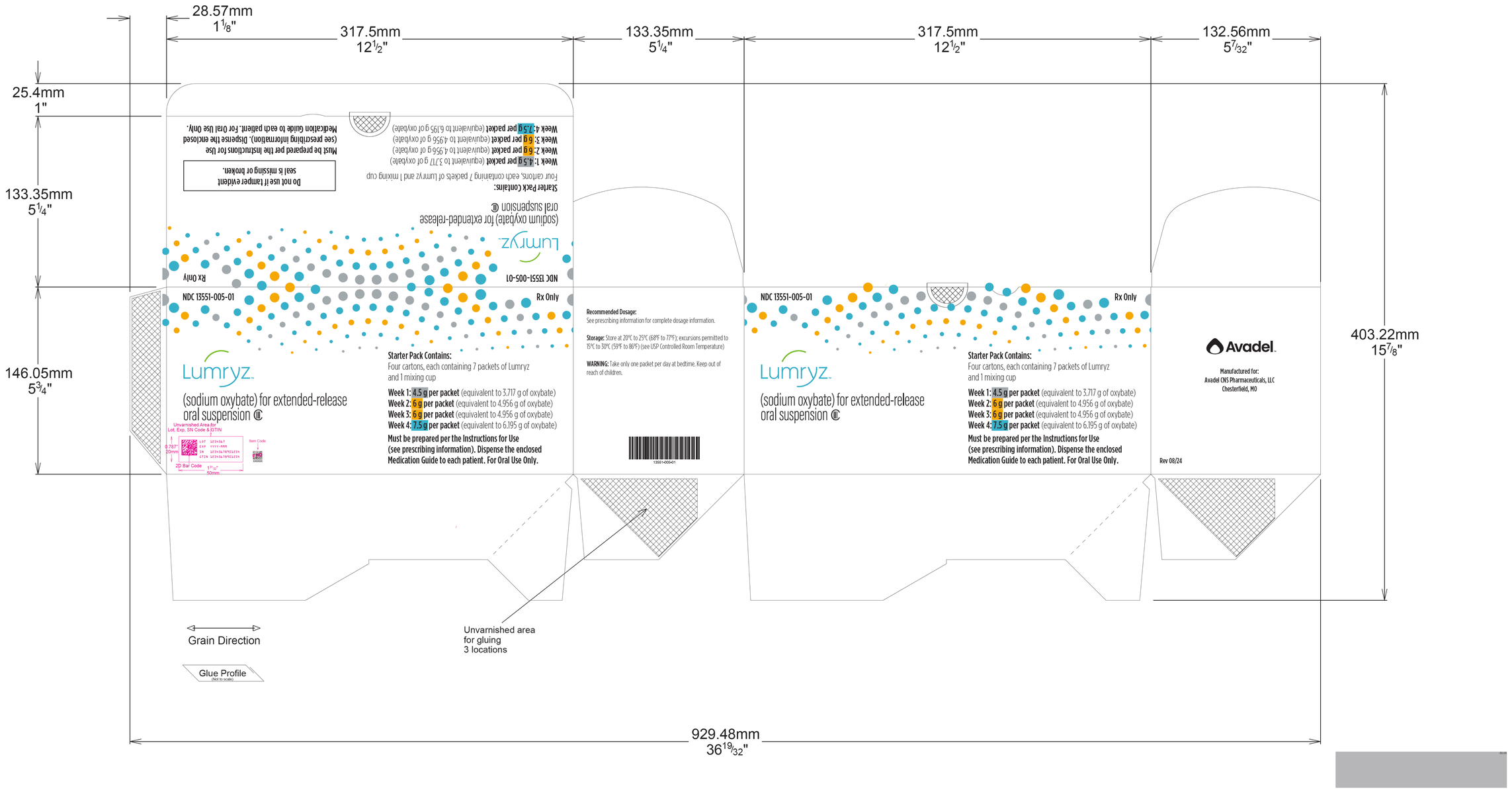


Lumryz™
(sodium oxybate) for extended-release oral suspension Ⓒ

Starter Pack Contains:
Four cartons, each containing 7 packets of Lumryz and 1 mixing cup

Week 1: 4.5 g per packet (equivalent to 3.717 g of oxybate)
Week 2: 6 g per packet (equivalent to 4.956 g of oxybate)
Week 3: 6 g per packet (equivalent to 4.956 g of oxybate)
Week 4: 7.5 g per packet (equivalent to 6.195 g of oxybate)

Must be prepared per the Instructions for Use (see prescribing information). Dispense the enclosed Medication Guide to each patient. For Oral Use Only.

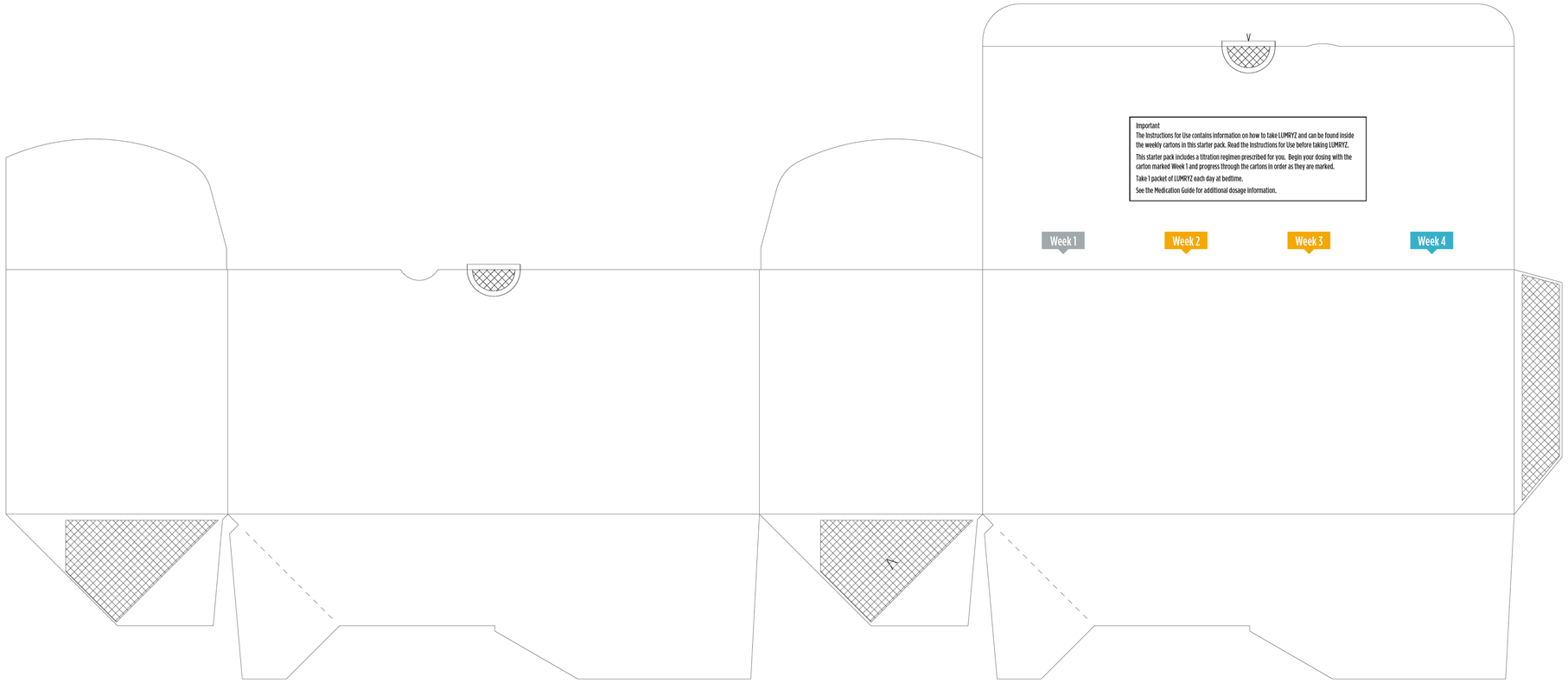
Do not use if tamper evident seal is missing or broken.

NDC 13551-005-01 Rx Only

Lumryz™
(sodium oxybate) for extended-release oral suspension Ⓒ

Reference ID: 5440567

INSIDE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Important
The Instructions for Use contains information on how to take LUMRYZ and can be found inside the weekly cartons in this starter pack. Read the Instructions for Use before taking LUMRYZ.
This starter pack includes a titration regimen prescribed for you. Begin your dosing with the carton marked Week 1 and progress through the cartons in order as they are marked.
Take 1 packet of LUMRYZ each day at bedtime.
See the Medication Guide for additional dosage information.
Week 1
Week 2
Week 3
Week 4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s007

REMS

Risk Evaluation and Mitigation Strategy (REMS) Document

LUMRYZ™ (sodium oxybate extended-release) REMS

I. Administrative Information

Risk: serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion
Application Number: NDA 214755
Application Holder: Avadel CNS Pharmaceuticals, LLC
Initial REMS Approval: 05/2023
Most Recent REMS Update: 09/2024

II. REMS Goal

The goal of the LUMRYZ REMS is to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of LUMRYZ by:

1. Informing prescribers, pharmacists, and patients of:
    a. The risk of significant central nervous system (CNS) and respiratory depression associated with LUMRYZ
    b. The contraindication of use of LUMRYZ with sedative hypnotics or alcohol
    c. The potential for abuse, misuse, and overdose associated with LUMRYZ
    d. The safe use, handling, and storage of LUMRYZ
2. Ensuring that pharmacy controls exist prior to filling prescriptions for LUMRYZ that:
    a. Screen for concomitant use of sedative hypnotics and other potentially interacting agents
    b. Monitor for inappropriate prescribing, misuse, abuse, and diversion of LUMRYZ
    c. Notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion

III. REMS Requirements

Avadel CNS Pharmaceuticals, LLC must ensure that healthcare providers, patients, pharmacies, and wholesalers, distributors, and other entities that distribute LUMRYZ comply with the following requirements:

1. Healthcare providers who prescribe LUMRYZ must:

To become certified to prescribe	1. Review the drug's Prescribing Information. 2. Review the following: Prescriber Brochure. 3. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS.

Before treatment initiation (first dose)	4. Assess the patient's health status to determine if LUMRYZ is medically appropriate by screening for history of alcohol and drug abuse, sleep-related breathing disorders, compromised respiratory function, depression or suicidality. Document and submit to a certified pharmacy using the Prescription Form. 5. Assess the patient's health status to determine if LUMRYZ is medically appropriate by screening for concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents. Document and submit to a certified pharmacy using the Prescription Form. 6. Counsel the patient on the serious risks and safe use, handling, and storage of LUMRYZ using the Patient Brochure. 7. Enroll the patient by completing and submitting the Patient Enrollment Form to the REMS. 8. Order the prescription using the Prescription Form and submit it to a certified pharmacy.
Before treatment re-initiation	9. For patients disenrolled for suspicion of abuse, misuse, or diversion: Communicate with the pharmacy regarding all relevant patient history and re-enroll the patient if the prescriber and pharmacist agree. 10. For patients with a lapse in treatment of 6 months or longer: Order the prescription using the Prescription Form and submit it to a certified pharmacy.
During treatment; within the first 3 months of starting treatment and recommended every 3 months thereafter	11. Assess the patient for concomitant use of sedative hypnotics, other CNS depressants, or potentially interacting agents, serious adverse events, and signs of abuse and misuse, including an increase in dose or frequency of dosing, reports of lost, stolen, or spilled medication, and drug-seeking behavior.
At all times	12. Report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death; and any cases of suspected abuse, misuse, or diversion to Avadel CNS Pharmaceuticals, LLC. 13. Assess the patient's potential for abuse, misuse, and diversion. Document and submit all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug using the Risk Management Report. 14. Report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the Risk Management Report.

2. Patients who are prescribed LUMRYZ:

Before treatment initiation	1. Review the Patient Brochure. 2. Receive counseling from the prescriber on the serious risks associated with LUMRYZ and safe use, handling, and storage of LUMRYZ using the Patient Brochure.

	3. Enroll in the REMS by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS. 4. Complete the Patient Counseling Checklist with the pharmacist.
During treatment	5. Adhere to the safe use conditions described in the Patient Brochure. 6. Complete the Patient Counseling Checklist with the pharmacist based on changes in medication and/or medical history.
During treatment; within the first 3 months of starting treatment and recommended every 3 months thereafter	7. Be monitored by your prescriber for concomitant use of sedative hypnotics, other CNS depressants, or potentially interacting agents; serious adverse events; signs of abuse and misuse, including an increase in dose or frequency of dosing; reports of lost, stolen, or spilled medication; and drug-seeking behavior.
Before treatment re-initiation, after lapse in treatment for 6 months or longer	8. Complete the Patient Counseling Checklist with the pharmacist.
At all times	9. Inform your prescriber and the pharmacy about any new medications you may be taking or medical conditions you may have.

3. Pharmacies that dispense LUMRYZ must:

To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy. 2. Have the authorized representative review Certified Pharmacy Training Program – Pharmacy Staff Module and Pharmacist Module. 3. Have the authorized representative successfully complete the Pharmacy Staff Knowledge Assessment and Pharmacist Knowledge Assessment and submit both to the REMS. 4. Have the authorized representative enroll in the REMS by completing and submitting the Pharmacy Enrollment Form. 5. Train all relevant staff involved in dispensing using the Certified Pharmacy Training Program – Pharmacy Staff Module. 6. Have all relevant staff involved in dispensing successfully complete the Pharmacy Staff Knowledge Assessment and submit it to the REMS. 7. Train all pharmacists involved in dispensing using the Certified Pharmacy Training Program – Pharmacy Staff Module and the Pharmacist Module. 8. Have all pharmacists involved in dispensing successfully complete the Pharmacy Staff Knowledge Assessment and Pharmacist Knowledge Assessment and submit both to the REMS.

	9. Establish processes and procedures to assess the patient's concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents that either are unknown to the prescriber or pose a high risk of serious interaction. 10. Establish processes and procedures to verify the following: the patient and prescriber are enrolled, the patient has no other active LUMRYZ prescriptions. 11. Establish processes and procedures to verify and document the following by contacting all other REMS for oxybate products: the patient has no other active prescriptions that overlap with the current prescription for LUMRYZ by obtaining oxybate prescription information of last dispense date, days' supply, and prescriber's name; and the patient and prescriber have not been disenrolled from any of the REMS for oxybate products for suspected abuse, misuse, or diversion. 12. Establish processes and procedures to verify all prescription information including patient name and two additional identifiers, prescriber name and information, dose, titration information (if applicable), number of refills, dosing directions, total quantity (days' supply), and concomitant medications. 13. Establish processes and procedures to assess the patient's potential for abuse, misuse, and diversion by reviewing the alerts and Risk Management Report histories in the REMS. 14. Establish processes and procedures to provide 24-7 toll-free access to a LUMRYZ REMS trained pharmacist; to dispense no more than a one-month supply for the initial shipment and no more than a three-month supply for subsequent shipments; and to ship, track, and verify receipt of LUMRYZ to the patient or patient-authorized adult designee using an overnight service. 15. Establish processes and procedures to report each prescription filled for LUMRYZ to all other REMS for oxybate products and document to the REMS. 16. Establish processes and procedures to reconcile LUMRYZ inventory using the pharmacy's inventory management system. 17. Establish processes and procedures to provide dispensing data and shipment and receipt dates to the REMS.
Before dispensing	18. For new patients and existing patients who restart treatment after not receiving LUMRYZ for 6 months or longer: Counsel the patient using the Patient Counseling Checklist. Document and submit to the REMS. 19. For patients who report a change in their medication use or medical history: Document and submit the change to the REMS using the Patient Counseling Checklist. 20. Assess the patient's concomitant use of sedative hypnotics, other CNS depressants, or potentially interacting agents that either are unknown to the prescriber or pose a high risk of serious interaction through the processes and procedures established as a requirement of the REMS. 21. Verify in this REMS that the patient has no other active LUMRYZ prescriptions through the processes and procedures established as a requirement of the REMS. Document and submit to the REMS.

	22. Verify the following by contacting all other REMS for oxybate products through the processes and procedures established as a requirement of the REMS: the patient has no other active prescriptions for oxybate products that overlap with the current prescription for LUMRYZ by obtaining oxybate prescription information of last dispense date, days' supply, and prescriber's name; and the patient and prescriber have not been disenrolled from any other REMS for oxybate products for suspected abuse, misuse, or diversion. Document and submit to the REMS. 23. Assess the patient's and their prescriber's potential for abuse, misuse, and diversion by reviewing the alerts and Risk Management Report history in the REMS. Document the confirmation to the REMS. 24. Obtain authorization by contacting the REMS to verify the pharmacy is certified, the prescriber is certified, the patient is enrolled, the Patient Counseling Checklist is completed as required, the alerts and Risk Management Report history for the patient and their prescriber are reviewed by the pharmacist, and the patient has no active, overlapping prescriptions for oxybate products. 25. For patients previously disenrolled for suspicion of abuse, misuse, or diversion: Communicate all relevant patient history to the prescriber and determine whether to re-enroll the patient if the prescriber and pharmacist agree. 26. Verify the patient's prescription information including patient name and two additional identifiers, prescriber name and information, dose, titration information (if applicable), number of refills, dosing directions, total quantity (days' supply), and concomitant medications through the processes and procedures established as a requirement of the REMS. 27. For patients who request an early refill or if abuse, misuse or diversion is suspected: Discuss the request or concern with the prescriber. 28. Dispense no more than a one-month (30 day) supply for the initial shipment. 29. Dispense no more than a three-month (90 day) supply for subsequent shipments.
After dispensing, within 1 business day	30. Report each prescription filled for LUMRYZ to all REMS for oxybate products through the processes and procedures established as a requirement of the REMS. Document and submit to the REMS.
Before shipping	31. Verify the patient's shipping address and that the patient or patient-authorized adult designee will be available to receive the shipment through the processes and procedures established as a requirement of the REMS. 32. Ship LUMRYZ directly to each patient or a patient-authorized adult designee through the processes and procedures established as a requirement of the REMS. 33. Provide new patients with the Patient Brochure with their first shipment.
After shipping	34. Track and verify receipt of each shipment of LUMRYZ through the processes and procedures established as a requirement of the REMS. 35. Document and submit the dispensing data, and shipment and receipt dates to the REMS.

To maintain certification to dispense	36. Have a new authorized representative review Certified Pharmacy Training Program – Pharmacy Staff Module and Pharmacist Module. 37. Have a new authorized representative successfully complete the Pharmacy Staff Knowledge Assessment and Pharmacist Knowledge Assessment and submit both to the REMS. 38. Have a new authorized representative enroll in the REMS by completing the Pharmacy Enrollment Form and submitting it to the REMS.
To maintain certification to dispense, every year	39. Train all relevant staff involved in dispensing LUMRYZ using the Certified Pharmacy Training Program – Pharmacy Staff Module. 40. Have all relevant staff involved in dispensing LUMRYZ successfully complete the Pharmacy Staff Knowledge Assessment and submit it to the REMS. 41. Train all pharmacists involved in dispensing LUMRYZ using the Certified Pharmacy Training Program – Pharmacy Staff Module and Pharmacist Module. 42. Have all pharmacists involved in dispensing LUMRYZ successfully complete the Pharmacy Staff Knowledge Assessment and Pharmacist Knowledge Assessment and submit both knowledge assessments to the REMS.
At all times	43. Provide 24-7 toll-free access to a REMS trained pharmacist. 44. Ship LUMRYZ directly to the patient or a patient-authorized adult designee using an overnight service. 45. Document and report all potential adverse events reported by all sources, including any CNS depression, respiratory depression, loss of consciousness, coma, and death to Avadel CNS Pharmaceuticals, LLC. 46. Report lost, stolen, destroyed, or spilled drug to the REMS using the Risk Management Report. 47. Monitor all instances of patient and prescriber behavior that give rise to a reasonable suspicion of abuse, misuse, and diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug. Report to the REMS by completing and submitting a Risk Management Report. 48. Report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the Risk Management Report. 49. Not distribute, transfer, loan, or sell LUMRYZ. 50. Not stock LUMRYZ in retail pharmacies. 51. Maintain records of staff training and completion of knowledge assessments. 52. Maintain records of inventory reconciliation using the pharmacy's inventory management system. 53. Maintain records of all processes and procedures including compliance with those processes and procedures.

	54. Comply with audits carried out by Avadel CNS Pharmaceuticals, LLC or a third party acting on behalf of Avadel CNS Pharmaceuticals, LLC to ensure all processes and procedures are in place and are being followed.

4. Wholesalers, distributors, and other entities that distribute LUMRYZ must:

To be able to distribute	1. Establish processes and procedures to ensure that the drug is distributed only to certified pharmacies. 2. Train all relevant staff involved in distributing LUMRYZ on the REMS requirements.
At all times	3. Distribute only to certified pharmacies. 4. Maintain records of all drug distributions. 5. Comply with audits carried out by Avadel CNS Pharmaceuticals, LLC or a third party acting on behalf of Avadel CNS Pharmaceuticals, LLC to ensure all processes and procedures are in place and are being followed.

Avadel CNS Pharmaceuticals, LLC must provide training to healthcare providers who prescribe LUMRYZ.
The training includes the following educational material: Prescriber Brochure. The training must be available on the REMS website and delivered by Avadel CNS Pharmaceuticals, LLC.

Avadel CNS Pharmaceuticals, LLC must provide training to the pharmacies that dispense LUMRYZ.
The training includes the following educational materials: Certified Pharmacy Training Program – Pharmacy Staff Module and Pharmacist Module, Pharmacy Staff Knowledge Assessment, and Pharmacist Knowledge Assessment. The training must be available on the REMS website and delivered by Avadel CNS Pharmaceuticals, LLC.

To inform healthcare providers about the REMS and the risks and safe use of LUMRYZ, Avadel CNS Pharmaceuticals, LLC must disseminate REMS communication materials according to the table below:

Target Audience	Communication Materials & Dissemination Plans
Healthcare providers who are likely to prescribe LUMRYZ	REMS Letters: Healthcare Provider REMS Letter, Professional Society REMS Letter, with attachments LUMRYZ Prescribing Information, Fact Sheet 1. Email within 14 calendar days of the date LUMRYZ is first commercially distributed and 30 calendar days later. a. Send by mail within 30 calendar days of the date the first email was sent if a healthcare provider's email address is not available or the email is undeliverable. b. Send a second email within 30 calendar days of the date the first email was sent if the first email is marked as unopened. c. Send by mail within 30 calendar days of the date the second email was sent if the second email is marked as unopened. 2. Disseminate through the following professional societies and request the letter or content be provided to their members: a. American Academy of Neurology, American College of Chest Physicians, Academy American of Sleep Medicine,

	National Institute of Neurological Disorders and Stroke, National Organization for Rare Disorders, American Psychiatric Association, Society of General Internal Medicine, American College of Physicians – Internal Medicine Society, American Academy of Family Physicians, American Academy of Physician Assistants, and American Association of Nurse Practitioners.

To support REMS operations, Avadel CNS Pharmaceuticals, LLC must:

1. Not stock LUMRYZ in retail pharmacies.

2. Authorize dispensing for each patient after verifying the pharmacy is certified, the prescriber is certified, the patient is enrolled, the Patient Counseling Checklist is completed as required, the alerts and Risk Management Report history for the patient and their prescriber are reviewed by the pharmacist, and the patient has no active, overlapping prescriptions for oxybate products.

3. Establish and maintain a REMS website: www.LUMRYZREMS.com. The REMS website must include the capability to complete prescriber certification online, complete pharmacy staff and pharmacist knowledge assessments, the capability to enroll and manage patients online, including the capability for pharmacies to obtain an authorization to dispense, complete the Risk Management Report, complete the Patient Counseling Checklist, and the option to print the Prescribing Information, Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS website. The REMS website must not link to promotional product website(s).

4. Make the REMS website fully operational and all REMS materials available through the REMS website and call center by the date LUMRYZ is first commercially distributed.

5. Establish and maintain a REMS call center for REMS participants at 1-877-453-1029.

6. Establish and maintain validated, secure, separate and distinct databases of all REMS participants enrolled, certified and/or disenrolled in the REMS, including a patient database, certified prescriber database, certified pharmacy database, and disenrolled prescriber database that will be queried independently through electronic verification.

7. Ensure prescribers are able to submit the Prescriber Enrollment Form online and by fax.

8. Ensure certified prescribers are able to submit the Patient Enrollment Form online and by fax.

9. Ensure certified prescribers are able to submit the Prescription Form by fax and mail to a certified pharmacy.

10. Ensure certified prescribers are able to add refills and renew prescriptions by phone, fax, mail, and electronically.

11. Ensure patients are able to change certified prescribers.

12. Ensure pharmacies are able to submit the Pharmacy Enrollment Form by fax.

13. Ensure certified pharmacies are able to obtain authorization to dispense LUMRYZ online, including through the pharmacy's pharmacy management system, and by phone.

14. Ensure certified pharmacies and prescribers are able to report lost, stolen, destroyed or spilled LUMRYZ by completing and submitting a Risk Management Report to the REMS online and by fax.

15. Ensure certified pharmacies are able to submit the Patient Counseling Checklist by fax and online.

16. Ensure certified pharmacies are able to verify that the patient has no other active, overlapping prescriptions for oxybate products and that the patient and prescriber have not been disenrolled from any REMS for oxybate products for suspected abuse, misuse, or diversion by phone.

17. Ensure certified pharmacies are able to report by phone and online that the patient has no other active, overlapping prescriptions of oxybate products and that the patient and prescriber have not been disenrolled from any REMS for oxybate products for suspected abuse, misuse, or diversion.

18. Ensure certified pharmacies and certified prescribers are able to create an alert in the patient's profile for repeated incidents of lost, stolen, destroyed, or spilled drug by completing and submitting a Risk Management Report online and by fax.

19. Ensure certified pharmacies and prescribers are able to access alerts and Risk Management Report histories by phone and online.

20. Ensure certified pharmacies are able to report completion of the review of alerts and Risk Management Report histories of the patient and their prescriber by the pharmacist by submitting confirmation by phone and online.

21. Ensure certified pharmacies and certified prescribers are able to request to disenroll patients for incidents suggestive of abuse, misuse, or diversion by completing and submitting a Risk Management Report online and by fax.

22. Ensure certified pharmacies are able to request to disenroll a prescriber for suspected abuse, misuse, or diversion by completing and submitting a Risk Management Report online and by fax.

23. Report patient and prescriber disenrollment in the LUMRYZ REMS due to suspected abuse, misuse, or diversion to all other REMS for oxybate products by phone. Document in the LUMRYZ REMS databases.

24. Maintain a process to provide LUMRYZ prescription information including last dispense date, days' supply, and prescriber's name, to other pharmacies upon request to verify that the named patient has no other active, overlapping prescriptions for oxybate products and that the patient and prescriber have not been disenrolled from the LUMRYZ REMS for suspected abuse, misuse, or diversion.

25. Notify prescribers and pharmacies within two (2) business days after they become certified in the REMS.

26. Provide the Prescriber Enrollment Form and the Prescriber Brochure to prescribers who (1) attempt to prescribe LUMRYZ and are not yet certified or (2) inquire about how to become certified.

27. Provide certified pharmacies access to the REMS databases of certified prescribers, enrolled patients, and disenrolled patients.

28. Provide wholesalers-distributors access to list of certified pharmacies.

To ensure REMS participants' compliance with the REMS, Avadel CNS Pharmaceuticals, LLC must:

29. Verify annually that the authorized representative's name and contact information correspond to those of the current designated authorized representative for the pharmacy. If different, the pharmacy must be required to re-certify with a new authorized representative.

30. Maintain adequate records to demonstrate REMS requirements have been met, including, but not limited to, records of: LUMRYZ distribution and dispensing; certification of prescribers and pharmacies; enrolled patients; and audits of REMS participants. These records must be readily available for FDA inspections.

31. Establish a plan for addressing noncompliance with REMS requirements.

32. Monitor certified prescribers, certified pharmacies, wholesaler-distributors, and other entities that distribute LUMRYZ on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if noncompliance is identified, including de-certification.

33. Monitor certified prescribers and pharmacies for timely reporting to Avadel CNS Pharmaceuticals, LLC of all potential adverse events and any behavior by patients or prescribers enrolled in the REMS that raises suspicion of abuse, misuse, or diversion.

34. Audit certified pharmacies within 90 calendar days after the pharmacy places its first order of LUMRYZ, and annually thereafter, to ensure all REMS processes and procedures are in place, functioning, and comply with REMS requirements.

35. Audit wholesalers, distributors, and other entities that distribute LUMRYZ within 90 calendar days after LUMRYZ is first commercially distributed and annually thereafter to ensure all REMS processes and procedures are in place, functioning, and comply with REMS requirements.

36. Take reasonable steps to improve operations of and compliance with the requirements in the REMS based on monitoring and evaluation of the REMS.

IV. REMS Assessment Timetable

Avadel CNS Pharmaceuticals, LLC must submit REMS Assessments at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Avadel CNS Pharmaceuticals, LLC must submit each assessment so it will be received by FDA on or before the due date.

V. REMS Materials

The following materials are part of the LUMRYZ REMS:

Enrollment Forms:

Prescriber:

1. Prescriber Enrollment Form

Patient:

2. Patient Enrollment Form

Pharmacy:

3. Pharmacy Enrollment Form

Training and Educational Materials:

Prescriber:

4. Prescriber Brochure

Patient:

5. Patient Brochure

Pharmacy:

6. Certified Pharmacy Training Program

7. Pharmacy Staff Knowledge Assessment

8. Pharmacist Knowledge Assessment

Patient Care Forms:

9. Prescription Form
10. Patient Counseling Checklist

Communication Materials:

11. Dear Healthcare Provider Letter
12. Dear Professional Society Letter
13. REMS Fact Sheet

Other Materials:

14. Risk Management Report
15. REMS Program Website

VI. Statutory Elements

This REMS is required under section 505-1 of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1) and consists of the following elements:

1. Elements to Assure Safe Use:
    - Health care providers who prescribe LUMRYZ are specially certified under 505-1(f)(3)(A).
    - Pharmacies that dispense LUMRYZ are specially certified under 505-1(f)(3)(B).
    - LUMRYZ is dispensed to patients with evidence or other documentation of safe-use conditions under 505-1(f)(3)(D).
2. Implementation System
3. Timetable for Submission of Assessments

LUMRYZ™ REMS | Prescriber Enrollment Form

Lumryz
(sodium oxybate) for extended-release oral suspension

Complete and submit this form online at www.LUMRYZREMS.com, OR fax to 1-877-206-3198 (toll free).

For more information, please call the LUMRYZ REMS at 1-877-453-1029.

TO BECOME A CERTIFIED PRESCRIBER IN THE LUMRYZ REMS AND PRESCRIBE LUMRYZ:

1. Review the LUMRYZ Prescribing Information.
2. Review the **Prescriber Brochure.**
3. Complete steps 1, 2 and 3 below and submit this **Prescriber Enrollment Form** to the LUMRYZ REMS.

