CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214755Orig1s006

Trade Name:	LUMRYZ
Generic or Proper Name:	(sodium oxybate)
Sponsor:	Avadel CNS
Approval Date:	October 16, 2024
Indication:	LUMRYZ is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 214755/S-006

SUPPLEMENT APPROVAL

Avadel CNS Pharmaceuticals, LLC
Attention: Marla E. Scarola, MS
Senior Vice President, Regulatory and Quality
16640 Chesterfield Grove Rd, Suite 200
Chesterfield, MO 63005

Dear Marla E. Scarola:

Please refer to your supplemental new drug application (sNDA) dated and received November 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) extended-release oral suspension.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated November 7, 2023.

This Prior Approval sNDA provides for expanding the indication of Lumryz to include pediatric patients 7 years of age or older with narcolepsy and proposed modifications to the approved Lumryz REMS to align with the expanded indication.

APPROVAL & LABELING

We have completed our review of this 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.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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]

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.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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 September 26, 2024. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of: changes to REMS Document and materials to align with the expanded indication to include patients 7 years of age and older with narcolepsy; addition of the Pediatric Patients and their Caregivers Brochure;

[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.

and removal of the Dear Healthcare Provider Letter, Dear Professional Society Letter, and Fact Sheet.

Your proposed modified REMS, submitted on November 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.

The revised REMS assessment plan must include, but is not limited to, the following: For each metric, provide the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted

Program Implementation and Operations

1. **REMS Implementation (1st assessment after approval)**
   a. REMS implementation date
   b. Date of first commercial distribution of Lumryz
   c. Date when the Lumryz REMS call center became operational
   d. Date when the Lumryz REMS website became live and operational
   e. Date(s) when the Dear Healthcare Provider Letter and Dear Professional Society Letter were provided
      i. Number of letters sent by method of distribution (mail/email)
      ii. Number of letters returned/undeliverable and number of unopened emails for each mailing

2. **REMS Enrollment and Certification Statistics**
   a. Patients
      i. Total number of enrolled patients
      ii. Number and percentage of newly enrolled patients stratified by age, geographic region (defined by US Census), and gender
      iii. Number and percentage of active patients enrolled (i.e., patients who received at least one shipment of Lumryz during the reporting period) stratified by age, geographic region (defined by US Census), and gender
      iv. Number and percentage of patients who have discontinued Lumryz after receiving at least one shipment of Lumryz. Include demographics of discontinued patients and reasons for discontinuation
   b. Healthcare Providers
      i. Total number of certified healthcare providers
      ii. Number and percentage of newly certified healthcare providers stratified by professional designation (i.e., MD, DO, PA, NP, Other), medical specialty, and geographic region (defined by US Census)

iii. Number and percentage of active certified healthcare providers (healthcare providers who have written at least one prescription for Lumryz during the reporting period) stratified by professional designation (i.e., MD, DO, PA, NP, Other), medical specialty, and geographic region (defined by US Census)

c. Certified Pharmacy
   i. Total number of certified pharmacies
   ii. Number of newly certified pharmacies
   iii. Number of active pharmacies (e.g., dispensed one or more Lumryz prescriptions)

d. Wholesalers/Distributors
   i. Total number of authorized wholesalers/distributors
   ii. Number and percentage of newly authorized wholesalers/distributors
   iii. Number and percentage of active wholesalers/distributors (i.e., have shipped Lumryz at least once during the reporting period)

3. Utilization Data

a. Number of shipments, including number of Lumryz packets, shipped by wholesalers, distributors, and other entities to pharmacies.
b. Number and percentage of Lumryz prescriptions (new and refill) dispensed by pharmacies to patients.
c. Number and percentage of Lumryz packets and shipments sent by pharmacies to patients stratified by dose strength.

4. REMS Operation and Performance Data

a. REMS Databases Report
   i. Number and percentage of contacts by stakeholder type (e.g., patients, healthcare providers, pharmacy, other)
   ii. Summary of reasons for contacts (e.g., enrollment questions) by reporter (e.g., authorized representative, patient, healthcare provider, other)
   iii. Summary of frequently asked questions by stakeholder type and topic
   iv. Summary of any REMS-related problems identified and a description of any corrective actions taken
   v. If the summary reason for the calls indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden (e.g., pharmacy calls to other REMS for oxybate products) or patient access issues (e.g., patient's therapy delayed due to unwillingness of other REMS for oxybate products to provide necessary information)
   vi. Summary of program or system problems and a description of any corrective actions taken

5. REMS Compliance

a. Audits: Summary of audit activities including but not limited to:
   i. A copy of the audit plan for certified pharmacies and wholesalers, distributors, and other entities that distribute Lumryz
   ii. The number of audits expected, and the number of audits performed
   iii. The number and type of deficiencies noted
   iv. For those with deficiencies noted, report the status of corrective and preventative action (CAPA) proposed to address the deficiencies, including completion dates
   v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
   vi. Provide details on deviations for the CAPA proposed, including timelines, and mitigating steps to address the deviations
   vii. Confirm documentation of completion of training for relevant staff
   viii. Review of cumulative findings to identify any trends of potential repeat issues, and steps to be taken to address these findings
   ix. A summary report of the processes and procedures that are implemented to be in compliance with the REMS requirements

b. A summary report of noncompliance, associated corrective and preventive actions (CAPA) plans, and the status of CAPA plans including but not limited to:
   i. A copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder, actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or decertified/disenrolled from the REMS
   ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:
      1. The unique ID(s) of the stakeholder(s) associated with the noncompliance event to enable tracking over time
      2. The source of the noncompliance data
      3. The results of root cause analysis
      4. What action(s) were taken in response

c. Healthcare Providers
   i. Number and percentage of certified healthcare providers who were decertified and reasons for decertification. Include if any healthcare providers were re-certified.
   ii. Number and percentage of Lumryz prescriptions filled from a healthcare provider who was not certified

d. Certified Pharmacies

i. Number and percentage of Lumryz prescriptions dispensed for more than a 30 days' supply (first fill) or more than a 90 days' supply (refills) and reasons
ii. Number and percentage of Lumryz shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and *Risk Management Reports* completed
iii. Number and percentage of initial Lumryz shipments sent to patients without completion of the Patient Counseling Checklist
iv. Number and percentage of Lumryz shipments sent to patients without completion of the Patient Counseling Checklist for patients that reinitiated therapy after a lapse of > 6 months
v. Number and percentage of Lumryz shipments sent to patients without completion of the Patient Counseling Checklist when the patient notified the pharmacy of a new or change in concomitant medication or comorbidity
vi. Number and percentage of pharmacy decertifications and reasons for decertification. Include if any pharmacies were re-certified.

e. Patients
i. Number and percentage of patients who were disenrolled from the program and reasons for disenrollment
ii. Number and percentage of patients who received prescriptions from more than one prescriber during their therapy
iii. Number and percentage of patients with overlapping Lumryz prescriptions (more than one active prescription shipped)
iv. Number of duplicate patients detected by certified pharmacies
v. Number and percentage of duplicate patients who were shipped Lumryz under more than one name or identifier
vi. Number and percentage of patients who were shipped Lumryz after being disenrolled
vii. Number of patients found to have active, overlapping prescriptions for Lumryz and any other oxybate product (e.g., Xywav, Xyrem, or generic Sodium Oxybate)
viii. Number and percentage of patients who requested an early refill of Lumryz and reason for the request
    1. Number and percentage of requests approved
    2. Number and percentage of requests denied by the prescriber
    3. Number and percentage of requests denied by the certified pharmacy
    4. Number and percentage of patients with multiple (i.e., more than 1) requests for early refills

Safe Use Behaviors

6. Pharmacy Notifications

a. A summary of the notifications by pharmacies to prescribers for Lumryz. Each of the following situations will include the number and percentage of notifications, number of unique patients, the outcome of the pharmacy notification (e.g., counseled patient, discussed with prescriber) and outcome of Lumryz prescription disposition (e.g., prescriber approved shipment, prescriber requested shipment hold, prescriber denied shipment, pharmacy approved shipment):

i. Use with prescription sedative-hypnotics indicated for sleep (e.g., eszopiclone, zaleplon, zolpidem, temazepam, suvorexant, quazepam, estazolam, flurazepam, triazolam, tasimelteon, ramelteon). Indicate specific actions taken by the prescriber and the prescriber rationale for continuing treatment in response to the notification including the following:

1. Treatment with Lumryz will be discontinued
2. Sedative hypnotic will be discontinued
3. Dosage of sedative hypnotic has been/will be reduced
4. Information unavailable
5. No action (continue sedative hypnotic with Lumryz)
6. Prescriber's rationale for continued use of sedative hypnotic with Lumryz
    a. Sedative hypnotic will not be taken at the same time as Lumryz
    b. Sedative hypnotic will be taken at the same time as Lumryz
    c. Sedative hypnotic will be taken as a sleep aid
    d. Sedative hypnotic will be taken for different indication per medical need
    e. Lumryz dose regimen changed
    f. No rationale provided
    g. Other rationale provided

ii. Benzodiazepines (e.g., diazepam, alprazolam or any not listed in metric 6.a.i.). Indicate specific actions taken by the prescriber and the prescriber rationale for continuing treatment in response to the notification including the following:

1. Treatment with Lumryz will be discontinued
2. Benzodiazepine will be discontinued
3. Dosage of benzodiazepine has been/will be reduced
4. Information unavailable
5. No action (continue benzodiazepine with Lumryz)
6. Prescriber's rationale for continued use of benzodiazepine with Lumryz
    a. Benzodiazepine will not be taken at the same time as Lumryz
    b. Benzodiazepine will be taken at the same time as Lumryz
    c. Benzodiazepine will be taken as a sleep aid

d. Benzodiazepine will be taken for different indication per medical need
e. Lumryz dose regimen changed
f. No rationale provided
g. Other rationale provided

iii. Use with other concomitant CNS depressant medications (i.e., sedating antidepressants or antipsychotics, sedating anti-epileptics, sedating antihistamines, general anesthetics, muscle relaxants, opioid analgesics, or illicit CNS depressants)
iv. Patient report of alcohol use
v. Patient report of diagnosis of sleep apnea
vi. Patient report of diagnosis of asthma, COPD, or other conditions affecting breathing
vii. Suspected abuse, misuse, or diversion
viii. Alerts regarding potential abuse, misuse, or diversion on the patient profiles
ix. Prescription error
x. Early refill requests

7. Risk Management Reports (RMRs)

a. Number and percentage of RMRs submitted
b. Number and percentage of unique patients with an RMR
c. Number and percentage of unique patients with multiple RMRs
d. Number and percentage of alerts generated from RMRs
e. Number and percentage of RMRs generated from early refill requests
f. Number and percentage of RMRs generated for other reasons, stratified by reasons
g. Number and percentage of prescriber-related RMRs
h. Number and percentage of RMRs that included reporting of an adverse event.

8. REMS Patient Counseling Checklist

a. Summary table from REMS Patient Counseling Checklists of the number and percentage of patients taking the following concomitant medications and who subsequently received at least one shipment of drug:
   i. Prescription sedative hypnotics indicated for sleep (e.g., eszopiclone, zaleplon, zolpidem, temazepam, suvorexant, quazepam, estazolam, flurazepam, triazolam, tasimelteon, ramelteon)
   ii. Alcohol
   iii. Other potentially interacting agents:

1. Benzodiazepines (e.g., diazepam, alprazolam, or any not listed in metric 8.a.i.)
2. Sedating antidepressants or antipsychotics, sedating anti-epileptics, and sedating antihistamines
3. General anesthetics
4. Muscle relaxants
5. Opioid analgesics
6. Illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB])

b. Summary table for Lumryz from REMS Patient Counseling Checklists of the number and percentage of patients who have been diagnosed with the following conditions and who subsequently received at least one shipment of drug:
   i. Sleep apnea
   ii. Asthma, COPD, or other conditions affecting the respiratory system

9. Verification of Disenrollment or Active Prescriptions in Other REMS for Oxybate Products (per reporting period)

a. Information on patient with active, overlapping prescription or disenrollment or deactivation for misuse, abuse, etc., in other REMS for oxybate products and outcomes
   i. For unsuccessful attempts or those that resulted in a treatment delay, indicate the REMS contacted
   ii. Number and dates of unsuccessful contact attempts to other REMS for oxybate products, including hold times per contact attempt
   iii. For contacts resulting in a delay, the total number of contact attempts, and time from receipt of prescription to successful contact with other REMS for oxybate products
   iv. The number of prescriptions delayed or unable to be filled divided by the number of valid prescriptions received.
   v. Reason not dispensed (e.g., active prescription in other REMS for oxybate products, other REMS for oxybate products unresponsive, patient disenrolled or discontinued due to abuse, misuse or diversion)
   vi. Reports of any negative outcomes due to any treatment delay
   vii. Number of prescriptions dispensed without verification of current overlapping prescription or disenrollment from other REMS for oxybate products

10. REMS Dispense Authorizations (RDAs)

a. Number of requested RDAs that were rejected and reasons for rejection
b. Number of prescriptions dispensed where all REMS and safe use requirements were not met, but an RDA was provided
c. Number of prescriptions dispensed without an RDA

d. The number of requested RDAs that were rejected and were subsequently approved and the duration of time from rejection of the requests to approval

Health Outcomes and/or Surrogates of Health Outcomes

11. Pharmacovigilance/surveillance (per reporting period)
    a. Analysis of serious adverse events and summary table for Lumryz of the number of reports of serious adverse events, including the following data fields: date, case report ID, age, gender, serious adverse event(s) outcome (hospitalization or death), associated factors (i.e., concurrent use with sedative hypnotics or alcohol, intentional misuse, abuse, overdose, diversion, or medication error) and if cases are considered related or not related to Lumryz. Tables will include an overall narrative summary and analysis of the adverse events and data fields reported.
        i. All cases of death – include narrative summary of each death
            1. Number, percentage, and type of RMRs, notifications, and alerts within 6 months of the reported deaths
            2. Calculation of the overall, and age- and gender-specific mortality rates.
            3. Calculation of the standardized mortality rates, adjusted for age and gender, using both the point estimates and the lower bounds of the 95% confidence intervals as the reference rates.
        ii. Serious adverse events with all outcomes of death, emergency department visits (when admitted to hospital), or hospitalizations resulting from or associated with the following:
            1. Use with concurrent sedative hypnotics
            2. Use with alcohol
            3. Intentional misuse
            4. Abuse
            5. Overdose
            6. Medication error
        iii. Cases of sexual abuse – include narrative summary of each case
        iv. Proportion of discontinued patients who were associated with a report of a serious adverse event, including death

Knowledge

12. Knowledge, Attitude, and Behavior (KAB) Surveys of Patients/ Caregivers, and Healthcare Providers, and Pharmacists (to be submitted annually)
    a. Assessment of patients'/ caregivers', and healthcare providers' and pharmacists' understanding of the following:
        i. The risk of significant CNS and respiratory depression associated with Lumryz even at recommended doses
        ii. The contraindicated uses of Lumryz with sedative hypnotics and alcohol

iii. The potential for abuse, misuse, and overdose associated with Lumryz
iv. The safe use, handling, and storage of Lumryz
v. The Lumryz REMS requirements

13. Certified Pharmacy Knowledge Assessments (per reporting period and cumulatively)
    a. Number of pharmacy staff who completed post-training Knowledge Assessments including method of completion and the number of attempts needed to complete
        i. Breakdown of scores within the Pharmacy Staff Knowledge Assessment and Pharmacist Knowledge Assessment
    b. Summary of the most frequently missed post-training Pharmacy Staff Knowledge Assessment questions
    c. Summary of the most frequently missed post-training Pharmacist Knowledge Assessment questions
    d. Summary of potential comprehension or perception issues identified with the post-training Knowledge Assessments
    e. Number of pharmacy staff and pharmacists who did not pass the Knowledge Assessments

Overall Assessment of REMS Effectiveness

14. The requirements for assessments of an approved REMS under section 505-1 (g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *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.

d) *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.

e) *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.

f) *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.

Additionally, we recommend that you submit your proposed healthcare provider, pharmacist and patient/caregiver knowledge surveys for FDA review within 60 days of this letter. Prominently identify the submissions containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission: "**REQUEST FOR REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW/ SURVEY METHODOLOGIES**", respectively, in **bold capital letters, at the top of your cover letter and at the top of the first page** of the main submission document.

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

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

[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]

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).

If you have any questions, contact C. Eugene Lee, Senior Regulatory Project Manager, at C.Eugene.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- 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
10/16/2024 04:19:36 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s006

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)

RECENT MAJOR CHANGES

Indications and Usage (1)	10/2024
Dosage and Administration (2.2)	10/2024
Warnings and Precautions (5.4, 5.5, 5.6, 5.7)	10/2024

INDICATIONS AND USAGE

LUMRYZ is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy (1).

DOSAGE AND ADMINISTRATION

Dosing for Adults:

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

Dosing for Pediatric Patients (7 Years of Age and Older):

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

Important Administration Information

- Prepare the dose of LUMRYZ prior to bedtime; suspend dose in approximately ⅓ cup of water in the mixing cup provided (2.3).
- Allow 2 hours after eating before dosing (2.3).
- Take LUMRYZ while in bed and lie down after dosing (2.3).

DOSAGE FORMS AND STRENGTHS

For extended-release oral suspension: Packets of 4.5 g, 6 g, 7.5 g, or 9 g (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

Most common adverse reactions for pediatric patients (≥ 5%) in a study with immediate-release sodium oxybate were nausea, enuresis, vomiting, headache, weight decreased, decreased appetite, dizziness, and sleepwalking (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact 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: 10/2024

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 patients 7 years of age and older with narcolepsy.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosing Information

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

2.2 Pediatric Dosing Information

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

Pediatric Patients 7 years and Older Weighing at least 45 kg

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

Pediatric Patients 7 years and Older Weighing Less than 45 kg

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

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

2.3 Important Administration Instructions

LUMRYZ is taken orally as a single dose at bedtime. Prepare the dose of LUMRYZ prior to bedtime. Prior to ingestion, the dose of LUMRYZ should be suspended in approximately 1/3 cup (approximately 80 mL) of water in the mixing cup provided *[see Instructions for Use]*. Do not use hot water *[see Clinical Pharmacology (12.3)]*. After mixing, consume LUMRYZ within 30 minutes.

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

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

2.4 Switching Patients from Immediate-Release Sodium Oxybate

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

LUMRYZ is contraindicated for use in:

- combination with sedative hypnotics *[see Warnings and Precautions (5.1)]*

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

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Depression

LUMRYZ is a central nervous system (CNS) depressant. Clinically significant respiratory depression and obtundation has occurred in patients treated with immediate-release sodium oxybate at recommended doses in clinical trials and may occur in patients treated with LUMRYZ at recommended doses. LUMRYZ is contraindicated in combination with alcohol and sedative hypnotics. The concurrent use of LUMRYZ with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating antiepileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with LUMRYZ is required, dose reduction or discontinuation of one or more CNS depressants (including LUMRYZ) should be considered. In addition, if short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with LUMRYZ should be considered. In addition to coadministration of LUMRYZ and alcohol being contraindicated because of respiratory depression, consumption of alcohol while taking LUMRYZ may also result in a more rapid release of the dose of sodium oxybate *[see Clinical Pharmacology (12.3)]*.

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

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

5.2 Abuse and Misuse

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

(e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy) *[see Warnings and Precautions (5.3) and Drug Abuse and Dependence (9.2)]*.

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

5.3 LUMRYZ REMS

LUMRYZ is available only through a restricted distribution program called the LUMRYZ REMS because of the risks of central nervous system depression and abuse and misuse *[see Warnings and Precautions (5.1, 5.2)]*.

Notable requirements of the LUMRYZ REMS include the following:

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

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

5.4 Respiratory Depression and Sleep-Disordered Breathing

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

Increased apnea and reduced oxygenation may occur with LUMRYZ administration. A significant increase in the number of central apneas and clinically significant oxygen desaturation may occur in patients with obstructive sleep apnea treated with LUMRYZ.

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

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

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

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

In adult clinical trials in 128 patients with narcolepsy administered immediate-release sodium oxybate, two subjects had profound CNS depression, which resolved after supportive respiratory intervention. Two other patients discontinued immediate-release sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea. In two controlled trials assessing polysomnographic (PSG) measures in adult patients with narcolepsy administered immediate-release sodium oxybate, 40 of 477 patients were included with a baseline apnea/hypopnea index of 16 to 67 events per hour, indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a clinically significant worsening of respiratory function, as measured by apnea/hypopnea index and pulse oximetry at doses of 4.5 g to 9 g per night.

Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not on hormone replacement therapy, and among patients with narcolepsy. Increased central apneas and clinically relevant desaturation events have been observed with immediate-release sodium oxybate administration in adult and pediatric patients.

5.5 Depression and Suicidality

Depression, and suicidal ideation and behavior, can occur in patients treated with LUMRYZ.

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

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

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

The emergence of depression in patients treated with LUMRYZ requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking LUMRYZ.

5.6 Other Behavioral or Psychiatric Adverse Reactions

Other behavioral and psychiatric adverse reactions can occur in patients taking LUMRYZ.

During adult clinical trials in patients with narcolepsy administered LUMRYZ, 2% of 107 patients treated with LUMRYZ experienced a confusional state. During adult clinical trials in patients with narcolepsy administered immediate-release sodium oxybate, 3% of 781 patients treated with immediate-release sodium oxybate experienced confusion, with incidence generally increasing with dose.

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

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

Other psychiatric reactions reported in adult clinical trials in patients with narcolepsy administered LUMRYZ included irritability, emotional disorder, panic attack, agitation, delirium, and obsessive thoughts. Other neuropsychiatric reactions reported in adult clinical trials in patients with narcolepsy administered immediate-release sodium oxybate and in the postmarketing setting for immediate-release sodium oxybate include hallucinations, paranoia, psychosis, aggression, and agitation.

In a clinical trial in pediatric patients with narcolepsy administered immediate-release sodium oxybate, neuropsychiatric reactions, including acute psychosis, confusion, and anxiety were reported while taking immediate-release sodium oxybate.

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

5.7 Parasomnias

Parasomnias can occur in patients taking LUMRYZ.

Sleepwalking, defined as confused behavior occurring at night and at times associated with wandering, was reported in 3% of 107 adult patients with narcolepsy treated with LUMRYZ. No patients treated with LUMRYZ discontinued due to sleepwalking. Sleepwalking was reported in 6% of 781 patients with narcolepsy treated with immediate-release sodium oxybate in adult controlled and long-term open-label studies, with <1% of patients discontinuing due to sleepwalking. In controlled trials, rates of sleepwalking were similar for patients taking placebo

and patients taking immediate-release sodium oxybate. It is unclear if some or all of the reported sleepwalking episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Five instances of sleepwalking with potential injury or significant injury were reported during a clinical trial of immediate-release sodium oxybate in patients with narcolepsy.

Parasomnias, including sleepwalking, have been reported in a pediatric clinical trial and in postmarketing experience with immediate-release sodium oxybate. Therefore, episodes of sleepwalking should be fully evaluated, and appropriate interventions considered.

5.8 Use in Patients Sensitive to High Sodium Intake

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

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Adult Patients

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

Adverse Reactions Leading to Treatment Discontinuation

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

Most Common Adverse Reactions

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

Adverse Reactions Occurring at an Incidence of 2% or Greater

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

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

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

Dose-Response Information

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

Additional Adverse Reactions

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

Pediatric Patients (7 Years of Age and Older)

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

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

Adverse Reactions Leading to Treatment Discontinuation

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

Adverse Reactions in the Pediatric Clinical Trial

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

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

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

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

6.2 Postmarketing Experience

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

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

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

7 DRUG INTERACTIONS

7.1 Alcohol, Sedative Hypnotics, and CNS Depressants

LUMRYZ is contraindicated for use in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of LUMRYZ *[see Warnings and Precautions (5.1)]*. In addition to coadministration of LUMRYZ and alcohol being contraindicated because of respiratory depression, consumption of alcohol while taking LUMRYZ may also result in a more rapid release of the dose of sodium oxybate *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Clinical Considerations

Labor or Delivery

LUMRYZ has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate, newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine

contractions 20 minutes after injection. Placental transfer is rapid and gamma-hydroxybutyrate (GHB) has been detected in newborns at delivery after intravenous administration of GHB to mothers. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

Data

Animal Data

Oral administration of sodium oxybate to pregnant rats (150, 350, or 1,000 mg/kg/day) or rabbits (300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity. The highest doses tested in rats and rabbits were approximately 1 and 3 times, respectively, the maximum recommended human dose (MRHD) of 9 g per night on a body surface area (mg/m^2) basis.

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

LUMRYZ has not been studied in a pediatric clinical trial. The safety and effectiveness of LUMRYZ in the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy is supported by evidence from a double-blind, placebo-controlled, randomized-withdrawal study of immediate-release sodium oxybate *[see Adverse Reactions* (*6.1) and Clinical Studies (14.2)]*.

In the pediatric clinical trial with immediate-release sodium oxybate administration in pediatric patients 7 years of age and older with narcolepsy, serious adverse reactions of central sleep apnea and oxygen desaturation documented by polysomnography evaluation; depression; suicidal ideation; neuropsychiatric reactions including acute psychosis, confusion, and anxiety; and parasomnias, including sleepwalking, have been reported *[see Warnings and Precautions (5.4, 5.5, 5.6, 5.7) and Adverse Reactions (6.1)]*.

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

Juvenile Animal Toxicity Data

In a study in which sodium oxybate (0, 100, 300, or 900 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 21 through 90), mortality was

observed at the two highest doses tested. Deaths occurred during the first week of dosing and were associated with clinical signs (including decreased activity and respiratory rate) consistent with the pharmacological effects of the drug. Reduced body weight gain in males and females and delayed sexual maturation in males were observed at the highest dose tested. The no-effect dose for adverse effects in juvenile rats is associated with plasma exposures (AUC) less than that at the maximum recommended human dose (9 g/night).

8.5 Geriatric Use

Clinical studies of LUMRYZ or immediate-release sodium oxybate in patients with narcolepsy did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects. In controlled trials of immediate-release sodium oxybate in another population, 39 (5%) of 874 patients were 65 years or older. Discontinuations of treatment due to adverse reactions were increased in the elderly compared to younger adults (21% vs. 19%). Frequency of headaches was markedly increased in the elderly (39% vs. 19%). The most common adverse reactions were similar in both age categories. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Because of an increase in exposure to LUMRYZ, LUMRYZ should not be initiated in patients with hepatic impairment because appropriate dosage adjustments for initiation of LUMRYZ cannot be made with the available dosage strengths *[see Clinical Pharmacology (12.3)]*. Patients with hepatic impairment who have been titrated to a maintenance dosage of another oxybate product can be switched to LUMRYZ if the appropriate dosage strength is available.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

9.2 Abuse

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

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

drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).

Illicit GHB is abused in social settings primarily by young adults. Some of the doses estimated to be abused are in a similar dosage range to that used for treatment of patients with cataplexy. GHB has some commonalities with ethanol over a limited dose range, and some cross tolerance with ethanol has been reported as well. Cases of severe dependence and craving for GHB have been reported when the drug is taken around the clock. Patterns of abuse indicative of dependence include: 1) the use of increasingly large doses, 2) increased frequency of use, and 3) continued use despite adverse consequences.

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

9.3 Dependence

Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the recommended dosage range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required. The discontinuation effects of LUMRYZ have not been systematically evaluated in controlled clinical trials. In the clinical trial experience with immediate-release sodium oxybate in narcolepsy/cataplexy patients at recommended doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time.

Tolerance

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to LUMRYZ has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended LUMRYZ dosage regimen. Clinical studies of immediate-release sodium oxybate in the treatment of alcohol

withdrawal suggest a potential cross-tolerance with alcohol. The safety and effectiveness of LUMRYZ in the treatment of alcohol withdrawal have not been established.

10 OVERDOSAGE

10.1 Human Experience

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

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

10.2 Signs and Symptoms

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

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

10.3 Recommended Treatment of Overdose

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

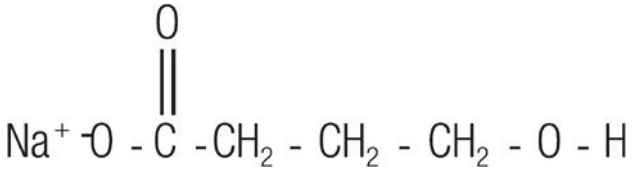
overdose, but have been reported in cases of acidosis associated with GHB ingestions of 125 g or greater; however, due to the rapid metabolism of sodium oxybate, these measures may not be warranted.

10.4 Poison Control Center

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

11 DESCRIPTION

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



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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Following oral administration of LUMRYZ, the plasma levels of GHB increased dose-proportionally for C_{max} and more than dose-proportionally for area under the plasma

concentration-time curve (AUC_{inf}) (respectively, 2-fold and 2.3-fold increases as total daily dose is doubled from 4.5 g to 9 g).

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

Absorption

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

Effect of Food

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

Effect of Ethanol

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

Effect of Water Temperature

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

Distribution

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

Elimination

Metabolism

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

Excretion

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

Specific Population

Geriatric Patients

There is limited experience with LUMRYZ in the elderly. Results from a pharmacokinetic study of immediate-release sodium oxybate (n=20) in another studied population indicate that the pharmacokinetic characteristics of GHB are consistent among younger (age 48 to 64 years) and older (age 65 to 75 years) adults.

Pediatric Patients

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

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

Male and Female Patients

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

Racial or Ethnic Groups

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

Patients with Renal Impairment

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

Patients with Hepatic Impairment

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

Drug Interaction Studies

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

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

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

- Diclofenac: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with diclofenac (50 mg/dose twice per day) showed no significant changes in systemic exposure to GHB. Co-administration did not appear to affect the pharmacokinetics of diclofenac.
- Ibuprofen: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with ibuprofen (800 mg/dose four times per day also dosed four hours apart) resulted in comparable systemic exposure to GHB, as shown by plasma C_{max} and AUC values. Co-administration did not affect the pharmacokinetics of ibuprofen.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

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

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

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

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

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

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

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

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

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

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

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

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

Dose	Treatment Group (N)	Change from Baseline*	Difference from Placebo [95% CI]	p-value
9 g (Week 13)	LUMRYZ (55)	-11.5	-6.7 [-9.32;-3.98]	<0.001
	Placebo (62)	-4.9	-	-

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

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

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

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

Patients entered the study either taking a stable dosage of immediate-release sodium oxybate or were immediate-release sodium oxybate-naïve. CNS stimulants were allowed at entry, and approximately 50% of patients continued taking a stable dose of stimulant throughout the stable-dose and double-blind periods. Immediate-release sodium oxybate-naïve patients were initiated and titrated based on body weight over a period of up to 10 weeks. The total nightly dose was administered in two divided doses, with the first dose given at nighttime and the second given 2.5 to 4 hours later. Once a stable dosage of immediate-release sodium oxybate had been achieved, these patients entered the 2-week stable-dose period; patients on a stable dosage of immediate-release sodium oxybate at study entry remained on this dosage for 3 weeks prior to randomization. Efficacy was established at dosages ranging from 3 g to 9 g of immediate-release sodium oxybate per night.