STEP 1: PRESCRIBER ATTESTATIONS

I have:
- Reviewed the Prescribing Information.
- Reviewed the **Prescriber Brochure**.

I understand:
- LUMRYZ is approved for the treatment of
  - Cataplexy in adults with narcolepsy.
  - Excessive daytime sleepiness (EDS) in adults with narcolepsy.
- LUMRYZ is a Schedule III central nervous system (CNS) depressant and can cause obtundation and clinically significant respiratory depression at recommended doses.
- LUMRYZ is contraindicated in combination with alcohol and sedative hypnotics.
- Concurrent use of LUMRYZ with certain other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.
- Patients who have sleep apnea or compromised respiratory function (e.g., asthma, COPD, etc.) may be at higher risk of developing respiratory depression, loss of consciousness, coma, and death with LUMRYZ use.

Before treatment initiation (first dose), I must:
- Assess the patient's health status to determine if LUMRYZ is medically appropriate by screening for history of alcohol and drug abuse, sleep-related breathing disorders, compromised respiratory function, depression, suicidality, concomitant use of sedative hypnotics and other CNS depressants or potentially interacting agents. Document and submit to a certified pharmacy using the **Prescription Form**.
- Counsel the patient on the serious risks and safe use, handling, and storage of LUMRYZ using the **Patient Brochure**.
- Enroll the patient by completing and submitting the **Patient Enrollment Form** to the REMS.
- Order the prescription using the **Prescription Form** and submit it to a certified pharmacy.

Before treatment re-initiation, I must:
- **For patients disenrolled for suspicion of abuse, misuse, or diversion:** Communicate with the pharmacy regarding all relevant patient history and re-enroll the patient if the pharmacist and I agree.
- **For patients with a lapse in treatment of 6 months or longer:** Order the prescription using the **Prescription Form** and submit it to a certified pharmacy.

Within the first 3 months of starting treatment, I must:
- •Assess the patient for concomitant use of sedative hypnotics, other CNS depressants, or potentially interacting agents, serious adverse events, and signs of abuse and misuse, including an increase in dose or frequency of dosing, reports of lost, stolen, or spilled medication, and drug-seeking behavior.

It is recommended that patients be re-assessed every 3 months while taking LUMRYZ.

At all times, I must:
1. Report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death; and any cases of suspected abuse, misuse, or diversion to Avadel CNS Pharmaceuticals, LLC.
2. Assess the patient's potential for abuse, misuse, and diversion. Document and submit all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug using the **Risk Management Report**.
3. Report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the **Risk Management Report**.

STEP 2: TO HELP EXPEDITE THE ENROLLMENT PROCESS, PLEASE COMPLETE ALL REQUIRED FIELDS (PLEASE PRINT)

PRESCRIBER INFORMATION (*denotes required field)

*First Name:	M.I.:	*Last Name:	*DEA No.:
Facility/Practice Name:		*State License No.:	*NPI No.:

*Professional Designation: ☐ MD ☐ DO ☐ PA ☐ NP ☐ Other_____

*Medical Specialty: ☐ Sleep Medicine ☐ Neurology ☐ Pulmonology ☐ Psychiatry ☐ Internal Medicine ☐ Other_____

*Address Line 1:		
Address Line 2:		
*City:	*State:	*Zip Code:
*Phone: ☐ Email ☐ Fax	*Fax:	*Email:
*Preferred Method of Contact:		

OFFICE CONTACT INFORMATION (If you should need to add more than three office contacts, please call the LUMRYZ REMS at 1-877-453-1029.)

Office Contact First Name:	Office Contact Last Name:	Office Contact Phone:	Office Contact Email:

STEP 3: PRESCRIBER SIGNATURE IS REQUIRED BELOW FOR ENROLLMENT IN THE LUMRYZ REMS

By signing below, I acknowledge the above attestations, and I understand my personally identifiable information provided above will be shared with Avadel CNS Pharmaceuticals, LLC, its agents, contractors, and affiliates and entered into a prescriber database for the LUMRYZ REMS. I agree that I may be contacted in the future by mail, email, fax, and/or telephone concerning LUMRYZ, the LUMRYZ REMS, and other LUMRYZ programs and services.

_____ *Prescriber Signature

_____ *Date

Report adverse events to Avadel CNS Pharmaceuticals, LLC at productsafety@avadel.com or 1-888-828-2335.

Avadel

Reference ID: 5446567

LUMRYZ™ REMS | Patient Enrollment Form

Lumryz
(sodium oxybate) for extended-release oral suspension C

Complete and submit this form online at www.LUMRYZREMS.com, OR fax to 1-877-206-3198 (toll free).

For more information, please call the LUMRYZ REMS at 1-877-453-1029.

In order to receive LUMRYZ, patients must be enrolled in the LUMRYZ REMS. To enroll a patient, the prescriber and the patient must complete, sign and submit this form to the LUMRYZ REMS.

To help expedite the enrollment process, please complete all required fields - please print (*denotes required field)

PATIENT INFORMATION

*First Name:	M.I.:	*Last Name:	*Primary Phone:
*Date of Birth (MM/DD/YYYY):	*Gender (select one): ☐ Male ☐ Female ☐ Other		Cell Phone:
*Address Line 1:			Work Phone:
Address Line 2:			
*City:	*State:	*Zip Code:	*Email:

REMS for Oxybate Products Participation

Is the patient currently enrolled in other REMS for oxybate products? ☐ Yes ☐ No

Was the patient previously enrolled in other REMS for oxybate products? ☐ Yes ☐ No

PRESCRIBER INFORMATION

*First Name:	*Last Name:	
*DEA No.:	*NPI No.:	
*Address Line 1:	Address Line 2:	
*City:	*State:	*Zip Code:
*Phone:	*Fax:	

PATIENT ATTESTATIONS:

Before I start treatment, I must:

- Review the **Patient Brochure**
- Receive counseling from my doctor/prescriber about the serious risks with LUMRYZ and the safe use, handling, and storage of LUMRYZ using the **Patient Brochure**
- Enroll in the REMS by completing the **Patient Enrollment Form** with my prescriber
- Complete the **Patient Counseling Checklist** with the pharmacist

During treatment

- Follow the safe use instructions explained to me by my doctor/prescriber
- Tell my pharmacist about any changes in the medicines I am taking and any changes in my medical history so I can be monitored for problems with the medicines I'm taking and signs of abuse and misuse of LUMRYZ

At all times

- I understand that my personally identifiable information provided above will be shared with the LUMRYZ REMS, its agents, contractors, and affiliates, and entered into a patient database for the LUMRYZ REMS
- I understand that my personally identifiable information provided above may be shared with other REMS for oxybate salt medicines, their agents, contractors, and affiliates
- I agree that Avadel CNS Pharmaceuticals, LLC and its agents may contact me or my doctor/prescriber via phone, mail, or email to support administration of the LUMRYZ REMS
- I agree to inform my doctor/prescriber and pharmacy about changes in my medication use or medical history

_____ *Patient/Guardian Signature

_____ *Date

* Printed Guardian Name, if applicable: First Name: _____ Last Name: _____

* Guardian Email, if applicable: _____

PRESCRIBER:

By signing below, I acknowledge that:

- I have counseled the patient about the serious risks associated with the use of LUMRYZ and the safe use conditions as described in the **Patient Brochure**
- I have provided the patient with the **Patient Brochure** (optional)

_____ *Prescriber Signature

_____ *Date

Phone: 1-877-453-1029 | www.LUMRYZREMS.com | Fax: 1-877-206-3198

Avadel

LUMRYZ™ REMS | Pharmacy Enrollment Form

Lumryz.
(sodium oxybate) for extended-release oral suspension C

Pharmacies must be certified in the LUMRYZ REMS to dispense LUMRYZ. To become certified, every pharmacy must designate an authorized representative to:

1. Complete certification using this **Pharmacy Enrollment Form** and fax the completed form to the LUMRYZ REMS at 1-877-206-3198.
2. Review the **Certified Pharmacy Training Program** and submit the completed **Pharmacy Staff Knowledge Assessment** and **Pharmacist Knowledge Assessment** online at www.LUMRYZREMS.com or by fax to 1-877-206-3198.
3. Provide relevant training to the pharmacy staff and pharmacists in each pharmacy and maintain a record of the training.
4. Ensure the pharmacy enables its Pharmacy Management System (PMS) to support electronic communication with the LUMRYZ REMS system using established telecommunication standards.

AUTHORIZED REPRESENTATIVE RESPONSIBILITIES

As the authorized representative, I must:

- Review the **Certified Pharmacy Training Program – Pharmacy Staff Module** and **Pharmacist Module.**
- Successfully complete the **Pharmacy Staff Knowledge Assessment** and **Pharmacist Knowledge Assessment** and submit both to the REMS.
- Complete and submit the **Pharmacy Enrollment Form**.
- Train all relevant staff involved in dispensing using the **Certified Pharmacy Training Program – Pharmacy Staff Module.**
- Have all relevant staff involved in dispensing successfully complete the **Pharmacy Staff Knowledge Assessment** and submit it to the REMS.
- Train all pharmacists involved in dispensing using the **Certified Pharmacy Training Program – Pharmacy Staff Module** and the **Pharmacist Module**.
- Have all pharmacists involved in dispensing successfully complete the **Pharmacy Staff Knowledge Assessment** and **Pharmacist Knowledge Assessment** and submit both to the REMS.
- Establish processes and procedures to assess the patient's concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents that either are unknown to the prescriber or pose a high risk of serious interaction.
- Establish processes and procedures to verify the patient and prescriber are enrolled and that the patient has no other active LUMRYZ prescriptions.
- Establish processes and procedures to verify and document the following by contacting all other REMS for oxybate products: the patient has no other active prescriptions that overlap with the current prescription for LUMRYZ by obtaining oxybate prescription information of last dispense date, days' supply, and prescriber's name; and the patient and prescriber have not been disenrolled from any of the REMS for oxybate products for suspected abuse, misuse, or diversion.
- Establish processes and procedures to verify all prescription information including patient name and two additional identifiers, prescriber name and information, dose, titration information (if applicable), number of refills, dosing directions, total quantity (days' supply), and concomitant medications.
- Establish processes and procedures to assess the patient's potential for abuse, misuse, and diversion by reviewing the alerts and **Risk Management Report** histories in the REMS.
- Establish processes and procedures to provide 24/7 toll-free access to a LUMRYZ REMS trained pharmacist; to dispense no more than a one-month supply for the initial shipment and no more than a three-month supply for subsequent shipments; and to ship, track, and verify receipt of LUMRYZ to the patient or patient-authorized adult designee using an overnight service.
- Establish processes and procedures to report each prescription filled for LUMRYZ to all other REMS for oxybate products and document to the LUMRYZ REMS.
- Establish processes and procedures to reconcile LUMRYZ inventory using the pharmacy's inventory management system.
- Establish processes and procedures to provide dispensing data and shipment and receipt dates to the REMS.

Before dispensing, all pharmacy staff must:

- For new patients and existing patients who restart treatment after not receiving LUMRYZ for 6 months or longer: Counsel the patient using the **Patient Counseling Checklist**. Document and submit to the REMS.
- For patients who report a change in their medication use or medical history: Document and submit the change to the REMS using the **Patient Counseling Checklist**.
- Assess the patient's concomitant use of sedative hypnotics, CNS depressants, or other potentially interacting agents either are unknown to the prescriber or pose a high risk of serious interaction through the processes and procedures established as a requirement of the REMS.
- Verify in this REMS that the patient has no other active LUMRYZ prescriptions through the processes and procedures established as a requirement of the REMS. Document and submit to the REMS.
- Verify the following by contacting all other REMS for oxybate products through the processes and procedures established as a requirement of the REMS: the patient has no other active, prescriptions for oxybate products that overlap with the current prescription for LUMRYZ by obtaining oxybate prescription information of last dispense date, days' supply, and prescriber's name; and the patient and prescriber have not been disenrolled from any other REMS for oxybate products for suspected abuse, misuse, or diversion. Document and submit to the REMS.
- Assess the patient's and their prescriber's potential for abuse misuse, and diversion by reviewing the alerts and **Risk Management Report** history in the REMS. Document the confirmation to the REMS.
- Obtain authorization by contacting the REMS to verify the pharmacy is certified, the prescriber is certified, the patient is enrolled, the **Patient Counseling Checklist** is completed as required, the alerts and **Risk Management Report** history for the patient and their prescriber are reviewed by the pharmacist, and the patient has no active, overlapping prescriptions for oxybate products.
- For patients previously disenrolled for suspicion of abuse, misuse, or diversion: Communicate all relevant patient history to the prescriber and determine whether to re-enroll the patient if the prescriber and patient agree.
- Verify the patient's prescription information including patient name and two additional identifiers, prescriber name and information, dose, titration information (if applicable), number of refills, dosing directions, total quantity (days' supply), and concomitant medications through the processes and procedures established as a requirement of the REMS.
- For patients who request an early refill or if abuse, misuse or diversion is suspected: Discuss the request or concern with the prescriber.
- Dispense no more than a one-month (30 day) supply for the initial shipment.
- Dispense no more than a three-month (90 day) supply for subsequent shipments.

After dispensing, within 1 business day:

- Report each prescription filled for LUMRYZ to all REMS for oxybate products through the processes and procedures established as a requirement of the REMS. Document and submit to the REMS.

Before shipping, all pharmacy staff must:

- Verify the patient's shipping address and that the patient or patient-authorized adult designee will be available to receive the shipment through the processes and procedures established as a requirement of the REMS.
- Ship LUMRYZ directly to each patient or a patient-authorized adult designee through the processes and procedures established as a requirement of the REMS.
- Provide new patients with the **Patient Brochure** with their first shipment.

CONTINUED >>

Lumryz.
(sodium oxybate) for extended-release oral suspension ℂ

After shipping, all pharmacy staff must:

- Track and verify receipt of each shipment of LUMRYZ through the processes and procedures established as a requirement of the REMS.
- Document and submit the dispensing data, and shipment and receipt dates to the REMS.

All pharmacy staff must:

- Provide 24-7 toll-free access to a REMS trained pharmacist .
- Ship LUMRYZ directly to the patient or a patient-authorized adult designee using an overnight service.
- Document and report all potential adverse events reported by all sources, including any CNS depression, respiratory depression, loss of consciousness, coma, and death to Avadel CNS Pharmaceuticals, LLC.
- Report lost, stolen, destroyed, or spilled drug to the REMS using the **Risk Management Report.**
- Monitor all instances of patient and prescriber behavior that give rise to a reasonable suspicion of abuse, misuse, and diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug. Report to the REMS by completing and submitting a **Risk Management Report**.
- Report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the **Risk Management Report**.
- Not distribute, transfer, loan, or sell LUMRYZ.
- Not stock LUMRYZ in retail pharmacies.
- Maintain records of staff training and completion of knowledge assessments.
- Maintain records of inventory reconciliation using the pharmacy's inventory management system.
- Maintain records of all processes and procedures including compliance with those processes and procedures.
- Comply with audits carried out by Avadel CNS Pharmaceuticals, LLC or a third party acting on behalf of Avadel CNS Pharmaceuticals, LLC to ensure all processes and procedures are in place and are being followed.
- To maintain certification to dispense, have a new Authorized Representative enroll in the REMS by reviewing the **Certified Pharmacy Training Program – Pharmacy Staff Module** and **Pharmacist Module**, successfully completing the **Pharmacy Staff Knowledge Assessment** and **Pharmacist Knowledge Assessment** and completing and submitting to the REMS the **Pharmacy Enrollment Form**.

To maintain certification to dispense LUMRYZ, every year the authorized representative must:

- Train all relevant staff involved in dispensing LUMRYZ using the **Certified Pharmacy Training Program – Pharmacy Staff Module**.
- Have all pharmacy staff involved in dispensing LUMRYZ successfully complete the **Pharmacy Staff Knowledge Assessment** and submit it to the REMS.
- Train all pharmacists involved in dispensing LUMRYZ using the **Certified Pharmacy Training Program – Pharmacy Staff Module** and **Pharmacist Module**.
- Have all pharmacists involved in dispensing LUMRYZ successfully complete the **Pharmacy Staff Knowledge Assessment** and **Pharmacist Knowledge Assessment** and submit both to the REMS.

PHARMACY INFORMATION

(*denotes required field)

*Pharmacy Name:		
*Address Line 1:		
Address Line 2:		
*City:	*State:	*Zip Code:
*NPI No.:	*DEA No.:	

AUTHORIZED REPRESENTATIVE INFORMATION

(All fields required)

First Name:	Last Name:	
Phone:	Fax:	Email:
Job Title/Role:	Credentials:	
Preferred Contact Method: ☐ Phone ☐ Fax ☐ Email		

_____ _____

***Authorized Representative Signature** ***Date**

Avadel

Reference ID: 5446567

LUMRYZ™ REMS

PRESCRIBER BROCHURE

Lumryz™

(sodium oxybate) for extended-release oral suspension Ⓒ

Reference ID: 5446567

Lumryz.

(sodium oxybate) for extended-release oral suspension

Dear Prescriber,

The LUMRYZ REMS was developed in collaboration with the Food and Drug Administration (FDA) as a Risk Evaluation and Mitigation Strategy (REMS). A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure the benefits of a drug outweigh its risks. The LUMRYZ REMS is a separate REMS and does not replace any other REMS for oxybate products. Certification in any other REMS for oxybate products is not reciprocal with the LUMRYZ REMS.

This brochure provides valuable information about the LUMRYZ REMS that includes important prescribing information, educational and counseling requirements, and materials necessary for REMS certification and prescribing LUMRYZ (sodium oxybate) for extended-release oral suspension, including:

- **Prescriber Enrollment Form**—a one-time certification is required for all prescribers of LUMRYZ.
- **Patient Enrollment Form**—a one-time patient enrollment in the LUMRYZ REMS is required for each new patient for whom LUMRYZ will be prescribed. Patient enrollment in any other REMS for oxybate products is not reciprocal with the LUMRYZ REMS. LUMRYZ may only be dispensed to enrolled patients in the LUMRYZ REMS.
- **Prescription Form**—This form must be used for treatment initiation and for patients re-initiating treatment after a lapse in treatment of six months or longer and are not required for refills and renewals of LUMRYZ prescriptions. A specialty pharmacy certified in the LUMRYZ REMS is responsible for processing prescriptions for this drug.
- **Patient Brochure**—answers important questions for adult patients about how to obtain LUMRYZ, how to use LUMRYZ properly, and how to store it safely. It also gives important information about the risks associated with LUMRYZ.

Healthcare providers who prescribe LUMRYZ must be certified in the LUMRYZ REMS. The **Prescriber Enrollment Form** and **Patient Enrollment Form** must be completed in full and sent to the LUMRYZ REMS. The **Prescription Form** must be completed in full and sent to a certified pharmacy. For your convenience, the **Prescriber Enrollment Form, Patient Enrollment Form,** and **Prescription Form** are available online at www.LUMRYZREMS.com. All forms can be requested by calling the LUMRYZ REMS toll-free at 1-877-453-1029. Only pharmacies certified in the REMS can process LUMRYZ prescriptions. A list of certified pharmacies is available in the secure certified prescriber website portal at www.LUMRYZREMS.com or by calling the LUMRYZ REMS.

Continue reading this brochure to learn more about the LUMRYZ REMS and your responsibilities as a prescriber of LUMRYZ. Please review the Prescribing Information for LUMRYZ.

LUMRYZ is approved for the treatment of:

- **Cataplexy in adults with narcolepsy**
- **Excessive daytime sleepiness (EDS) in adults with narcolepsy**

If you require any additional assistance or information, please call the LUMRYZ REMS at 1-877-453-1029 or visit www.LUMRYZREMS.com.

Sincerely,

Avadel CNS Pharmaceuticals, LLC

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

LUMRYZ is contraindicated for use in:

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

WARNINGS AND PRECAUTIONS

Central Nervous System Depression

- LUMRYZ is a central nervous system (CNS) depressant. 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.
  - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with LUMRYZ should be considered.
- Patients who have sleep apnea or compromised respiratory function may be at a higher risk of developing respiratory depression, loss of consciousness, coma, and death with LUMRYZ use.
- 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., impaired 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.

Abuse and Misuse

- LUMRYZ is a Schedule III controlled substance.
- The active ingredient in 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. Illicit GHB has also been associated with drug-facilitated sexual assault.
- 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).
- You 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; reports of lost, stolen, or spilled medication; drug-seeking behavior; feigned cataplexy).

LUMRYZ REMS

- LUMRYZ is to be prescribed only to patients enrolled in the LUMRYZ REMS. LUMRYZ is available only through a restricted distribution program called the LUMRYZ REMS because of the risks of central nervous system depression and abuse and misuse. Notable requirements of the LUMRYZ REMS include the following:
  - Healthcare providers who prescribe LUMRYZ are specially certified. To be certified, prescribers must complete the **Prescriber Enrollment Form** and comply with the LUMRYZ REMS requirements.
  - 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. To be enrolled, patients must sign the **Patient Enrollment Form** and acknowledge that they have been counseled on the serious risks and safe use of LUMRYZ.

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

Depression, Suicidality, and Other Behavioral / Psychiatric Adverse Reactions

- Depression, suicidal ideation and behavior, and other behavioral and psychiatric adverse reactions can occur in patients taking LUMRYZ.
- 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. Psychiatric reactions reported in adult clinical trials in patients with narcolepsy administered LUMRYZ included irritability, emotional disorder, panic attack, agitation, delirium, and obsessive thoughts. Patients should be instructed to call their healthcare provider if they experience any of these events.
- Anxiety can also occur in patients treated with LUMRYZ.

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.

Most Common Adverse Events

- In the placebo-controlled clinical trial for LUMRYZ, the most common adverse reactions reported for any dose of LUMRYZ were nausea, dizziness, enuresis, headache, and vomiting.

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 the 6 g, 4.5% on the 7.5 g, and 3.9% on 9 g dose.

For complete safety information, please see the Prescribing Information for LUMRYZ.

Reference ID: 5446567

TABLE OF CONTENTS

Prescribing Information is also included.

PRESCRIBING LUMRYZ—A BRIEF GUIDE

The procedure for writing and dispensing prescriptions for LUMRYZ is outlined below.

PRESCRIBERS OF LUMRYZ

Prescribing LUMRYZ requires a one-time certification

- If you are prescribing LUMRYZ for the first time, complete the **Prescriber Enrollment Form**, found either accompanying this **Prescriber Brochure** or online at www.LUMRYZREMS.com. Please:
  - Submit the form online at www.LUMRYZREMS.com, or
  - Fax to 1-877-206-3198
- On the **Prescriber Enrollment Form**, please confirm that:
  - You understand LUMRYZ is approved for:
    - Treatment of cataplexy in adults with narcolepsy
    - Treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy
  - You have read and understand the Prescribing Information and this **Prescriber Brochure**

SCREEN

- You agree to assess the patient's health statusto determine if LUMRYZ is medically appropriate by screening each patient for the following and document and submit to a certified pharmacy using the **Prescription Form:**
  - History of alcohol and drug abuse
  - History of sleep-related breathing disorders
  - History of compromised respiratory function
  - Concomitant use of sedative hypnotics, other CNS depressants or potentially interacting agents
  - History of depression and suicidality

COUNSEL

- You agree to counsel your patients on:
  - The serious risks associated with LUMRYZ
  - Contraindications (alcohol and sedative hypnotics)
  - Risks of concomitant use of LUMRYZ with alcohol and/or certain CNS depressants
  - Risk of operating hazardous machinery, including automobiles or airplanes, for at least 6 hours after taking LUMRYZ
  - Preparation and dosing instructions for LUMRYZ
  - Risk of abuse and misuse associated with use of LUMRYZ
  - Safe use, handling, and storage of LUMRYZ

ENROLL

- You will enroll each patient in the LUMRYZ REMS by completing the one-time **Patient Enrollment Form** and submitting the form to the LUMRYZ REMS.
- You will evaluate each patient within the first 3 months of starting LUMRYZ, including an evaluation of the following. It is recommended that patients be reevaluated every 3 months thereafter while on LUMRYZ therapy:
  - Concomitant use of sedative hypnotics, other CNS depressants or other potentially interacting agents
  - Serious adverse events
  - Signs of abuse, misuse, and diversion, such as an increase in dose or frequency of dosing; reports of lost, stolen, or spilled medication; and/or drug-seeking behavior

REPORT

- You will report all potential serious adverse events including CNS depression, respiratory depression, loss of consciousness, coma, and death, and any cases of suspected abuse, misuse, or diversion to Avadel CNS Pharmaceuticals, LLC at productsafety@avadel.com or 1-888-828-2335.
- You will document and submit all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug using the **Risk Management Report**. The **Risk Management Report** can be completed online or downloaded and faxed to the LUMRYZ REMS.
- Report requests to disenroll a patient for suspected abuse, misuse, or diversion to the LUMRYZ REMS using the **Risk Management Report**.
- Patient alerts and **Risk Management Report** histories are available for review at www.LUMRYZREMS.com or by calling the LUMRYZ REMS at 1-877-453-1029.

Reference ID: 5446567

PATIENT ENROLLMENT

All patients must be enrolled one time in the LUMRYZ REMS.

- On the **Patient Enrollment Form**, please:
  - Verify you have provided counseling to the patient about the serious risks associated with the use of LUMRYZ and the safe use conditions as described in the **Patient Brochure**.
  - Obtain a mandatory patient or guardian signature acknowledging the patient i) has been counseled on the serious risks and safe use conditions of LUMRYZ, ii) has had the opportunity to ask you any questions he/she may have about LUMRYZ, iii) grants you the authority to release personal information to the LUMRYZ REMS, other REMS for oxybate products, and partners and agents of the LUMRYZ REMS, including the certified pharmacy that will fill the prescription, and iv) agree that Avadel CNS Pharmaceuticals, LLC and agents may contact him/her to support administration of the REMS.
- Complete the **Patient Enrollment Form** online at www.LUMRYZREMS.com or fax the completed form to the LUMRYZ REMS at 1-877-206-3198.

PRESCRIBING REQUIREMENTS

The **Prescription Form** must be completed for treatment initiation and before treatment re-initiation for patients with a lapse in treatment of six months or longer. The **Prescription Form** may not satisfy all legal requirements for prescribing LUMRYZ in your state. Please submit all prescriptions in accordance with applicable state laws or as required by institutional policy. The **Prescription Form** completion is not required for refill or renewals of LUMRYZ.

- Fill out the **Prescription Form** completely and clearly to ensure timely fulfillment of your patient's prescription.

Verify that you have screened your patient for:

- History of alcohol or substance abuse
- History of sleep-related breathing disorders
- History of compromised respiratory function
- Concomitant use of sedative hypnotics, other CNS depressants or other potentially interacting agents
- History of depression or suicidality

Verify that you have counseled the patient regarding:

- The serious risks associated with LUMRYZ
- Contraindications (alcohol or sedative hypnotics)
- Risk of concomitant use of LUMRYZ with alcohol and/or certain other CNS depressants
- Preparation and dosing instructions for LUMRYZ
- Risk of abuse and misuse associated with use of LUMRYZ
- Risk of operating hazardous machinery, including automobiles or airplanes, for at least 6 hours after taking a dose of LUMRYZ
- Safe use, handling, and storage of LUMRYZ

Provide a list of all current prescription and non-prescription medications and dosages that the patient is currently taking to the best of your knowledge. Additionally, indicate the presence of relevant comorbid medical conditions.

NOTE: Prior to dispensing each LUMRYZ prescription (including refills), the certified pharmacy responsible for dispensing LUMRYZ to the patient will complete the patient counseling process and will ask the patient about the use of other medicines. If the patient's certified pharmacy learns the patient has a previous undisclosed comorbid condition or is taking a previously undisclosed contraindicated medication (sedative hypnotics), an opioid, more than one CNS depressant, or other potentially interacting agent and the prescriber has not indicated awareness of the comorbid condition or concomitant medication, the patient's certified pharmacy will contact and inform the prescriber of the comorbid condition or concomitant medication use prior to dispensing LUMRYZ. The patient's certified pharmacy may also contact the prescriber about other concomitant medications of concern.

- Verify you have informed the patient that his/her certified pharmacy will send him/her a copy of the **Patient Brochure** with his/her first LUMRYZ prescription fill. This material is available through the LUMRYZ REMS at www.LUMRYZREMS.com.
- Access the secure certified prescriber website portal at www.LUMRYZREMS.com to look up the certified pharmacies.
- Fax the completed **Prescription Form** and all renewal/refill prescriptions to a certified pharmacy.

PATIENT EVALUATION

- Evaluate each patient within the first 3 months of starting LUMRYZ therapy, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while they are taking LUMRYZ.
    - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
    - Serious adverse events
    - Signs of abuse, misuse, and diversion, such as an increase in dose or frequency of dosing; reports of lost, stolen, or spilled medication; and/or drug-seeking behavior. You may use information that can be obtained by reviewing patient alerts and **Risk Management Report** histories by accessing www.LUMRYZREMS.com or by calling 1-877-453-1029
- Monitor each patient for all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, and diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug. Document and submit to the REMS using the **Risk Management Report**.
- Pharmacies and prescribers can request disenrollment for a patient based on suspected abuse, misuse, or diversion by completing a **Risk Management Report** and submitting the completed form to the REMS.
- Pharmacies and prescribers can request through submission of the **Risk Management Report** that a patient is monitored by placing an alert on the patient's record if serious or repeated events give rise to reasonable suspicion of misuse abuse or diversion.
- The LUMRYZ REMS will contact the prescriber if an enrollment form is received for a patient previously disenrolled from the program; or for suspicion of abuse, misuse, or diversion, and will provide the prescriber with all relevant patient history.
- Follow up frequently during titration to review symptom response and adverse reactions. A follow up of every three months is recommended.

REFILL PRESCRIPTIONS

- Up to 5 refills are allowed on a LUMRYZ prescription (per DEA regulations for Schedule lll controlled substances).

- Prescription refills and renewals may be conveyed by phone, fax, mail, and online through a prescribing system to the patient's certified pharmacy. For treatment re-initiation for patients with a lapse in treatment of six months, a completed **Prescription Form** is required.
    - Fill out the **Prescription Form** completely and clearly to ensure timely fulfillment of your patient's prescription.
    - Prior to prescribing or authorizing additional refills or renewals, you may review the alerts and **Risk Management Report** history of the patient as needed by www.LUMRYZREMS.com or by calling the LUMRYZ REMS at 1-877-453-1029.