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

sleepiness. The overall change in narcolepsy condition was assessed by the Clinical Global Impression of Change for narcolepsy overall. Efficacy was assessed during or at the end of the 2-week double-blind treatment period, relative to the last 2 weeks or end of the stable-dose period (see Tables 6 and 7).

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

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

Treatment Group	Baseline[*,†]	Double-blind Treatment Period[‡,§]	Median Change from Baseline	Comparison to Placebo (p-value[¶])
Median Number of Cataplexy Attacks (attacks/week)				
Placebo (n=32)	4.7	21.3	12.7	-
Immediate-release Sodium Oxybate (n=31)	3.5	3.8	0.3	<0.0001
Median Epworth Sleepiness Scale (Child and Adolescent) Score				
Placebo (n=31[**])	11	12	3	-
Immediate-release Sodium Oxybate (n=30[**])	8	9	0	0.0004

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

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

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

Worsened, %[†]	CGIc Cataplexy Severity[*]	CGIc Narcolepsy Overall[*]

	Placebo (n=32)	Immediate-release Sodium Oxybate (n=29)[‡]	Placebo (n=32)	Immediate-release Sodium Oxybate (n=29)[‡]
Much worse or very much worse	66%	17%	59%	10%
p-value[§]	0.0001		<0.0001	

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

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

Table 8: LUMRYZ Carton Configurations

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

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

Table 9: LUMRYZ Starter Pack Contents

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

16.2 Storage

Keep out of reach of children.

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

Suspensions should be consumed within 30 minutes.

16.3 Handling and Disposal

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

17 PATIENT COUNSELING INFORMATION

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

Central Nervous System Depression

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

Abuse and Misuse

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

LUMRYZ REMS

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

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

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

Alcohol or Sedative Hypnotics

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

Sedation

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

Food Effects on LUMRYZ

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

Respiratory Depression and Sleep-Disordered Breathing

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

Depression and Suicidality

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

Other Behavioral or Psychiatric Adverse Reactions

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

Sleepwalking

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

Sodium Intake

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

Distributed By:

Avadel CNS Pharmaceuticals, LLC
Chesterfield, MO

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

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

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

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

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

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

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

What is LUMRYZ?

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

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

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

Do not take LUMRYZ if you or your child:

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

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

- have a history of drug abuse.
- have short periods of not breathing while sleeping (sleep apnea).
- have trouble breathing or have lung problems. You or your child may have a higher chance of having serious breathing problems when taking LUMRYZ.
- have or had depression or have tried to harm yourself. You or your child should be watched carefully for new symptoms of depression.
- have or had behavior or other psychiatric problems such as:
  - anxiety
  - seeing or hearing things that are not real (hallucinations)
  - feeling more suspicious (paranoia)

- being out of touch with reality (psychosis)
- acting aggressive
- agitation

- have liver problems.
- are on a salt-restricted diet. LUMRYZ contains a lot of sodium (salt) and may not be right for you or your child.
- have high blood pressure.
- have heart failure.
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if LUMRYZ can harm your unborn baby.
- are breastfeeding or plan to breastfeed. LUMRYZ passes into breast milk. You and your doctor should decide if you or your child will take LUMRYZ or breastfeed.

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

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

How should I take or give LUMRYZ?

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

What are the possible side effects of LUMRYZ?

LUMRYZ can cause serious side effects, including:

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

  People who already have breathing or lung problems have a higher chance of having breathing problems when they use LUMRYZ.
- **mental health problems, including:**
  - confusion
  - seeing or hearing things that are not real (hallucinations)
  - unusual or disturbing thoughts (abnormal thinking)
  - feeling anxious or upset
  - depression
  - thoughts of killing yourself or trying to kill yourself
  - increased tiredness
  - feelings of guilt or worthlessness
  - difficulty concentrating

  Call your doctor right away if you or your child has symptoms of mental health problems, or a change in weight or appetite.
- **sleepwalking.** Sleepwalking can cause injuries. Call your doctor if you start or your child starts sleepwalking. Your doctor should check you or your child.

The most common side effects of LUMRYZ in adults include:

- nausea
- dizziness
- bedwetting

- headache
- vomiting

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

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

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

How should I store LUMRYZ?

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

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

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

What are the ingredients in LUMRYZ?
Active ingredients: sodium oxybate
Inactive ingredients: carrageenan, hydrogenated vegetable oil, hydroxyethyl cellulose, magnesium stearate, malic acid, methacrylic acid copolymer, microcrystalline cellulose, povidone, xanthan gum.

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. Revised: 10/2024

INSTRUCTIONS FOR USE

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

Avadel™

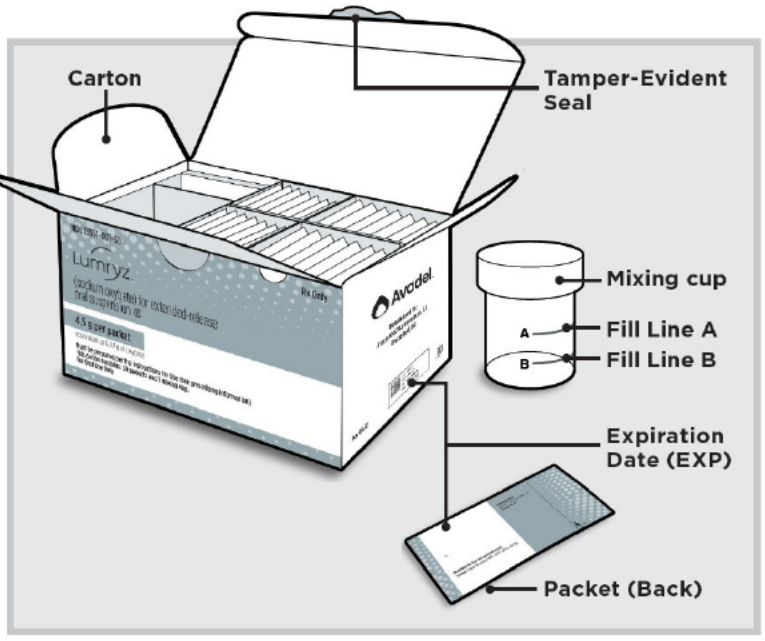
This Instructions for Use contains information on how to take LUMRYZ. Read this Instructions for Use before you (or your child) take LUMRYZ and each time you (or your child) get a refill. There may be new information.

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

Important information when taking LUMRYZ

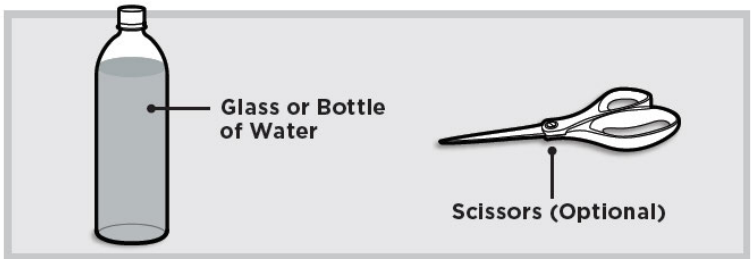
- Take (or give) 1 packet of LUMRYZ each day at bedtime.
- You will need to mix LUMRYZ with water before you take or give your child the dose.
- You (or your child) should avoid getting out of bed after taking LUMRYZ. Some people fall asleep within 5 minutes of taking LUMRYZ and most will fall asleep within 15 minutes. The time it takes to fall asleep might be different from night to night.
- Medicines that cause sleepiness should not be used while taking LUMRYZ.
- **Do not** use LUMRYZ with alcohol.
- **Do not** drive or operate heavy machinery within 6 hours of taking LUMRYZ. Those activities should not be done until you know how LUMRYZ affects you.
- Mix and take (or give) LUMRYZ within 30 minutes. If not taken or given within 30 minutes of mixing, throw it away (dispose of it) and prepare a new dose.

LUMRYZ carton and contents



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

Additional supplies needed



How should I store LUMRYZ?

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

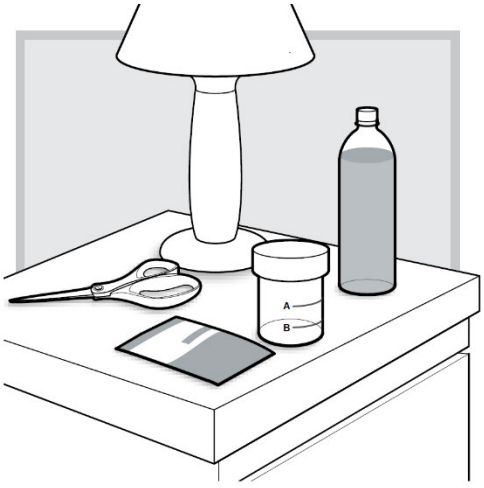
Before using LUMRYZ

- Before using a new LUMRYZ carton, check the tamper-evident seal on the carton lid to make sure it is not missing or broken.
- **Do not** use if the tamper-evident seal is missing or broken.
- Check the expiration date (EXP) on the LUMRYZ carton.
- **Do not** use LUMRYZ after the expiration date (EXP) on the label has passed.
- Open the LUMRYZ carton by tearing the tamper-evident seal with your hands or by using a pair of scissors.

Before each use

- Clean the mixing cup by rinsing it with water and letting it dry before each use.
- **Do not** use a measuring device other than the mixing cup that comes in your LUMRYZ carton to measure and take a dose of LUMRYZ.
- Check the expiration date (EXP) on the packet label. **Do not** use the LUMRYZ packet after the expiration date (EXP) has passed.

Important: Make sure to prepare LUMRYZ at bedside.



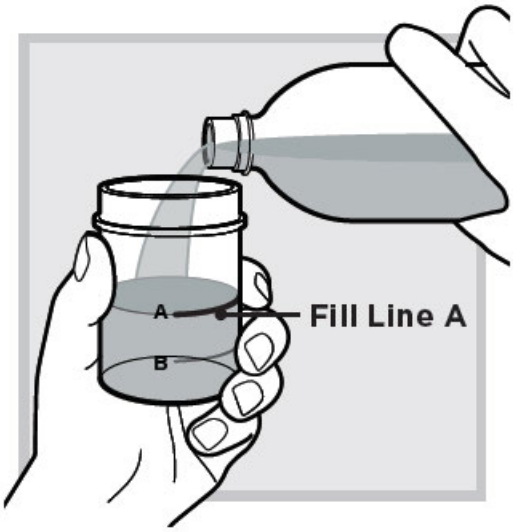
Gather the following supplies and place them on a flat surface at your (or your child's) bedside:

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

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

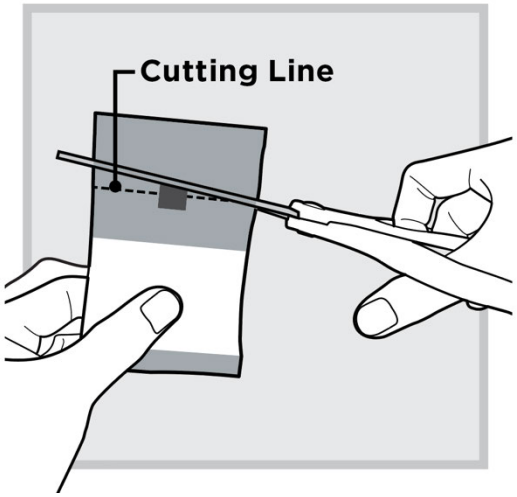
1.) At your (or your child's) bedside, open the mixing cup by twisting the cap to the left (counter-clockwise) to remove it.

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



3.) Open 1 packet:

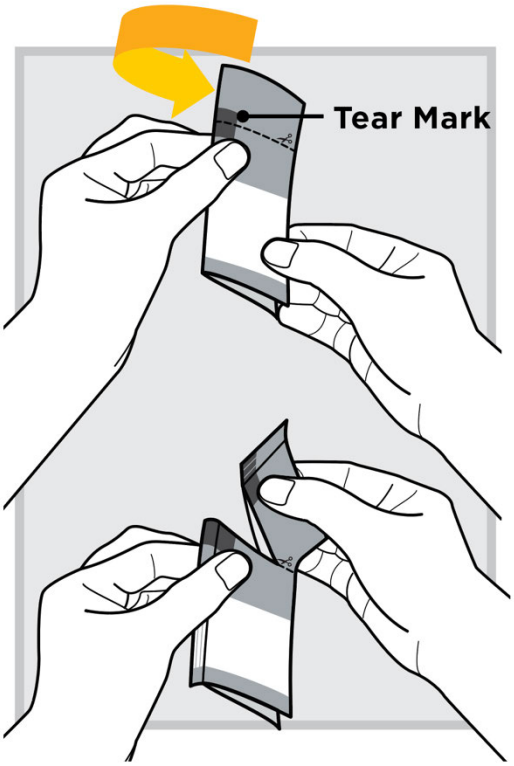
Use scissors to cut open the packet along the **Cutting Line**, located on the back of the packet.



-or-

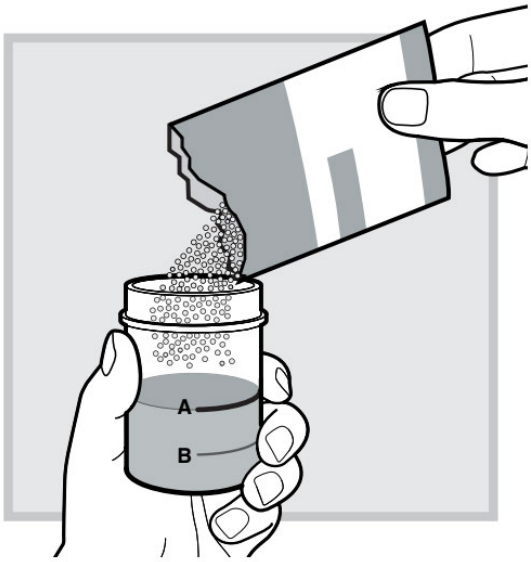
Fold the packet in half at the gray **Tear Mark** located on the back of the packet.

Tear the packet open with your hands.

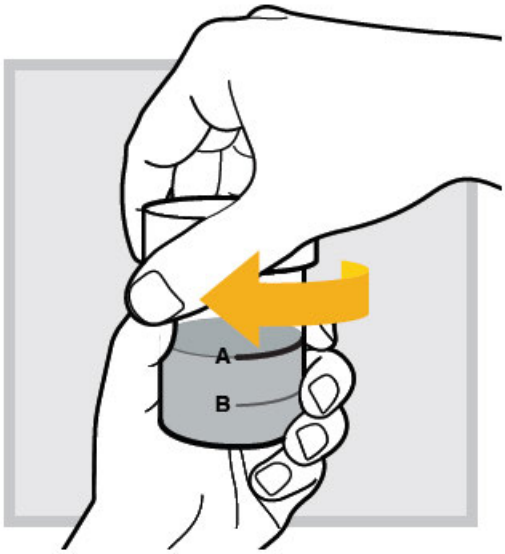


4.) Pour the entire content from the packet into the water-filled mixing cup.