Certified Pharmacy

FOLLOWING RECEIPT OF A PATIENT'S PRESCRIPTION THE CERTIFIED PHARMACY WILL:

- Provide you with confirmation of each new LUMRYZ prescription received from your office
- Contact the patient's insurance provider to verify LUMRYZ prescription benefits
- Prior to the first shipment, contact the patient to:
  - Verify he/she will receive a copy of the **Patient Brochure**
  - Counsel the patient using the **Patient Counseling Checklist** on expectations about LUMRYZ therapy and how to prepare and take LUMRYZ doses safely and effectively
  - Review important LUMRYZ safety information and precautions for LUMRYZ use
  - Review LUMRYZ safe handling and storage procedures
  - Review the adverse events associated with LUMRYZ use
  - Review the patient's use of concomitant medications
    - You will be notified of any potential for drug interactions based on patient counseling
  - Review the patient's comorbid medical conditions
  - Ask if the patient has any questions about LUMRYZ and answer the questions and/or refer the patient back to the prescriber, as appropriate
  - Provide 24/7 toll-free telephone access to pharmacist support for prescribers, office staff, and patients by answering questions about safety, dosing, and patient care
  - Dispense and ship LUMRYZ by overnight service to the patient or his/her authorized adult designee
  - Remind patients about weekly or monthly refills, as applicable
  - Contact the prescriber if a prescription refill or renewal is required

For your convenience, materials and information regarding the LUMRYZ REMS are available online at www.LUMRYZREMS.com

Please be sure to review the Prescribing Information prior to prescribing LUMRYZ for your patients.

DOSING LUMRYZ

- LUMRYZ is for oral suspension in water and taken in a single dose orally at bedtime
- The recommended starting dose is 4.5 g once per night
- The recommended dosage range is 6 g to 9 g once per night
- Doses higher than 9 g per night have not been studied and should not ordinarily be administered
- The dose of LUMRYZ should be titrated to effect
  - LUMRYZ should be titrated in increments of 1.5 g per night at weekly intervals
  - The dosage may be gradually titrated based on efficacy and tolerability
- Improvement may occur during the first weeks of therapy; however, titration to an optimal dose may take longer
- Inform the patient that they should be seen by the prescriber frequently to review dose titration, symptom response, and adverse reactions; a follow-up of every three months is recommended.

NOTE: The patient's first shipment of LUMRYZ cannot exceed a 1-month (30-day) supply and future shipments cannot exceed a 3-month (90-day) supply.

DOSING AND TITRATION	
	Total Single Dose
Recommended Starting Dose	4.5 g
Effective Dosage Range	6 g
	7.5 g
	9 g

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).

Please see the LUMRYZ Prescribing Information for additional guidelines for dosing and titration.

PATIENT DOSING INFORMATION

- Inform patients that each packet of LUMRYZ contains LUMRYZ powder, which will need to be mixed with water for once-nightly dosing
- Patients should prepare the dose of LUMRYZ prior to bedtime
  - Instruct patients to make sure the LUMRYZ mixing cup is clean prior to preparing each dose
  - Each packet of LUMRYZ should be mixed with approximately 80 mL of water (to Fill Line A) in the mixing cup provided
  - After drinking the contents of the mixing cup, the patient should rinse the LUMRYZ mixing cup with an additional 25 mL of water (to Fill Line B) and drink that as well to ensure all medication is ingested
  - Patients should be instructed to store LUMRYZ in a secure place out of the reach of children and pets
- LUMRYZ should be taken at least 2 hours after eating
- LUMRYZ should be taken while in bed

Additional Information About LUMRYZ

LUMRYZ has been placed in a bifurcated federal schedule. LUMRYZ is a Schedule III controlled substance when used for legitimate medical purposes, as prescribed. The active ingredient of LUMRYZ, sodium oxybate, is gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Your patients should be informed that federal law prohibits the transfer of LUMRYZ to any persons other than the patient for whom it was prescribed. If you have any questions regarding this, please call the LUMRYZ REMS toll-free at 1-877-453-1029.

Illicit use and abuse of GHB have been reported, including drug-facilitated sexual assault. Prescribers should carefully evaluate patients for a history of drug abuse and follow patients closely, observing them for signs of misuse or abuse of GHB (e.g., increase in size or frequency of dosing, reports of lost, stolen, or spilled medication, drug-seeking behavior, etc.).

WHEN PRESCRIBING A CONTROLLED SUBSTANCE

- Be judicious when deciding to increase a dose. Make sure the appropriate medical indicators for increasing or altering a dose are present.
- Be suspicious of a pattern of excuses for additional refills or repeated requests for additional refills on an emergency basis.
- Be vigilant. Recognize there is potential to abuse LUMRYZ. It is important you know the LUMRYZ REMS maintains records about who is prescribing LUMRYZ. These records will be made available to any state or federal agency that requests them.

DEPENDENCE AND TOLERANCE

Dependence

- Cases of severe dependence and craving for GHB have been reported when the drug is taken around the clock
- There have been case reports of withdrawal after illicit use of GHB at frequent repeated doses
    - Doses (18 g to 250 g per day) were in excess of recommended dosage range

Tolerance

- There have been some case reports of symptoms of tolerance developing after illicit use at doses far in excess of the recommended LUMRYZ dosage regimen
- Discontinuation effects and tolerance of LUMRYZ have not been systematically evaluated in controlled clinical trials

For your convenience, materials and information regarding the LUMRYZ REMS are available online at www.LUMRYZREMS.com

Use in Specific Populations

PREGNANCY

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.

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.

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 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.

LACTATION

GHB is excreted in human milk after oral administration of sodium oxybate. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUMRYZ and any potential adverse effects on the breastfed infant from LUMRYZ or from the underlying maternal condition.

PEDIATRIC USE

Safety and effectiveness of LUMRYZ in pediatric patients have not been established.

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.

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.

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. 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.

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.

Please read accompanying Prescribing Information.
The LUMRYZ REMS is here to support you, your staff, and your patients.
For assistance, call 1-877-453-1029.

Reference ID: 5446567

Patient Counseling Information

Prior to initiating therapy, counsel each patient regarding the serious risks and safe use, handling, and storage of LUMRYZ using the **Patient Brochure.**

- Inform patients that LUMRYZ is available only through certified pharmacies under a restricted distribution program called the LUMRYZ REMS and provide them with the telephone number and website for more information about LUMRYZ and the LUMRYZ REMS.
- Confirm that patients understand the serious risks and safe use conditions of LUMRYZ and that you have answered any questions the patient has about LUMRYZ by having the patient sign and date the **Patient Enrollment Form**. Inform the patient that regular follow-up is recommended.

To ensure safe and effective use of LUMRYZ, you should provide your patient with the following guidance:

ALCOHOL OR SEDATIVE HYPNOTICS

Advise patients that alcohol and other sedative hypnotics should not be taken with LUMRYZ.

SEDATION

Inform patients they are likely to fall asleep quickly after taking LUMRYZ (often within 5 minutes 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 resulting in injuries, in some cases requiring hospitalization. Instruct patients to remain in bed following ingestion of LUMRYZ.

FOOD EFFECT

Inform patients that LUMRYZ should be taken at least 2 hours after eating.

RESPIRATORY DEPRESSION

Inform patients that LUMRYZ can be associated with respiratory depression even at recommended doses and with concurrent use of LUMRYZ with certain other CNS depressants.

OPERATING HAZARDOUS MACHINERY

Inform patients that, until they are reasonably certain LUMRYZ does not affect them adversely (e.g., impair judgment, thinking, or motor skills), they should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating hazardous machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking LUMRYZ.

SUICIDALITY

Instruct patients to contact a healthcare provider immediately if the patient develops 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.

SLEEPWALKING

Instruct patients that LUMRYZ has been associated with sleepwalking and other behaviors during sleep, and to contact their healthcare provider if this occurs.

SODIUM INTAKE

Instruct patients 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.

SAFE USE, HANDLING, STORAGE, AND DISPOSAL

- Discuss safe and proper use of LUMRYZ and dosing information with patients prior to the initiation of treatment.
- Instruct patients to store LUMRYZ packets in a secure place, out of reach of children and pets.
- Instruct patients to take one dose nightly at bedtime. Patients should not divide dose.
- Inform patients they should be seen by their healthcare provider frequently to review dose titration, symptom response, and adverse reactions.
- Instruct patients to store LUMRYZ at room temperature, between 59°F and 86°F. Inform patients they may safely dispose of LUMRYZ down the sink.
- Inform patients they must report all instances of lost or stolen LUMRYZ to the local police and to the LUMRYZ REMS.

Reference ID: 5446567

Lumryz™

(sodium oxybate) for extended-release oral suspension CIII

Avadel™

Phone: 1-877-453-1029 | www.LUMRYZREMS.com | Fax: 1-877-206-3198

MED-US-LUM-2100004
10/2023

LUMRYZ™ REMS

PATIENT BROCHURE

Important information about the safe use and handling of LUMRYZ (sodium oxybate) for extended-release oral suspension

Lumryz™

(sodium oxybate) for extended-release oral suspension [C-III]

Learn more scan to enroll.

Reference ID: 5446567

Lumryz.

(sodium oxybate) for extended-release oral suspension C

Dear Patient,

You are receiving these materials because your healthcare provider has prescribed LUMRYZ (sodium oxybate) for extended-release oral suspension for you. LUMRYZ is a medicine used to treat excessive daytime sleepiness and/or cataplexy in adults with narcolepsy.

The Food and Drug Administration (FDA) has required a special safety program called a Risk Evaluation and Mitigation Strategy (REMS) for LUMRYZ because of the serious risks associated with LUMRYZ. The purpose of the LUMRYZ REMS is to make sure the benefits of LUMRYZ outweigh the risks. All patients must be enrolled in the LUMRYZ REMS to receive LUMRYZ. This **Patient Brochure** contains information you need to know about LUMRYZ and will help you to use LUMRYZ correctly. Read this **Patient Brochure** before you start taking LUMRYZ.

After your healthcare provider sends your enrollment form to the LUMRYZ REMS and your first prescription for LUMRYZ to your certified pharmacy, you will receive a call from your certified pharmacy to tell you how to get started with taking LUMRYZ and to answer any questions you may have about LUMRYZ.

You will also speak with appropriate staff at a certified pharmacy, who will go over your insurance information with you. Before you can receive your first shipment of LUMRYZ, a pharmacist at a certified pharmacy must confirm whether you have read and understood this **Patient Brochure**, ask you about your medical history and other medications you may be taking, and give you advice on how to prepare and take your LUMRYZ and how to store it safely. **You must take this call before you can get your LUMRYZ.**

Please call your healthcare provider if you have questions about LUMRYZ, or you can contact the LUMRYZ REMS toll free at 1-877-453-1029. You can reach your certified pharmacy 24 hours a day, 7 days a week with any questions. We hope you find this information and the LUMRYZ REMS services helpful.

Sincerely,

Avadel CNS Pharmaceuticals, LLC

WARNING: LUMRYZ can cause serious side effects.
Do not drink alcohol or take other medicines that make you sleepy.

LUMRYZ is a prescription medicine used to treat adults with narcolepsy to reduce excessive daytime sleepiness and/or cataplexy (suddenly weak or paralyzed muscles).

IMPORTANT INFORMATION ABOUT LUMRYZ INCLUDES THE FOLLOWING:

- When taking LUMRYZ, **do not** drink alcohol or take other medicines that slow your breathing or mental activity or make you sleepy. You could have serious side effects.
- LUMRYZ can cause serious side effects, including trouble breathing while asleep, confusion, unusual or disturbing thoughts, depression, and passing out, even at recommended doses. Tell your healthcare provider if you have any of these problems while taking LUMRYZ.
- Abuse of LUMRYZ can lead to dependence (a physical need to take the drug), craving for the medicine, and severe withdrawal symptoms (symptoms that start when the drug is stopped, especially when it is stopped suddenly).
- Each packet of LUMRYZ contains LUMRYZ powder, which will need to be mixed with water for once-nightly dosing prior to bedtime.
- Take 1 packet of LUMRYZ each day at bedtime.
- Mix and take LUMRYZ within 30 minutes. If not taken within 30 minutes of mixing, throw it away (dispose of it) and prepare a new dose.
- Avoid getting out of your 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 you to fall asleep might be different from night to night.
- **Do not** drive a car, use heavy machinery, fly an airplane, or do anything dangerous or that requires you to be alert for at least 6 hours after taking LUMRYZ. When you first start taking LUMRYZ, be careful until you know how LUMRYZ affects you.
- Keep LUMRYZ out of the reach of children and pets. Get emergency medical help right away if a child ingests LUMRYZ.
- Report all side effects to your healthcare provider.

WHAT WILL YOU FIND IN THIS BROCHURE?

This brochure answers important questions about how to get your LUMRYZ, how to use LUMRYZ properly, and how to store it safely. It also gives you important information about LUMRYZ.

WHAT IS THE LUMRYZ REMS?

The FDA has required a special program called a REMS for LUMRYZ because of the serious risks associated with LUMRYZ. Enrollment in the LUMRYZ REMS by prescribers, pharmacies, and patients is required by the FDA to ensure the benefits of LUMRYZ outweigh the risks associated with LUMRYZ. You are enrolled in the REMS when your healthcare provider sends the **Patient Enrollment Form** you signed to the LUMRYZ REMS. Your healthcare provider can then send your prescription for LUMRYZ to a certified pharmacy.

You will receive a call from a pharmacist at a certified pharmacy who will review important information about LUMRYZ with you. They will also answer any questions you have about LUMRYZ.

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ENROLLING IN THE LUMRYZ REMS

WHAT AM I REQUIRED TO DO IN THIS REMS?

As a patient, your responsibility is to discuss the safe use of LUMRYZ with your healthcare provider and to read this **Patient Brochure** before receiving your first LUMRYZ prescription. Be sure to let your healthcare provider know if you are taking other medications or if you have any conditions that might affect your breathing.

DO I HAVE TO ENROLL IN THIS REMS?

Yes. You and your healthcare provider will be required to sign a **Patient Enrollment Form** in order to receive LUMRYZ. You must verify that you have been counseled by your healthcare provider on the serious risks and safe use of LUMRYZ and that you were able to ask your healthcare provider any questions you have about LUMRYZ.

WHY SHOULD I CONTACT THIS REMS?

You should contact the LUMRYZ REMS at 1-877-453-1029 for any questions regarding enrollment in the LUMRYZ REMS. For questions regarding your medication, please contact your certified pharmacy or prescriber.

FILLING YOUR LUMRYZ PRESCRIPTION

HOW IS MY PRESCRIPTION FILLED?

All LUMRYZ prescriptions are filled only by pharmacies certified in the LUMRYZ REMS.

WHAT DOES A CERTIFIED PHARMACY DO?

Your healthcare provider sends your LUMRYZ prescription directly to a certified pharmacy.

After your healthcare provider sends in your first prescription of LUMRYZ, you will receive a call from your certified pharmacy to tell you how to get started with taking LUMRYZ and to answer any questions you may have about LUMRYZ. A staff member from your certified pharmacy will call you to complete a **Patient Counseling Checklist**. The **Patient Counseling Checklist** will include information about other medications you are taking and other medical conditions that might increase your risk of serious side effects. Your certified pharmacy will go over the information about how to use LUMRYZ safely and provide a copy of this brochure with your first shipment.

Your certified pharmacy will always ask you where and when you would like your LUMRYZ delivered and who will sign for the shipment. LUMRYZ will be shipped by an overnight service. When the courier arrives, you or an adult you designate must sign for your LUMRYZ.

WHAT WILL I GET WITH MY LUMRYZ PRESCRIPTION?

With each prescription, you will get a carton containing individual, dose packets of LUMRYZ (each child-resistant dose packet contains one single dose of LUMRYZ, all of the same dose strength), a LUMRYZ-specific mixing cup for mixing your LUMRYZ dose with water in preparation for drinking the mixture, and a cap to close the mixing cup and assist with mixing (e.g., shaking or otherwise agitating the LUMRYZ and water after being placed in the mixing cup).

HOW DO I GET MY LUMRYZ REFILLS?

Your certified pharmacy will contact you when it is close to your refill time. You may also call your certified pharmacy to schedule your refills.

CAN MY LOCAL PHARMACY PROVIDE LUMRYZ?

No. You can get your LUMRYZ only from a LUMRYZ REMS certified pharmacy. You may be able to have your LUMRYZ shipped to your home, place of work or to a local overnight carrier hub for pickup. Saturday deliveries may also be an option for you. Your certified pharmacy will work with you on the options available.

INSURANCE COVERAGE

WILL INSURANCE PAY FOR MY LUMRYZ?

In most cases, yes. A staff member from your certified pharmacy will call and work with your insurance company to help you get coverage for LUMRYZ. In the unlikely event your insurance does not cover LUMRYZ or you can't afford the out-of-pocket costs, ask the certified pharmacy about available financial assistance programs.

WHAT IS THE PHARMACY'S ROLE WITH MY INSURANCE?

An experienced pharmacy staff member will:

- Contact you to go over your prescription benefits and coverage
- Tell you what your co-pay is, if applicable
- Tell you about any LUMRYZ prescription savings plans for which you may qualify
- Work with your healthcare provider on prior authorizations, if required by your insurance company
- Provide information about any financial help that may be available to you

Your certified pharmacy's attempt to get coverage from a third-party payer does not guarantee that you will get coverage.

WHAT SHOULD I DO WHEN I GET MY LUMRYZ CARTON?

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

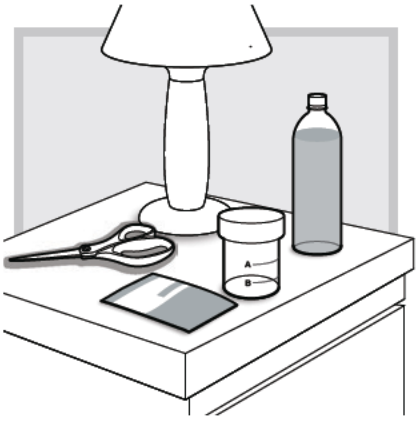
Open the LUMRYZ carton by tearing the tamper-evident seal with your hands or by using a pair of scissors.

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 bedside:



- 1 bottle or glass of water (1/3 cup). Do not use hot water.
- 1 LUMRYZ packet
- 1 clean mixing cup. - The cap is not child resistant.
- 1 pair of scissors (optional)

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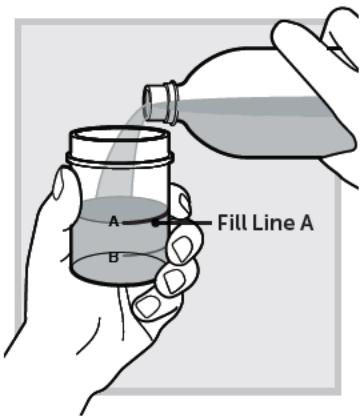
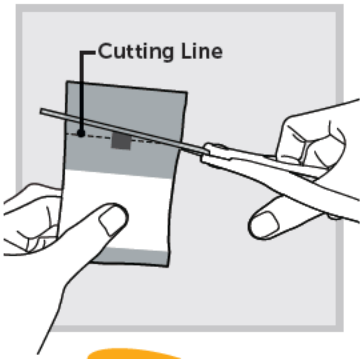
HOW DO I TAKE MY LUMRYZ?

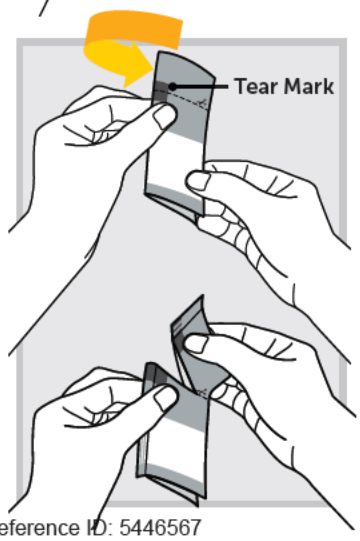
MIX THE LUMRYZ SOLUTION AT YOUR BEDSIDE

1. At your 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.



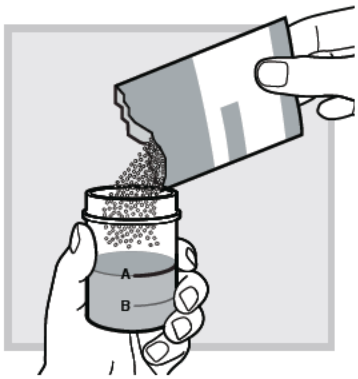


3. Open 1 packet:

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

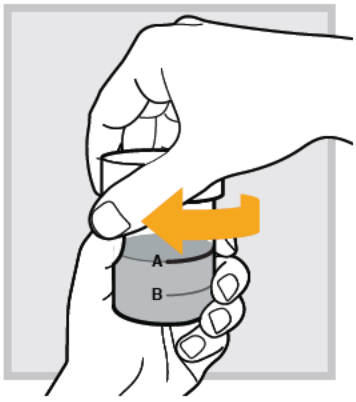
-or-

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

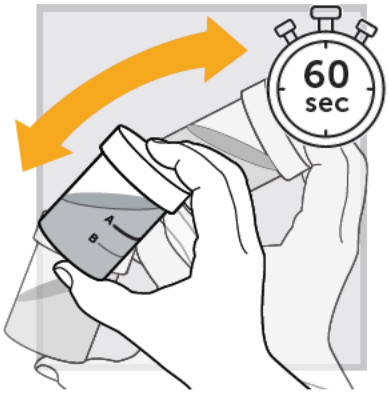


4. Pour the entire content from the packet into the water-filled mixing cup.

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.

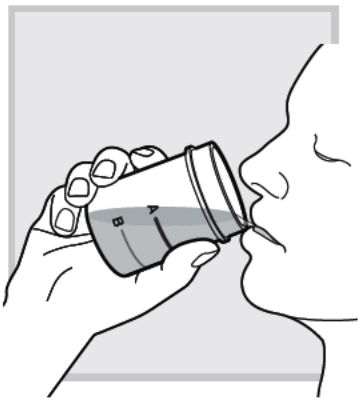
The mixed solution will appear slightly milky with some lumps.

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.

HOW DO I TAKE MY LUMRYZ?

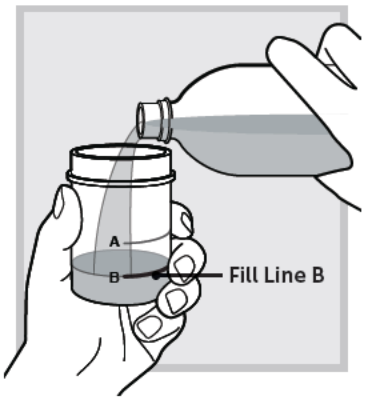
TAKE THE LUMRYZ SOLUTION AT YOUR BEDSIDE

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



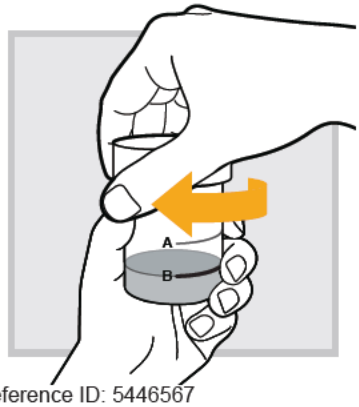
9 While sitting in bed drink the mixed solution within **30 minutes** of mixing.

Make sure to drink all the mixed solution in the mixing cup.

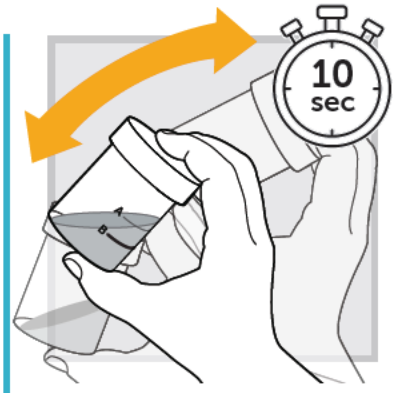


10 Immediately refill your mixing cup with water up to **Fill Line B** (lower line) to mix in any medicine left in the mixing cup.

Do not open another packet of LUMRYZ. Take only 1 packet each day at bedtime.



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

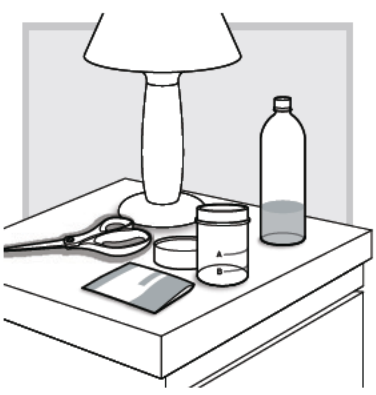


12 Shake well again for **10 seconds.**

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

14 Drink the mixed solution immediately after mixing.

Make sure to drink all the mixed solution in the mixing cup.



15 Leave the empty mixing cup at your bedside and immediately lie down to go to sleep.

Avoid getting out of your bed after taking your dose.

Reference ID: 5446567

WHAT SHOULD I DO IF I MISS A DOSE?

It is very important to take only one single dose of LUMRYZ each day at bedtime, as prescribed. If you miss a dose, skip that dose.

- Do not take LUMRYZ again until the next day at bedtime.

Empty any unused LUMRYZ solution that you prepared but did not take down the sink the next day. Clean the mixing cup by rinsing it with water and letting it dry before each use.

HOW SOON WILL I SEE A CHANGE IN MY SYMPTOMS?

After starting LUMRYZ, it may take a few weeks or longer to see your symptoms improve. It may also take time to find the right dose that works for you. It is important that you talk with your healthcare provider often when you first start taking LUMRYZ.

Tell your healthcare provider if you don't feel any improvements while taking LUMRYZ. LUMRYZ may not be right for you.

WHAT ARE THE SIDE EFFECTS OF LUMRYZ?

LUMRYZ can cause serious side effects, including breathing problems (slower breathing, trouble breathing, and short periods of no breathing while asleep), mental health problems (confusion, seeing or hearing things that are not real, unusual or disturbing thoughts, feeling anxious or upset, depression, thoughts of suicide, increased tiredness, feelings of guilt or worthlessness, difficulty concentrating), and sleepwalking. If you have any of these side effects, call your healthcare provider right away.

The most common side effects with LUMRYZ are nausea, dizziness, bedwetting, headache, and throwing up.

These are not the only possible side effects with LUMRYZ. If you are worried about any possible side effects with LUMRYZ, talk with your healthcare provider or a pharmacist at a certified pharmacy.

ARE THERE ANY PRECAUTIONS I SHOULD TAKE WHILE ON LUMRYZ?

- While taking LUMRYZ, do not drink alcohol or take medicines that cause sleepiness.
- Do not drive a car, use heavy machinery, or do anything that is dangerous or requires you to be alert, for the first 6 hours after taking LUMRYZ.
- When you first start taking LUMRYZ, be careful until you know how it will affect you.
- Before starting LUMRYZ, tell your healthcare provider if you are pregnant, or plan to become pregnant, or if you are breastfeeding. It is not known whether LUMRYZ can pass through your breast milk.
- Keep LUMRYZ in a safe place, out of the reach of children.
- Take LUMRYZ while in bed.

Tell your healthcare provider and pharmacist about any other medicines you are taking, including prescription and non-prescription medicines, vitamins, and supplements.

Reference ID: 5446567

It is also important to tell other healthcare providers, including pharmacists, that you are taking LUMRYZ before you start or change any medications.

HOW OFTEN SHOULD MY HEALTHCARE PROVIDER CHECK MY PROGRESS WITH LUMRYZ?

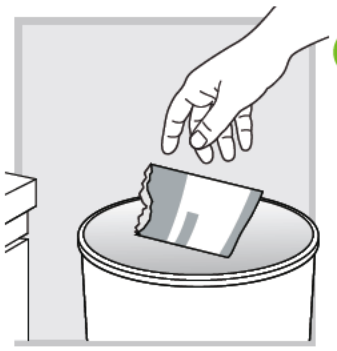
When you first start taking LUMRYZ, you may need to talk to your healthcare provider often until he/she determines the best dose for you. It is possible your dose may need to be adjusted. Your healthcare provider will evaluate you within the first 3 months of taking LUMRYZ and may reevaluate you every 3 months while you are taking LUMRYZ.

STORAGE AND SAFETY TIPS AT HOME

HOW DO I STORE LUMRYZ?

- Always store LUMRYZ in its original carton in a clean dry place.
- Store LUMRYZ at room temperature, between 68°F to 77°F (20°C to 25°C), and do not refrigerate or allow near fire.
- Keep LUMRYZ and all medicines out of reach of children and pets. If a child or pet ingests LUMRYZ, get emergency medical help (call 911) right away.

HOW DO I THROW AWAY (DISPOSE OF) LUMRYZ?



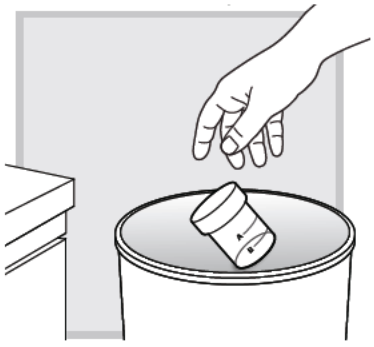
1 The next day, place the empty LUMRYZ packet in the trash.

If any LUMRYZ remains in the packet, rinse it down the sink prior to disposal.

2 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 finish all of the packets in your LUMRYZ carton



After you have finished your last packet in the carton, throw away the rinsed mixing cup in the trash.

Reference ID: 5446567

DRUG TAKEBACK PROGRAM

LUMRYZ patients can return any unused, leftover or expired drug product through a drug takeback program. To obtain information, please contact the LUMRYZ REMS at 1-877-453-1029.

WHAT IF I HAVE CONCERNS ABOUT HAVING LUMRYZ IN MY HOME?

- If your LUMRYZ is lost or stolen, report the incident right away to the local police and to your certified pharmacy.
- Use LUMRYZ only as your healthcare provider tells you. Remember that use of your LUMRYZ by others is illegal.
- If you have any questions or concerns, or if you need advice about LUMRYZ, call your healthcare provider or your certified pharmacy.

GETTING MORE INFORMATION

WHERE CAN I GET MORE INFORMATION ABOUT LUMRYZ?

For more information about LUMRYZ, contact the LUMRYZ REMS:

Phone: 1-877-453-1029

Fax: 1-877-206-3198

Website: www.LUMRYZREMS.com

NOTES

KEEP THIS BOOKLET AS A HELPFUL REMINDER

If you have questions or need information, contact the LUMRYZ REMS at 1-877-453-1029.

Lumryz™

(sodium oxybate) for extended-release oral suspension CIII

Avadel™

Phone: 1-877-453-1029 | www.LUMRYZREMS.com | Fax: 1-877-206-3198

MED-US-LUM-2100005
09/2023

LUMRYZ™ REMS

Certified Pharmacy Training — Pharmacy Staff and Pharmacists

All LUMRYZ REMS authorized representatives, certified pharmacy staff, and pharmacists involved in dispensing LUMRYZ must complete the **Pharmacy Staff Module** and the **Pharmacy Staff Knowledge Assessment**. All authorized representatives and pharmacists must also complete the **Pharmacist Module** and the **Pharmacist Knowledge Assessment**.

Lumryz™

(sodium oxybate) for extended-release oral suspension Ⓒ

Reference ID: 5446567

Lumryz™

(sodium oxybate) for extended-release oral suspension [C]

Dear LUMRYZ REMS Certified Pharmacy Staff,

The LUMRYZ REMS has been approved by the Food and Drug Administration (FDA) as a Risk Evaluation and Mitigation Strategy (REMS).