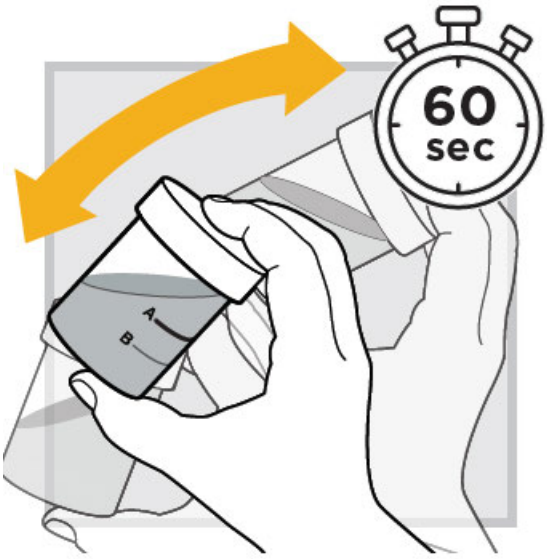
Make sure there is no powder left in the packet.



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

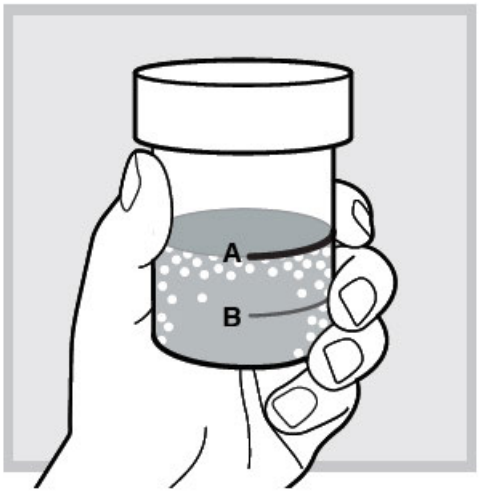


6.) Mix the water and powder solution by shaking the closed mixing cup well for at least **60 seconds (1 minute)**.



7.) Make sure the solution is mixed thoroughly.

The mixed solution will appear slightly milky with some lumps.



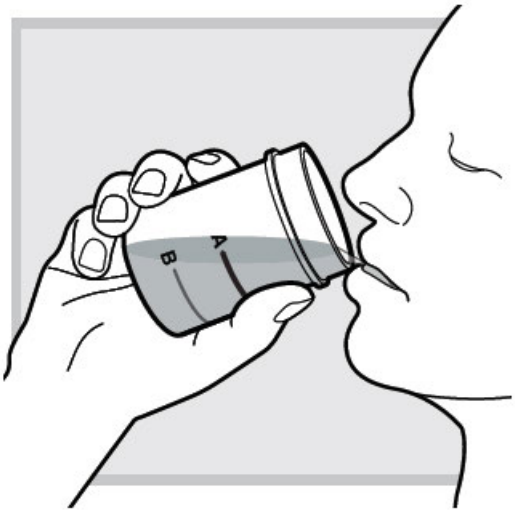
The mixing cup cap is not child resistant. If the mixed solution is not drank immediately, then do not remove the cap, and keep out of reach of children.

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

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

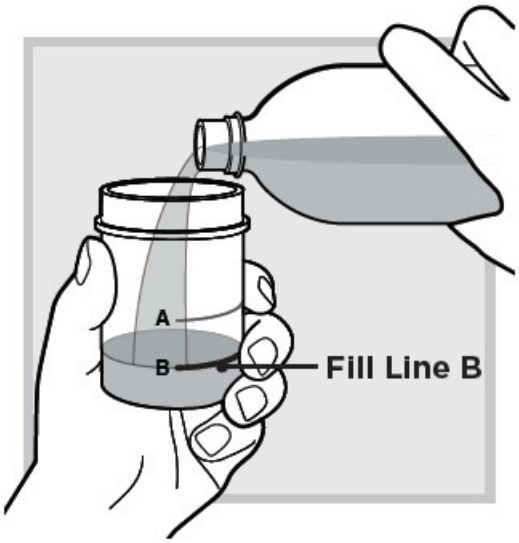
9.) While sitting in bed drink (or have your child drink) the mixed solution within **30 minutes** of mixing.

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

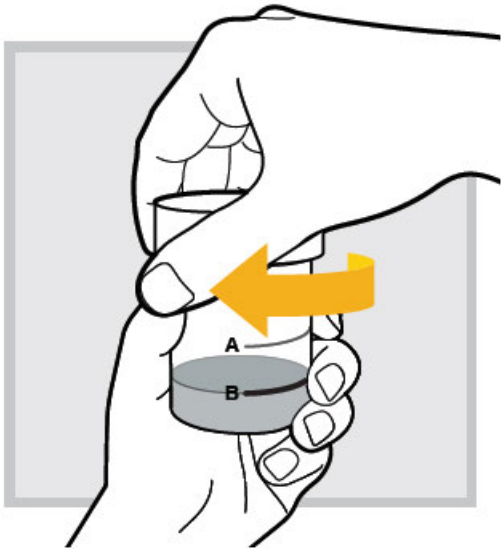


10.) Immediately refill the mixing cup with water up to **Fill Line B** (lower line) to mix in any medicine left in the mixing cup.

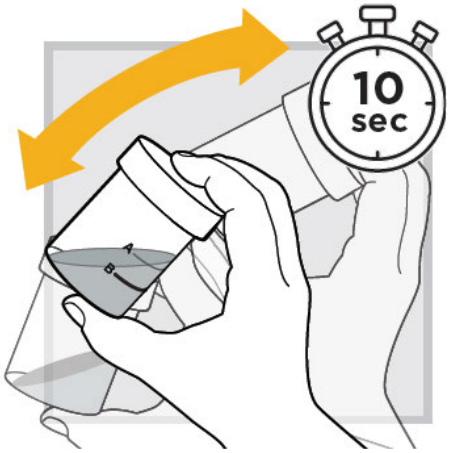
Do not open another packet of LUMRYZ. Take (or give) only 1 packet each day at bedtime.



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



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



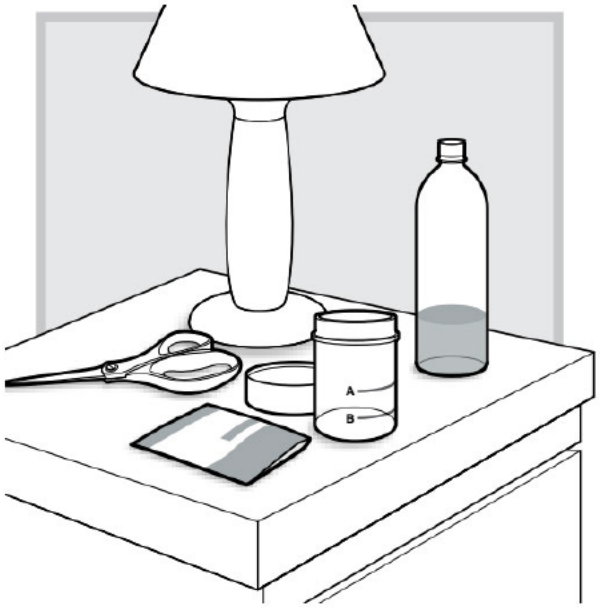
13.) Open the mixing cup by twisting the cap to the left (counter-clockwise) and remove it.

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

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

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

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

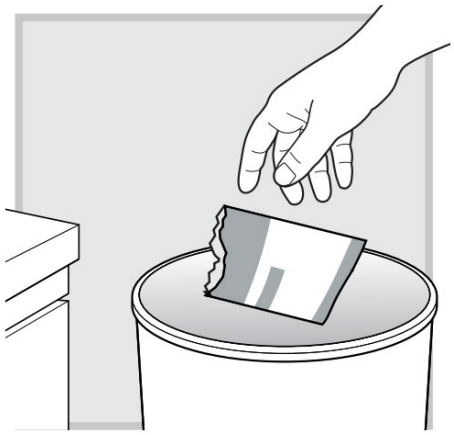


Continue to Step 16

How do I throw away (dispose of) LUMRYZ?

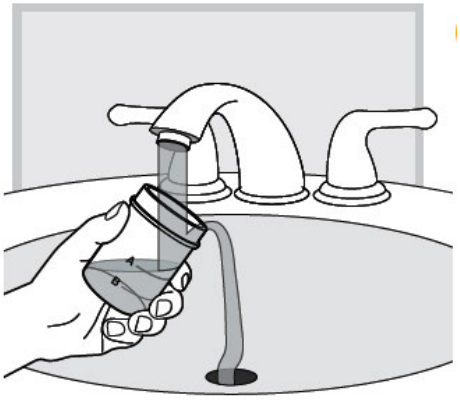
16.) The next day, place the empty LUMRYZ packet in the trash.

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



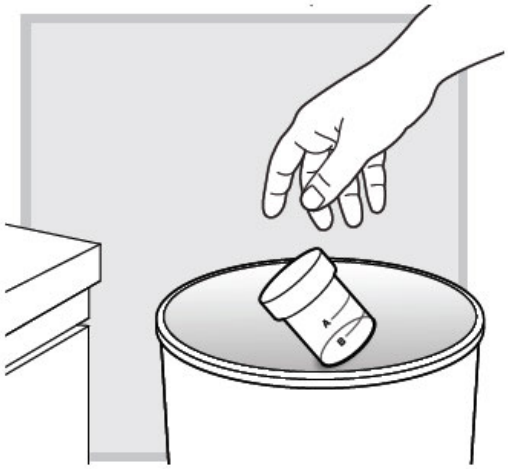
17.) Empty any unused LUMRYZ down the sink drain the next day.

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



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

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



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

You can also contact:
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: 10/2024

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s006

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: 10/2024

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 or the Pediatric Patients and their Caregivers 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 or the Pediatric Patients and their Caregivers 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 or the Pediatric Patients and their Caregivers 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 or the Pediatric Patients and their Caregivers 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 or the Pediatric Patients and their Caregivers 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 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 pediatric patients are able to change caregivers provided that the new caregiver has been counseled by a certified pharmacy on the serious risks and safe use of the drug and acknowledges that he/she had any questions about LUMRYZ answered before drug product is dispensed and shipped.

12. Ensure patients are able to change certified prescribers.

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

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

15. 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.

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

17. 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.

18. 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.

19. 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.

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

21. 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.

22. 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.

23. 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.

24. 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.

25. 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.

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

27. 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.

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

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

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

30. 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.

31. 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.

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

33. 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.

34. 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.

35. 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.

36. 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.

37. 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
6. Pediatric Patients and their Caregivers Brochure

Pharmacy:

7. Certified Pharmacy Training Program
8. Pharmacy Staff Knowledge Assessment
9. Pharmacist Knowledge Assessment

Patient Care Forms:

10. Prescription Form
11. Patient Counseling Checklist

Other Materials:

12. Risk Management Report
13. 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 patients 7 years of age and older with narcolepsy.
  - Excessive daytime sleepiness (EDS) in patients 7 years of age and older 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** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients.
- 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 (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.

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

Avadel

Reference ID: 5463592

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 and/or caregiver 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:
*Caregiver First Name (required for pediatric patient):	*Caregiver Last Name (required for pediatric patient):		*Caregiver Relationship to Patient (required for pediatric patient):
Caregiver Phone: (if different from above)	* Caregiver Email (required for pediatric patient):		

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:

A parent or caregiver of a patient under the age 18 must also read and understand each item before signing this enrollment form.

Before starting treatment, I must:

- Review the **Patient Brochure** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients
- 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** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients
- Enroll in the REMS by completing the **Patient Enrollment Form** with my prescriber
- Complete the **Patient Counseling Checklist** with the pharmacist

During treatment, I will:

- Follow the safe use instructions explained to me by my doctor/prescriber
- Tell my pharmacist about any changes in the medicines I am/the patient is taking and any changes in my medical history so I/the patient can be monitored for problems with the medicines I'm taking/the patient is 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/Caregiver Signature: _____ *Date

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

PRESCRIBER:

By signing below, I acknowledge that:

- I have counseled the patient and/or caregiver about the serious risks associated with the use of LUMRYZ and the safe use conditions as described in the **Patient Brochure** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients
- I have provided the patient and/or caregiver with the **Patient Brochure** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients (optional)

_____ *Prescriber Signature _____ *Date

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** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients 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.

LUMRYZ™ REMS

PRESCRIBER BROCHURE

Lumryz™

(sodium oxybate) for extended-release oral suspension Ⓒ

Reference ID: 5463592

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 and pediatric 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.
- **Pediatric Patients and their Caregivers Brochure**—answers important questions for caregivers of pediatric patients and pediatric patients on 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 patients 7 years of age and older with narcolepsy**
- **Excessive daytime sleepiness (EDS) in patients 7 years of age and older 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 or caregivers 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 and/or caregivers should be instructed to call the patient's healthcare provider if the patient experiences 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

- Adult Patients: 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.
- Pediatric Patients (7 years of age and older): In the pediatric clinical trial with immediate-release sodium oxybate, the most common adverse reactions were nausea, enuresis, vomiting, headache, weight decreased, decreased appetite, dizziness, and sleepwalking.

Adverse Reactions Leading to Treatment Discontinuation

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

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

Reference ID: 5463592

TABLE OF CONTENTS

Prescribing Information is also included.

Reference ID: 5463592

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 patients 7 years of age and older with narcolepsy
    - Treatment of excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy
  - You have read and understand the Prescribing Information and this **Prescriber Brochure**

SCREEN

- You agree to assess the patient's health status to 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 and/or caregivers for pediatric patients on:
  - The serious risks associated with LUMRYZ
  - Contraindications (alcohol and sedative hypnotics)
  - Risks of concomitant use of LUMRYZ with alcohol and/or certain other 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 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: 5463592

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 and/or caregiver for pediatric patients about the serious risks associated with the use of LUMRYZ and the safe use conditions as described in the **Patient Brochure** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients.
  - Obtain a mandatory patient or caregiver 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 potentially interacting agents
- History of depression or suicidality

Verify that you have counseled the patient and/or caregiver for pediatric patients 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 and/or caregiver counseling process and will ask the patient and/or caregiver 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 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 and/or caregiver that his/her certified pharmacy will send him/her a copy of the **Patient Brochure** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients with the patient's 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 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.

Responsibilities of the LUMRYZ REMS 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 and/or caregiver to:
  - Verify the patient will receive a copy of the **Patient Brochure** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients
  - Counsel the patient and/or caregiver 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 and/or caregiver counseling
  - Review the patient's comorbid medical conditions
  - Ask if the patient and/or caregiver has any questions about LUMRYZ and answer the questions and/or refer the patient and/or caregiver back to the prescriber, as appropriate
  - Provide 24/7 toll-free telephone access to pharmacist support for prescribers, office staff, and patients and/or caregivers 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 and/or caregivers 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.

Guidelines for Dosing and Titrating LUMRYZ

DOSING LUMRYZ

The information presented is for adult patients with narcolepsy. Please see page 13 for additional important information on dosing for pediatric patients (7 years of age and older) with narcolepsy.

- 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

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

  - 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.

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

Reference ID: 5463592

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 and/or caregivers 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

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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

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

In the pediatric clinical trial with immediate-release sodium oxybate administration in patients with narcolepsy, serious adverse reactions of central sleep apnea and oxygen desaturation documented by polysomnography evaluation; depression; suicidal ideation; neuropsychiatric reactions including acute psychosis, confusion, and anxiety; and parasomnias, including sleepwalking, have been reported. The safety profile in pediatric patients with LUMRYZ is expected to be similar to that of adult patients treated with LUMRYZ and to that of pediatric patients treated with immediate-release sodium oxybate.

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

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 and/or caregivers.
For assistance, call 1-877-453-1029.

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Patient Counseling Information

Prior to initiating therapy, counsel each patient and/or caregiver for pediatric patients 7 years of age or older regarding the serious risks and safe use, handling, and storage of LUMRYZ using the **Patient Brochure** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients.

- Inform patients and/or caregivers 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 and/or caregivers understand the serious risks and safe use conditions of LUMRYZ and that you have answered any questions the patient and/or caregiver has about LUMRYZ by having the patient and/or caregiver 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 and/or caregiver with the following guidance:

ALCOHOL OR SEDATIVE HYPNOTICS

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

SEDATION

Inform patients and/or caregivers that the patient is 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 and/or caregivers that patients should remain in bed following ingestion of LUMRYZ.

FOOD EFFECT

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

RESPIRATORY DEPRESSION

Inform patients and/or caregivers 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 and/or caregivers that, until they are reasonably certain LUMRYZ does not affect patients 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 hazardous machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking LUMRYZ.

SUICIDALITY

Instruct patients and/or caregivers 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 and/or caregivers that LUMRYZ has been associated with sleepwalking and other behaviors during sleep, and to contact the patient's healthcare provider if this occurs.

SODIUM INTAKE

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

SAFE USE, HANDLING, STORAGE, AND DISPOSAL

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

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Pediatric Patient Supplement

This pediatric patient supplement provides information specifically for pediatric patients and/or their caregivers about the LUMRYZ REMS, including important prescribing information, educational and counseling requirements, and materials necessary for REMS enrollment and prescribing LUMRYZ. **If you are prescribing LUMRYZ for a pediatric patient, please read the Prescriber Brochure in its entirety, including this Pediatric Patient Supplement.**

PRESCRIBING LUMRYZ FOR PEDIATRIC PATIENTS

In addition to the procedure for writing and dispensing prescriptions for LUMRYZ described above, prescribing LUMRYZ to pediatric patients requires the following:

- Verify that you have counseled the caregiver on the serious risks and safe use conditions as described in the **Pediatric Patients and their Caregivers Brochure** and encourage him/her to read the LUMRYZ Medication Guide.

RESPONSIBILITIES OF THE LUMRYZ REMS CERTIFIED PHARMACY FOR PEDIATRIC PATIENTS

In addition to the responsibilities described above, for pediatric patients a LUMRYZ certified pharmacy will:

- Counsel the caregiver of each pediatric patient on the serious risks and safe use of LUMRYZ.

Each pediatric patient receiving LUMRYZ must have a caregiver

GUIDELINES FOR DOSING AND TITRATING LUMRYZ FOR PEDIATRIC PATIENTS

- The recommended starting dose, titration regimen, and maximum total nightly dosage are based on patient weight.
  - Pediatric Patients 7 years and Older Weighing at least 45 kg
    - The recommended starting dose for pediatric patients 7 years and older weighing at least 45 kg is 4.5 g once per night administered orally
    - Increase the dosage by 1.5 g per night at weekly intervals to the maximum recommended dosage of 9 g once per night orally
    - The dosage may be gradually titrated based on efficacy and tolerability
    - Pediatric patients 7 years and older weighing at least 45 kg 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)
  - Pediatric Patients 7 years and Older Weighing Less than 45 kg
    - Because the recommended starting dosage in pediatric patients 7 years and older weighing less than 45 kg cannot be achieved with the available strengths of LUMRYZ, use another sodium oxybate product to initiate treatment
      - Refer to the Prescribing Information of other sodium oxybate products for the recommended dosage for those products
    - The maximum recommended dosage for patients 7 years and older weighing 20 kg to < 30 kg is 6 g once per night orally, and the maximum recommended dosage for patients 7 years and older weighing 30 kg to <45 kg is 7.5 g once per night orally
    - There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg
    - Pediatric patients 7 years and older weighing less than 45 kg who have been titrated to a maintenance dosage of an immediate-release sodium oxybate product can be switched to LUMRYZ if the appropriate dosage strength is available

Reference ID: 5463592

Pediatric Patient Supplement

PEDIATRIC PATIENT DOSING INFORMATION

- Inform patient and/or caregivers that they should ensure that all LUMRYZ doses are kept in a safe place until given
- Inform patient and/or caregivers that each packet of LUMRYZ contains LUMRYZ powder, which will need to be mixed with water for once-nightly dosing
- Patient and/or caregivers should prepare the dose of LUMRYZ prior to bedtime
    - Instruct patient and/or caregivers 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
    - Patient and/or caregivers 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

Lumryz.

(sodium oxybate) for extended-release oral suspension

Avadel

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

MED-US-LUM-2100004
10/2024

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: 5463592

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 patients 7 years of age and older 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 in people 7 years of age or older to treat the following symptoms of narcolepsy:

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

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), 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.

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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.

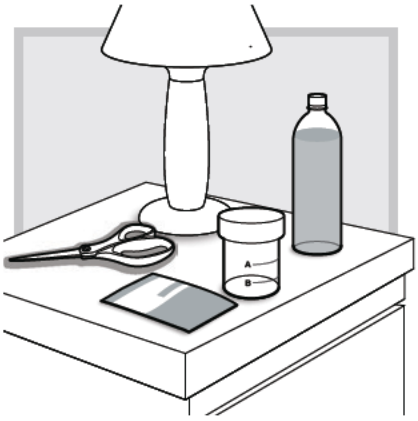
Open the LUMRYZ carton by tearing the tamper-evident seal with your hands or by using a pair of scissors.

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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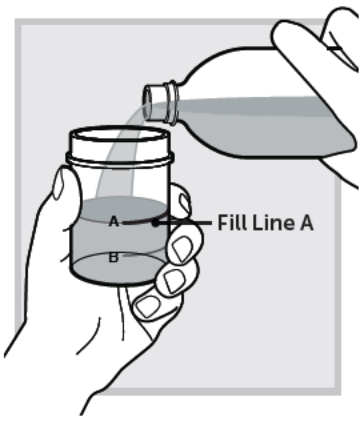
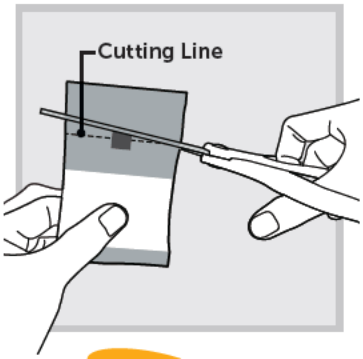
HOW DO I TAKE MY LUMRYZ?

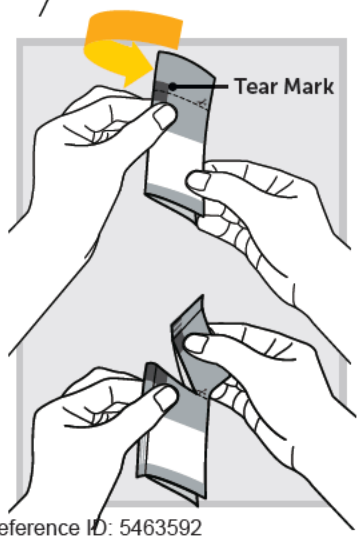
MIX THE LUMRYZ SOLUTION AT YOUR BEDSIDE

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.



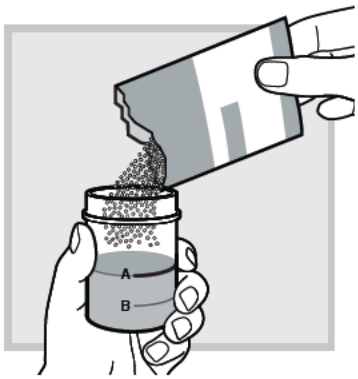


3. Open 1 packet:

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

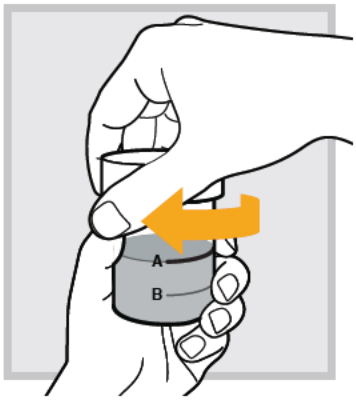
-or-

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

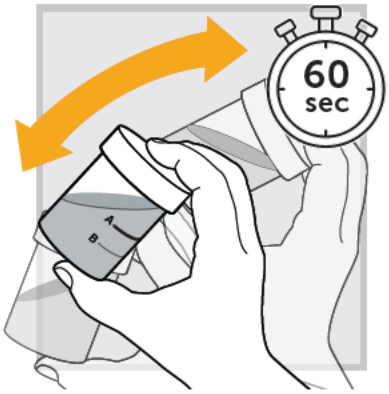


4. Pour the entire content from the packet into the water-filled mixing cup.

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.

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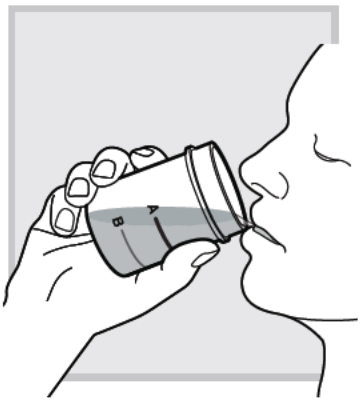
HOW DO I TAKE MY LUMRYZ?

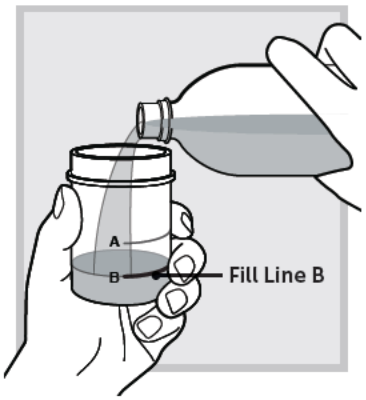
TAKE THE LUMRYZ SOLUTION AT YOUR BEDSIDE

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



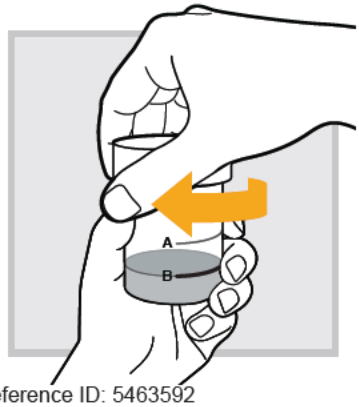
9 While sitting in bed drink the mixed solution within **30 minutes** of mixing.

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

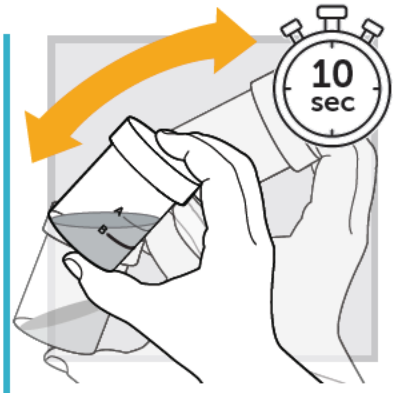


10 Immediately refill your mixing cup with water up to **Fill Line B** (lower line) to mix in any medicine left in the mixing cup.

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.

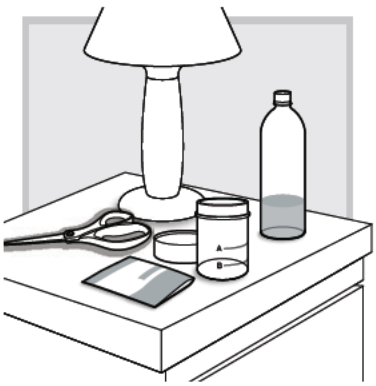


12 Shake well again for **10 seconds.**

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.

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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 in adults 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.

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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?

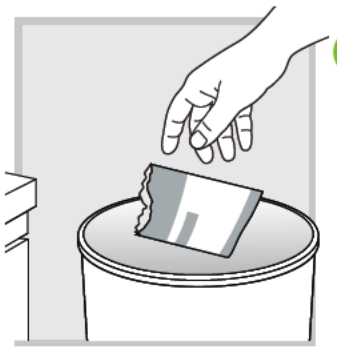
When you first start taking LUMRYZ, you may need to talk to your healthcare provider often until he/she determines the best dose for you. It is possible your dose may need to be adjusted. Your healthcare provider will evaluate you within the first 3 months of taking LUMRYZ and may reevaluate you every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

STORAGE AND SAFETY TIPS AT HOME

HOW DO I STORE LUMRYZ?

- Always store LUMRYZ in its original packet prior to mixing with water.
- 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?



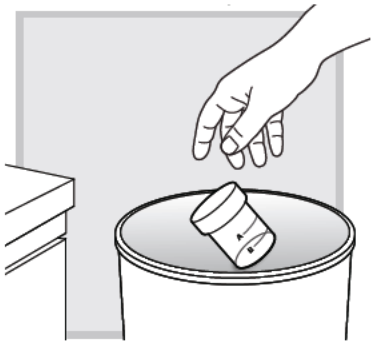
1. The next day, place the empty LUMRYZ packet in the trash.

   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.

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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

Reference ID: 5463592

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
10/2024

LUMRYZ™ REMS

Pediatric Patients and their Caregivers 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

Learn more scan to enroll.

Reference ID: 5463592

Lumryz.

(sodium oxybate) for extended-release oral suspension C

Dear Caregiver,

You are receiving these materials because your child's healthcare provider has prescribed LUMRYZ (sodium oxybate) for extended-release oral suspension for your child. LUMRYZ is a medicine used to treat excessive daytime sleepiness and/or cataplexy in patients 7 years of age and older 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. Each pediatric patient must have a caregiver who is counseled on the serious risks and safe use of LUMRYZ. This **Pediatric Patients and their Caregivers Brochure** contains information you need to know about LUMRYZ and will help your child to use LUMRYZ correctly. Read this **Pediatric Patients and their Caregivers Brochure** before your child starts taking LUMRYZ.

After your child's healthcare provider sends your child's enrollment form to the LUMRYZ REMS and your child's first prescription for LUMRYZ to the certified pharmacy, you will receive a call from the certified pharmacy to tell you how to get your child 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 child's insurance information with you. Before you can receive your child's first shipment of LUMRYZ, a pharmacist at a certified pharmacy must confirm whether you have read and understood this **Pediatric Patients and their Caregivers Brochure**, ask you about your child's medical history and other medications your child may be taking, and give you advice on how to prepare and give LUMRYZ to your child and how to store it safely. **You must take this call before you can get your child's LUMRYZ.**

Please call your child's 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 child's 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 in people 7 years of age or older to treat the following symptoms of narcolepsy:

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

IMPORTANT INFORMATION ABOUT LUMRYZ INCLUDES THE FOLLOWING:

- When taking LUMRYZ, your child **should not** drink alcohol or take other medicines that slow his or her breathing or mental activity or make him or her sleepy. Your child 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 child's healthcare provider if he or she has 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.
- Give 1 packet of LUMRYZ each day at bedtime.
- Mix and give LUMRYZ within 30 minutes. If not taken within 30 minutes of mixing, throw it away (dispose of it) and prepare a new dose.
- Your child should avoid getting out of their bed after taking LUMRYZ. Some people fall asleep within 5 minutes of taking LUMRYZ and most will fall asleep within 15 minutes. The time it takes to fall asleep might be different from night to night.
- **Your child should not** drive a car, use heavy machinery, fly an airplane, or do anything dangerous or that requires him or her to be alert for at least 6 hours after taking LUMRYZ. When your child first starts taking LUMRYZ, be careful until you know how LUMRYZ affects your child.
- Keep LUMRYZ out of the reach of children and pets. Get emergency medical help right away if a child who has not been prescribed LUMRYZ ingests it.
- Report all side effects to your child's healthcare provider.