The LUMRYZ REMS

The FDA has determined that a REMS is necessary to ensure that the benefits of LUMRYZ (sodium oxybate) for extended-release oral suspension outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of LUMRYZ by:

1. **Informing prescribers, pharmacists, and patients of:**
   - The risk of significant central nervous system (CNS) and respiratory depression associated with LUMRYZ
   - The contraindication of use of LUMRYZ with sedative hypnotics or alcohol
   - The potential for abuse, misuse, and overdose associated with LUMRYZ
   - The safe use, handling, and storage of LUMRYZ
2. **Ensuring that pharmacy controls exist prior to filling prescriptions for LUMRYZ that:**
   - Screen for concomitant use of sedative hypnotics and other CNS depressants
   - Monitor for inappropriate prescribing, misuse, abuse, and diversion of LUMRYZ
   - Notify prescribers when patients are receiving concomitant contraindicated medications or when there are signs of potential abuse, misuse, or diversion

This training provides information about the LUMRYZ REMS that includes important information about LUMRYZ and the responsibilities of certified pharmacy staff involved in the dispensing of LUMRYZ.

LUMRYZ is approved for:

- Treatment of cataplexy in adults with narcolepsy
- Treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy

LUMRYZ may be prescribed only by prescribers certified in the LUMRYZ REMS and dispensed only by pharmacies certified in the LUMRYZ REMS to patients enrolled in the LUMRYZ REMS. Please contact the LUMRYZ REMS with any questions at www.LUMRYZREMS.com or 1-877-453-1029.

Sincerely,

Avadel CNS Pharmaceuticals, LLC

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Reference ID: 5446567

CERTIFIED PHARMACY TRAINING — PHARMACY STAFF MODULE

LUMRYZ™ REMS

Training for the Authorized Representative, Pharmacy Staff, and Pharmacists Involved in the LUMRYZ REMS

All authorized representatives, pharmacy staff, and pharmacists within a LUMRYZ REMS certified pharmacy involved in dispensing LUMRYZ must complete training on the **Pharmacy Staff Module** successfully complete the **Pharmacy Staff Knowledge Assessment**. Training must be completed annually.

Lumryz™

(sodium oxybate) for extended-release oral suspension Ⓒ

Reference ID: 5446567

IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

- LUMRYZ (sodium oxybate) for extended-release oral suspension is a central nervous system (CNS) depressant that is indicated for the following:
  - Treatment of cataplexy in adults with narcolepsy
  - Treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy

HOW SUPPLIED

- LUMRYZ is shipped from a LUMRYZ REMS certified pharmacy directly to patients. Each shipment to a patient will contain:
  - A carton with the prescribed amount of LUMRYZ packets at the prescribed dose (each child-resistant package contains a packet of LUMRYZ 4.5 g, 6 g, 7.5 g, or 9 g)
  - A mixing cup for preparation of each single dose (LUMRYZ dose mixed with water)
  - For a new patient, the **Patient Brochure**

CONTROLLED SUBSTANCE SCHEDULING

- The active ingredient in LUMRYZ is sodium oxybate or gamma-hydroxybutyrate (GHB, a known drug of abuse). GHB has been used to facilitate sexual assaults. Because of its rapid sedative effects (particularly when mixed with alcohol) and its colorless and odorless appearance, GHB has been used to "spike" the drinks of unsuspecting victims. Because of its abuse potential, GHB is designated a controlled substance by the Drug Enforcement Administration (DEA) and has been placed in a bifurcated federal schedule.
- GHB products approved by the FDA, such as sodium oxybate, and used as prescribed for therapeutic purposes are Schedule Ill drugs.
- The active ingredient of LUMRYZ, sodium oxybate, is the sodium salt of GHB, a Schedule I controlled substance.
- Federal law prohibits the transfer of LUMRYZ to any persons other than the patient for whom it was prescribed.

BOXED WARNING

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

- **Central Nervous System Depression**

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

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

Because of the risks of CNS depression and abuse and misuse, LUMRYZ is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the LUMRYZ REMS. For further information go to www.LUMRYZREMS.com or call 1-877-453-1029.

Reference ID: 5446567

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- LUMRYZ is contraindicated for use in:
  - combination with sedative hypnotics.
  - combination with alcohol.
  - patients with succinic semialdehyde dehydrogenase deficiency, a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.

WARNINGS AND PRECAUTIONS

Central Nervous System Depression

- LUMRYZ is a CNS depressant.
- 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.
  - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with LUMRYZ should be considered.
- Patients who have sleep apnea or compromised respiratory function may be at a higher risk of developing respiratory depression, loss of consciousness, coma, and death with LUMRYZ use.
- 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.

Abuse, Misuse and Diversion

- LUMRYZ is a Schedule III controlled substance.
- The active ingredient of LUMRYZ, sodium oxybate, is the sodium salt of 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).
- Patients should be carefully evaluated 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, reports of lost, stolen, or spilled medication, drug-seeking behavior, feigned cataplexy).

For complete safety information, please see the Prescribing Information for LUMRYZ.

LUMRYZ REMS REQUIREMENTS

LUMRYZ may be prescribed only by prescribers certified in the LUMRYZ REMS and dispensed only to patients enrolled in the LUMRYZ REMS. Because of the risks of CNS depression, abuse, misuse, and diversion, LUMRYZ is available only through a restricted program called the LUMRYZ REMS.

Notable requirements of this REMS include:

- Use of a certified pharmacy.
- Healthcare providers who prescribe LUMRYZ must have completed the **Prescriber Enrollment Form** and must comply with the requirements of the LUMRYZ REMS.
- To receive LUMRYZ, patients must be enrolled in the LUMRYZ REMS and be counseled on the serious risks and safe use of LUMRYZ treatment. Patients are enrolled by certified prescribers who must fill out and submit the **Patient Enrollment Form**. Prescribers must also complete and submit the **Prescription Form** to a certified pharmacy for all new LUMRYZ prescriptions and for LUMRYZ prescriptions for patients restarting LUMRYZ treatment after not receiving LUMRYZ for 6 months or more.
- Lumryz must not be stocked in retail pharmacies.

Further information is available at www.LUMRYZREMS.com.

OVERVIEW OF CERTIFIED PHARMACY RESPONSIBILITIES

PRESCRIPTION PROCESSING

- A certified pharmacy must validate all prescriptions prior to dispensing LUMRYZ. Before a prescription for LUMRYZ can be shipped to a patient, the certified pharmacy must:
  - Verify that the **Prescription Form** is complete and signed by the prescriber.
  - Verify that the **Prescription Form** was received from the prescriber's office.
  - Verify the prescription is dated according to state-controlled substance regulations.
  - Verify the prescription is for no more than a 1-month (30-day) supply on a patient's first LUMRYZ fill and no more than a 3-month (90-day) supply on subsequent fills.
  - Verify there are no discrepancies or concerns with the dosing and titration.
    - If there are discrepancies or concerns, the certified pharmacy must contact the prescriber to revise and resubmit the prescription.
  - Review the **Prescription Form** for medications and comorbidities
    - * Note: A pharmacy processing a refill (e.g., transferred prescription) or a renewal (e.g., prescription sent from a prescriber) for an existing patient with the previous fill at another certified pharmacy must contact the previous pharmacy for the most recent **Prescription Form** for the patient that contains the medication and comorbidities list. A pharmacy may view an existing patient's previous RDA history and REMS activity online at www.LUMRYZREMS.com or by calling the LUMRYZ REMS at 1-877-453-1029.
  - Complete the **Patient Counseling Checklist** with the patient and review the patient information contained in the LUMRYZ REMS patient database using the secure web viewing portal and the **Prescription Form,** including:
    - Comorbid conditions and concomitant use of sedative hypnotics, certain other CNS depressants or other potentially interacting agents that either are unknown to the prescriber or pose a high risk of serious interaction with LUMRYZ.
      - If comorbid conditions or patient use of a contraindicated medication is confirmed and if the prescriber has not indicated prior knowledge, then the pharmacist will notify and consult the prescriber about the comorbid conditions and risks of concomitant medication use and document the call and the prescriber's treatment rationale on the **Patient Counseling Checklist**.
    - Alerts and **Risk Management Reports (RMRs)** regarding potential abuse, misuse, or diversion.
  - Contact all other REMS for oxybate products by phone to:
    - Verify that the patient has no other active, overlapping prescriptions for oxybate products that overlap with the current prescription.
    - Verify that the patient and prescriber have not been disenrolled from any other REMS for oxybate products for suspected abuse, misuse, or diversion.
  - Document that the calls to all other REMS for oxybate products were completed by submitting confirmation to the LUMRYZ REMS through the REMS dispense authorization (RDA) process.
  - Obtain a RDA from the LUMRYZ REMS for each dispense.
  - The issuance of a RDA informs the pharmacy that all the REMS safe us conditions are met:
    - The pharmacy is certified
    - The prescriber is certified
    - The patient is enrolled
    - The patient has no other active, overlapping LUMRYZ prescriptions
    - The **Patient Counseling Checklist** has been completed for the required patients

- ◊ The Pharmacist confirmed that the alerts and **RMR** history for patient and prescriber have been reviewed
- ◊ The pharmacy confirmed that the call was made to all other REMS for oxybate products to verify:
  - The patient has no other active, overlapping prescriptions for oxybate products that overlap with the current prescription for LUMRYZ
  - The patient and prescriber have not been disenrolled from any other REMS for oxybate products for suspected abuse, misuse, or diversion

o The certified pharmacy will process all LUMRYZ prescriptions, regardless of payment method, through the pharmacy management system (PMS) and obtain a RDA online on the LUMRYZ REMS website or by calling the REMS to verify the safe use conditions as described above.

- ◊ To obtain an RDA, provide the following information prior to dispensing LUMRYZ.
  - Patient information:
    - Patient First Name
    - Patient Last Name
    - Patient Date of Birth
    - Patient Zip Code
  - Prescriber information:
    - Prescriber DEA
  - Completed **Patient Counseling Checklist** for required patients
  - Confirmation that alerts and **RMR** have been reviewed for patient and prescriber
  - Confirmation that a call was made to all other REMS for oxybate products
    - Initial date / time of outreach to all other REMS for oxybate products
    - Number of attempts to contact all other REMS for oxybate products
    - Confirmation that the patient and prescriber are not disenrolled in any other REMS for oxybate products for misuse, abuse, or diversion
    - Confirmation that the patient does not have an overlapping prescription in any other REMS for oxybate products
- ◊ If all safe use conditions are met;
  - A RDA will be generated by the LUMRYZ REMS
  - The RDA will be recorded by the pharmacy
  - The RDA will be maintained in the LUMRYZ REMS patient database
  - Upon receiving the RDA code, the certified pharmacy is authorized to dispense LUMRYZ

- If the safe use conditions are **not met**, a RDA will not be issued, and the pharmacy will be notified of the reason, and the product will not be dispensed.
- If a certified pharmacy receives information regarding active, overlapping prescriptions for an oxybate product for a patient, the certified pharmacy responsible for dispensing the current prescription will notify and consult each prescriber.

o Prescriptions are considered overlapping when more than one prescription for an oxybate product is received for a patient within an overlapping timeframe.

- ◊ If a certified pharmacy suspects abuse, misuse, or diversion, the prescription should not be filled, the certified pharmacy must complete and submit a **RMR** to the LUMRYZ REMS, and the prescriber will be notified.
- ◊ There are valid reasons why a patient may have overlapping prescriptions on file or on hold, including if the patient moves or changes prescribers, or if the prescriber sends in a new prescription prior to the completion of all refills.
- ◊ A certified pharmacy responsible for dispensing LUMRYZ to a patient must ensure that under these situations a patient does not receive multiple overlapping shipments of an oxybate product.
- ◊ If there are valid reasons why a patient may need an overlapping dispense of an oxybate product, including if the prescriber is changing the patient's treatment, to avoid delivery issues, if there is a valid early refill (e.g., lost or stolen medication), or for titration timing.

- Once a RDA is obtained from the LUMRYZ REMS, patient information has been reviewed in the patient database using the secure web viewing portal has been performed, and the other REMS for oxybate products have been contacted, the certified pharmacy will contact the patient to schedule shipment.
  - For a new patient, the certified pharmacy provides the **Patient Brochure**.
  - A pharmacist must counsel the patient by completing the **Patient Counseling Checklist** prior to the initial dispensing of LUMRYZ.
    - The certified pharmacy must submit the **Patient Counseling Checklist** to the LUMRYZ REMS online at www.LUMRYZREMS.com or complete a print version and fax to the LUMRYZ REMS at 1-877-206-3198.
- The certified pharmacy must report each prescription filled for LUMRYZ to all REMS for oxybate products
  - Product information:
    - Date of Fill
    - Days' Supply
    - Quantity
    - Product/NDC

SHIPPING

All LUMRYZ is shipped to patients (or their adult designee) by an overnight service with receipt signature required. Certified pharmacies must provide confirmation of receipt of each prescription of LUMRYZ to the LUMRYZ REMS electronically.

- The patient may request an alternate shipping address, which is subject to approval by a pharmacist.
- See **How Supplied** for details of the contents of each LUMRYZ shipment.
- Daily tracking reports are generated to confirm the receipt of each order shipped.
- Lost shipments are investigated.

MONITORING FOR INAPPROPRIATE PRESCRIBING, ABUSE, MISUSE, AND DIVERSION

Certified pharmacies must conduct detailed monitoring on an ongoing basis of patients and prescribers for signs of inappropriate prescribing, abuse, misuse and diversion. Each certified pharmacy will:

- Document early refill requests and instances of patient and prescriber behavior that suggest potential abuse, misuse, or diversion by completing and submitting a **RMR** to the LUMRYZ REMS online at www.LUMRYZREMS.com or complete a print version and fax to the LUMRYZ REMS at 1-877-206-3198. This information is maintained in the prescriber and/or patient databases in the LUMRYZ REMS.
  - Request the LUMRYZ REMS to disenroll a patient or a prescriber who has demonstrated behavior that suggests potential abuse, misuse, or diversion by completing and submitting a **RMR** to the LUMRYZ REMS.
- Review the patient's **RMR** history and alerts in the LUMRYZ REMS using the secure pharmacy web viewing portal for the patient database prior to granting an early refill request or if abuse, misuse, or diversion is suspected.
- Discuss early refill requests or other patient incidents with the prescriber so that the prescriber can make a decision to allow or deny the early refill, or to take some other action based on the patient's behavior and history.
- Report all **RMRs** to the LUMRYZ REMS by completing and submitting the **RMR** online at www.LUMRYZREMS.com or by fax to 1-877-206-3198.
- Determine whether an alert should be placed in the patient's profile in the patient database within the LUMRYZ REMS for repeated reports of lost, stolen, destroyed, or spilled drug for review prior to shipping LUMRYZ.
- Inform a pharmacist immediately if certified pharmacy staff suspects patients or prescribers of abuse, misuse, or diversion.

ADVERSE EVENT REPORTING

- Everyone on staff in each certified pharmacy has an essential role to play in the process of collecting information on potential adverse events for reporting to the LUMRYZ REMS.
  - Document and report all potential adverse events reported by all sources, including any CNS depression, respiratory depression, loss of consciousness, coma, and death by contacting Avadel CNS Pharmaceuticals, LLC at productsafety@avadel.com or 1-888-828-2335.
  - Report all potential adverse events related to suspected abuse, misuse, or diversion, by completing and submitting the **RMR** to the LUMRYZ REMS online at www.LUMRYZREMS.com or by fax to 1-877-206-3198.

ONGOING PATIENT EDUCATION

Patients in the LUMRYZ REMS have access to ongoing education while taking LUMRYZ through:

- A 24-hour/7 day a week toll-free telephone help line staffed by a pharmacist trained in the LUMRYZ REMS,
- Continued contact with the certified pharmacy for every refill, and
- The LUMRYZ REMS website (www.LUMRYZREMS.com).

DRUG TAKEBACK PROGRAM

- LUMRYZ patients can return any unused, leftover or expired drug product through a drug takeback program. To obtain information, please contact the LUMRYZ REMS at 1-877-453-1029.

CERTIFIED PHARMACY TRAINING — PHARMACIST MODULE

LUMRYZ™ REMS

Training for Authorized Representatives and Pharmacists Involved in the Dispensing of LUMRYZ

All LUMRYZ REMS authorized representatives and certified pharmacy pharmacists involved in dispensing LUMRYZ must complete training on the **Pharmacist Module** (in addition to the **Pharmacy Staff Module**) and successfully complete the **Pharmacist Knowledge Assessment** and **Pharmacy Staff Knowledge Assessment**. Training must be completed annually.

Lumryz™

(sodium oxybate) for extended-release oral suspension Ⓒ

Reference ID: 5446567

Authorized representatives and all pharmacists involved in dispensing LUMRYZ must complete the following additional training at least annually. The LUMRYZ REMS requires that pharmacists within a certified pharmacy are thoroughly trained on the requirements of the LUMRYZ REMS. Training will be conducted by reviewing the LUMRYZ REMS materials and successfully completing the **Knowledge Assessments** on the requirements of certified pharmacies and pharmacists working within a certified pharmacy.

To complete pharmacy certification, Authorized Representatives must submit the **Pharmacy Enrollment Form** to the LUMRYZ REMS.

Pharmacist duties will include:

- Review of the LUMRYZ Prescribing Information.
- Review of certified pharmacy's internal processes and procedures established to support the LUMRYZ REMS with an experienced pharmacist.
- Execution of the **Patient Counseling Checklist** for new patients, existing patients who restart treatment after not receiving LUMRYZ for 6 months or longer, and patients who report a change in their medication or medical history.
- Detailed monitoring including completion of a **RMR**, as needed.
- Follow-up interactions with patients and prescribers.
- LUMRYZ REMS documentation and processes.

LUMRYZ REMS REQUIREMENTS

For information on the LUMRYZ REMS requirements see **Pharmacy Staff Module- LUMRYZ REMS Requirements**.

CERTIFIED PHARMACY RESPONSIBILITIES

Certified pharmacies will:

- Limit the first prescription fill to no more than a 1-month (30-day) supply of LUMRYZ and no more than a 3-month (90-day) supply for subsequent prescription fills.
- Report potential adverse events to Avadel CNS Pharmaceuticals, LLC at productsafety@avadel.com or 1-888-828-2335.
- Notify prescribers when there are signs of potential abuse or misuse or when patients are taking sedative hypnotics, other CNS depressants, or other potentially interacting agents of which the prescriber is not already aware.
- Certified pharmacies must complete and submit a **RMR** to the LUMRYZ REMS for all instances of potential abuse, misuse, or diversion.
- Certified pharmacies must provide confirmation that each Lumryz prescription filled was reported to all REMS for oxybate products by submitting the confirmation electronically to the LUMRYZ REMS.
- Utilize the LUMRYZ REMS, which has access to the secure, validated, separate and distinct LUMRYZ REMS databases (patient database, certified prescriber database, certified pharmacy database, and disenrolled prescriber database) that will only be queried independently through electronic verification, to verify the following:
    - Complete patient enrollment information
    - Complete prescriber certification information
    - Patient information including:
        - Name and two additional identifiers (date of birth, phone number, address, gender)
        - Current and previous prescribers
        - Comorbid conditions and concomitant medications reported by the patient
        - Prescription history

- Prescription information including:
  - Date
  - Dose
  - Titration instructions (as applicable)
  - Number of refills
  - Directions
  - Total quantity (dose packets and number of days' supply)
  - Concomitant medications
- **RMRs**
- Shipment information, including:
  - Dates of shipments
  - Dates of shipment receipts
  - Patient addresses
  - Designee information
  - Number of shipments sent daily
  - Quantities of LUMRYZ dispensed daily
- Documentation of interactions with prescribers, patients, and other parties

These data must be available to the LUMRYZ REMS for review on an ongoing basis to ensure that LUMRYZ is dispensed to enrolled patients only after completion and documentation of safe use conditions. In certain cases, a pharmacist must access a patient's or prescriber's historical data in the LUMRYZ REMS using the certified pharmacy secure web viewing portal for the patient database and review it prior to dispensing LUMRYZ.

PATIENT COUNSELING AND SCREENING

- Certified pharmacies must complete the **Patient Counseling Checklist** and submit to the LUMRYZ REMS prior to dispensing LUMRYZ for new patients, existing patients who restart treatment after not receiving LUMRYZ for 6 months or longer, and patients who report a change in their medication or medical history.
- For new patients (first shipment of LUMRYZ), and for patients who are restarting LUMRYZ treatment after not receiving product for 6 months or longer, the **Patient Counseling Checklist** must be completed in its entirety.
- For prescription renewals and refills, if the patient has indicated a change in their medication use or medical history, the patient will be transferred to the pharmacist to determine if further counseling and prescriber outreach is required. Steps 1, 3, 4 and 5 of the **Patient Counseling Checklist** must be completed if the patient indicates that the patient is taking a new medication or has a new comorbid medical condition that is listed in Step 4 of the **Patient Counseling Checklist.**
- Each time a pharmacist completes the **Patient Counseling Checklist**, the pharmacist must:
  - Verify that early refill requests have been thoroughly questioned and approved through the **RMR** procedure (see below).
  - Screen the patient for concomitant use of contraindicated medications (sedative hypnotics), alcohol, other CNS depressants or other potentially interacting agents.
    - The pharmacist asks the patient if he or she is taking any other medications and can consult external pharmacy databases to identify drug interactions or prescriptions for other drug products that might have been filled at different pharmacies before filling the LUMRYZ prescription.
    - If patient use of a contraindicated medication is confirmed, and if the prescriber has not indicated prior knowledge, then the pharmacist will notify and consult the prescriber about the risks of concomitant medication use prior to shipping LUMRYZ.
    - Instruct the patient to alert the pharmacy to any new medication the patient begins as soon as possible.
  - Screen the patient for other medical conditions.
    - The pharmacist asks the patient what other medical conditions he/she has.
    - If the patient indicates that he/she has a certain medical condition listed on the **Patient Counseling Checklist**, the pharmacist counsels the patient and notifies the prescriber, if there is no confirmation of prior prescriber knowledge, about the medical condition prior to shipping LUMRYZ.
  - Document the results of the patient screening, all reported concomitant medications and comorbid medical conditions, the action(s) taken, and the date the **Patient Counseling Checklist** is completed in the LUMRYZ REMS.
  - Counsel the patient on proper drug disposal if patient has unused oxybate product from a prior prescription (e.g., receiving an early refill for a dosage increase, alternative dose form of oxybate products, etc.).
  - Submit the **Patient Counseling Checklist** to the LUMRYZ REMS online at www.LUMRYZREMS.com or complete a print version and fax to the LUMRYZ REMS at 1-877-206-3198.
- Certified pharmacies must provide patients with 24/7 access to a LUMRYZ REMS trained pharmacist.

CLINICAL USAGE CLARIFICATIONS

The pharmacist must:

- Review the information on each **Prescription Form**.
- Notify and consult the prescriber if there are any clinical usage clarifications required, such as:
  - Dose over recommended dosage range (6 g to 9 g per night)
  - Non-standard doses or instructions
  - Possible errors in dosing or titration amounts or directions

If the issue is not resolved with the prescriber, the pharmacist may consult with the Pharmacist-in-Charge at his/her certified pharmacy and with the LUMRYZ REMS.

PRESCRIPTION REFILLS

* Note: A pharmacy processing a refill (e.g., transferred prescription) or a renewal (e.g., prescription sent from a prescriber) for an existing patient with the previous fill at another certified pharmacy must contact the previous pharmacy for the most recent **Prescription Form** for the patient that contains the medication and comorbidities list. A pharmacy may view an existing patient's previous RDA history and REMS activity online at www.LUMRYZREMS.com or by calling the LUMRYZ REMS at 1-877-453-1029.

- Up to 5 refills are allowed on a LUMRYZ prescription (per DEA regulations for Schedule lll controlled substances).
- Refills may be submitted from the prescriber to the certified pharmacy by phone, fax, mail, and online through a prescribing system. When the prescription information is entered into the PMS, the LUMRYZ REMS will verify eligibility and issue a RDA.
- For information on the prescription processing requirements see **Prescription Processing** – in the Pharmacy Staff Module.
- Refill orders should be opened at a patient's certified pharmacy when the patient has approximately 10 days of therapy remaining from the previous shipment.
  - Certified pharmacy staff will contact the patient and schedule a shipment. The pharmacy staff will ask the patient if there has been any change in his/her medications or medical history.
  - If the patient reports a change in their medication or medical history, the pharmacy staff will then transfer the patient to a pharmacist who must complete the **Patient Counseling Checklist**. The patient should be counseled on the use or diagnosis of:
    - Sedative hypnotics (for example, diazepam, phenobarbital, zolpidem, etc.)
    - CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating antiepileptic drugs, general anesthetics, and muscle relaxants
    - Alcohol
    - Sleep apnea
    - Asthma, COPD, or other conditions affecting his or her breathing
    - Other current medical conditions
  - The pharmacist completes refill counseling and confirmation of prescriber consultation or notification by completing and submitting the **Patient Counseling Checklist** as applicable to the LUMRYZ REMS online at www.LUMRYZREMS.com or by fax to 1-877-206-3198.
- All patient requests for early refills are to be questioned and documented by the pharmacist.
  - An early refill request is a request for LUMRYZ shipment prior to the date of the next shipment.
  - Requests to accommodate shipment logistics (scheduled delivery date falls on a Sunday, holiday, or vacation) are not considered early refills.
  - If the early refill is required due to a dosage increase, a pharmacist must:
    - Confirm the new dosage with the prescriber prior to processing the prescription.
  - If an early refill is requested for any other reason, a pharmacist must:

- Discuss the request with the patient to evaluate his/her compliance with therapy, assessing for misuse, abuse, and diversion.
- Evaluate the patient's record in the LUMRYZ REMS using the certified pharmacy secure web viewing portal for the patient database and review the patient's prior **RMR** history to identify previous reports of early refills or other incidents suggestive of abuse, misuse, and diversion.
- Contact the prescriber to discuss the request and any prior early refill requests or incidents suggestive of abuse, misuse, and diversion.
- Send new shipments of LUMRYZ to the patient only if approved by the prescriber.
- Send new shipments to replace LUMRYZ reported stolen by a patient only after obtaining a copy of the police report filed by the patient.
- Document the discussion and outcome by completing and submitting the **RMR** to the LUMRYZ REMS online at www.LUMRYZREMS.com or by fax to 1-877-206-3198.

MONITORING AND ASSESSING FOR SIGNS OF ABUSE, MISUSE, AND DIVERSION

- Risk management events must be documented in the LUMRYZ REMS.
  - Risk management events are reported or discovered events outside the norm that give rise to a reasonable suspicion of abuse, misuse, or diversion.
  - Examples of events that should generate a **RMR** include but are not limited to:
    - Requests for early refills
    - Patient's misuse or abuse of product
    - Lost, stolen, destroyed, or spilled drug
    - Delivery to incorrect address and not returned
    - Patient claims that product was not delivered while carrier shows receipt of delivery
    - Product tampering
    - Counterfeit product
    - Contaminated product
    - Inquiries and/or arrests by law or regulatory enforcement agencies associated with the misuse, abuse, or diversion of the product
    - Crimes related to the product
  - **RMRs** must document:
    - Patient and/or prescriber identifying information
    - Reason for report
    - Certified Pharmacy actions
    - Prescriber contact
    - Supporting documentation (if applicable, such as a police report, fire report, DEA Form 106, or shipper investigation report)
  - Pharmacies can request that a patient be monitored by the LUMRYZ REMS if serious or repeated events give rise to reasonable suspicion of misuse, abuse or diversion.
  - If abuse, misuse, or diversion is suspected, the pharmacist must review the patient's **RMR** history and discuss the incident with the prescriber prior to shipping LUMRYZ.
  - Repeated reports of lost, stolen, destroyed, or spilled drug will be documented as an alert to the patient record stored in the patient database of the LUMRYZ REMS and will be accessible to the dispensing pharmacist using the secure web viewing portal for the patient database for review prior to shipping drug.
  - Certified pharmacies and/or prescribers may request the LUMRYZ REMS to disenroll a patient after review and discussion of incidents suggestive of abuse, misuse, or diversion by completing and submitting a **RMR** to the LUMRYZ REMS. Avadel CNS Pharmaceuticals, LLC will review the information and determine if the patient should be disenrolled.

- Pharmacies may recommend that a prescriber be disenrolled by submitting a **RMR** to the LUMRYZ REMS. Avadel CNS Pharmaceuticals, LLC will review the information and determine if the prescriber should be disenrolled.
- All **RMRs** must be reported to the LUMRYZ REMS online at www.LUMRYZREMS.com or by fax to 1-877-206-3198.

SHIPPING PROCEDURES

- LUMRYZ must be shipped via an overnight service with receipt signature required.
  - LUMRYZ is shipped directly to the patient or adult designee (18 years, or 21 years if required by carrier) if the patient is not available to receive the order.
- The patient may request an alternate shipping address, which is then subject to approval by a pharmacist.
- If the patient requests Saturday delivery, his/her certified pharmacy will verify with the overnight shipping service that Saturday delivery is available for the shipping address.
- Each LUMRYZ shipment must include:
  - A carton with the prescribed amount of LUMRYZ packets at the prescribed dose (each child-resistant packet contains a single dose of LUMRYZ 4.5 g, 6 g, 7.5 g, or 9 g).
  - A mixing cup for preparation of each single dose (LUMRYZ dose mixed with water).
  - The **Patient Brochure** (new patients only).
- Daily tracking reports must be generated by each certified pharmacy to confirm the receipt of each order shipped during the previous 48 hours. Saturday deliveries are confirmed the following Monday.
  - A patient will be contacted if there is no proof of patient or designee signature, if the patient or designee on file did not sign for the shipment, or if there is a potential incomplete delivery.
  - If a shipment is reported lost, an investigation will be launched to find it.
  - Receipt of each shipment of LUMRYZ by a patient must be reported to the LUMRYZ REMS by the patient's certified pharmacy electronically. This will include confirmation that the LUMRYZ prescription filled was reported to all REMS for oxybate products.

INVENTORY CONTROL

The LUMRYZ inventory must be reconciled every two weeks and recorded in the pharmacy management system. A physical count must match the count in the pharmacy management system. If the LUMRYZ inventory cannot be reconciled, no other patient orders can be processed until an investigation is completed and approved by the Pharmacist in Charge. Documentation must be made available in the event of an audit.

LUMRYZ™ REMS | Pharmacy Staff Knowledge Assessment

Lumryz.
(sodium oxybate) for extended-release oral suspension

For immediate processing, please go to www.LUMRYZREMS.com.

To submit this form via fax, please complete all required fields below and fax to 1-877-206-3198. You will receive a confirmation of your successful completion of the Knowledge Assessment via email.

PHARMACY STAFF INFORMATION

(*denotes required field)

*First Name:	*Last Name:	
*Phone:	*Fax:	*Email:
*Pharmacy Name:		
*NPI No.:		

LUMRYZ REMS TRAINING: PHARMACY STAFF MODULE

SELECT THE BEST ANSWER FOR EACH OF THE FOLLOWING QUESTIONS.