WHAT WILL YOU FIND IN THIS BROCHURE?

This brochure answers important questions about how to get your child's 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. Your child is enrolled in the REMS when your child's healthcare provider sends the **Patient Enrollment Form** you signed to the LUMRYZ REMS. Your child's healthcare provider can then send your child's 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 caregiver, your responsibility is to discuss the safe use of LUMRYZ with your child's healthcare provider and to read this **Pediatric Patients and their Caregivers Brochure** before receiving your child's first LUMRYZ prescription. Be sure to let your child's healthcare provider know if your child is taking other medications or if your child has any conditions that might affect their breathing.

DO I HAVE TO ENROLL IN THIS REMS?

Yes. You and your child's 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 child's healthcare provider on the serious risks and safe use of LUMRYZ and that you were able to ask your child's 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 child's medication, please contact the certified pharmacy or your child's prescriber.

FILLING YOUR CHILD'S LUMRYZ PRESCRIPTION

HOW IS MY CHILD'S PRESCRIPTION FILLED?

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

WHAT DOES A CERTIFIED PHARMACY DO?

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

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

Your child's certified pharmacy will always ask you where and when you would like your child's 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 child's LUMRYZ.

WHAT WILL I GET WITH MY CHILD'S 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), a LUMRYZ-specific mixing cup for mixing your child's 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 CHILD'S LUMRYZ REFILLS?

The certified pharmacy will contact you when it is close to your child's LUMRYZ refill time. You may also call the certified pharmacy to schedule refills.

CAN MY LOCAL PHARMACY PROVIDE LUMRYZ?

No. You can get your child's LUMRYZ only from a LUMRYZ REMS certified pharmacy. You may be able to have your child's 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. The certified pharmacy will work with you on the options available.

INSURANCE COVERAGE

WILL INSURANCE PAY FOR MY CHILD'S LUMRYZ?

In most cases, yes. A staff member from the certified pharmacy will call and work with your child's insurance company to help your child get coverage for LUMRYZ. In the unlikely event your child's 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 CHILD'S INSURANCE?

An experienced pharmacy staff member will:

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

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

WHAT SHOULD I DO WHEN I GET MY CHILD'S 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.

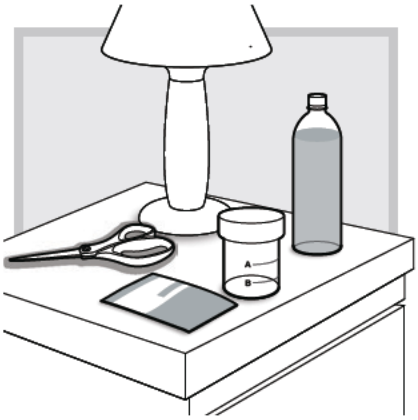
Open the LUMRYZ carton by tearing the tamper-evident seal with your hands or by using a pair of scissors.

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 child's 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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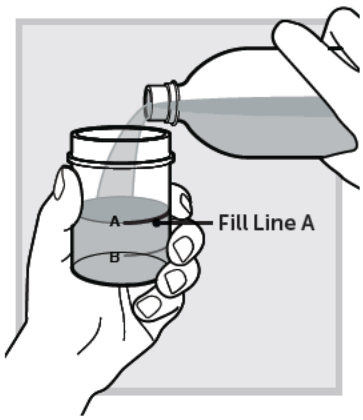
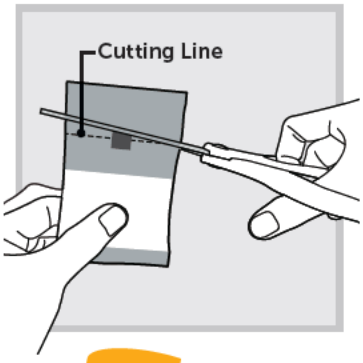
HOW DOES MY CHILD TAKE THEIR LUMRYZ?

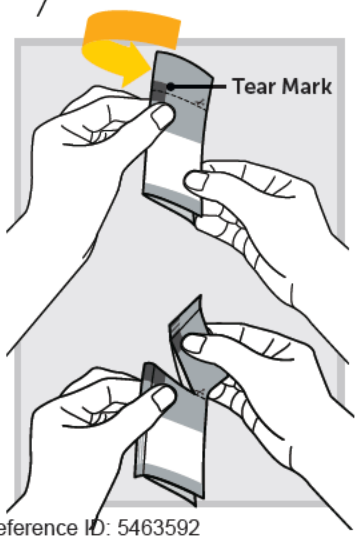
MIX THE LUMRYZ SOLUTION AT YOUR CHILD'S BEDSIDE

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



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



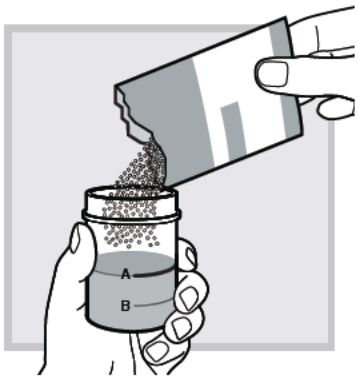


3 Open 1 packet:

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

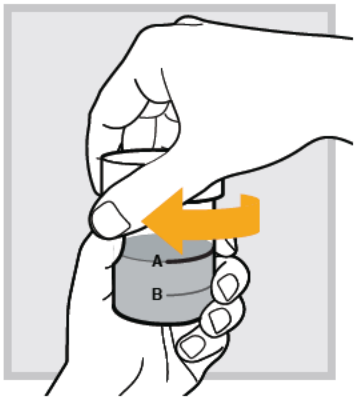
-or-

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

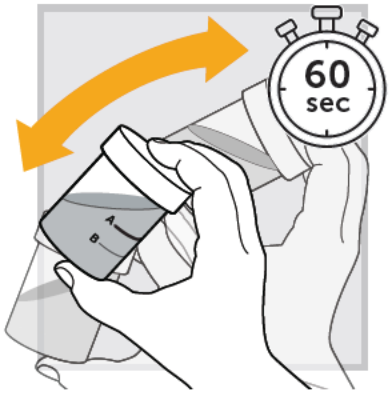


4 Pour the entire content from the packet into the water-filled mixing cup.

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.

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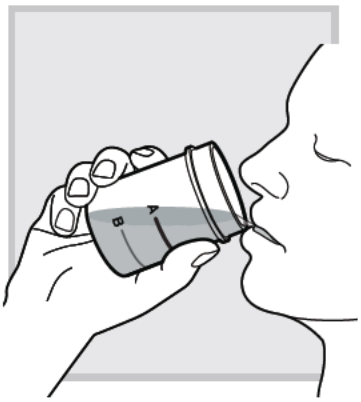
HOW DOES MY CHILD TAKE THEIR LUMRYZ?

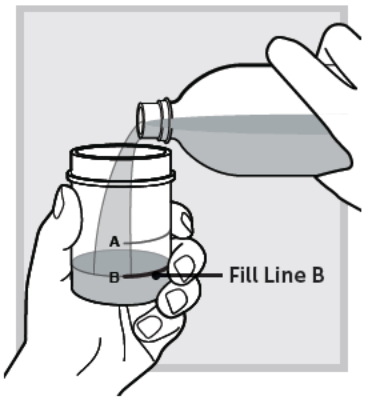
GIVE THE LUMRYZ SOLUTION AT YOUR CHILD'S BEDSIDE

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



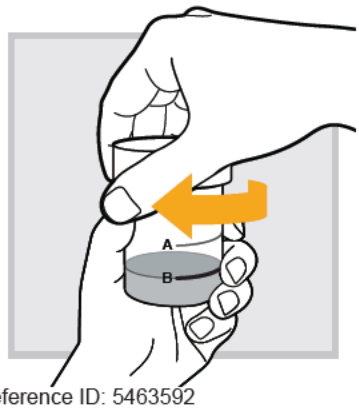
9 While sitting in bed have your child drink the mixed solution within **30 minutes** of mixing.

Make sure your child drinks all the mixed solution in the mixing cup.

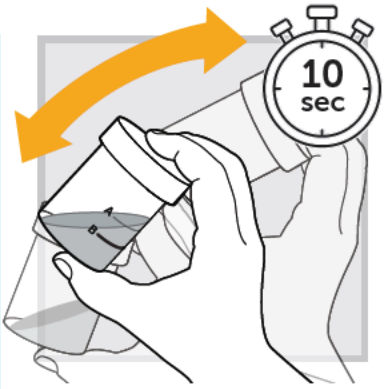


10 Immediately refill your mixing cup with water up to **Fill Line B** (lower line) to mix in any medicine left in the mixing cup.

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



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

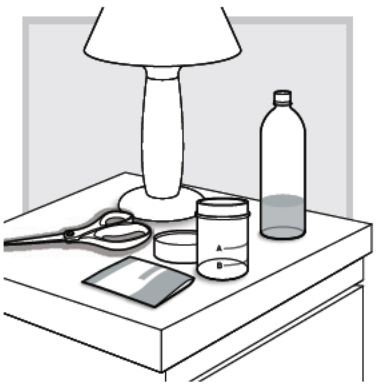


12 Shake well again for **10 seconds.**

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

14 Have your child drink the mixed solution immediately after mixing.

Make sure your child drinks all the mixed solution in the mixing cup.



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

Avoid having your child get out of bed after taking LUMRYZ.

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WHAT SHOULD I DO IF MY CHILD MISSES A DOSE?

It is very important to give only one single dose of LUMRYZ each day at bedtime, as prescribed. If your child misses a dose, skip that dose.

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

Empty any unused LUMRYZ solution that you prepared but did not give your child 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 CHILD'S SYMPTOMS?

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

Tell your child's healthcare provider if your child doesn't feel any improvements while taking LUMRYZ. LUMRYZ may not be right for your child.

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 your child has any of these side effects, call your child's healthcare provider right away.

The most common side effects with LUMRYZ in children are nausea, bedwetting, throwing up, headache, weight decreased, decreased appetite, dizziness, and sleepwalking.

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

ARE THERE ANY PRECAUTIONS MY CHILD SHOULD TAKE WHILE ON LUMRYZ?

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

Tell your child's healthcare provider and pharmacist about any other medicines your child is taking, including prescription and non-prescription medicines, vitamins, and supplements.

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It is also important to tell other healthcare providers, including pharmacists, that your child is taking LUMRYZ before your child starts or changes any medications.

HOW OFTEN SHOULD MY CHILD'S HEALTHCARE PROVIDER CHECK THEIR PROGRESS WITH LUMRYZ?

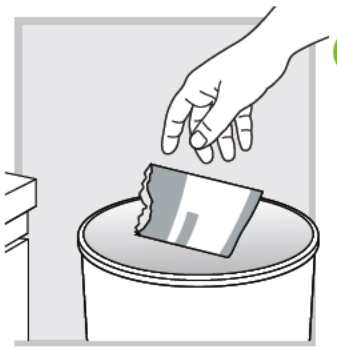
When your child first starts taking LUMRYZ, you may need to talk to your child's healthcare provider often until he/she determines the best dose for your child. It is possible your child's dose may need to be adjusted. Your child's healthcare provider will evaluate your child within the first 3 months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

STORAGE AND SAFETY TIPS AT HOME

HOW DO I STORE LUMRYZ?

- Always store LUMRYZ in its original packet prior to mixing with water.
- 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 not prescribed LUMRYZ ingests it, get emergency medical help (call 911) right away.

HOW DO I THROW AWAY (DISPOSE OF) LUMRYZ?



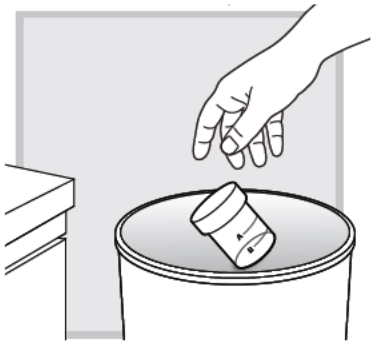
1. The next day, place the empty LUMRYZ packet in the trash.

   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 child's LUMRYZ carton



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

Reference ID: 5463592

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

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

Reference ID: 5463592

These pages are intended to help teach your child what they need to know about taking LUMRYZ.

WHAT KEY POINTS SHOULD MY CHILD KNOW ABOUT TAKING LUMRYZ?

Prepare For Bed

- **Finish your regular bedtime routine before you get in bed and drink your LUMRYZ**

Reference ID: 5463592

Stay In Bed

- Drink your LUMRYZ while sitting in bed. Lie down as soon as you are done drinking your LUMRYZ
- Do not get out of bed after taking LUMRYZ. Ask an adult if you want to get out of bed
- Falling asleep may happen quickly or take some time after taking LUMRYZ

Reference ID: 5463592

Be Careful Getting Up

- You should be careful getting up in the morning
- If you still feel sleepy in the morning, ask for help

Reference ID: 5463592

Things To Remember

- Don’t let anyone else take your LUMRYZ. This is just yours!
- Only drink LUMRYZ from your LUMRYZ cup
- If something feels different, tell an adult

Reference ID: 5463592

HOW CAN I HELP MY CHILD HANDLE LUMRYZ IN A SAFE MANNER?

It is essential for your child to be actively involved in safe practices when using their LUMRYZ. This is particularly important for teenagers and those heading off to college. This brochure assists you in talking with your child about responsible LUMRYZ usage.

Before your child leaves home, such as for college, it is important to consult their healthcare provider and the certified pharmacy for additional guidance on ensuring safe use, handling, and storage. To aid in this transition, ensure your child receives counseling from their healthcare provider or a pharmacist regarding the serious risks and safe use of LUMRYZ.

Encourage your child to read this brochure and to ask their healthcare provider any questions they may have.

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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.

Reference ID: 5463592

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-2300057
10/2024

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: 5463592

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 patients 7 years of age and older with narcolepsy
- Treatment of excessive daytime sleepiness (EDS) in patients 7 years of age and older 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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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** and successfully complete the **Pharmacy Staff Knowledge Assessment**. Training must be completed annually.

Lumryz™

(sodium oxybate) for extended-release oral suspension Ⓒ

Reference ID: 5463592

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 patients 7 years of age and older with narcolepsy
  - Treatment of excessive daytime sleepiness (EDS) in patients 7 years of age and older 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** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients

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 III 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.

- <u>Central Nervous System Depression</u>

  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.
- <u>Abuse and Misuse</u>

  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: 5463592

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.

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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 patients and/or caregivers for pediatric patients must 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/or caregiver for pediatric patients 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
  - A pharmacist must counsel the patient and/or caregiver for pediatric patients 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.
- 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.

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- ◊ 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 , document and submit the valid reason for overlapping prescription through the RDA process online at www.LUMRYZREMS.com or by calling the LUMRYZ REMS at 1-877-453-1029.

- 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** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients.
- 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 and/or caregiver 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 AND CAREGIVER EDUCATION

Patients and caregivers in the LUMRYZ REMS have access to ongoing education during LUMRYZ treatment 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: 5463592

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 and/or caregivers who report a change in the patient's medication or medical history.
- Detailed monitoring including completion of a **RMR**, as needed.
- Follow-up interactions with patients and/or caregivers 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/or caregivers for pediatric 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 AND/OR CAREGIVER 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 a new caregiver of an already enrolled pediatric patient, confirmation should be obtained, that he or she has been counseled on the serious risks and safe use of LUMRYZ and that he or she has asked any questions he or she has about LUMRYZ.
- For prescription renewals and refills, if the patient and/or caregiver has indicated a change in the patient's 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 and/or caregiver 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 and/or caregiver if the patient 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 and/or caregiver 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 and/or caregiver what other medical conditions the patient has.
    - If the patient and/or caregiver indicates that the patient has a certain medical condition listed on the **Patient Counseling Checklist**, the pharmacist counsels the patient and/or caregiver 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 and/or caregiver for pediatric patients 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 and/or caregivers 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/or caregiver and schedule a shipment. The pharmacy staff will ask the patient and/or caregiver if there has been any change in the patient's medications or medical history.
  - If the patient and/or caregiver reports a change in the patient's medication or medical history, the pharmacy staff will then transfer the patient and/or caregiver to a pharmacist who must complete the **Patient Counseling Checklist**. The patient and/or caregiver 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 and/or caregiver 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 and/or caregiver 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 and/or caregiver only after obtaining a copy of the police report filed by the patient and/or caregiver.
  - 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 and/or caregiver 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 and/or caregiver may request an alternate shipping address, which is then subject to approval by a pharmacist.
- If the patient and/or caregiver requests Saturday delivery, the patient's 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).
  - New patients only: The **Patient Brochure** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients.
- 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 and/or caregiver 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 and/or caregiver 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 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.

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 patients 7 years of age and older 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 the patient and/or caregiver for pediatric patients must 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 a patient who is 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 and/or caregivers for pediatric 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 and/or caregiver for pediatric patients 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 and/or caregivers who report a change in the patient's 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 and/or caregiver for pediatric patients 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 and/or caregiver 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** for new adult patients only or a **Pediatric Patients and their Caregivers Brochure** for new pediatric 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/or caregiver for pediatric 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

Avadel™

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.

Please Print (*denotes required field)

PRESCRIBER INFORMATION

*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

*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 and/or caregiver for pediatric patients that the LUMRYZ REMS will send the patient a **Patient Brochure** for adult patients or a **Pediatric Patients and their Caregivers Brochure** for pediatric patients 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 patients 7 years of age and older with narcolepsy.
  - Excessive daytime sleepiness (EDS) in patients 7 years of age and older 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** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients.
- 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.

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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 and/or caregivers who report a change in the patient's 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:

CAREGIVER INFORMATION (Required for pediatric patients) (All fields required)

First Name:	Last Name:

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 and/or caregivers who report a change in their medication use or medical history, listed in Step 4 of this checklist)

- ☐ New/restart
- ☐ Scheduled refill (change in medication use or medical history)
- ☐ Early refill approved through **Risk Management Report (RMR)** process
- ☐ Change of care responsibility (new caregiver for an already enrolled pediatric patients)

STEP 2: COUNSELING

(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 for patients that report a change of care responsibility)

- ☐ Verify that the patient and/or caregiver will receive the **Patient Brochure** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients.
- ☐ Verify that the patient and/or caregiver for pediatric patients 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 (or your child's) doctor will determine the dose that is appropriate.
  - Be sure to talk to your (or your child's) doctor about any troubling side effects or if you (or your child) doesn't feel any benefits while taking LUMRYZ.
  - For any prescription changes, have your (or your child's) doctor call or fax the new prescription change to the pharmacy. NEVER attempt to change the dose yourself.
- ☐ Verify that the patient and/or caregiver has been counseled on **Preparation and Administration** information below:
  - LUMRYZ should be taken as directed by your (or your child's) doctor (review prescriber's instructions with patient and/or caregiver).
  - LUMRYZ should be taken at least 2 hours after eating.
  - Prepare the dose of LUMRYZ as follows:
    - Before going to bed, gather the following supplies and place them on a flat surface at your (or your child's) bedside:
      - 1 bottle or glass of water (1/3 cup). Do not use hot water;
      - 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 the 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 you (or your child) drink(s) all the mixed solution in the mixing cup.

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

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- Immediately after the mixed solution is taken, 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 you (or your child) are in bed, make sure you (or your child) 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 (or your child's) bedside and you (or your child) should immediately lie down to go to sleep. Avoid getting out of bed after taking LUMRYZ.

- Refer to the LUMRYZ Medication Guide for additional information on preparation of your (or your child's) LUMRYZ dose.
- Feel free to call your (or your child's) certified pharmacy if you have any questions about preparing your (or your child's) dose or how to take your (or your child's) 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 (or your child's) 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 and/or caregiver for pediatric patients 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 (or your child's) 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 (or your child's) doctor if you (or your child):
  - Are pregnant or plan to become pregnant. It is not known if LUMRYZ can harm your (or your child's) unborn baby.
  - Are breastfeeding or plan to breastfeed. LUMRYZ passes into breast milk. You and your doctor should decide if you (or your child) will take LUMRYZ or breastfeed.
  - Have or had depression or tried to harm yourself. You (or your child) should be watched carefully for new symptoms of depression.
  - Have liver problems.
  - Have short periods of not breathing while you sleep (sleep apnea), trouble breathing, or lung problems. You (or your child) 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 (or your child).

☐ Verify that the patient and/or caregiver for pediatric patients has been counseled on **Side Effects** below:

- Adult Patients: 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.
- Pediatric Patients (7 years of age and older): In the pediatric clinical trial with immediate-release sodium oxybate, the most common adverse reactions were nausea, enuresis (bedwetting), vomiting, headache, weight decreased, decreased appetite, dizziness, and sleepwalking.
- 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 (or your child's) doctor if you (or your child) has any of these problems while taking LUMRYZ.
- Remember that you (or your child) 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 (or your child) sleepy unless specifically prescribed by your (or your child's) 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 (or your child) might experience. Contact your (or your child's) doctor if you are concerned about any possible side effects. Refer to the LUMRYZ Medication Guide for additional information on possible side effects.

☐ For situations involving a change of care responsibility:

- Inform caregiver/patient that this completes this section of the checklist. Confirm that the caregiver/patient has asked any questions he or she has about LUMRYZ.

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

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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 and/or Caregiver

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 and/or Caregiver

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 and/or Caregiver

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

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 and/or Caregiver

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

Drug	Dose

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

☐ Yes ☐ No If Yes, ☐ Counseled Patient and/or Caregiver

Please list the condition(s), if known:

Condition

8. Does the patient and/or Caregiver have any clinical questions about LUMRYZ?

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

Please list the question(s):

Question

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

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

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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 and/or caregiver for pediatric patients using this **Patient Counseling Checklist**.
- I will submit this checklist to the LUMRYZ REMS.

_____ _____

Pharmacist Signature **Date**

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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:

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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 and Caregivers

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 patients 7 years of age and older 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/or caregiver for pediatric patients 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** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients
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 patients 7 years of age and older with narcolepsy.
  - Excessive daytime sleepiness (EDS) in patients 7 years of age and older 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** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients.
- 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 patients 7 years of age and older with narcolepsy.
  - Excessive daytime sleepiness (EDS) in patients 7 years of age and older 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** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients.
- 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 patients 7 years of age and older with narcolepsy.
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- LUMRYZ is a Schedule III central nervous system (CNS) depressant and can cause obtundation and clinically significant respiratory depression at recommended doses.
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- 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:
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- Counsel the patient on the serious risks and safe use, handling, and storage of LUMRYZ using the **Patient Brochure** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients.
- 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.

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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** for adult patients or the **Pediatric Patients and their Caregivers Brochure** for pediatric patients
   - The benefits and serious risks associated with LUMRYZ
   - The safe use, handling, and storage of LUMRYZ

4. Enroll the patient 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 and Caregivers

- Patient Brochure
- Pediatric Patients and their Caregivers 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.

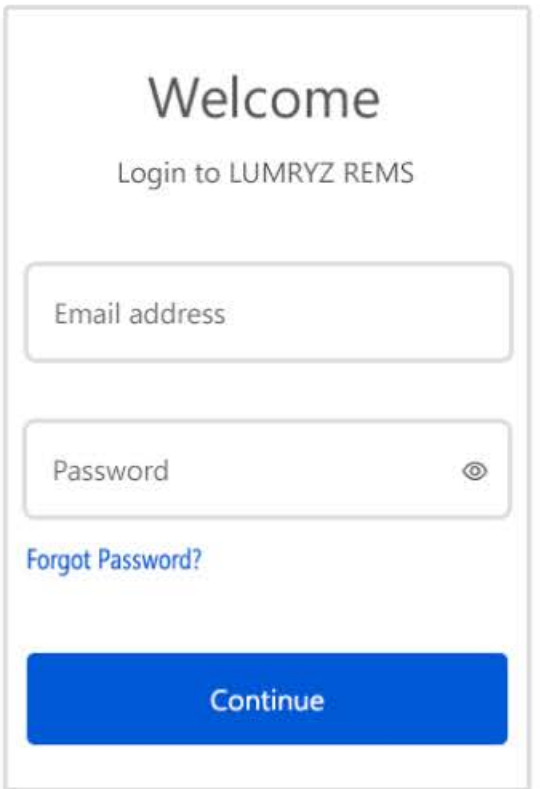
If you do not receive the email within the next few hours, or would like to update your information at any time, please contact the LUMRYZ REMS for assistance at 1-877-453-1029.

Lumryz

(sodium oxybate) for extended-release oral suspension ℂ

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.



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s006

MULTI-DISCIPLINE REVIEW

Summary Review
Cross Discipline Team Leader Review Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	214755/S-006
Priority or Standard	Standard
Submit Date(s)	11/07/2023
Received Date(s)	11/07/2023
PDUFA Goal Date	09/07/2024
Division/Office	Division of Psychiatry / Office of Neuroscience
Review Completion Date	10/16/2024
Established/Proper Name	Sodium oxybate
(Proposed) Trade Name	Lumryz
Pharmacologic Class	Central nervous system depressant
Code name	N/A
Applicant	Avadel CNS Pharmaceuticals, LLC
Dosage form	Oral suspension
Applicant proposed Dosing Regimen	For pediatric patients weighing 45 kg or more, starting dosage of 4.5 g once per night administered orally, increasing by 1.5 g per night at weekly intervals (b) (4) (b) (4) 9 g once per night orally
Applicant Proposed Indication(s)/Population(s)	Treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	60380001 Narcolepsy (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	60380001 Narcolepsy (disorder)
Recommended Dosing Regimen	For pediatric patients weighing 45 kg or more, starting dosage of 4.5 g once per night administered orally, increasing by 1.5 g per night at weekly intervals to the maximum recommended dosage range of 9 g once per night orally. For pediatric patients weighing 20 to <45 kg who are switching from immediate-release sodium oxybate, those weighing 20 kg to <30 kg is 6 g once per night orally, and the maximum

	recommended dosage for those weighing 30 kg to <45 kg is 7.5 g once per night orally.

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Table of Contents

Table of Tables

No tables included in the review.

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Table of Figures

No figures included in the review.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	C. Eugene Lee, PharmD
Nonclinical Reviewer	James Miller, PhD
Nonclinical Team Leader	Amy Avila, PhD
Nonclinical Supervisor	Aisar Atrakchi, PhD
Office of Clinical Pharmacology Reviewer(s)	Li Tan, PhD
Office of Clinical Pharmacology Team Leader(s)	Venkateswaran Chithambaram Pillai, PhD
Clinical Reviewer	Cathy Southammakosane, MD
Clinical Team Leader	Jean Kim, MD
Statistical Reviewer	N/A
Statistical Team Leader	N/A
Cross-Disciplinary Team Leader	Jean Kim, MD
Deputy Division Director (Psychiatry)	Bernard Fischer, MD
Division Director (Psychiatry), signatory	Tiffany R. Farchione, MD

Additional Reviewers of Application

Office of Pharmaceutical Quality (OPQ)	Joyce Crich, PhD
Microbiology	N/A
Office of Prescription Drug Promotion (OPDP)	Rachael Oyewole, PharmD
Office of Scientific Investigations (OSI)	N/A
Office of Surveillance and Epidemiology (OSE)/ Division of Epidemiology (DEPI)	N/A
OSE/ Division of Medication Error Prevention and Analysis (DMEPA)	Loretta Holmes, BSN, PharmD
OSE/ Division of Risk Management (DRM)	Stephanie Olumba, PharmD

Signatures

See archived signatory memos for each discipline.

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Glossary

AE	adverse event
BA	bioavailability
BLA	biologics license application
CFR	Code of Federal Regulations
CNS	central nervous system
CSF	cerebrospinal fluid
EDS	excessive daytime sleepiness
ETASU	elements to assure safe use
FDA	Food and Drug Administration
GHB	gamma-hydroxybutyrate
HLA	human leukocyte antigen
IND	Investigational New Drug
LD	listed drug
MSLT	Multiple Sleep Latency Test
NDA	new drug application
PK	pharmacokinetics
PMR	postmarketing requirement
PPSR	proposed pediatric study request
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
sNDA	supplemental new drug application
SOREMP	sleep-onset rapid eye movement periods

1 Executive Summary

1.1. Product Introduction

Lumryz, sodium oxybate extended-release powder for oral solution, is the sodium salt of gamma-hydroxybutyrate (GHB), which is, in turn, an endogenous metabolite of the GABA neurotransmitter. The mechanism of action for this drug in the treatment of narcolepsy is not known but is hypothesized to be related to activity with norepinephrine, dopamine, and thalamocortical neurons. It was approved on May 1, 2023, for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy (NDA 214755).

Xyrem, sodium oxybate immediate-release oral solution, and Xywav, calcium, magnesium, potassium, and sodium oxybates immediate-release oral solution, are approved for this indication in both adults and children 7 years of age and older and are administered nightly in two doses separated by an interval of 2.5 to 4 hours. Lumryz, sodium oxybate extended-release is administered nightly as a single dose.

All oxybate products are designated as Schedule III controlled substances under the Federal Controlled Substances Act and were approved with a boxed warning for central nervous system (CNS) depression and abuse and misuse and with an associated risk evaluation and mitigation strategy (REMS). The REMS involves a restricted distribution program comprising healthcare provider certification, distribution through specially certified central pharmacies, and patient enrollment.

Additional warnings and precautions in the oxybate labels include respiratory depression and sleep-disordered breathing, depression and suicidality, other behavioral or psychiatric adverse reactions, and parasomnias. Sodium oxybate labels also include a warning and precaution regarding use in patients sensitive to high sodium intake. In the sodium oxybate immediate-release labels, pediatric data for respiratory depression and sleep-disordered breathing, depression and suicidality, other behavioral or psychiatric adverse reactions, and parasomnias are also included in the warnings and precautions.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The efficacy and safety of oxybate in treating cataplexy or EDS in narcolepsy in children 7 years of age and older has been confirmed in clinical trials of the listed drug (LD) sodium oxybate immediate-release (Xyrem). This application relies on the Agency's previous findings of safety and effectiveness for the LD based on a single-dose, randomized, two-sequence, crossover, comparative bioavailability (BA) study, which provided an acceptable scientific bridge between sodium oxybate extended-release (Lumryz) to sodium oxybate immediate-release (LD) with no unexpected safety signals. Additional evidence comes from a prior randomized, double-blind,

placebo-controlled efficacy and safety study of sodium oxybate extended-release in adults with cataplexy and EDS in narcolepsy.

APPEARS THIS WAY ON ORIGINAL

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Pediatric narcolepsy is a rare, serious, chronic condition with a range of symptoms including excessive daytime sleepiness (EDS), cataplexy, hypnagogic and hypnopompic hallucinations, disrupted nighttime sleep, and sleep paralysis. EDS is a core symptom in all patients with narcolepsy and can be associated with significant impairment in function and in quality of life. Cataplexy, which is sudden loss of muscle tone, impacts a subset of patients with narcolepsy (narcolepsy type 1). Cataplexy episodes can be frequent, unpredictable, occurring spontaneously or triggered by strong emotions, and can lead to psychological distress and additional functional impairment. There are few available pharmacologic therapies for the treatment of EDS or cataplexy in narcolepsy.