1. LUMRYZ (sodium oxybate) for extended-release oral suspension is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.
   ☐ A. True ☐ B. False
2. LUMRYZ contains the sodium salt of gamma-hydroxybutyrate (GHB) and is a controlled substance because:
   ☐ A. It can make the patient sleepy quickly
   ☐ B. It must be taken while in bed
   ☐ C. It has abuse and misuse potential
   ☐ D. It requires preparing a suspension before dosing
3. LUMRYZ is contraindicated in patients who:
   ☐ A. Take sedative hypnotics
   ☐ B. Drink alcohol while using LUMRYZ
   ☐ C. Have succinic semialdehyde dehydrogenase deficiency, a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia
   ☐ D. All of the above
4. Healthcare providers should caution patients about operating hazardous machinery for at least six (6) hours after taking a dose of LUMRYZ.
   ☐ A. True ☐ B. False
5. The LUMRYZ REMS has which of the following requirements?
   ☐ A. Use of a limited number of certified pharmacies
   ☐ B. Healthcare providers who prescribe LUMRYZ must be certified in the REMS and must comply with the requirements of the LUMRYZ REMS
   ☐ C. For patients to receive LUMRYZ, they must be enrolled in the LUMRYZ REMS and be counseled on the serious risks and safe use of LUMRYZ
   ☐ D. All of the above
6. When must a healthcare provider complete and submit a Prescription Form to the pharmacy EXCEPT:
   ☐ A. For a patient's initial prescription of LUMRYZ
   ☐ B. For patient who are restarting LUMRYZ after a lapse in therapy of 6-months or longer
   ☐ C. For all refills and renewals of LUMRYZ
7. The issuance of an RDA informs of all of the following, EXCEPT:
   ☐ A. That the pharmacy is certified, prescriber is certified, and the patient is enrolled in the LUMRYZ REMS
   ☐ B. That the patient is not allergic to LUMRYZ
   ☐ C. That the pharmacy confirmed contact to all other REMS for oxybate products to verify the patient has no other active, overlapping prescriptions for oxybate products and that the patient and prescriber has not been disenrolled from any other REMS for oxybate products for suspected abuse, misuse, or diversion were completed
   ☐ D. That the pharmacist has completed the **Patient Counseling Checklist** with the required patients
   ☐ E. That the pharmacist has reviewed the alerts and **Risk Management Report (RMR)** history for the patient and prescriber
8. A certified pharmacy must not stock LUMRYZ in retail pharmacies.
   ☐ A. True
   ☐ B. False
9. In monitoring patients and prescribers for signs of inappropriate prescribing, abuse, misuse, and diversion, the certified pharmacy staff will:
   ☐ A. Document early refill requests and instances of patient and prescriber behavior that suggest potential abuse, misuse, or diversion by completing a **RMR**
   ☐ B. Review the patient's RMR history and alerts in the LUMRYZ REMS
   ☐ C. Inform a pharmacist immediately if certified pharmacy staff suspects a patient or prescriber of abuse, misuse, or diversion
   ☐ D. Determine whether an alert should be placed in the patient's profile in the patient database within the LUMRYZ REMS
   ☐ E. All of the above
10. Certified pharmacy staff must report all potential adverse events reported by all sources including any CNS depression, respiratory depression, loss of consciousness, coma, and death to Avadel CNS Pharmaceuticals, LLC.
    ☐ A. True
    ☐ B. False
11. Which of the following must be completed when contacting all other REMS for oxybate products with each prescription dispense?
    ☐ A. Verify that the patient has no other active prescriptions for oxybates products that overlap with the current prescription
    ☐ B. Verify that the patient/prescriber has not been disenrolled from any other REMS for oxybate products for suspected abuse, misuse, or diversion
    ☐ C. Report each prescription filled for LUMRYZ
    ☐ D. All of the above
12. LUMRYZ is a CNS depressant. Which of the following warnings related to CNS depressants is false?
    ☐ A. Concurrent use with other CNS depressants may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death
    ☐ B. Patients who have sleep apnea or compromised respiratory function may be at higher risk of developing respiratory depression, loss of consciousness, coma, and death with LUMRYZ
    ☐ C. All surgeries and procedures must be reported as adverse events
    ☐ D. 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., impaired judgment, thinking, or motor skills)

Avadel™

LUMRYZ™ REMS | Pharmacist Knowledge Assessment

Lumryz.
(sodium oxybate) for extended-release oral suspension C

For immediate processing, please go to www.LUMRYZREMS.com.

To submit this form via fax, please complete all required fields below and fax to 1-877-206-3198. You will receive a confirmation of your successful completion of the Knowledge Assessment via email.

PHARMACIST INFORMATION

(*denotes required field)

*First Name:	*Last Name:	
*Phone:	*Fax:	*Email:
*Pharmacy Name:		
*NPI No.:		

LUMRYZ REMS TRAINING: PHARMACISTS MODULE

SELECT THE BEST ANSWER FOR EACH OF THE FOLLOWING QUESTIONS.

1. Prior to dispensing LUMRYZ to a patient, the certified pharmacy will process all LUMRYZ prescriptions, regardless of payment method, through the pharmacy management system and obtain a REMS dispense authorization (RDA) via electronic verification to verify the prescriber is certified, the patient is enrolled and the patient has no other active, overlapping LUMRYZ prescriptions.
   A. True B. False
2. Certified pharmacies must reconcile LUMRYZ inventory every two weeks and record in the pharmacy management system. Documentation must be made available in the event of an audit.
   A. True B. False
3. Certified pharmacies in the LUMRYZ REMS will:
   A. Limit the patient's first prescription fill of LUMRYZ to no more than a one-month (30-day) supply and subsequent prescription fills to no more than a three-month (90-day) supply
   B. Report potential adverse events to Avadel CNS Pharmaceuticals, LLC
   C. Notify prescribers when there are signs of potential abuse or misuse or when patients are taking sedative hypnotics, other CNS depressants, or other potentially interacting agents of which the prescriber is not already aware
   D. All of the above
4. Certified pharmacies in the LUMRYZ REMS must perform all of the following EXCEPT:
   A. Validate all prescriptions prior to dispensing LUMRYZ
   B. Counsel the patient by completing the **Patient Counseling Checklist** prior to dispensing LUMRYZ to new patients, existing patients who are restarting LUMRYZ treatment after not receiving product for 6 months or longer, and patients who report a change in their medication or medical history
   C. Contact the patient's prescriber prior to every dispense of LUMRYZ
   D. Monitor patients and prescribers for signs of inappropriate prescribing, abuse, misuse, and diversion and complete a **Risk Management Report Form** if needed
5. If there are clinical usage clarifications needed for a prescription, the pharmacist will:
   A. Document via the REMS Dispense Authorization
   B. Notify and consult the patient's prescriber
   C. Fill out a **Risk Management Report Form**
   D. Disenroll the prescriber
6. Which of the following is NOT true for the prescription refill process?
   A. Up to 5 refills are allowed on a LUMRYZ prescription
   B. Patient counseling must be completed and submitted to the REMS using the **Patient Counseling Checklist** if the patient reports a change in their medication or medical history
   C. Refill orders should be opened when the patient has approximately 10 days of therapy remaining from the previous shipment
   D. All refills must be countersigned by the prescriber
7. If the pharmacist identifies the patient is taking a potentially interacting agent that may present a risk to the patient, the pharmacist should consider which of the following actions before filling the prescription?
   A. Notifying law enforcement
   B. Taking no action
   C. Consulting with the patient's prescriber
   D. Consulting with the patient's insurance provider
8. In monitoring and assessing for signs of abuse, misuse, or diversion, a pharmacist should complete a **Risk Management Report (RMR)** for which of the following events?
   A. Early refill requests (excluding requests to accommodate shipment logistics)
   B. Lost, stolen, destroyed, or spilled drug
   C. Patient claims that product was not delivered while carrier shows receipt of delivery
   D. Patient's misuse or abuse of product
   E. All of the above
9. Each shipment of LUMRYZ must include:
   - A carton with the prescribed amount of LUMRYZ packets at the prescribed dose (each child-resistant packet contains LUMRYZ 4.5 g, 6 g, 7.5 g, or 9 g)
   - A mixing cup for preparation of each single dose (LUMRYZ dose mixed with water)
   - A **Patient Brochure** (new patients only)

   A. True B. False
10. All LUMRYZ prescriptions must be shipped to the patient or adult designee via:
    A. Certified mail with receipt signature
    B. Overnight service with receipt signature required
    C. Medical courier
    D. United States Postal Service with delivery receipt
11. Pharmacist duties include:
    A. Execution of the **Patient Counseling Checklist** with new patients and patients who have not received LUMRYZ for 6 months or longer
    B. Detailed monitoring, including completion of a **Risk Management Report (RMR)**
    C. Follow-up interactions with patients and prescribers
    D. All of the above
12. If the LUMRYZ inventory cannot be reconciled, no other patient orders can be processed until an investigation is completed and approved by the Pharmacist in Charge.
    A. True B. False

Reference ID: 5446567

Lumryz.
(sodium oxybate) for extended-release oral suspension C

LUMRYZ™ REMS | LUMRYZ Prescription Form

LUMRYZ (sodium oxybate) for extended-release oral suspension

Fax completed form to one of the certified pharmacies. A list of certified pharmacies is available to certified prescribers at www.LUMRYZREMS.com or by calling the LUMRYZ REMS at 1-877-453-1029. For more information, please call the LUMRYZ REMS at 1-877-453-1029.

PRESCRIBER INFORMATION Please Print (*denotes required field)

*First Name:	M.I.:	*Last Name:	
*NPI No.:	*DEA No.:	*State License No.:	
*Street Address:		*Phone:	
*City:	*State:	*Zip Code:	*Fax:
Office Contact Name:		Office Contact Phone:	

PATIENT INFORMATION Please Print (*denotes required field)

*First Name:	M.I.:	*Last Name:	*Primary Phone:
*Date of Birth (MM/DD/YYYY):	*Gender: ☐ Male ☐ Female ☐ Other		Cell Phone:
*Address:			Work Phone:
*City:	*State:	*Zip Code:	Email:

***Medications:** (list all known current prescription and non-prescription medications and dosages or submit as a separate page)
☐ Check box if separate page(s) attached. Total number of additional pages: _____

Comorbidities: (list all known comorbidities or submit as a separate page)
☐ Check box if separate page(s) attached. Total number of additional pages: _____

*Indication for Use (Select One): ☐ G47.411 Narcolepsy with cataplexy ☐ G47.419 Narcolepsy without cataplexy ☐ Other (please specify) _____

LUMRYZ (sodium oxybate) for extended-release oral suspension
The available strengths of LUMRYZ are 4.5 g, 6 g, 7.5 g and 9 g in box quantities of 7 or 30 packets or a Starter Pack containing 28 packets (7 packets of 4.5 g, 14 packets of 6 g and 7 packets of 7.5 g).

Please complete one of the below prescription options (either Starter Pack, Titrated Dose, or Maintenance Dose):

Medication	Package Type & Strength	Quantity	# of Refills
_____ *Please specify medication name above*	☐ Starter Pack NDC: 13551-005-01 Starter Pack includes 4.5 g (Week 1), 6 g (Week 2 and Week 3) and 7.5 g packets (Week 4)	_____ Starter Pack box of seven (7) 4.5 g fourteen (14) 6 g, seven (7) 7.5 g packets	N/A
	☐ Titrated Dose Week 1 _____ g Week 2 _____ g Week 3 _____ g Week 4 _____ g	_____ box(es) of seven (7) _____ box(es) of seven (7) _____ box(es) of seven (7) _____ box(es) of seven (7)	N/A
	☐ Maintenance Dose _____ g	_____ box(es) of thirty (30)	_____

Dispensing Instructions: ***Initial prescription fill cannot exceed 1 month of therapy; refills cannot exceed 3 months' supply of therapy.***

Directions: ☐ Take contents of one packet mixed with water in provided mixing cup once per night orally at bedtime.
Note: Prepare the dose of LUMRYZ at bedtime according to label instructions. The LUMRYZ shipment does not include water for mixing.

Special Instructions:

PRESCRIBER PRESCRIPTION VERIFICATION: I understand and agree that, as the prescriber, I will comply with my state-specific prescription requirements such as e-prescribing, state-specific prescription form, fax language, etc. Non-compliance with state-specific requirements could result in outreach to me, as the prescriber. Prescriber attests this is his/her legal signature. NO STAMPS.

_____ *Prescriber Signature _____ *Date

PRESCRIBER REMS VERIFICATION: My signature below signifies that: I understand the statements and agree to the LUMRYZ REMS requirements which are found on page 2 of this form; LUMRYZ is medically appropriate for this patient; and, I have informed the patient that the LUMRYZ REMS will send him/her a Patient Brochure with his or her first prescription fill.

_____ *Prescriber Signature _____ *Date

Printed Supervising Physician Name (if required by state law):

_____ Supervising Physician Signature _____ Date

PHARMACY VERIFICATION – My signature below signifies that: I understand the statements and agree to the LUMRYZ REMS requirements which are found on page 2 of this form.

_____ *Pharmacist Signature _____ *Date

Prescriber and Pharmacist: Signature verification is required on the first page of this **Prescription Form** as acknowledgment that you have an understanding of and/or agree to the following:

PRESCRIBER ATTESTATIONS

I understand that:

- LUMRYZ is approved for the treatment of
  - Cataplexy in adults with narcolepsy.
  - Excessive daytime sleepiness (EDS) in adults with narcolepsy.
- LUMRYZ is a Schedule III central nervous system (CNS) depressant and can cause obtundation and clinically significant respiratory depression at recommended doses.
- LUMRYZ is contraindicated in combination with alcohol and sedative hypnotics.
- Concurrent use of LUMRYZ with certain 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.
- Patients who have sleep apnea or compromised respiratory function (e.g., asthma, COPD, etc.) may be at higher risk of developing respiratory depression, loss of consciousness, coma, and death with LUMRYZ use.

Before treatment initiation (first dose), I must:

- Assess the patient's health status to determine if LUMRYZ is medically appropriate by screening for history of alcohol and drug abuse, sleep-related breathing disorders, compromised respiratory function, depression, suicidality, concomitant use of sedative hypnotics and other CNS depressants or potentially interacting agents. Document and submit to a certified pharmacy using the **Prescription Form**.
- Counsel the patient on the serious risks and safe use, handling, and storage of LUMRYZ using the **Patient Brochure**.
- Enroll the patient by completing and submitting the **Patient Enrollment Form** to the REMS.
- Order the prescription using the **Prescription Form** and submit it to a certified pharmacy.

Before treatment re-initiation, I must:

- **For patients disenrolled for suspicion of abuse, misuse, or diversion:** Communicate with the pharmacy regarding all relevant patient history and re-enroll the patient if the pharmacist and I agree.
- **For patients with a lapse in treatment of 6 months or longer:** Order the prescription using the **Prescription Form** and submit it to a certified pharmacy.

Within the first 3 months of starting treatment, I must:

- Assess the patient for:
  - Concomitant use of sedative hypnotics, other CNS depressants, or potentially interacting agents
  - Serious adverse events
  - Signs of abuse and misuse, including an increase in dose or frequency of dosing, reports of lost, stolen, or spilled medication, and/or drug-seeking behavior

It is recommended that patients be re-assessed every 3 months while taking LUMRYZ.

At all times, I must:

- Report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death; and any cases of suspected abuse, misuse, or diversion to Avadel CNS Pharmaceuticals, LLC.
- Assess the patient's potential for abuse, misuse, and diversion. Document and submit all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug using the **Risk Management Report**.
- Report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the **Risk Management Report**.

PHARMACIST ATTESTATIONS

As the pharmacist, I must

- Verify that the patient has no other active, overlapping prescriptions for an oxybate product that overlap with the current LUMRYZ prescription.
- Verify the patient and prescriber have not been disenrolled in any other REMS for oxybate products for suspected abuse, misuse, or diversion.
- Report this prescription filled for LUMRYZ to the LUMRYZ REMS and all other REMS for oxybate products.

Lumryz.
(sodium oxybate) for extended-release oral suspension C

To be completed by the pharmacist online at www.LUMRYZREMS.com
or
by printing and faxing the completed form to the LUMRYZ REMS at 1-877-206-3198 prior to dispensing LUMRYZ to new patients, existing patients who are restarting LUMRYZ treatment after not receiving product for 6 months or longer, and patients who report a change in their medication or medical history. Include additional requirements (if any) per federal or state requirements that need to be collected as part of the patient counseling process.

PHARMACIST INFORMATION (All fields required)

Pharmacist First Name:	Pharmacist Last Name:
Phone:	Email.:
Pharmacy Name:	NPI No:

PATIENT INFORMATION (All fields required)

First Name:	Last Name:
Date of Birth (MM/DD/YYYY):	REMS ID Number:

ALL STEPS BELOW ARE REQUIRED AND MUST BE COMPLETED BY CHECKING THE BOXES AND INITIALING/DATING THE BOTTOM OF EACH PAGE.

STEP 1: PATIENT INFORMATION (Select One)

(Complete this section for new patients (first shipment of LUMRYZ), existing patients who are restarting LUMRYZ treatment after not receiving product for 6 months or longer, and patients who report a change in their medication use or medical history listed in Step 4 of this checklist)

- ☐ New/restart
- ☐ Scheduled refill
- ☐ Early refill approved through **Risk Management Report (RMR)** process

STEP 2: COUNSELING

(Complete this section for new patients (first shipment of LUMRYZ) and existing patients who are restarting LUMRYZ treatment after not receiving product for 6 months or longer)

- ☐ Verify that the patient will receive the **Patient Brochure**.
- ☐ Verify that the patient has been counseled on **Therapy Expectations** below:
  - During clinical trials with LUMRYZ, many patients with narcolepsy saw some improvement with excessive daytime sleepiness and/or cataplexy in the first weeks after beginning LUMRYZ therapy. However, the response to LUMRYZ can vary from patient to patient. It may also take time to find the right dose that works for you. Your doctor will determine the dose that is appropriate for you.
  - Be sure to talk to your doctor about any troubling side effects or if you don't feel any benefits while taking LUMRYZ.
  - For any changes to your prescription, have your doctor call or fax the new prescription change to the pharmacy. NEVER attempt to change the dose yourself.
- ☐ Verify that the patient has been counseled on **Preparation and Administration** information below:
  - LUMRYZ should be taken as directed by your doctor (review prescriber's instructions with patient).
  - LUMRYZ should be taken at least 2 hours after eating.
  - Prepare your dose of LUMRYZ as follows:
    - Before going to bed, gather the following supplies and place them on a flat surface at your bedside:
      - 1 bottle or glass of water (1/3 cup). Do not use hot water;
      - 1 LUMRYZ packet from the carton;
      - 1 clean mixing cup; and
      - 1 pair of scissors (optional).
    - Fill the mixing cup with water up to Fill Line A (top line) and set the mixing cup on a flat surface at your bedside.
    - Open one LUMRYZ packet (by either tearing at the tear mark or cutting with scissors) and pour the entire content from the packet into the water-filled mixing cup.
    - Place the cap on the mixing cup and shake well for at least 60 seconds (1 minute). The mixed solution should appear slightly milky and may contain some lumps. Make sure to drink all the mixed solution in the mixing cup.
    - Immediately after drinking the mixed solution, refill the mixing cup with water up to Fill Line B (lower line) to mix in any medicine left in the mixing cup.
    - Place the cap on the mixing cup and shake well for at least 10 seconds. Again, while in bed, make sure to drink all the mixed solution in the mixing cup within 30 minutes of mixing. If not taken within 30 minutes of mixing, throw it away (dispose of it) and prepare a new dose.
    - Leave the empty mixing cup at your bedside and immediately lie down to go to sleep. Avoid getting out of bed after taking LUMRYZ.

Pharmacist Initials: _____ Date (mm/dd/yyyy): _____

Lumryz.
(sodium oxybate) for extended-release oral suspension C

- Refer to the LUMRYZ Medication Guide for additional information on preparation of your LUMRYZ dose.
- Feel free to call your certified pharmacy if you have any questions about preparing your dose or how to take your LUMRYZ doses. The LUMRYZ REMS is also available Monday through Friday, from 8 am to 8 pm Eastern Time, at 877-453-1029, and a pharmacist is always available 24 hours a day, 7 days a week at your certified pharmacy, if needed.
- Patients usually fall asleep in about 5 to 15 minutes, although some patients have reported falling asleep more quickly (without first feeling drowsy) and others may take longer to fall asleep. The time it takes to fall asleep might be different from night to night.
- Be sure to store LUMRYZ in the original carton in a safe and secure place out of the reach of children and pets. Get emergency help (call 911) right away if a child ingests LUMRYZ.
- LUMRYZ should be stored at room temperature.

Note to pharmacist: If patient has unused sodium oxybate from a prior prescription (e.g., receiving an early refill for a dosage increase, alternative dose form of sodium oxybate), counsel the patient on proper drug disposal.

☐ Verify that the patient has been counseled on **Precautions Needed for LUMRYZ Use** below:

- LUMRYZ is classified as a controlled substance medication. LUMRYZ must be used only by the person for whom it is prescribed and as directed by the prescriber. All lost or stolen medication must be reported to local police and your pharmacy.
- Federal law prohibits the transfer of LUMRYZ to any person other than the patient for whom it was prescribed.
- LUMRYZ is sodium oxybate. The active ingredient in sodium oxybate is gamma-hydroxybutyrate (GHB), which is associated with serious adverse reactions with illicit use and abuse. GHB has been associated with drug-facilitated sexual assault (e.g., date rape).
- Abuse of GHB can lead to dependence (a physical need to take the drug), craving for the medicine, and severe withdrawal symptoms (symptoms that start when the drug is stopped, especially when it is stopped suddenly). Abuse of GHB, with or without other CNS depressants (for example, nortriptyline, oxycodone, or heroin) including alcohol can lead to seizure, trouble breathing, decreases in the level of consciousness, coma, and death.
- Tell your doctor if you:
  - 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 will take LUMRYZ or breastfeed.
  - Have or had depression or tried to harm yourself. You should be watched carefully for new symptoms of depression.
  - Have liver problems.
  - Have short periods of not breathing while you sleep (sleep apnea), snoring, trouble breathing, or lung problems. You may have a higher chance of serious breathing problems with LUMRYZ.
  - Have mental health problems.
  - Have experienced sleepwalking.
  - Are on a salt-restricted diet, have high blood pressure, heart failure, or kidney problems. LUMRYZ contains sodium (salt) and may not be right for you.

☐ Verify that the patient has been counseled on **Side Effects** below:

- In the placebo-controlled clinical trial for LUMRYZ, the most common adverse reactions reported for any dose of LUMRYZ were nausea, dizziness, enuresis (bedwetting), headache, and vomiting.
- LUMRYZ can cause serious side effects, including trouble breathing while sleeping, confusion, unusual or disturbing thoughts, depression, thoughts of killing yourself or trying to kill yourself, and sleepwalking, even at recommended doses. Tell your doctor if you have any of these problems while taking LUMRYZ.
- Remember that you must not drive a car, operate heavy machinery, or perform any activity that is dangerous or that requires mental alertness or motor coordination for at least 6 hours after taking LUMRYZ.
- When taking LUMRYZ, do not drink alcohol or take medicines that make you sleepy unless specifically prescribed by your doctor for use with LUMRYZ, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating antiepileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants.
- These are not all of the side effects that you might experience. Contact your doctor if you are concerned about any possible side effects. Refer to the LUMRYZ Medication Guide for additional information on possible side effects.

Pharmacist Initials: _____ Date (mm/dd/yyyy): _____

Lumryz.
(sodium oxybate) for extended-release oral suspension C

STEP 3: SCREENING

(Complete this section for new patients (first shipment of LUMRYZ), existing patients who are restarting LUMRYZ treatment after not receiving product for 6 months or longer, and patients who report a change in their medication or medical history listed in Step 4 of this checklist)

1. Is the patient taking sedative hypnotics (for example, eszopiclone, zaleplon, zolpidem, temazepam, suvorexant, quazepam, estazolam, flurazepam, triazolam, tasimelteon, ramelteon)?

☐ Yes ☐ No If Yes, ☐ Counseled Patient

Please list the drug(s) and dose of each:	Drug	Dose

2. Is the patient taking benzodiazepines (for example, diazepam, alprazolam or any not listed in question 1), sedating antidepressants or antipsychotics, sedating antiepileptics, general anesthetics, muscle relaxants, opioid analgesics, or illicit CNS depressants (for example, heroin, GHB, etc.)?

☐ Yes ☐ No If Yes, ☐ Counseled Patient

Please list the drug(s) and dose of each:	Drug	Dose

3. What other prescription and non-prescription drugs is the patient taking? ☐ None

Please list the drug(s) and dose of each:	Drug	Dose

4. Does the patient drink alcohol? ☐ Yes ☐ No If Yes, ☐ Counseled Patient

5. Has the patient been diagnosed with sleep apnea (short periods of not breathing while asleep)? ☐ Yes ☐ No If Yes, ☐ Counseled Patient

6. Does the patient have a diagnosis of or suffer from asthma, COPD, or other conditions affecting his/her breathing (slower breathing, trouble breathing)?

☐ Yes ☐ No If Yes, ☐ Counseled Patient

Please list the drug(s) used to treat and dose of each, if known:	Drug	Dose

7. Does the patient have any other current medical/psychiatric conditions for which the patient is under a healthcare provider's care?

☐ Yes ☐ No If Yes, ☐ Counseled Patient

Please list the condition(s), if known:	Condition

8. Does the patient have any clinical questions about LUMRYZ?

☐ Yes ☐ No If Yes, ☐ Counseled Patient **and/or** ☐ Referred Patient to Prescriber

Please list the question(s):	Question

Pharmacist Initials: _____ Date (mm/dd/yyyy): _____

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STEP 4: CONCOMITANT MEDICATION & COMORBIDITY SUMMARY

(Complete this section for new patients (first shipment of LUMRYZ), existing patients who are restarting LUMRYZ treatment after not receiving product for 6 months or longer, and patients who report a change in their medication or medical history listed in this step of this checklist)

Medication Type:

- ☐ Sedative hypnotics
- ☐ Benzodiazepines
- ☐ Alcohol
- ☐ Sedating antidepressants, antipsychotics, or antiepileptics
- ☐ General anesthetics
- ☐ Muscle relaxants
- ☐ Opioid analgesics
- ☐ Illicit CNS depressants (e.g., heroin, GHB, etc.)
- ☐ None of the above

Medical Conditions:

- ☐ Sleep apnea
- ☐ Asthma
- ☐ COPD
- ☐ Other conditions affecting their breathing
- ☐ History of depression or suicidality
- ☐ History of alcohol and drug abuse
- ☐ Seizure disorders
- ☐ Hepatic impairment
- ☐ High blood pressure, heart problems, kidney problems, or are on a salt-restricted diet
- ☐ None of the above

If any of the medication types or medical conditions listed above are checked, or any of the questions in Step 3 were answered yes and there is no confirmation of prior prescriber knowledge, call the prescriber to consult:

Is a prescriber consult required? ☐ Yes ☐ No

If no, please provide reason:_____

_____

If yes, action(s) taken (check all that apply and document details in "Prescriber consult outcome" section below):

☐ Contacted prescriber: _____/_____/_____ (Date - mm/dd/yyyy) ☐ Other: _____/_____/_____ (Date - mm/dd/yyyy)

Is prescriber consult due to concomitant sedative hypnotics or benzodiazepines?

If yes, complete all of the following questions at the conclusion of the consult. If no, complete step 5 only. ☐ No ☐ Yes

If yes, is treatment with LUMRYZ to be continued? ☐ No ☐ Yes

If yes, what action will be taken? (select one)

- ☐ Concomitant medication will be discontinued
- ☐ Dosage of concomitant medication has been/will be reduced
- ☐ No action (continue concomitant medication with LUMRYZ)
  - Prescriber's rationale for continuing concomitant medication with LUMRYZ (select one):
    - ☐ Medication will not be taken at the same time as LUMRYZ
    - ☐ Medication will be taken at the same time as LUMRYZ (select one):
      - ☐ Medication will be taken as a sleep aid
      - ☐ Medication will be taken for a different indication per medical need
      - ☐ Information unavailable
    - ☐ LUMRYZ dose regimen changed
    - ☐ No rationale provided or Information unavailable
    - ☐ Other (specify):

CONSULTING PRESCRIBER INFORMATION

First Name:	Last Name:	
Prescriber Identifier (provide at least one):	NPI:	DEA:

Overall Prescriber consult outcome:_____

_____

_____

Pharmacist Initials: _____ Date (mm/dd/yyyy): _____

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STEP 5: COMPLETION SUMMARY

(Complete this section for new patients (first shipment of LUMRYZ), existing patients who are restarting LUMRYZ treatment after not receiving product for 6 months or longer, and patients who report a change in their medication or medical history listed in Step 4 of this checklist)

Checklist Completed: ☐ Yes ☐ No (LUMRYZ cannot be dispensed until checklist is completed.)

If yes, date checklist completed (mm/dd/yyyy): _____/_____/_____

If no, document the reason for non-completion:_____

_____

_____

My signature below signifies:

- I understand the counseling requirements of the LUMRYZ REMS and have counseled the patient using this **Patient Counseling Checklist**
- I will submit this checklist to the LUMRYZ REMS.

_____ _____

Pharmacist Signature **Date**

Phone: 1-877-453-1029 | www.LUMRYZREMS.com | Fax: 1-877-206-3198

Avadel

Lumryz™
(sodium oxybate) for extended-release oral suspension

SUBJECT:
- **Serious Risks with Use of LUMRYZ™ (sodium oxybate) for extended-release oral suspension:**
  - **Central Nervous System (CNS) Depression**
  - **Abuse and Misuse**
- **FDA Required LUMRYZ REMS**

FDA-REQUIRED REMS SAFETY INFORMATION

Dear Healthcare Provider:

This letter is to inform you about the risks of CNS depression, abuse and misuse associated with LUMRYZ and the LUMRYZ REMS. LUMRYZ is a new once-at-bedtime therapy indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.

The U.S. Food and Drug Administration (FDA) has determined that a **Risk Evaluation and Mitigation Strategy (REMS)** is necessary to manage the risks of CNS depression, abuse, and misuse. LUMRYZ is only available through a restricted distribution program called the LUMRYZ REMS.

Risks of LUMRYZ

- Serious adverse outcomes from inappropriate prescribing, misuse, abuse and diversion
- Significant central nervous system (CNS) and respiratory depression
- Contraindication of use of LUMRYZ with sedative hypnotics or alcohol

LUMRYZ REMS Requirements

- Prescribers of LUMRYZ must be certified in the LUMRYZ REMS in order to prescribe LUMRYZ.
- Additional details about the requirements of the LUMRYZ REMS are outlined in the *Fact Sheet* included with this letter.
- To certify in the LUMRYZ REMS, visit www.LUMRYZREMS.com.

For additional details about the REMS, visit www.LUMRYZREMS.com or contact the LUMRYZ REMS at 1-877-453-1029.

The information in this letter is not intended as a complete description of the benefits and risks associated with the use of LUMRYZ. Please see the accompanying Prescribing Information including the Medication Guide.

Adverse Event Reporting

Report serious adverse events of LUMRYZ to Avadel CNS Pharmaceuticals, LLC at productsafety@avadel.com or 1-888-828-2335 and/or the FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Sincerely,

Avadel CNS Pharmaceuticals, LLC

Lumryz™
(sodium oxybate) for extended-release oral suspension Ⓒ

SUBJECT:
- **Serious Risks with Use of LUMRYZ™ (sodium oxybate) for extended-release oral suspension:**
  - **Central Nervous System (CNS) Depression**
  - **Abuse and Misuse**
- **FDA Required LUMRYZ REMS**

FDA-REQUIRED REMS SAFETY INFORMATION

Dear Professional Society:

We request that you share the following with your members.

This letter is to inform prescribers about the risks of CNS depression, abuse and misuse associated with LUMRYZ and the LUMRYZ REMS. LUMRYZ is a new once-at-bedtime therapy indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.

The U.S. Food and Drug Administration (FDA) has determined that a **Risk Evaluation and Mitigation Strategy (REMS)** is necessary to manage the risks of CNS depression, abuse, and misuse. LUMRYZ is only available through a restricted distribution program called the LUMRYZ REMS.

Risks of LUMRYZ

- Serious adverse outcomes from inappropriate prescribing, misuse, abuse and diversion
- Significant central nervous system (CNS) and respiratory depression
- Contraindication of use of LUMRYZ with sedative hypnotics or alcohol

LUMRYZ REMS Requirements for Prescribers

- Prescribers of LUMRYZ must be certified in the LUMRYZ REMS in order to prescribe LUMRYZ.
- Additional details about the requirements of the LUMRYZ REMS are outlined in the *Fact Sheet* included with this letter.
- To certify in the LUMRYZ REMS, prescribers should visit www.LUMRYZREMS.com.

For additional details about the REMS, visit www.LUMRYZREMS.com or contact the LUMRYZ REMS at 1-877-453-1029.

The information in this letter is not intended as a complete description of the benefits and risks associated with the use of LUMRYZ. Please see the accompanying Prescribing Information including the Medication Guide.

Adverse Event Reporting

Prescribers are to report serious adverse events of LUMRYZ to Avadel CNS Pharmaceuticals, LLC at productsafety@avadel.com or 1-888-828-2335 and/or the FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Sincerely,

Avadel CNS Pharmaceuticals, LLC

Lumryz.
(sodium oxybate) for extended-release oral suspension C

LUMRYZ™ REMS Fact Sheet

LUMRYZ REMS OVERVIEW

What is the LUMRYZ REMS (Risk Evaluation and Mitigation Strategy)?

The LUMRYZ REMS is a safety program that manages the risk of serious adverse outcomes from inappropriate prescribing, misuse, abuse, and diversion of LUMRYZ. The LUMRYZ REMS is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. The LUMRYZ REMS is a restricted distribution program. The LUMRYZ REMS is a separate REMS program and does not replace other REMS for oxybate products. Certification in other REMS for oxybate products is not reciprocal with the LUMRYZ REMS.

PRESCRIBERS must be certified in the LUMRYZ REMS

PHARMACIES must be certified in the LUMRYZ REMS

PATIENTS must be enrolled in the LUMRYZ REMS

Scan to access

WHAT IS THE RISK?

LUMRYZ:

- Is a central nervous system (CNS) depressant and can cause obtundation and clinically significant respiratory depression at recommended doses
- Has a known potential for abuse and misuse, 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

How Can Prescribers Manage the Risk?

- Assess the patient's health status by screening the patient for history of alcohol, drug abuse, sleep-related breathing disorders, compromised respiratory function, depression, suicidality, concomitant use of sedative hypnotics, other CNS depressants or other potentially interacting agents
- Counsel each patient prior to initiating therapy on the serious risks and safe use, handling, and storage of LUMRYZ
- Assess the patient's potential for abuse, misuse, and diversion and report any suspected cases to the REMS

How Can Pharmacies Manage the Risk?

- Screen for concomitant use of sedative hypnotics and potentially interacting agents
- Notify prescribers when there are signs of potential abuse or misuse or when patients are taking sedative hypnotics, other CNS depressants, or other potentially interacting agents of which the prescriber is not already aware
- Report all potential adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death to Avadel CNS Pharmaceuticals, LLC
- Monitor and report all instances of patient and prescriber behavior that gives rise to a reasonable suspicion of abuse, misuse, or diversion

TO ENROLL IN THE LUMRYZ REMS,
call 1-877-453-1029 or go to www.LUMRYZREMS.com.

Avadel

Reference ID: 5446567

Lumryz.
(sodium oxybate) for extended-release oral suspension C

WHAT ARE THE KEY REQUIREMENTS OF THE LUMRYZ REMS?

PRESCRIBERS

- Review the LUMRYZ Prescribing Information and **Prescriber Brochure**
- Complete and submit the **Prescriber Enrollment Form**

PHARMACIES

- Designate an authorized representative to carry out the certification process
  - Review **Certified Pharmacy Training Program – Pharmacy Staff Module and Pharmacist Module** and successfully complete the **Pharmacy Staff Knowledge Assessment and Pharmacist Knowledge Assessment** and submit both to the LUMRYZ REMS.
  - Complete and submit the **Pharmacy Enrollment Form**
    - Train all relevant staff in dispensing requirements using the appropriate **Certified Pharmacy Training Program Module**.

REPORTING ADVERSE EVENTS

Report adverse events to Avadel CNS Pharmaceuticals, LLC at productsafety@avadel.com or 1-888-828-2335 and/or to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

This **Fact Sheet** does not contain the complete safety information for LUMRYZ. For complete safety information, please see the full Prescribing Information, including Boxed Warning, available at www.LUMRYZREMS.com.

MED-US-LUM-2100015
10/2023

**TO ENROLL IN THE LUMRYZ REMS,
call 1-877-453-1029 or go to www.LUMRYZREMS.com.**

Avadel

Reference ID: 5446567

Lumryz.
(sodium oxybate) for extended-release oral suspension C

INSTRUCTIONS

Risk Management Reports (RMRs) are completed by prescribers or pharmacies that are certified in the LUMRYZ REMS to document and report events that give rise to a reasonable suspicion of abuse, misuse, diversion, or any behavior or information that may indicate LUMRYZ is not being used according to the prescriber's instructions. For immediate reporting, **RMRs** can be completed by the pharmacist online at www.LUMRYZREMS.com. Alternatively, a pharmacist can complete a print version and fax to the LUMRYZ REMS at 1-877-206-3198.

The **RMR** history allows for the review of prior events of suspected abuse, misuse, or diversion and gives the pharmacist and prescriber a more complete picture of the patient's and/or prescriber's history. The availability of individual patient and prescriber **RMRs** enables the pharmacist to track and monitor for trends suggesting abuse, misuse, or diversion. A trend or pattern of behavior in a patient's and/or prescriber's **RMR** history can be an indicator of abuse, misuse, or diversion and identifies patients/prescribers who may require additional scrutiny when another event, such as an early refill request, occurs. In these cases, the **RMR** history informs actions of the pharmacist.

Examples of events that would require completion of an RMR under the LUMRYZ REMS include, but are not limited to, the following:

- Patient requests for early refills and/or prescriber approval of early refill requests.
- Patient's loss/misuse of the product.
- Patient claims he/she did not receive the product, but the delivery service shows receipt of delivery, or that the shipment was lost, stolen, or delivered to an incorrect address and was not returned.
- Tampering with, counterfeiting or contamination of the product.
- Inquiries and/or arrests by law and regulatory enforcement agencies associated with the misuse or diversion of the product, or crimes related to the product.
- Prescribers whose DEA and/or state license numbers cannot be validated and the prescriber is submitting a **Prescription Form** and/or LUMRYZ prescription.

To complete an RMR:

- Complete investigation of the event, which may include contacting the patient, prescriber, law enforcement agency, or other parties.
- Complete review, follow-up, and sign the **RMR**.
  - When the event involves suspected abuse, misuse, or diversion, the prescriber will be contacted, as appropriate, and an alert may be placed in the prescriber database or patient database of the LUMRYZ REMS to ensure prescriber and pharmacist awareness.
  - The LUMRYZ REMS will monitor any associated patient or prescriber activity during the course of the investigation and for a period after the investigation, where appropriate.
  - The LUMRYZ REMS will work with Avadel CNS Pharmaceuticals, LLC to determine the need to notify local, state, or federal authorities.
- Attach any additional documentation required to support the investigation, including but not limited to the following: DEA Form 106, police or fire report, or report from the shipping service.
- Complete and submit the **RMR**, and any attachments, online at www.LUMRYZREMS.com or by fax to 1-877-206-3198 within one business day of awareness of the event.

If the **RMR** includes a potential adverse event, the potential adverse event is reported to Avadel CNS Pharmaceuticals, LLC at 1-888-828-2335 or productsafety@avadel.com.

ALL SECTIONS REQUIRED TO BE COMPLETED

REPORTER INFORMATION			
Type of Reporter (Select one): ☐ Prescriber ☐ Pharmacist			
Name of Reporter:	First Name:	Last Name:	
Date Reported:		Reporter Phone:	
Reporter Address:			
Reporter City:		Reporter State:	Reporter Zip Code:

Lumryz.
(sodium oxybate) for extended-release oral suspension ℂ

PATIENT AND/OR PRESCRIBER BEING REPORTED

☐ Patient	First Name:	Last Name:	Date of Birth (MM/DD/YYYY):
☐ Prescriber	First Name:	Last Name:	DEA No.:

ALL SECTIONS REQUIRED TO BE COMPLETED

LUMRYZ REMS RISK MANAGEMENT REPORT

Addendum to an Existing RMR: ☐ Yes ☐ No

Nature of Report:
☐ Early Refill Request ☐ Lost/Stolen Product ☐ Package Not Received ☐ Abuse ☐ Misuse
☐ Diversion ☐ Product tampering by an individual in contact with product ☐ Counterfeit/contaminated product
☐ Unexplained irreconcilable inventory ☐ Prescriber's DEA and/or state license is invalid
☐ Suicide attempt and/or ideation and/or death ☐ Multiple prescribers ☐ Potential or actual dose increase
☐ Excess medication on hand ☐ Other (specify):_____

If early refill request, what is the reason?
☐ Dose Increase ☐ Spilled Medication ☐ Lost/Stolen Product
☐ Other (specify):_____

Have the alerts and **RMR** history been reviewed for the patient? ☐ Yes ☐ No | Date(s) of RMR Event:

RMR Event (please provide detail):

Potential adverse event (AE) associated with report? ☐ Yes ☐ No
If yes, date AE reported to Avadel CNS Pharmaceuticals, LLC:_____
If yes, AE report number (if available):_____

Prescriber Contacted? ☐ Yes ☐ No
If yes, what was the outcome? ☐ Early Refill Approved ☐ Early Refill Denied
☐ Recommend to Disenroll Patient ☐ Other (specify):_____
If no, what is the reason? ☐ Unable to Contact ☐ Other (specify):_____

Summary of investigation:

Attachments, if applicable:
☐ DEA Form 106 ☐ Police/Fire Report ☐ Shipping Service Report ☐ Other (specify):_____
Total number of additional pages: _____

Should patient be monitored (alert placed)?
☐ Yes ☐ No
Should prescriber be monitored (alert placed)?
☐ Yes ☐ No

Are you requesting disenrollment for suspected abuse, misuse, or diversion? ☐ Yes ☐ No
If yes, for whom? ☐ Patient ☐ Prescriber

_____ Signature

_____ Date

Report adverse events to Avadel CNS Pharmaceuticals, LLC at 1-888-828-2335 or productsafety@avadel.com.

Avadel

LUMRYZ™ REMS (Risk Evaluation and Mitigation Strategy)

The LUMRYZ REMS (Risk Evaluation and Mitigation Strategy) is a safety program that manages the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of LUMRYZ. The LUMRYZ REMS is required by the Food and Drug Administration (FDA) to ensure the potential benefits of LUMRYZ outweigh its risks.

Prescribers

Prescribers must become certified in the LUMRYZ REMS to prescribe LUMRYZ.

Learn about Prescriber Certification

LEARN MORE

Patients

Patients who are prescribed LUMRYZ must be enrolled in the LUMRYZ REMS.

Learn about Patient Enrollment

LEARN MORE

If you have questions about the LUMRYZ REMS or need help with certification or enrollment, call 1-877-453-1029 Monday-Friday, 8:00 AM – 8:00 PM ET

To learn more about the serious risks associated with LUMRYZ, please refer to the Prescribing Information including Boxed Warning and the Medication Guide.

INDICATION

LUMRYZ is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.

Prescribers

LUMRYZ is only available through the LUMRYZ REMS. In order for prescribers to prescribe LUMRYZ, they must become certified.

To become certified in the LUMRYZ REMS, prescribers must:

1. Review the LUMRYZ Prescribing Information and the **Prescriber Brochure**
2. Complete, sign and submit a **Prescriber Enrollment Form** to the LUMRYZ REMS:
   - Online
   - By fax to 1-877-206-3198

To enroll a patient in the LUMRYZ REMS:

1. Complete the **Patient Enrollment Form** with each patient and submit it to the LUMRYZ REMS:
   - Online
   - By fax to 1-877-206-3198

Administration Requirements:

Before treatment initiation, the prescriber will:

1. Assess the patient's health status to determine if LUMRYZ is medically appropriate by screening for:
   - History of alcohol and drug abuse, sleep-related breathing disorders, compromised respiratory function, depression and suicidality
   - Concomitant use of sedative hypnotics, other CNS depressants or other potentially interacting agents
   - Document and submit to a certified pharmacy using the **Prescription Form**
2. Counsel the patient on:
   - The serious risks and safe use, handling and storage of LUMRYZ using the **Patient Brochure**
3. Submit a **Prescription Form** to a certified pharmacy

During treatment, within the first 3 months of starting treatment and recommended every 3 months thereafter, the prescriber will:

1. Assess the patient for concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents, serious adverse events, and signs of abuse and misuse, including an increase in dose or frequency of dosing, reports of lost, stolen, or spilled medication, and/or drug-seeking behavior

At all times, the prescriber will:

1. Report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death; and any cases of suspected abuse, misuse, or diversion to Avadel CNS Pharmaceuticals, LLC.
2. Assess the patient's potential for abuse, misuse, and diversion. Document and submit all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug using the **Risk Management Report**.
3. Report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the **Risk Management Report**.

LUMRYZ™ REMS Prescriber Enrollment Form

Complete and submit this form online at www.LUMRYZREMS.com,
OR fax to 1-877-206-3198 (toll free).
For more information, please call the LUMRYZ REMS at 1-877-453-1029.

TO BECOME A CERTIFIED PRESCRIBER IN THE LUMRYZ REMS AND PRESCRIBE LUMRYZ:

1. Review the LUMRYZ Prescribing Information.
2. Review the **Prescriber Brochure**.
3. Complete steps 1, 2 and 3 below and submit this **Prescriber Enrollment Form** to the LUMRYZ REMS.

STEP 1 PRESCRIBER ATTESTATIONS

I have:
- Reviewed the Prescribing Information.
- Reviewed the **Prescriber Brochure**.

I understand:
- LUMRYZ is approved for the treatment of
  - Cataplexy in adults with narcolepsy.
  - Excessive daytime sleepiness (EDS) in adults with narcolepsy.
- LUMRYZ is a Schedule III central nervous system (CNS) depressant and can cause obtundation and clinically significant respiratory depression at recommended doses.
- LUMRYZ is contraindicated in combination with alcohol and sedative hypnotics.
- Concurrent use of LUMRYZ with certain other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.
- Patients who have sleep apnea or compromised respiratory function (e.g., asthma, COPD, etc.) may be at higher risk of developing respiratory depression, loss of consciousness, coma, and death with LUMRYZ use.

Before treatment initiation (first dose), I must:
- Assess the patient's health status to determine if LUMRYZ is medically appropriate by screening for history of alcohol and drug abuse, sleep-related breathing disorders, compromised respiratory function, depression, suicidality, concomitant use of sedative hypnotics and other CNS depressants or potentially interacting agents. Document and submit to a certified pharmacy using the **Prescription Form**.
- Counsel the patient on the serious risks and safe use, handling, and storage of LUMRYZ using the **Patient Brochure.**
- Enroll the patient by completing and submitting the **Patient Enrollment Form** to the REMS.
- Order the prescription using the **Prescription Form** and submit it to a certified pharmacy.

Before treatment re-initiation, I must:
- **For patients disenrolled for suspicion of abuse, misuse, or diversion**: Communicate with the pharmacy regarding all relevant patient history and re-enroll the patient if the pharmacist and I agree.
- **For patients with a lapse in treatment of 6 months or longer**: Order the prescription using the **Prescription Form** and submit it to a certified pharmacy.

Within the first 3 months of starting treatment, I must:
- Assess the patient for concomitant use of sedative hypnotics, other CNS depressants, or potentially interacting agents, serious adverse events, and signs of abuse and misuse, including an increase in dose or frequency of dosing, reports of lost, stolen, or spilled medication, and drug-seeking behavior.

It is recommended that patients be re-assessed every 3 months while taking LUMRYZ.

At all times, I must:
- Report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death; and any cases of suspected abuse, misuse, or diversion to Avadel CNS Pharmaceuticals, LLC.
- Assess the patient's potential for abuse, misuse, and diversion. Document and submit all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug using the **Risk Management Report**.
- Report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the **Risk Management Report**.

STEP 2 TO HELP EXPEDITE THE ENROLLMENT PROCESS, PLEASE COMPLETE ALL REQUIRED FIELDS

Prescriber Information (* *denotes required field*)

*NPI No.

CONTINUE

LUMRYZ™ REMS Prescriber Enrollment Form

Complete and submit this form online at www.LUMRYZREMS.com,
OR fax to 1-877-206-3198 (toll free).
For more information, please call the LUMRYZ REMS at 1-877-453-1029.

TO BECOME A CERTIFIED PRESCRIBER IN THE LUMRYZ REMS AND PRESCRIBE LUMRYZ:

1. Review the LUMRYZ Prescribing Information.
2. Review the **Prescriber Brochure**.
3. Complete steps 1, 2 and 3 below and submit this **Prescriber Enrollment Form** to the LUMRYZ REMS.

STEP 1 PRESCRIBER ATTESTATIONS

I have:
- Reviewed the Prescribing Information.
- Reviewed the **Prescriber Brochure**.

I understand:
- LUMRYZ is approved for the treatment of
  - Cataplexy in adults with narcolepsy.
  - Excessive daytime sleepiness (EDS) in adults with narcolepsy.
- LUMRYZ is a Schedule III central nervous system (CNS) depressant and can cause obtundation and clinically significant respiratory depression at recommended doses.
- LUMRYZ is contraindicated in combination with alcohol and sedative hypnotics.
- Concurrent use of LUMRYZ with certain other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.
- Patients who have sleep apnea or compromised respiratory function (e.g., asthma, COPD, etc.) may be at higher risk of developing respiratory depression, loss of consciousness, coma, and death with LUMRYZ use.

Before treatment initiation (first dose), I must:
- Assess the patient's health status to determine if LUMRYZ is medically appropriate by screening for history of alcohol and drug abuse, sleep-related breathing disorders, compromised respiratory function, depression, suicidality, concomitant use of sedative hypnotics and other CNS depressants or potentially interacting agents. Document and submit to a certified pharmacy using the **Prescription Form**.
- Counsel the patient on the serious risks and safe use, handling, and storage of LUMRYZ using the **Patient Brochure.**
- Enroll the patient by completing and submitting the **Patient Enrollment Form** to the REMS.
- Order the prescription using the **Prescription Form** and submit it to a certified pharmacy.

Before treatment re-initiation, I must:
- **For patients disenrolled for suspicion of abuse, misuse, or diversion**: Communicate with the pharmacy regarding all relevant patient history and re-enroll the patient if the pharmacist and I agree.
- **For patients with a lapse in treatment of 6 months or longer**: Order the prescription using the **Prescription Form** and submit it to a certified pharmacy.

Within the first 3 months of starting treatment, I must:
- Assess the patient for concomitant use of sedative hypnotics, other CNS depressants, or potentially interacting agents, serious adverse events, and signs of abuse and misuse, including an increase in dose or frequency of dosing, reports of lost, stolen, or spilled medication, and drug-seeking behavior.

It is recommended that patients be re-assessed every 3 months while taking LUMRYZ.

At all times, I must:
- Report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death; and any cases of suspected abuse, misuse, or diversion to Avadel CNS Pharmaceuticals, LLC.
- Assess the patient's potential for abuse, misuse, and diversion. Document and submit all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug using the **Risk Management Report**.
- Report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the **Risk Management Report**.

STEP 2 TO HELP EXPEDITE THE ENROLLMENT PROCESS, PLEASE COMPLETE ALL REQUIRED FIELDS

Prescriber Information (* *denotes required field*)

*NPI No.
1234567890

*First Name: John | M.I. | *Last Name: Smith | *DEA No.

Facility/Practice Name | *State License No.

*Professional Designation
☐ MD ☐ DO ☐ PA ☐ NP ☐ Other

*Medical Specialty
☐ Sleep Medicine ☐ Neurology ☐ Pulmonology ☐ Psychiatry ☐ Internal Medicine ☐ Other

*Address Line 1: 123 Main Street | Address Line 2

*City: Philadelphia | *State: PA | *Zip Code: 99999

*Phone | *Fax | *Email

*Preferred Method of Contact
☐ Email ☐ Fax

Office Contact Information

If you should need to add more than three office contacts, please call the LUMRYZ REMS at 1-877-453-1029.

Office Contact First Name | Office Contact Last Name | Office Contact Phone
Office Contact Email

Office Contact First Name | Office Contact Last Name | Office Contact Phone
Office Contact Email

Office Contact First Name | Office Contact Last Name | Office Contact Phone
Office Contact Email

STEP 3 PRESCRIBER SIGNATURE IS REQUIRED BELOW FOR ENROLLMENT IN THE LUMRYZ REMS

By signing below, I acknowledge the above attestations, and I understand my personally identifiable information provided above will be shared with Avadel CNS Pharmaceuticals, LLC, its agents, contractors, and affiliates and entered into a prescriber database for the LUMRYZ REMS. I agree that I may be contacted in the future by mail, email, fax, and/or telephone concerning LUMRYZ, the LUMRYZ REMS, and other LUMRYZ programs and services.

☐ *Prescriber Signature

CANCEL | SUBMIT

Report adverse events to Avadel CNS Pharmaceuticals, LLC at productsafety@avadel.com or 1-888-828-2335.

LUMRYZ™ REMS Prescriber Enrollment Form

Complete and submit this form online at www.LUMRYZREMS.com,
OR fax to 1-877-206-3198 (toll free).
For more information, please call the LUMRYZ REMS at 1-877-453-1029.

TO BECOME A CERTIFIED PRESCRIBER IN THE LUMRYZ REMS AND PRESCRIBE LUMRYZ:

1. Review the LUMRYZ Prescribing Information.
2. Review the **Prescriber Brochure**.
3. Complete steps 1, 2 and 3 below and submit this **Prescriber Enrollment Form** to the LUMRYZ REMS.

STEP 1 PRESCRIBER ATTESTATIONS

I have:
- Reviewed the Prescribing Information.
- Reviewed the **Prescriber Brochure**.

I understand:
- LUMRYZ is approved for the treatment of
  - Cataplexy in adults with narcolepsy.
  - Excessive daytime sleepiness (EDS) in adults with narcolepsy.
- LUMRYZ is a Schedule III central nervous system (CNS) depressant and can cause obtundation and clinically significant respiratory depression at recommended doses.
- LUMRYZ is contraindicated in combination with alcohol and sedative hypnotics.
- Concurrent use of LUMRYZ with certain other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.
- Patients who have sleep apnea or compromised respiratory function (e.g., asthma, COPD, etc.) may be at higher risk of developing respiratory depression, loss of consciousness, coma, and death with LUMRYZ use.

Before treatment initiation (first dose), I must:
- Assess the patient's health status to determine if LUMRYZ is medically appropriate by screening for history of alcohol and drug abuse, sleep-related breathing disorders, compromised respiratory function, depression, suicidality, concomitant use of sedative hypnotics and other CNS depressants or potentially interacting agents. Document and submit to a certified pharmacy using the **Prescription Form**.
- Counsel the patient on the serious risks and safe use, handling, and storage of LUMRYZ using the **Patient Brochure.**
- Enroll the patient by completing and submitting the **Patient Enrollment Form** to the REMS.
- Order the prescription using the **Prescription Form** and submit it to a certified pharmacy.

Before treatment re-initiation, I must:
- **For patients disenrolled for suspicion of abuse, misuse, or diversion**: Communicate with the pharmacy regarding all relevant patient history and re-enroll the patient if the pharmacist and I agree.
- **For patients with a lapse in treatment of 6 months or longer**: Order the prescription using the **Prescription Form** and submit it to a certified pharmacy.

Within the first 3 months of starting treatment, I must:
- Assess the patient for concomitant use of sedative hypnotics, other CNS depressants, or potentially interacting agents, serious adverse events, and signs of abuse and misuse, including an increase in dose or frequency of dosing, reports of lost, stolen, or spilled medication, and drug-seeking behavior.

It is recommended that patients be re-assessed every 3 months while taking LUMRYZ.

At all times, I must:
- Report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death; and any cases of suspected abuse, misuse, or diversion to Avadel CNS Pharmaceuticals, LLC.
- Assess the patient's potential for abuse, misuse, and diversion. Document and submit all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug using the **Risk Management Report**.
- Report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the **Risk Management Report**.

STEP 2 TO HELP EXPEDITE THE ENROLLMENT PROCESS, PLEASE COMPLETE ALL REQUIRED FIELDS

Prescriber Information (* *denotes required field*)

*NPI No.
1234567890

*First Name: John | M.I. | *Last Name: Smith | *DEA No.

Facility/Practice Name | *State License No.

*Professional Designation: ☐ MD ☐ DO ☐ PA ☐ NP ☑ Other

*Medical Specialty: ☐ Sleep Medicine ☐ Neurology ☐ Pulmonology ☐ Psychiatry ☐ Internal Medicine ☑ Other

*Professional Designation Other: RN

*Medical Specialty Other: Internist

*Address Line 1: 123 Main Street | Address Line 2

*City: Philadelphia | *State: PA | *Zip Code: 99999

*Phone | *Fax | *Email

*Preferred Method of Contact: ☐ Email ☐ Fax

Office Contact Information

If you should need to add more than three office contacts, please call the LUMRYZ REMS at 1-877-453-1029.

Office Contact First Name | Office Contact Last Name | Office Contact Phone

Office Contact Email

Office Contact First Name | Office Contact Last Name | Office Contact Phone

Office Contact Email

Office Contact First Name | Office Contact Last Name | Office Contact Phone

Office Contact Email

STEP 3 PRESCRIBER SIGNATURE IS REQUIRED BELOW FOR ENROLLMENT IN THE LUMRYZ REMS

By signing below, I acknowledge the above attestations, and I understand my personally identifiable information provided above will be shared with Avadel CNS Pharmaceuticals, LLC, its agents, contractors, and affiliates and entered into a prescriber database for the LUMRYZ REMS. I agree that I may be contacted in the future by mail, email, fax, and/or telephone concerning LUMRYZ, the LUMRYZ REMS, and other LUMRYZ programs and services.

☐ *Prescriber Signature

CANCEL | SUBMIT

Report adverse events to Avadel CNS Pharmaceuticals, LLC at productsafety@avadel.com or 1-888-828-2335.

LUMRYZ REMS Prescriber Enrollment Successful

You have successfully completed and submitted the **Prescriber Enrollment Form**. A confirmation of this submission has been sent via your preferred method of contact.

You can expect to receive an email containing a link to login and instructions for creating a password. Please login with the username provided. You will then be prompted to create a password.

If you do not receive the email within the next few hours, or would like to update your enrollment information at any time, please contact the LUMRYZ REMS for assistance at 1-877-453-1029.

Patients

LUMRYZ is available only through the LUMRYZ REMS. For a patient to receive LUMRYZ, the prescriber must enroll the patient in the LUMRYZ REMS.

To become enrolled in the LUMRYZ REMS, patients must:

1. Discuss the benefits, risks and safe use of LUMRYZ with your prescriber

2. Ask your prescriber any questions you have about taking LUMRYZ and about the LUMRYZ REMS

3. Make sure you understand:
   - How to enroll and take part in the LUMRYZ REMS
   - The information in the **Patient Brochure**
   - The benefits and serious risks associated with LUMRYZ
   - The safe use, handling, and storage of LUMRYZ

4. Enroll in the REMS by completing the **Patient Enrollment Form** with your prescriber. Enrollment information will be provided to the REMS
   - **Patient Enrollment Form**

5. Complete the **Patient Counseling Checklist** with the pharmacist

6. Your healthcare provider will evaluate you within the first 3 months of taking LUMRYZ and may reevaluate you every 3 months while you are taking LUMRYZ
   - Inform your prescriber and the pharmacy about any changes in your medications or medical conditions

Resources

Resources for Prescribers

- **Prescriber Brochure**
- Fact Sheet
- **Prescriber Enrollment Form**
- **Patient Enrollment Form**
- **Prescription Form**
- **Dear Healthcare Provider Letter**
- **Dear Professional Society Letter**

Resources for Pharmacies

- **Certified Pharmacy Training Program**
- **Patient Counseling Checklist**

Resources for Patients

- **Patient Brochure**
- Medication Guide
- **Patient Enrollment Form**

Contact Us

Phone: 1-877-453-1029

Fax: 1-877-206-3198

Hours of Operation: Monday - Friday
8:00 AM — 8:00 PM Eastern Time

To learn more about the serious risks associated with LUMRYZ, please refer to the Prescribing Information including Boxed Warning and the Medication Guide.

Pharmacy Staff Registration

Please contact your pharmacy's authorized representative for the LUMRYZ REMS if you do not know your Pharmacy Identifier.

Required fields are denoted by "*".

Pharmacy Staff User Information

* Pharmacy Identifier

CANCEL CONTINUE

Pharmacy Staff Registration

Please contact your pharmacy's authorized representative for the LUMRYZ REMS if you do not know your Pharmacy Identifier.

Required fields are denoted by "*".

Pharmacy Staff User Information

*Pharmacy Identifier

1111

You are registering for the below pharmacy. If this pharmacy is incorrect, please check the Pharmacy Identifier and if in error, click "Clear".

ABC Pharmacy

*I am a Pharmacist

○ Yes ○ No

*First Name

*Last Name

*Email Address

*Phone

CLEAR SUBMIT

Pharmacy Staff Registration

Your registration has been successfully submitted.

You can expect to receive an email containing a link to login and instructions for creating a password. Please login with the username provided. You will then be prompted to create a password.

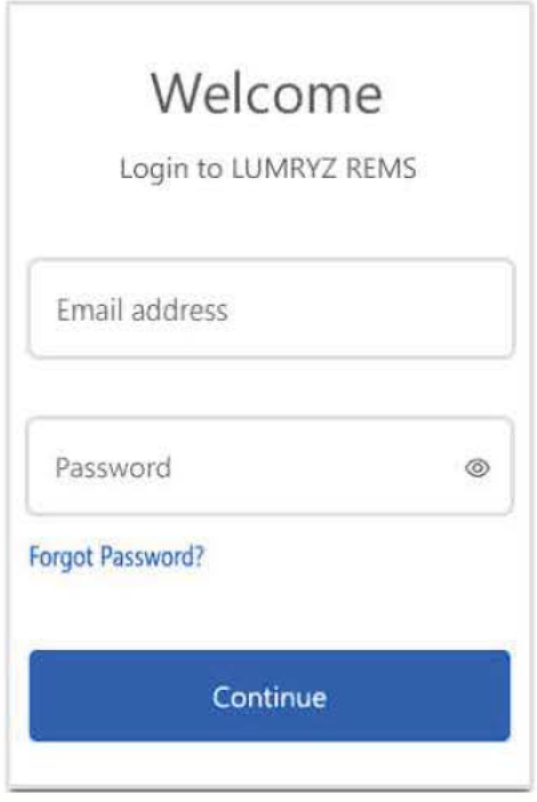
If you do not receive the email within the next few hours, or would like to update your information at any time, please contact the LUMRYZ REMS for assistance at 1-877-453-1029.

Lumryz

(sodium oxybate) for extended-release oral suspension Ⓒ

Login is available to certified prescribers to enroll patients and submit **Risk Management Reports**, and to certified pharmacy users to complete and submit **Knowledge Assessments, Risk Management Reports** and **Patient Counseling Checklists**.

Certified pharmacies are also able to verify patient REMS requirements are met prior to dispensing LUMRYZ.



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

/s/

TIFFANY R FARCHIONE
09/26/2024 02:39:22 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s007

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
LABELING REVIEW

DRUG/NDA: Lumryz (sodium oxybate) 4.5 mg, 6 mg 7.5 mg, 9 mg Extended-Release for Oral Suspension (NDA 214755)
Sponsor: Avadel CNS Pharmaceuticals, LLC
Indications: Treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy

Pending and Last Approved Supplements:

NDA	Supplement	Dated	Provides for	Status
NDA 214755	Original NDA	12/15/2020; RS 03/01/2023	treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy	Approved 05/01/2023
214755	S-003	05/04/23	Modifications to the REMS (no labeling changes)	Approved 10/31/23
214755	S-006	11/07/23	Treatment of cataplexy or excessive daytime sleepiness down to 7 years old	Pending
214755	S-007	12/07/23	Addition of carton and container labeling for new starter pack and edits to the REMS documents	Pending

BACKGROUND

- A Prior Approval supplement was submitted on 12/07/23 to add Lumryz starter pack. Carton and container labeling and corresponding changes to the Prescribing Information and REMS documents (Instructions for Use) were included.
- The last approved labeling was approved in an Agency letter dated 05/01/23.
- This review will only encompass the pending PA supplement 007 listed above.

REVIEW

1. The following reviews were conducted on the content of labeling:
   - OSE/DMEPA (Loretta Holmes, BSN, PharmD, Yevgeniya Kogan, PharmD, BSCP) review finalized in DARRTS 5/31/24, amended 09/06/2024
   - OSE/DRM (Stephanie Olumba, PharmD, MPH, BCPS, Carolyn Tieu, PharmD, MPH) review finalized in DARRTS 8/8/24, addendum finalized in DARRTS 8/9/24.
   - OPDP (Rachael Oyewole, PharmD, Susannah O'Donnell, MPH, RAC) review finalized in DARRTS 07/12/24.
   - Clinical (David Millis, MD, Jean Kim, MD) reviewed changes to labeling.
   - ADL (Kimberly Updegraff, RPh, MHS, MS) reviewed the team's edits.
2. The changes to labeling are captured in the attached tracked changes document.

DISCUSSION

1. The review teams reviewed the labeling supplement submission as outlined above.

2. The Agency's proposed PI & IFU labeling revisions were sent to the Applicant on 08/09/24.
3. The Agency's proposed carton label revisions were sent to the Applicant on 09/05/2024.
4. The Applicant provided agreement to PI & IFU via email on 08/13/24.
5. Carton label agreement reached on 09/06/2024.
6. No changes were made to MG, as compared to last approved.

CONCLUSIONS

1. This PA labeling supplement only provides for those revisions as stated above when compared to the last approved labeling (Agency letter dated 05/01/23).
2. The Agency agrees with the Applicant's proposed labeling.
3. I recommend that an approval letter issue for this pending supplemental application.

{See appended electronic signature page}

LCDR Shin-Ye Chang, Pharm.D., M.S., RAC
Regulatory Project Manager

{See appended electronic signature page}

CAPT Keith J. Kiedrow, Pharm.D., MS, RAC
Chief, Project Management Staff

{See appended electronic signature page}

Kimberly Updegraff, R.Ph., M.S., RAC
Associate Director for Labeling

Attachment: annotated labeling, agreement email

40 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

From: Lee, C. Eugene
To: Marla Scarola
Cc: Chang, ShinYe; Sohn, Ann J
Subject: RE: [EXTERNAL] RE: [EXTERNAL EMAIL] NDA 214755/S-007 (Lumryz): Carton Label Information Request
Date: Friday, September 6, 2024 9:23:30 AM
Attachments: image001.png

Good morning Marla,

Your plan for the outer carton is acceptable.

Thanks,

C. Eugene Lee, Pharm.D.
Senior Regulatory Health Project Manager
Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research
Tel: 240-402-9386
C.Eugene.Lee@fda.hhs.gov

From: Marla Scarola <mscarola@avadel.com>
Sent: Thursday, September 5, 2024 4:20 PM
To: Lee, C. Eugene <C.Eugene.Lee@fda.hhs.gov>
Cc: Chang, ShinYe <ShinYe.Chang@fda.hhs.gov>; Sohn, Ann J <Ann.Sohn@fda.hhs.gov>
Subject: [EXTERNAL] RE: [EXTERNAL EMAIL] NDA 214755/S-007 (Lumryz): Carton Label Information Request

Hi, Eugene,

Due to the size of the outer carton, the width of the box (12.5”) is too wide to transverse the conveyor in the right orientation to allow for printing on either of the smaller side panels. Please note that the current placement of the product identifier information is on the back of the carton as indicated by the opening (see placement of lift tab and tamper evident seals). Would you please advise whether this is acceptable?

Best,
Marla

MARLA SCAROLA
Senior Vice President Regulatory and Quality

avadel.com
Office: +1 636-237-7091
Mobile: (b) (6)

From: Lee, C. Eugene <C.Eugene.Lee@fda.hhs.gov>
Sent: Thursday, September 5, 2024 3:02 PM
To: Marla Scarola <mscarola@avadel.com>
Cc: Chang, ShinYe <ShinYe.Chang@fda.hhs.gov>; Sohn, Ann J <Ann.Sohn@fda.hhs.gov>
Subject: [EXTERNAL EMAIL] NDA 214755/S-007 (Lumryz): Carton Label Information Request

Hello Marla,

I'm filling in for Ann while she's away this week.

With regard to NDA 214755/S-007, please refer to your 08/13/24, starter pack carton labeling submission for Lumryz. We have the following comments and request your response as soon as possible but no later than 09/11/24.

Starter Pack Carton Label:

We note that the placeholder for the product identifier containing both human-readable and 2D machine-readable formats is located on a principal display panel (PDP). In this location, the information is distracting and competes in prominence with critical information on the PDP. Therefore, we request that you move the placeholder information to one of the side panels.

Submit your response to the NDA and send us a courtesy electronic copy.

Thanks,

C. Eugene Lee, Pharm.D.
Senior Regulatory Health Project Manager
Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research
Tel: 240-402-9386
C.Eugene.Lee@fda.hhs.gov

From: Chang, ShinYe
To: Marla Scarola
Subject: RE: [EXTERNAL] RE: [EXTERNAL EMAIL] NDA 214755/S-007 Lumryz
Date: Tuesday, September 24, 2024 4:08:00 PM
Attachments: image001.png

Hi Marla,

I just wanted to close the loop on this, and let you know that we have no more comments/revisions to the labeling and consider the PI, IFU agreed upon.

Best,

Sandy

From: Marla Scarola <mscarola@avadel.com>
Sent: Friday, August 23, 2024 10:08 AM
To: Sohn, Ann J <Ann.Sohn@fda.hhs.gov>
Cc: Chang, ShinYe <ShinYe.Chang@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: [EXTERNAL EMAIL] NDA 214755/S-007 Lumryz

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Happy Friday, Ann! Are you able to provide me with an update on the review of NDA 214755/S-007?

Thanks,
Marla

MARLA SCAROLA
Senior Vice President Regulatory and Quality

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Office: +1 636-237-7091
Mobile: (b) (6)

From: Sohn, Ann J <Ann.Sohn@fda.hhs.gov>
Sent: Wednesday, August 14, 2024 1:20 PM

To: Marla Scarola <mscarola@avadel.com>
Cc: Chang, ShinYe <ShinYe.Chang@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: [EXTERNAL EMAIL] NDA 214755/S-007 Lumryz

Thanks Marla, submission received. The team is reviewing. I will let you know if we have any questions or comments.

Thanks,
Ann

From: Marla Scarola <mscarola@avadel.com>
Sent: Wednesday, August 14, 2024 11:48 AM
To: Sohn, Ann J <Ann.Sohn@fda.hhs.gov>
Cc: Chang, ShinYe <ShinYe.Chang@fda.hhs.gov>
Subject: [EXTERNAL] RE: [EXTERNAL EMAIL] NDA 214755/S-007 Lumryz

Hi, Ann,

We submitted a response to NDA 214755 yesterday that addressed the comments on the outer carton, PI and IFU. Please let me know if you need any additional information or if there are any comments on the Med Guide.

Best,
Marla

MARLA SCAROLA
Senior Vice President Regulatory and Quality

avadel.com
Office: +1 636-237-7091
Mobile: (b) (6)

From: Sohn, Ann J <Ann.Sohn@fda.hhs.gov>
Sent: Friday, August 9, 2024 5:49 PM
To: Marla Scarola <mscarola@avadel.com>

Cc: Chang, ShinYe <ShinYe.Chang@fda.hhs.gov>
Subject: [EXTERNAL EMAIL] NDA 214755/S-007 Lumryz

Hi Marla,

Please find attached our comments fpr the Prescribing Information and Instructions for Use in the labeling for NDA 214755/S-007. This is in reference to S-007 only and is separate from labeling negotiations for S-006. Eugene Lee will be communicating with you regarding S-006.

Please submit your responses by COB Tuesday, August 13, 2024 and confirm receipt of this email.

Thanks,

Ann Sohn, PharmD, MS
LCDR, United States Public Health Service
Senior Regulatory Project Manager

Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research
ann.sohn@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

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

/s/

SHIN-YE CHANG
09/25/2024 03:16:05 PM

KEITH J KIEDROW
09/25/2024 03:18:11 PM

KIMBERLY S UPDEGRAFF
09/25/2024 05:19:55 PM

MEMORANDUM
REVIEW OF REVISED LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 6, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 214755/S-007
Product Name, Dosage Form, and Strengths:	Lumryz (sodium oxybate) for extended-release oral suspension, 4.5 g, 6 g, 7.5 g, and 9 g per packet
Applicant Name:	Avadel CNS Pharmaceuticals, LLC
FDA Received Date:	August 13, 2024
TTT ID #:	2024-7721-1
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Avadel CNS Pharmaceuticals, LLC submitted revised carton labeling received on August 13, 2024 for Lumryz. The Division of Psychiatry (DP) requested that we review the revised carton labeling for Lumryz (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labeling review.[a]

2 CONCLUSION

On September 5, 2024, an Information Request (IR) was sent via email to Avadel CNS Pharmaceuticals, LLC (Avadel) to request relocation of the placeholder for the product identifier containing both human-readable and 2D machine-readable formats from a principal display panel to one of the side panels.[b] Avadel provided the following email response:

Due to the size of the outer carton, the width of the box (12.5") is too wide to transverse the conveyor in the right orientation to allow for printing on either of the smaller side panels. Please note that the current placement of the product identifier information is on the back of the carton as indicated by the opening (see placement of lift tab and tamper evident seals). Would you please advise whether this is acceptable?

Given the aforementioned difficulty with relocating the placeholder information to a side panel, we find the current placement acceptable (see Appendix A). Therefore, we have no additional recommendations at this time.

---

[a] Holmes, L. Labeling Packaging and URRA Review for Lumryz (NDA 214755/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 May 31. TTT ID: 2024-7721.

[b] The following IR was sent to Avadel via email on August 5, 2024: *Reference is made to your August 13, 2024 submission of the starter pack carton labeling under Lumryz (NDA 214755/S-007). We note that the placeholder for the product identifier containing both human-readable and 2D machine-readable formats is located on a principal display panel (PDP). In this location, the information is distracting and competes in prominence with critical information on the PDP. Therefore, we request that you move the placeholder information to one of the side panels. Please respond no later than September 11, 2024.*

APPENDIX A. IMAGE OF LABELING RECEIVED ON AUGUST 13, 2024

Carton Labeling (not to scale)

(Carton labeling available from: \\CDSESUB1\EVSPROD\nda214755\0151\m1\us\114-labeling\114a-draft-label\corp-lbl-000058v1.pdf)

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

/s/

LORETTA HOLMES
09/06/2024 03:11:51 PM

YEVGENIYA M KOGAN
09/06/2024 03:40:35 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 12, 2024

To: Sandy Chang, PharmD, Regulatory Project Manager, Division of Psychiatry (DP)

David Millis, MD, Medical Reviewer, DP

Kimberly Updegraff, MS, RAC, Associate Director for Labeling, DP

From: Rachael Oyewole, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC Team Leader, OPDP

Subject: OPDP Labeling Comments for LUMRYZ (sodium oxybate) for extended-release oral suspension, CIII (Lumryz)

NDA: 214755, S-007

Background:
In response to DP's consult request dated July 9, 2024, OPDP has reviewed the proposed Instructions for Use (IFU), and carton and container labeling for Supplement 007 for Lumryz. This supplement provides for the inclusion of a starter pack (carton & container labeling), minor edits to Section 16 of the USPI, and modification to the REMS Prescription Form.

IFU:
OPDP's review of the proposed IFU is based on the draft labeling emailed to OPDP on July 10, 2024, and we do not have any comments at this time.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on July 10, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Rachael Oyewole, PharmD at (301)-796-0586 or rachael.oyewole@fda.hhs.gov.

22 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

RACHAEL O OYEWOLE
07/12/2024 03:33:15 PM

LABELING PACKAGING AND URRA REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 31, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 214755/S-007
Product Name, Dosage Form, and Strength:	Lumryz (sodium oxybate) for extended-release oral suspension, 4.5 g, 6 g, 7.5 g, and 9 g per packet
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Avadel CNS Pharmaceuticals, LLC (Avadel)
FDA Received Date:	December 7, 2023 and April 15, 2024
TTT ID #:	2024-7721
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Acting Team Leader	Matthew Barlow, RN, BSN
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 INTRODUCTION

Avadel CNS Pharmaceuticals, LLC submitted a Prior Approval Supplement (PAS) for Lumryz (sodium oxybate) for extended-release oral suspension. With this labeling supplement, Avadel proposes a starter pack. Subsequently, the Division of Psychiatry (DP) requested that we review the proposed Lumryz Prescribing Information (PI), Instructions for Use (IFU), Medication Guide (MG), and carton labeling (outer carton and inner cartons) for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Lumryz (sodium oxybate) is currently available in 4.5 g, 6 g, 7.5 g, and 9 g strengths. All strengths are supplied in 7-count and 30-count cartons. With this supplement, Avadel proposes a starter pack as "an additional packaging configuration to better facilitate a patient's needs during the titration phase." According to Avadel, "The proposed packaging configuration allows for a gradual increase in dose that mirrors the dose escalation used in the Phase 3 REST-ON study (CLFT218-1501) that served as the basis of demonstration of efficacy and safety for the LUMRYZ NDA approval. It contains one week (7 packets) of the starting dose (4.5 g), two weeks (14 packets) of the 6 g dose, and one week (7 packets) of the 7.5 g dose." Avadel also stated, "The proposed starter kit configuration would allow prescribers to titrate by 1.5 g weekly increments as outlined in the dosing instructions for the first three weeks or they can dose escalate as it was done in the pivotal REST-ON study, as outlined in Section 14 of the Prescribing Information." We note that if the starter pack is used to titrate according to the dosing instructions in the PI, the patient would have a 6 g 7-count carton left over. The clinical team is aware of Avadel's rationale for the starter pack.

Avadel submitted the starter pack outer carton labeling as well as the carton labeling for four 7-count weekly inner cartons. The inner cartons will be contained within the starter pack outer carton.

On November 2, 2022, Avadel participated in a Type C Meeting to discuss the regulatory pathway for the addition of a starter pack configuration. They also discussed the need for human factors (HF) testing of the starter pack configuration. In a post-meeting comment provided to Avadel via email on November 30, 2022, the Agency agreed that based on review of the Use Failure Modes and Effects Analysis (uFMEA), proposed mitigations, and supporting information, the results of an additional HF validation study are not required to be submitted to support the starter pack supplement. However, with this supplement, Avadel submitted a Human Factors Justification for Starter Pack Supplement (see Section 2.1) and a use Failure Modes Effect Analysis (URRA) (see Section 2.2). Although the Instructions for Use (IFU) and Medication Guide (MG) were also submitted with this supplement, no changes to the IFU and MG have been proposed. We note that this product has a Risk Evaluation and Mitigation Strategy (REMS).

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 214755/S-007.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labeling	B
Previous DMEPA Reviews	C
Human Factors Justification for Starter Pack Supplement, Use Related Risk Analysis (URRA), Information Request (IR)	D

2.1 HUMAN FACTORS JUSTIFICATION FOR STARTER PACK SUPPLEMENT

According to the Human Factors Justification for Starter Pack Supplement document, "the greatest risk to patients introduced by the starter pack is that the wrong strength is selected and the patient takes a higher than prescribed dose." To control for this risk, Avadel implemented the following:

- The different strengths are differentiated by the use of color on the inner 7-count cartons and individual packets.
- Each inner 7-count carton has a tamper-evident seal making it obvious when a patient is opening a new carton.
- Each inner 7-count carton label includes an indication of the week number (1, 2, 3, or 4) during which the strength should be administered.
- The starter pack outer carton is color-coded with trade dress matching the strength specific colors to indicate the contents.
- The starter pack outer carton is configured so that the 7-count cartons increase in strength from left to right.
- The inside of the top flap of the outer carton is printed with a legend depicting the configuration of the 7-count cartons.
- Both the inner 7-count carton and outer carton include language describing the contents and referencing the Instructions for Use and Medication Guide.

Additionally, "The proposed starter pack contains an outer carton containing four complete 7-count cartons packaged starting with the lowest dose on the left to the highest dose on the right. Each 7-count carton is packaged with the approved 7-count carton label inclusive of the tamper evident seal and the full contents including IFU, PI, Medication Guide, and mixing aid. The cartons will be labeled Week 1-4 on the top of the 7-count carton." Furthermore, "The starter pack provides one week (7 packets) of each of the 4.5 g strength, two weeks (14 packets) of the 6 g strength, and one week (7 packets) of the 7.5 g strength, for a total of 4 weeks of treatment. Each strength is provided in an individual 7-count tamper-evident sealed carton."

2.2 USE RELATED RISK ANALYSIS (URRA)

The Applicant included a use Failure Modes Effect Analysis (hereafter referred to as URRA) in this supplement; however, it was not clear if the URRA was identical to the URRA we reviewed under IND 126321. As such, on April 9, 2024, we issued an information request (IR) asking for the following:

- Specify if the product user interface of the proposed starter pack in your December 7, 2023, submission is identical to the product user interface in your September 19, 2022, submission. If there are any changes, please indicate what changes you made to the product user interface and provide a side-by-side comparison highlighting the changes.
- Specify if the URRA for the proposed starter pack submitted on December 7, 2023, is the same as the URRA for the proposed starter pack submitted on September 19, 2022. If there are any changes, please specify the changes made to the URRA and provide a side-by-side comparison highlighting the changes.

The Applicant confirmed, in their April 15, 2024 information request (IR) response, that the URRA submitted on December 7, 2023 is identical to the URRA submitted on September 19, 2022 under IND 126321. Additionally, the Applicant indicated they made the following changes to the Lumryz proposed starter pack user interface:

- The "week 1-4 is printed directly on the inner 7-count cartons rather than applied as a sticker."
- The "NDC number was updated" on the inner and outer carton labeling
- The statement "Not for Individual Sale" was added to the inner carton labeling.
- The statement "See the Medication Guide for additional dosage information" was added to the outer carton labeling.
- The "Strength-correlated color-coding was changed from highlighting the count to highlighting strength and to black text on colored background rather than white text.".

Based on the aforementioned information, we agree that the user interface changes do not impact the risk mitigations/control measures, do not change critical task categorization, and do not present new, differing, or unique risks associated with the proposed product. As such, we maintain that the tasks evaluated appear to be comprehensive and appropriate based on what the Applicant proposes for the design and intended use of this product. Therefore, we maintain that the Applicant does not need to submit human factors (HF) validation results with their supplement for the Lumryz proposed starter pack.

3 CONCLUSION

Based on our evaluation of the carton labeling for the starter pack, we determined that from a medication error perspective, the Instructions for Use and Medication Guide do not require additional changes to accommodate this supplement. Additionally, based on the Use Related Risk Analysis (URRA), the Applicant does not need to submit human factor (HF) validation results with their supplement for the proposed Lumryz starter pack.

However, the proposed Lumryz Prescribing Information (PI) and outer carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Psychiatry (DP) in Section 4 and for Avadel CNS Pharmaceuticals, LLC in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF PSYCHIATRY (DP)

Table 2. Identified Issues and Recommendations for the Division of Psychiatry (DP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Comment			
1.	In their rationale for the starter pack, Avadel states, "The proposed starter kit configuration would allow prescribers to titrate by 1.5 g weekly increments as outlined in the dosing instructions for the first three weeks or they can dose escalate as it was done in the pivotal REST-ON study, as outlined in Section 14 of the Prescribing Information."	If the starter pack is used to titrate according to the dosing instructions in the PI, the patient would have a 6 g 7-count carton left over.	We defer to the Division on this issue.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The description of the 28-day starter pack contents states: "The 28-day starter pack contains four 7-count cartons, (b) (4) (b) (4) Prescribing Information and Medication Guide, and Instructions for Use."	The description of the starter pack contents is incomplete.	We recommend that the description be revised to read as follows (or use similar language): "The 28-day starter pack contains four 7-count cartons, each containing a mixing cup, Prescribing Information and Medication Guide, and Instructions for Use."

5 RECOMMENDATIONS FOR AVADEL CNS PHARMACEUTICALS, LLC

Table 3. Identified Issues and Recommendations for Avadel CNS Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Outer Carton Labeling			
1.	The "Starter Pack Contains" information does not provide a full description of the starter pack contents.	The lack of a full description of the starter pack contents may lead to confusion.	Revise the "Starter Pack Contains" information to read as follows: Starter Pack Contains: Four cartons, each containing 7 packets of Lumryz and 1 mixing cup Week 1: 4.5 g per packet (equivalent to XX) Week 2: 6 g per packet (equivalent to XX) Week 3: 6 g per packet (equivalent to XX) Week 4: 7.5 g per packet (equivalent to XX)
2.	The following statements on the front and back panels lack prominence: Must be prepared per… Dispense (b) (4) enclosed… For oral use…	The lack of prominence of these statements may potentially cause them to be overlooked.	Increase the size of the following statements on the outer carton labeling: Must be prepared per… Dispense the enclosed… For Oral Use…
3.	The box containing the text "Do not use if tamper evident seal…" lacks prominence.	The box and text lack prominence and are difficult to see because they are too small.	Increase the size of the box and the text that it contains.
4.	The established name, dosage form, and controlled substance symbol are presented in a light gray font that is difficult to see against the white background.	The poor contrast of the gray font against white background decreases the visibility of the information.	Consider the use of a darker font to improve the visibility of the established name, dosage form, and controlled substance symbol.
5.	The product identifier is missing.	In June 2021, FDA finalized the Guidance for Industry	We recommend that you review the guidance to determine if the

Table 3. Identified Issues and Recommendations for Avadel CNS Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.
6.	The placeholder for the expiration date is missing.	The label of an official drug product shall bear an expiration date per USP General Chapter <7>.	Add the placeholder for the expiration date in accordance with USP General Chapter <7>. The USP Chapter <7>Labeling requires the expiration date to appear on the immediate container and all other packaging. When all-numeric dates are used, they must be formatted using the year, the month, and, if applicable, the day, separated by hyphens or forward slashes in one of the following formats: YYYY-MM-DD or YYYY-MM. When alphanumeric dates are used, months must be displayed using at least three letters in one of the following formats: YYYY-MMM-DD or YYYY-MMM. We recommend you ensure that there are no other numbers located in close proximity to the expiration date. To minimize

Table 3. Identified Issues and Recommendations for Avadel CNS Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			confusion and reduce the risk for deteriorated drug medication errors, identify the expiration date format you intend to use.
7.	The placeholder for the lot number is missing.	Lot number statement is required on the carton labeling when there is sufficient space per 21 CFR 201.10(i)(1).	Add the placeholder for the lot number in accordance with 21 CFR 201.10(i)(1).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Lumryz received on December 7, 2023 from Avadel CNS Pharmaceuticals, LLC.

Table 4. Relevant Product Information for Lumryz	
Initial Approval Date	05/01/2023
Active Ingredient	sodium oxybate
Indication	Treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.
Dosage Form	for extended-release oral suspension
Strengths	4.5 g, 6 g, 7.5 g, and 9 g per packet
Route of Administration	Oral
Dose and Frequency	The recommended starting dosage 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.
How Supplied	Each carton contains either 7 or 30 packets of Lumryz, a mixing cup, Prescribing Information and Medication Guide, and Instructions for Use. Proposed: The 28-day starter pack contains four 7-count cartons, (b) (4), Prescribing Information and Medication Guide, and Instructions for Use. Dose packets contain a single dose of LUMRYZ provided in 4.5 g, 6 g, 7.5 g, or 9 g doses.

<table>
<tr><th colspan="2">Table 4. Relevant Product Information for Lumryz</th></tr>
<tr><td></td><td>
<table>
<tr><th>Strength</th><th>Package Size</th><th>NDC Number</th></tr>
<tr><td rowspan="2">4.5 g</td><td>7 packets</td><td>NDC 13551-001-07</td></tr>
<tr><td>30 packets</td><td>NDC 13551-001-30</td></tr>
<tr><td rowspan="2">6 g</td><td>7 packets</td><td>NDC 13551-002-07</td></tr>
<tr><td>30 packets</td><td>NDC 13551-002-30</td></tr>
<tr><td rowspan="2">7.5 g</td><td>7 packets</td><td>NDC 13551-003-07</td></tr>
<tr><td>30 packets</td><td>NDC 13551-003-30</td></tr>
<tr><td rowspan="2">9 g</td><td>7 packets</td><td>NDC 13551-004-07</td></tr>
<tr><td>30 packets</td><td>NDC 13551-004-30</td></tr>
</table>
<u>Proposed:</u>
<table>
<tr><th>Starter Pack</th><th>Strength</th><th>Package Size</th><th>NDC Number</th></tr>
<tr><td>Week 1</td><td>4.5 g</td><td>7 packets</td><td rowspan="4">NDC 13551-005-01</td></tr>
<tr><td>Week 2</td><td>6 g</td><td>7 packets</td></tr>
<tr><td>Week 3</td><td>6 g</td><td>7 packets</td></tr>
<tr><td>Week 4</td><td>7.5 g</td><td>7 packets</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>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).</td></tr>
</table>

APPENDIX B. LABELING

B.1 List of Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Lumryz labeling submitted by Avadel CNS Pharmaceuticals, LLC. on December 7, 2023.

- Prescribing Information
- Medication Guide
- Instructions for Use
- Carton Labeling

The above labeling are available from: \\Cdsesub1\evsprod\NDA214755\0117\m1\us\114-labeling\114a-draft-label

B.2 Carton Labeling Images (not to scale)

7-count Inner Carton Labeling

Week 1

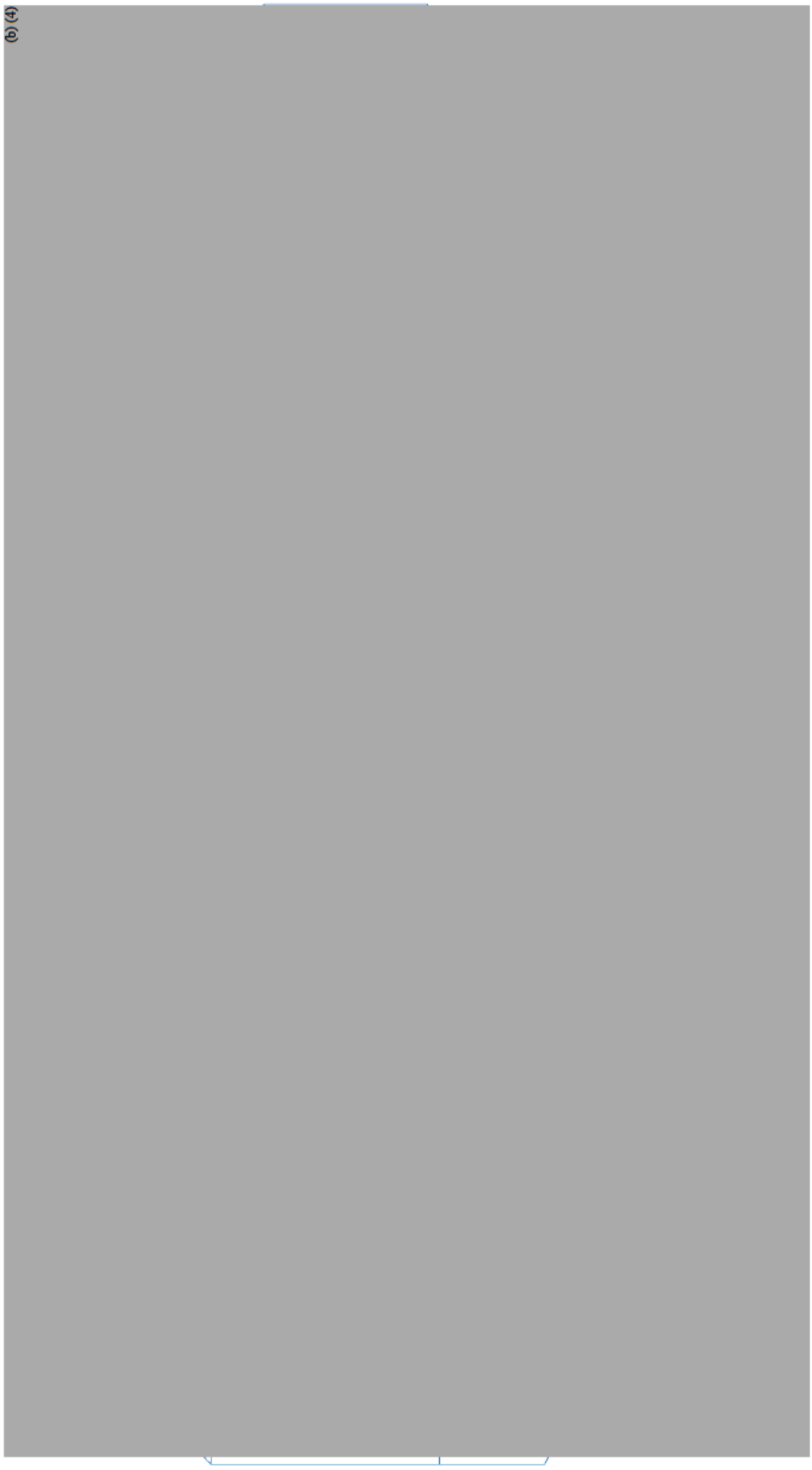
[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Week 2

Week 3

Week 4

Outer Carton Labeling



APPENDIX C. PREVIOUS DMEPA REVIEWS

On May 20, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 214755. Our search identified one relevant previous review[b] and we considered our previous recommendations to see if they are applicable for this current review.

APPEARS THIS WAY ON ORIGINAL

[b] Morris, C. Label and Labeling Review for Lumryz (NDA 214755). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 Apr 26. TTT ID No.: NDA 214755.

APPENDIX D.

HUMAN FACTORS JUSTIFICATION FOR STARTER PACK SUPPLEMENT

Human Factors Justification For Starter Pack Supplement, received on December 7, 2023, available from:
\\CDSESUB1\EVSPROD\nda214755\0117\m5\53-clin-stud-rep\535-rep-effic-safety-stud\forthetreatmentofcataplexyandexcessivedaytimesleepinessinnarcole\5354-other-stud-rep\humanfactors\hf-justification-starter-pack.pdf

USE RELATED RISK ANALYSIS

Use Related Risk Analysis, received on December 7, 2023, available from:
\\CDSESUB1\EVSPROD\nda214755\0117\m5\53-clin-stud-rep\535-rep-effic-safety-stud\forthetreatmentofcataplexyandexcessivedaytimesleepinessinnarcole\5354-other-stud-rep\humanfactors\d9721-004-ft218-ufmea.pdf

RESPONSE TO INFORMATION REQUEST

Response to Information Request, received on April 15, 2024, available from:
\\Cdsesub1\evsprod\NDA214755\0136\m1\us

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

/s/

LORETTA HOLMES
05/31/2024 04:34:47 PM

MATTHEW J BARLOW
05/31/2024 04:39:21 PM

YEVGENIYA M KOGAN
05/31/2024 04:54:04 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s007

RISK ASSESSMENT AND RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214755
Supplement Number, Date Received	Supplement 7 received December 7, 2023 (sequence 117), and amended on April 22, 2024 (sequence 137)
Action Date	June 7, 2024
Nexus TTT #	2024-7722
Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	August 09, 2024
Subject	Addendum to the review of proposed Minor REMS Modification
Established Name	Sodium oxybate for extended-release
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals
Therapeutic Class	Central Nervous System Depressant
Formulation(s)	Powder for extended-release oral suspension: packets of 4.5 g, 6 g, 7.5 g, and 9 g

1. Introduction

This review serves as an addendum to the Division of Risk Management (DRM) review dated May 13, 2024[1], which reviewed the proposed modifications to the Risk Evaluation and Mitigation Strategy (REMS) for Lumryz (sodium oxybate extended-release), New Drug Application (NDA) 214755, submitted by Avadel CNS Pharmaceuticals (Applicant) on December 7, 2023 and was amended April 22, 2024.

The Applicant submitted a labeling supplement to include the proposed 28-day starter pack containing 7 packets of 4.5 g (for week 1), 14 packets of 6 g (for weeks 2 and 3), and 7 packets of 7.5 g (for week 4).

In the May 31, 2024 labeling review[2] from the Division of Medication Error Prevention and Analysis 1 (DMEPA 1), it was stated that if the starter pack is used to titrate according to the dosing instructions in the prescribing information, the patient would have a 6 g 7-count carton left over. As a result, there were concerns about whether unused packets from the starter pack on the risks of abuse and misuse, which is the focus of this review.

2. Discussion

Lumryz is approved for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy. It is currently available as 4.5 grams, 6 grams, 7.5 grams, and 9 grams, and all strengths are supplied as packages of 7 or 30 packets. Prescribers will initiate Lumryz at 4.5 grams once per night orally and titrate to effect in increments of 1.5 g per night at weekly intervals to the recommended dosage range of 6 grams to 9 grams per night orally as a chronic use medication.

Patients being treated with Lumryz are expected to experience changes in their dosage regimen based on efficacy and tolerability. Like with other chronic medications, unused medications are likely to occur as a result. Additionally, prescribers may prescribe for a 30-day supply when initiating Lumryz or a 90-day supply for maintenance under the Lumryz REMS.[3] Thus, unused medications can also occur when a patient receives a 30-day or 90-day supply, but the patient's dose was changed before completing that supply.

DRM does not believe that the proposed starter pack is introducing a new safety risk and that the proposed starter pack could potentially reduce unused drug supply when prescribers are titrating a patient's dose as compared to the currently available 30-day or 90 day-supply. Additionally, unused medications are currently being addressed in Lumryz REMS by educating patients on proper drug disposal, such as information on a drug takeback program for any unused, leftover, or expired drug product. This aligns with other REMS programs with drugs that have similar risk of misuse and abuse. Although the REMS doesn't track leftover medications, we were not made aware of any issues in the Lumryz REMS assessment report regarding unused medications.

Based on the available information, no further changes are needed to Lumryz REMS regarding the proposed starter pack. As currently, prescribers will have to use their clinical judgment on selecting the appropriate regimen when initiating Lumryz or changing dose.

---

[1] Olumba, S. Review of Proposed Minor REMS Modification for Lumryz. NDA 214755. DARRTED May 13, 2024; accessed at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807443a6

[2] Holmes, L. Labeling Packaging and URRA Review for Lumryz. NDA 214755. DARRTED May 31, 2024; accessed at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80749ede

[3] REMS@FDA: FDA Approved Drug Products. Lumryz (sodium oxybate extended-release) REMS. Accessed on August 8, 2024 at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=401

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/s/

STEPHANIE N OLUMBA
08/09/2024 02:22:06 PM

CYNTHIA L LACIVITA on behalf of CAROLYN N TIEU
08/09/2024 03:38:47 PM

CYNTHIA L LACIVITA
08/09/2024 03:38:57 PM

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214755
Supplement Number, Date Received	Supplement 7 received December 7, 2023 (sequence 117), and amended on April 22, 2024 (sequence 137)
Action Date	June 7, 2024
Nexus TTT #	2024-7722
Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS Kate Oswell, MA
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	May 13, 2024
Subject	Review of proposed Minor REMS Modification
Established Name	Sodium oxybate for extended-release
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals
Therapeutic Class	Central Nervous System Depressant
Formulation(s)	Powder for extended-release oral suspension: packets of 4.5 g, 6 g, 7.5 g, and 9 g

TABLE OF CONTENTS

1. Introduction

This review evaluates the proposed modifications to the Risk Evaluation and Mitigation Strategy (REMS) for Lumryz (sodium oxybate extended-release), New Drug Application (NDA) 214755, submitted by Avadel CNS Pharmaceuticals (Applicant) on December 7, 2023 and was amended April 22, 2024.

The Applicant submitted a labeling supplement to include the proposed starter pack package. As part of this supplement, the Applicant proposed REMS modifications to include the starter pack as a prescription option on the **Prescription Form**.

2. Background

2.1. PRODUCT INFORMATION

Lumryz is a central nervous system depressant approved for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.[1] Lumryz is supplied as granules for extended-release oral suspension in single dose packets of 4.5 grams, 6 grams, 7.5 grams, and 9 grams. The recommended starting dosage is 4.5 grams once per night orally. The dosage may be increased by 1.5 grams per night at weekly intervals to the recommended dosage range of 6 grams to 9 grams once per night orally.

Lumryz was approved on May 1, 2023 with a REMS to ensure that the benefits of the drug outweigh the increased risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion[a] of Lumryz.[2]

The goal of the Lumryz REMS is to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Lumryz by:

1. Informing prescribers, pharmacists, and patients of:
    a. The risk of significant central nervous system (CNS) and respiratory depression associated with Lumryz.
    b. The contraindication of use of Lumryz with sedative hypnotics or alcohol.
    c. The potential for abuse, misuse, and overdose associated with Lumryz.
    d. The safe use, handling, and storage of Lumryz.
2. Ensuring that pharmacy controls exist prior to filling prescriptions for LUMRYZ that:
    a. Screen for concomitant use of sedative hypnotics and other potentially interacting agents.
    b. Monitor for inappropriate prescribing, misuse, abuse, and diversion of Lumryz.
    c. Notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion.

The most recently approved Lumryz REMS (October 31, 2023) consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS. The ETASU include prescriber certification (ETASU A), pharmacy certification (ETASU B), and documentation of safe use conditions (ETASU D).

[a] The goal of mitigating diversion in this REMS refers to preventing the sale or transfer of the drug outside the framework of the REMS in order to mitigate the risks of central nervous system depression, respiratory depression, abuse, and misuse.

2.2. REGULATORY HISTORY

The following is a summary of the regulatory history relevant to this review:

- **05/01/23:** Lumryz approved with REMS for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.
- **10/31/23:** Lumryz REMS modification approved to support compliance with pharmacy requirements that must be completed before dispensing and to align with other REMS for oxybate products that utilize multiple pharmacies and a separate REMS administrator.
- **12/07/23:** Applicant submitted a labeling supplement to propose a starter pack package and include the starter pack as a prescription option on the **Prescription Form**.
- **04/16/24:** Information Request sent to Applicant with comments on the **Prescription Form.**
- **04/22/24**: Applicant submitted a REMS amendment containing edits to the **Prescription Form** in response to DRM's April 16, 2024 Information Request.

3. Review of Proposed REMS Modifications

3.1. REMS Requirements

The Applicant did not propose changes to the REMS goal, REMS Document, REMS elements, or Applicant requirements.

3.1.1. REMS Participant Requirements and Materials

Only the affected participants and their associated materials are reviewed below.

3.1.1.1. Healthcare Providers that Prescribe

The Applicant proposed to include the starter pack as a prescription option on the **Prescription Form.** The starter pack is the proposed 28-day package containing seven packets of 4.5 g for week 1, 14 packets of 6 g for week 2 and 3, and seven packets of 7.5 g for week 4.

Reviewer's Comments: *Refer to our April 16, 2024 review where we provided additional clarifications on the* ***Prescription Form.*** [3] *The Applicant has addressed our comments. The proposed changes to the* ***Prescription Form*** *are acceptable.*

3.2. REMS ASSESSMENT TIMETABLE

The timetable for submission of assessments of the REMS remains the same as that approved on May 1, 2023.

4. Supporting Document

The Applicant did not propose changes to the Supporting Document.

5. REMS Assessment Plan

The Applicant did not propose changes to the REMS Assessment Plan.

There are no changes to the REMS Assessment Plan described in the October 31, 2023 Approval letter.

6. Conclusions and Recommendations

DRM finds the proposed REMS modification for Lumryz submitted on December 7, 2023, and last amended on April 22, 2024, and appended to this review to be acceptable and recommends approval.

The timetable for submission of assessments of the REMS remains the same as that approved on May 1, 2023.

The REMS Assessment Plan is not changing and will remain the same as that described in the October 31, 2023 Approval Letter.

7. References

[1] Lumryz (sodium oxybate) for extended-release oral solution Prescribing Information. Avadel CNS Pharmaceuticals, Inc. May 01, 2023; accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214755Orig1s000lbl.pdf

[2] Approval Letter for Lumryz (sodium oxybate) for extended-release oral suspension NDA 214755. May 01, 2023; accessed at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/214755Orig1s000ltr.pdf

[3] Olumba, S. Interim Review of Proposed Minor REMS Modification for Lumryz. NDA 214755. DARRTED April 16, 2024; accessed at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8073b3b7

8. Appendix

REMS Document

Enrollment Forms

Prescriber:

- Prescriber Enrollment Form

Patient:

- Patient Enrollment Form

Pharmacy:

- Pharmacy Enrollment Form

Training and Educational Materials

Prescriber:

- Prescriber Brochure

Patient:

- Patient Brochure

Pharmacy:

- Certified Pharmacy Training Program
- Pharmacy Staff Knowledge Assessment
- Pharmacist Knowledge Assessment

Patient Care Forms

- Prescription Form
- Patient Counseling Checklist

Communication Materials

- Dear Healthcare Provider Letter
- Dear Professional Society Letter
- REMS Fact Sheet

Other Materials

- Risk Management Report
- REMS Program Website

88 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

STEPHANIE N OLUMBA
05/13/2024 03:17:26 PM

KATE H OSWELL
05/13/2024 03:20:16 PM

CAROLYN N TIEU
05/13/2024 03:23:33 PM

CYNTHIA L LACIVITA
05/13/2024 10:38:01 PM

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214755
Supplement Number, Date Received	Supplement 7 received December 7, 2023 (sequence 117), and amended on April 22, 2024 (sequence 137)
Action Date	June 7, 2024
Nexus TTT #	2024-7722
Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	August 09, 2024
Subject	Addendum to the review of proposed Minor REMS Modification
Established Name	Sodium oxybate for extended-release
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals
Therapeutic Class	Central Nervous System Depressant
Formulation(s)	Powder for extended-release oral suspension: packets of 4.5 g, 6 g, 7.5 g, and 9 g

1. Introduction

This review serves as an addendum to the Division of Risk Management (DRM) review dated May 13, 2024[1], which reviewed the proposed modifications to the Risk Evaluation and Mitigation Strategy (REMS) for Lumryz (sodium oxybate extended-release), New Drug Application (NDA) 214755, submitted by Avadel CNS Pharmaceuticals (Applicant) on December 7, 2023 and was amended April 22, 2024.

The Applicant submitted a labeling supplement to include the proposed 28-day starter pack containing 7 packets of 4.5 g (for week 1), 14 packets of 6 g (for weeks 2 and 3), and 7 packets of 7.5 g (for week 4).

In the May 31, 2024 labeling review[2] from the Division of Medication Error Prevention and Analysis 1 (DMEPA 1), it was stated that if the starter pack is used to titrate according to the dosing instructions in the prescribing information, the patient would have a 6 g 7-count carton left over. As a result, there were concerns about whether unused packets from the starter pack on the risks of abuse and misuse, which is the focus of this review.

2. Discussion

Lumryz is approved for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy. It is currently available as 4.5 grams, 6 grams, 7.5 grams, and 9 grams, and all strengths are supplied as packages of 7 or 30 packets. Prescribers will initiate Lumryz at 4.5 grams once per night orally and titrate to effect in increments of 1.5 g per night at weekly intervals to the recommended dosage range of 6 grams to 9 grams per night orally as a chronic use medication.

Patients being treated with Lumryz are expected to experience changes in their dosage regimen based on efficacy and tolerability. Like with other chronic medications, unused medications are likely to occur as a result. Additionally, prescribers may prescribe for a 30-day supply when initiating Lumryz or a 90-day supply for maintenance under the Lumryz REMS.[3] Thus, unused medications can also occur when a patient receives a 30-day or 90-day supply, but the patient's dose was changed before completing that supply.

DRM does not believe that the proposed starter pack is introducing a new safety risk and that the proposed starter pack could potentially reduce unused drug supply when prescribers are titrating a patient's dose as compared to the currently available 30-day or 90 day-supply. Additionally, unused medications are currently being addressed in Lumryz REMS by educating patients on proper drug disposal, such as information on a drug takeback program for any unused, leftover, or expired drug product. This aligns with other REMS programs with drugs that have similar risk of misuse and abuse. Although the REMS doesn't track leftover medications, we were not made aware of any issues in the Lumryz REMS assessment report regarding unused medications.

Based on the available information, no further changes are needed to Lumryz REMS regarding the proposed starter pack. As currently, prescribers will have to use their clinical judgment on selecting the appropriate regimen when initiating Lumryz or changing dose.

---

[1] Olumba, S. Review of Proposed Minor REMS Modification for Lumryz. NDA 214755. DARRTED May 13, 2024; accessed at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807443a6

[2] Holmes, L. Labeling Packaging and URRA Review for Lumryz. NDA 214755. DARRTED May 31, 2024; accessed at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80749ede

[3] REMS@FDA: FDA Approved Drug Products. Lumryz (sodium oxybate extended-release) REMS. Accessed on August 8, 2024 at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=401

APPEARS THIS WAY ON ORIGINAL

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

/s/

STEPHANIE N OLUMBA
08/09/2024 02:22:06 PM

CYNTHIA L LACIVITA on behalf of CAROLYN N TIEU
08/09/2024 03:38:47 PM

CYNTHIA L LACIVITA
08/09/2024 03:38:57 PM

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214755
Supplement Number, Date Received	Supplement 7 received December 7, 2023 (sequence 117)
Action Date	June 7, 2024
Nexus TTT #	2024-7722
Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS Kate Oswell, MA
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	April 16, 2024
Subject	Review of proposed Minor REMS Modification
Established Name	Sodium oxybate for extended-release
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals
Therapeutic Class	Central Nervous System Depressant
Formulation(s)	Powder for extended-release oral suspension: packets of 4.5 g, 6 g, 7.5 g, and 9 g

TABLE OF CONTENTS

1. Introduction

This review evaluates the proposed modifications to the Risk Evaluation and Mitigation Strategy (REMS) for Lumryz (sodium oxybate extended-release), New Drug Application (NDA) 214755, submitted by Avadel CNS Pharmaceuticals (Applicant) on December 7, 2023.

Lumryz is a central nervous system depressant approved for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.[1] Lumryz was approved on May 1, 2023 with a REMS to ensure that the benefits of the drug outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion[a] of Lumryz.[2]

The Applicant submitted a labeling supplement to include the proposed starter pack package. As part of this supplement, the Applicant proposed REMS modifications to include the starter pack as a prescription option on the **Prescription Form**.

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- **05/01/23:** Lumryz approved with REMS for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.
- **10/31/23:** Lumryz REMS modification approved to support compliance with pharmacy requirements that must be completed before dispensing and to align with other REMS for oxybate products that utilize multiple pharmacies and a separate REMS administrator.
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3. Review of Proposed REMS Modifications

3.1. REMS Requirements

The Applicant did not propose changes to the REMS goal, REMS Document, REMS elements, or Applicant requirements.

3.1.1. REMS Participant Requirements and Materials

Only the affected participants and their associated materials are reviewed below.

3.1.1.1. Healthcare Providers that prescribe

The Applicant proposed to include the starter pack as a prescription option on the **Prescription Form.** The starter pack is the proposed 28-day package containing seven packets of 4.5 g for week 1, 14 packets of 6 g for week 2 and 3, and seven packets of 7.5 g for week 4.

[a] The goal of mitigating diversion in this REMS refers to preventing the sale or transfer of the drug outside the framework of the REMS in order to mitigate the risks of central nervous system depression, respiratory depression, abuse, and misuse.

Reviewer's Comments: *We have provided additional clarifications on the* ***Prescription Form*** *that only one of the prescription options should be selected (i.e., either starter pack, titrated dose, or maintenance dose) and specified the weeks for each packet for the starter pack option. Proposed changes to the* ***Prescription Form*** *will need to align with the final agreed upon prescribing information.*

4. Conclusions and Recommendations

DRM does not find the proposed REMS modifications for Lumryz (sodium oxybate) extended-release as submitted on December 7, 2023 to be acceptable, as described in this review. Please send the comments in Section 5 to the Applicant in an Information Request and instruct the Applicant to submit a REMS amendment within 5 business days.

5. Comments to the Applicant

We have the following comments on the proposed REMS modification for Supplement 7, submitted on December 7, 2023. Review of the REMS proposal is ongoing; these comments should not be considered final. Your proposed changes will have to align with the final agreed upon prescribing information.

Prescription Form

- We provided additional clarifications that only one of the prescription options should be selected (i.e., either starter pack, titrated dose, or maintenance dose) and specified the weeks for each packet for the starter pack option. See redlined document.

Resubmission Instructions

Submit a REMS amendment within 5 business days that addresses our comments. Accept the track changes with which you agree in the Word documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous).

Include one compiled PDF file that includes the REMS Document and all REMS materials (excluding the Supporting Document) in their final format. Submit the Supporting Document as a separate document in Clean Word, Tracked Word (if proposing any changes), and pdf formatted version.

6. References

[1] Lumryz (sodium oxybate) for extended-release oral solution Prescribing Information. Avadel CNS Pharmaceuticals, Inc. May 01, 2023; accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214755Orig1s000lbl.pdf

[2] Approval Letter for Lumryz (sodium oxybate) for extended-release oral suspension NDA 214755. May 01, 2023(accessed at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/214755Orig1s000ltr.pdf)

7. Appendix

Prescription Form

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

STEPHANIE N OLUMBA
04/16/2024 09:10:26 AM

KATE H OSWELL
04/16/2024 09:34:55 AM

CAROLYN N TIEU
04/16/2024 09:36:19 AM

CYNTHIA L LACIVITA
04/16/2024 12:41:39 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s007

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

From: Lee, C. Eugene
Sent: Thu 05 Sep 2024 03:01:36 PM -0400 UTC
To: Marla Scarola
Cc: Chang, ShinYe; Sohn, Ann J
Subject: NDA 214755/S-007 (Lumryz): Carton Label Information Request
Categories: IR/Advice

Hello Marla,

I'm filling in for Ann while she's away this week.

With regard to NDA 214755/S-007, please refer to your 08/13/24, starter pack carton labeling submission for Lumryz. We have the following comments and request your response as soon as possible but no later than 09/11/24.

Starter Pack Carton Label:

> *We note that the placeholder for the product identifier containing both human-readable and 2D machine-readable formats is located on a principal display panel (PDP). In this location, the information is distracting and competes in prominence with critical information on the PDP. Therefore, we request that you move the placeholder information to one of the side panels.*

Submit your response to the NDA and send us a courtesy electronic copy.

Thanks,

C. Eugene Lee, Pharm.D.
Senior Regulatory Health Project Manager
Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research
Tel: 240-402-9386
C.Eugene.Lee@fda.hhs.gov

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

/s/

CHRISTOPHER E LEE
09/05/2024 03:06:38 PM

From: Sohn, Ann J
Sent: Fri 09 Aug 2024 03:41:55 PM -0400 UTC
To: mscarola@avadel.com
Cc: Chang, ShinYe
Subject: NDA 214755/S-007 Lumryz Carton Labeling
Attachments: 214755 S7 IR 8 9 24.docx

Hi Marla,

I'm covering for Sandy this week while she is out of the office. Please refer to your NDA 214755/S-007. We have identified issues included in the attached table in the Outer Carton Labeling, and provided recommendations.

Please submit your response to the NDA by COB Tuesday, August 13, 2024 and also confirm receipt of this email.

Thank you,

Ann Sohn, PharmD, MS
LCDR, United States Public Health Service
Senior Regulatory Project Manager

Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research
ann.sohn@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

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/s/

ANN J SOHN
08/09/2024 03:47:30 PM

From: Sohn, Ann J
Sent: Fri 09 Aug 2024 05:48:41 PM -0400 UTC
To: Marla Scarola
Cc: Chang, ShinYe
Subject: NDA 214755/S-007 Lumryz
Attachments: 214755 S7 PI 8 9 24.docx, 214755 S007 IFU 8 9 24.docx

Hi Marla,

Please find attached our comments fpr the Prescribing Information and Instructions for Use in the labeling for NDA 214755/S-007. This is in reference to S-007 only and is separate from labeling negotiations for S-006. Eugene Lee will be communicating with you regarding S-006.

Please submit your responses by COB Tuesday, August 13, 2024 and confirm receipt of this email.

Thanks,

Ann Sohn, PharmD, MS
LCDR, United States Public Health Service
Senior Regulatory Project Manager

Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research
ann.sohn@fda.hhs.gov

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/s/

ANN J SOHN
08/09/2024 05:51:29 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **CDER-OPDP-RPM**	FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Psychiatry Medical Reviewer: David Millis, MD Project Manager: Shin-Ye Sandy Chang, PharmD

REQUEST DATE:	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
July 9, 2024		214755/S-007	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Lumryz (sodium oxybate) ER suspension		CNS depressant	

NAME OF FIRM:	
Avadel CNS Pharmaceuticals, LLC	PDUFA Date: June 4, 2024

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PRESCRIBING INFORMATION (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☒ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☒ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☒ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

For OSE USE ONLY
☐ REMS

EDR link to submission: \\CDSESUB1\evsprod\NDA214755\0117

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: On December 7, 2023, Avadel submitted a prior approval labeling supplement which provides for the inclusion of a starter pack (carton & container labeling), minor edits to Section 16 of the USPI, and modification to the REMS Prescription Form. Applicant did not propose any changes to existing IFU, however, DP would appreciate your feedback on the proposed carton/container and input on whether revisions should be made to account for the starter pack.

Thank you,

Sandy

SIGNATURE OF REQUESTER	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one)

	☒ eMAIL ☐ HAND

APPEARS THIS WAY ON ORIGINAL

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/s/

SHIN-YE CHANG
07/09/2024 03:05:44 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)
Division of Psychiatry
Medical Reviewer: David Millis, MD
Project Manager: Shin-Ye Sandy Chang, PharmD

REQUEST DATE:
July 8, 2024

NDA/BLA NO.:
214755/S-007

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:
Lumryz (sodium oxybate) ER suspension

PRIORITY CONSIDERATION:

CLASSIFICATION OF DRUG:
CNS depressant

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)

SPONSOR:
Avadel CNS Pharmaceuticals, LLC

PDUFA Date: June 7, 2024

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☒ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA/ANDA
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission: \\CDSESUB1\evsprod\NDA214755\0117

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS: On December 7, 2023, Avadel submitted a prior approval labeling supplement which provides for the inclusion of a starter pack (carton & container labeling), minor edits to Section 16 of the USPI, and modification to the REMS Prescription Form. Applicant did not propose any changes to existing IFU, however, DP would appreciate your input on whether revisions should be made to account for the starter pack.

Thank you,

Sandy

SIGNATURE OF REQUESTER
Shin-Ye Chang

SIGNATURE OF RECEIVER

Version: 06/06/2016

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/s/

SHIN-YE CHANG
07/08/2024 10:47:16 AM

From: Lee, C. Eugene
To: Marla Scarola
Subject: NDA 214755/S-007 (Lumryz): REMS Information Request
Date: Tuesday, April 16, 2024 2:53:00 PM
Attachments: 17-rems-prescription-form-starter-pack.docx
image001.png

Good afternoon Marla,

With regard to NDA 214755 please refer to your 12/07/23, new supplement (S-007) submission containing proposed REMS modifications for Lumryz. We have the following comments/questions and request your response as soon as possible but no later than COB on 04/23/24.

REMS:

Prescription Form

- *We provided additional clarifications that only one of the prescription options should be selected (i.e., either starter pack, titrated dose, or maintenance dose) and specified the weeks for each packet for the starter pack option. See redlined document.*

Resubmission Instructions

- *Submit a REMS amendment within 5 business days that addresses our comments. Accept the track changes with which you agree in the Word documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous).*
- *Include one compiled PDF file that includes the REMS Document and all REMS materials (excluding the Supporting Document) in their final format. Submit the Supporting Document as a separate document in Clean Word, Tracked Word (if proposing any changes), and pdf formatted version.*

Submit your response to the NDA and send me a courtesy electronic copy.

Thanks,

C. Eugene Lee, Pharm.D.
Senior Regulatory Health Project Manager
Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research
Tel: 240-402-9386
C.Eugene.Lee@fda.hhs.gov

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

CHRISTOPHER E LEE
04/16/2024 02:58:11 PM

From:	Nguyen, Phuong B (OSE SRPM)
To:	Marla Scarola
Cc:	Lee, C. Eugene; Lyons, Darrell; Kang, Sue
Subject:	Request for Product Samples: NDA 214755/S-007 Lumryz (sodium oxybate) ER Susp.
Date:	Wednesday, March 27, 2024 4:41:20 PM
Importance:	High

Dear Marla,

Please refer to your supplemental new drug application (sNDA), dated and received January 4, 2024, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Lumryz (sodium oxybate) Extended-Release Suspension.

We are reviewing your submission and have the following information requests. We request a prompt response in order to continue our evaluation of your submission.

Please submit:

- Two (2) placebo only intend-to-market samples of product within 2 business days from the receipt of this information request
- For RLD request, placebo samples of the reference listed product
- In the event that a sample with placebo cannot be submitted or is not available, it is acceptable to provide 2 empty samples (do not contain active drug or placebo) that represent the intend-to-market samples of product. If empty samples will be sent, please include a description of how the drug's characteristics (e.g., drug viscosity, color) may impact a user's interaction with the product and completion of critical tasks
- Material Safety Data Sheet (MSDS). Indicate if your sample contain any hazardous ingredients. If so, please include any special instructions for handling the samples

Please expedite the shipment. Address the samples to the following:

OSE Human Factors Sample Steward

ATTN: Phuong Nguyen

Food and Drug Administration

10903 New Hampshire Avenue, Bldg 22, Room 4477

Silver Spring, MD

Use zip code 20903 if shipping via United States Postal Service (USPS).

Use zip code 20993 if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx)

Please ensure that the Application Number and Product Name is included with the samples.

Please instruct the package carrier that a signature is NOT required for delivery if the package is dropped off at the designated inbox.

Please notify us with the delivery carrier's tracking number for the package and the location of shipping origin of the sample prior to shipment.

Please confirm your receipt of this communication. If you have any questions, please let me know.

Kind Regards,

Phuong

Phuong B. Nguyen, R.Ph., GWCPM, CQIA
Safety Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
U.S. Food and Drug Administration
Office: 240-402-5827
Phuong.Nguyen1@fda.hhs.gov

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/s/

PHUONG B NGUYEN
03/27/2024 11:52:31 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE – DMEPA

FROM: Division of Psychiatry
Medical Reviewer: Paul Bossie, MD, 240-402-9145
Project Manager: Shin-Ye Sandy Chang, 301-796-3971

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 4, 2024		214755 S-007	PAS Labeling supplement	December 7, 2023

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lumryz (sodium oxybate) ER suspension		CNS depressant	May 10, 2024 PDUFA: June 22, 2024

NAME OF FIRM: Avadel CNS Pharmaceuticals, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MEDICATION ERRORS
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: On December 7, 2023, Avadel submitted a prior approval labeling supplement to include a starter pack.

EDR Location: \\CDSESUB1\evsprod\NDA214755\0117

DP is requesting for OSE DEMPA to review the carton/container labeling, and provide feedback/revisions to the proposed labeling changes in
SP: N214755 S007

Thank you,

Sandy

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply)
Shin-Ye Sandy Chang, PharmD	☐ MAIL ☒ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	

	SIGNATURE OF DELIVERER

06/18/2013

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/s/

SHIN-YE CHANG
01/04/2024 12:13:08 PM