Lumryz, sodium oxybate extended-release powder for oral solution, is the sodium salt of gamma-hydroxybutyrate (GHB), which is, in turn, an endogenous metabolite of the GABA neurotransmitter. It is approved for the treatment of cataplexy or EDS in adults with narcolepsy. This supplemental new drug application (sNDA), expanding the indication to include patients down to 7 years of age, is supported by pharmacokinetic (PK) bridging to sodium oxybate immediate-release, which is approved already in the pediatric population with EDS in narcolepsy ages 7 and older. Additional supplemental evidential support also comes from previous efficacy and safety data for sodium oxybate extended-release for the approved indication in adults with cataplexy and EDS in narcolepsy. No novel clinical trial data were submitted with this sNDA.

This application does not alter the indication, population, or total nightly dosage compared to the relied-upon LD. The modification of once nightly dosing may provide greater ease of use for patients and their families. Overall, the benefit-risk assessment for this product is not appreciably different from the LD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Narcolepsy is a rare, chronic, and serious pediatric and adult neurologic disorder. • Available estimates suggest that narcolepsy affects 20 to 50 pediatric patients per 100,000. • Narcolepsy is diagnosed in pediatric or adult patients as type 1 or type	Narcolepsy is a serious and chronic neurologic condition typically beginning in childhood, adolescence, or young adulthood, characterized by EDS, cataplexy, and other symptoms that have a significant impact on

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	2. For both types, the International Classification of Sleep Disorders – 3 diagnostic criteria require symptoms of EDS for ≥3 months and threshold findings on the multiple sleep latency test (MSLT). • A diagnosis of NT1 requires the presence of cataplexy or low (i.e., below threshold) cerebrospinal fluid (CSF) orexin-A (hypocretin-1) concentration. • For an NT2 diagnosis, CSF orexin (hypocretin) has not been measured or is not below the threshold, and the hypersomnolence and/or MSLT findings are not better explained by other causes. • Symptoms typically manifest during childhood, adolescence, or young adulthood. • The core symptoms of narcolepsy have a significant impact on patients' quality of life, increasing the risk of injury, accidents, and falls and impacting daily functioning. In pediatric patients, narcolepsy may affect their ability to engage with school, social, and family activities and lead to negative academic, emotional, and behavioral outcomes.	patients' quality of life and ability to function in multiple spheres.
Current Treatment Options	• Sodium oxybate (Xyrem) oral solution and calcium, magnesium, potassium, and sodium oxybates (Xywav) oral solution are approved for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy. • Both oxybate products are CNS depressants administered orally twice nightly (i.e., with the first dose at bedtime and the second dose 2.5 to 4 hours later). • Pitolisant, a histamine-3 receptor antagonist/inverse agonist, is indicated for the treatment of EDS or cataplexy in adult patients with narcolepsy and EDS in patients 6 years of age and older with narcolepsy.	There are few approved pharmacologic treatment options for the treatment of EDS or cataplexy in pediatric patients with narcolepsy. Pediatric patients with narcolepsy would benefit from additional approved treatment options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The CNS stimulants methylphenidate and amphetamines (including certain products containing amphetamine, dextroamphetamine, mixed amphetamine salts) include an indication for the treatment of narcolepsy without specification as to pediatric or adult population. • Off-label pharmacologic treatments include modafinil, solriamfetol, and certain antidepressants, but the evidence supporting the use of these drugs in pediatric patients is limited.	
Benefit	• Sodium oxybate extended-release is approved for the treatment of EDS or cataplexy in adult patients with narcolepsy. • This application relies on the Agency's findings of effectiveness for the LD based on a prior single-dose, randomized, two-sequence, crossover, comparative BA study, which scientifically bridged sodium oxybate extended-release to sodium oxybate immediate-release. Supplemental support comes from a prior randomized, double-blind, placebo-controlled efficacy and safety study of sodium oxybate extended-release in adults with cataplexy and EDS in narcolepsy.	This application does not alter the indication, population, or total nightly dosage compared to the relied-upon LD. The modification of once-nightly dosing is expected to provide greater ease of use for patients and their families. Generally, the benefit-risk assessment for this product is not appreciably different from the LD.
Risk and Risk Management	• This application relies on the Agency's findings of safety for the LD based on a prior comparative BA study, which scientifically bridged sodium oxybate extended-release to sodium oxybate immediate-release with no unexpected safety signals. Supplemental support comes from a prior randomized, double-blind, placebo-controlled efficacy and safety study of sodium oxybate extended-release in adults with cataplexy and EDS in narcolepsy	The benefit-risk assessment for this product is not appreciably different from the LD. Labeling will be updated to include pediatric safety data from the pediatric clinical study conducted with the LD.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
✓	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Narcolepsy is a lifelong neurological disease estimated, in Western countries, to occur in 20 to 50 pediatric patients per 100,000.[1,2] The age of onset of narcolepsy ranges from early childhood to middle age with a peak around 14 to 15 years. Onset before 15 years of age occurs in approximately 33% of patients, and some exhibit symptoms before 5 years of age. Etiology is not well-established, but there appears to be an association with the loss of orexin (hypocretin) neurons along with genetic and immune factors, specifically involvement of the DQB1*0602 human leukocyte antigen (HLA) haplotype. The cardinal symptoms of narcolepsy are as follows:

- EDS is experienced by all patients and is typically the first symptom of narcolepsy. Severity ranges from intermittent drowsiness to irresistible "sleep attacks." In the pediatric population, EDS may manifest as napping outside of the expected age range, irritability, or disturbance in concentration or memory.

- Cataplexy occurs in approximately 70 to 80% of pediatric patients with narcolepsy and is specific to the diagnosis. It is characterized by abrupt and symmetric loss of muscle tone without loss of consciousness and is typically in response to strong emotions. Episodes are transient—usually lasting less than 1 minute—and the patient is often fully functional afterwards. Weakness may be partial or full and may occur multiple times throughout the day.

- Sleep-related hallucinations occur in 50 to 60% of pediatric narcolepsy patients and are described as vivid imagery at sleep onset (hypnagogic) or upon awakening (hypnopompic).

- Sleep paralysis occurs in 50 to 60% of pediatric narcolepsy patients and is characterized as the brief inability to move or speak upon awakening or at sleep onset.

- Disrupted nighttime sleep may include mid-night awakenings or motor behaviors.

The diagnosis of narcolepsy type 1 in the pediatric population mirrors adult criteria:[3]

- Daily irrepressible need to sleep or daytime lapses into sleep for at least 3 months and one or both of the following:

[1] Maski, K and Kotagal, S. Clinical features and diagnosis of narcolepsy in children. In: Connor RF, editor, UpToDate: Wolters Kluwer. (Accessed on March 5, 2024.)
[2] Chung, I., et al. (2022). Pediatric Narcolepsy-A Practical Review. Children, 9(7). doi: 10.3390/children9070974
[3] Sateia, MJ. (2014). International Classification of Sleep Disorders-Third Edition. Chest, 146(5), 1387-1394. https://doi.org/10.1378/chest.14-0970

- Cataplexy and one of the following:
  - Mean sleep latency of <8 minutes and two or more sleep-onset rapid eye movement periods (SOREMP) on an MSLT
  - SOREMP within 15 minutes of sleep onset on nocturnal polysomnogram
- CSF orexin concentration <110 picograms/mL

- Signs and symptoms not better explained by another disorder or medication/substance

Narcolepsy type 2 is diagnosed in the absence of cataplexy or low orexin concentration.

Unique narcolepsy features in the pediatric population include atypical cataplexy (facial hypotonia or positive motor signs), sudden weight gain (approximately 66% of pediatric patients are overweight or obese), and precocious puberty (occurring in approximately 17% of pediatric patients).

As is the case with adults, the symptoms of narcolepsy, including cataplexy, are frequently disruptive to the lives of children and adolescents, both at school and in other settings. The diagnosis of pediatric narcolepsy is typically delayed, potentially prolonging impairment, distress, and decreased quality of life. Among several consequences of narcolepsy in the pediatric population are impaired learning, academic performance, and socialization; injury; and emotional and behavioral disturbances. Psychological manifestations include depression, anxiety, attention-deficit/hyperactivity disorder, oppositional defiant disorder, and other behavioral dysregulation. These consequences in the pediatric population are particularly notable given the potential for greater impact of earlier disease on the patient's lifelong trajectory and on the lives of caregivers and other family members.

2.2. Analysis of Current Treatment Options

There is no curative treatment for narcolepsy; rather, existing therapies can only address symptoms. Although behavioral and lifestyle interventions are important in the management of pediatric narcolepsy, pharmacotherapy is also warranted in nearly all patients. Two oxybate immediate-release oral solution products (Xyrem (NDA 021196) and Xywav (NDA 212690)) are approved for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy, and pitolisant (Wakix (NDA 211150)) is approved for the treatment of EDS in pediatric patients 6 years of age and older with narcolepsy. Pitolisant has a warning for QT interval prolongation, and common adverse reactions in pediatric patients are headache and insomnia. The CNS stimulants methylphenidate (first approved in 1955) and amphetamines (including certain products containing amphetamine, dextroamphetamine, mixed amphetamine salts, first approved in 1960) include an indication for the treatment of narcolepsy without specification as to pediatric or adult population. Risks associated with stimulants include increased blood pressure and heart rate, psychiatric adverse reactions,

decreased appetite, long-term suppression of growth in pediatric patients, and insomnia. Although other drugs such as tricyclic antidepressants, selective serotonin reuptake inhibitors, modafinil, and solriamfetol are used in pediatric patients for narcolepsy, evidence supporting the use of these drugs is limited.

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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

On December 15, 2020, Avadel CNS Pharmaceuticals, LLC submitted NDA 214755, pursuant to section 505(b)(2) of the FDCA, for sodium oxybate oral solution for the treatment of cataplexy and EDS in adults with narcolepsy, using Xyrem (NDA 021196) as the LD. Because the 45-day period described in section 505(c)(3)(C) of the FD&C Act had not yet expired, the application was granted tentative approval for the treatment of cataplexy or EDS in adults with narcolepsy on July 18, 2022. It was granted final approval on May 1, 2023, with the requirement for a REMS. See the original review of NDA 214755 for more regulatory background information on this development program.

3.2. Summary of Presubmission/Submission Regulatory Activity

On May 16, 2018, the Agency held a Type B end-of-phase 2 meeting with the Sponsor. During the meeting, exemption from PREA was confirmed due to the orphan drug designation for sodium oxybate oral solution for the treatment of cataplexy and EDS in narcolepsy. The Agency also informed the Sponsor that while in most instances, the demonstration that one product is safer than another product in the same context would require direct ("head-to-head") comparisons of the two products in the same clinical trial, a direct comparison of the safety of sodium oxybate oral solution and Xyrem in the same clinical trial may not be required for obtaining exclusivity for sodium oxybate oral solution, based on the information available. Major contribution to patient care (MCTPC) may be used to demonstrate clinical superiority for the purpose of obtaining exclusivity. It was also agreed upon that a shared REMS was acceptable.

On July 22, 2020, a Proposed Pediatric Study Request (PPSR) was submitted for the treatment of EDS and cataplexy in patients with narcolepsy ages 7 years and older. On November 11, 2020, the Agency issued an Inadequate PPSR Letter, stating the Sponsor did not provide pharmacokinetic data from the pivotal relative bioavailability study (PKFT218-1801) in healthy adult subjects comparing the final to-be-marketed product and the reference LD (Xyrem). The Sponsor submitted another PPSR on March 18, 2021. On August 17, 2021, another Inadequate PPSR Letter was issued, stating clinical studies of sodium oxybate oral solution in pediatric patients with narcolepsy may not be needed. The use of sodium oxybate oral solution in children ages 7 years and older with cataplexy or EDS in narcolepsy has the potential to be supported by currently available efficacy and safety data in adults with cataplexy and EDS in narcolepsy from Study CLFT218-1501 and by pharmacokinetic bridging from Study PKFT218

-1801. Because there were not additional pediatric studies needed to adequately label the product for pediatric use for the indication of the treatment of cataplexy and EDS in narcolepsy, the Agency was unable to issue a WR.

On October 12, 2022, a Type B pre-NDA meeting was held to discuss aspects of the pediatric development plan. The Agency confirmed that pediatric clinical studies of sodium oxybate oral solution in children 7 years of age and older with a minimum weight of 45 kg may not be needed. It was recommended that the Applicant conduct a HF validation study of 15 pediatric subjects ages 10 to 16 years of age or 15 pediatric patient-adult caregiver pairs; however, after the Sponsor provided a detailed justification for not needing further human factor (HF) study data and the Agency agreed.

On May 9, 2023, IND 126321 was transferred from the Division of Neurology 1 to the Division of Psychiatry.

On August 25, 2023, in a pre-sNDA written response, the Agency confirmed that an Integrated Summary of Safety and Integrated Summary of Efficacy would not be necessary.

On November 7, 2023, the Division received sNDA 214755 S-006 with a user fee goal date of November 7, 2024.

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4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Not applicable; no clinical studies submitted with this sNDA.

4.2. Product Quality

Not applicable.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical information was submitted in support of this supplement, which aims to expand the current indication for sodium oxybate extended-release powder for oral solution to include patients 7 years of age and older. The Applicant is relying on the Agency's previous finding of safety for the LD (Xyrem), for nonclinical information needed to support the indication for pediatric patients. No changes to the drug formulation were made for this supplement, as the approved product is an oral solution. The acceptability of amount of one of the excipients, [redacted] (b) (4), for use in the pediatric population is discussed below. Overall, the nonclinical data relied upon to support approval of the LD are adequate to support approval of this supplement. A minor change to the nonclinical labeling was made in section 8.4 to include safety margins for the juvenile animal study to maintain consistency with the LD label.

Under the original NDA application, the Applicant submitted a number of legacy toxicity studies to support the amount of the excipient, [redacted] (b) (4) methacrylic acid [redacted] (b) (4) [redacted] (b) (4) co-polymer (for a detailed review see Pharmacology/Toxicology Review and Evaluation, NDA 214755, June 17, 2022). The maximum daily intake of this excipient exceeds the levels contained in previously approved drug products as listed in the FDA's Inactive Ingredient Database. Due to histologic findings indicating potential thyroid activation in the toxicity studies, two nonclinical post-marketing studies were required (PMRs), to assess the safety of [redacted] (b) (4) The first PMR (PMR #1) was to conduct an oral absorption study for the excipient and the second (PMR #2) was to conduct a 6-month rodent toxicity study if appreciable absorption of [redacted] (b) (4) occurred. In order to address the PMRs, the Applicant submitted a 6-month rat toxicity study report [redacted] (b) (4) that was conducted on behalf of the excipient manufacturer, to NDA 214755 on May, 15, 2023. The results of this study are described below. With the submission of the 6-month rat toxicity study, PMR #2 was considered fulfilled and PMR #1 was considered no longer needed and was released.

Adult rats (15/sex/group) were orally administered [redacted] (b) (4) once daily up to a maximum feasible dose of 1500 mg/kg/day for a duration of 6 months with a 4-week non-dosing recovery period. Standard general toxicity endpoints were evaluated including clinical signs, body weight, food consumption, clinical pathology (hematology, clinical chemistry, urinalysis), gross pathology, and histopathology including an adequate battery of tissues. Additionally, thyroid hormone levels (TSH, T3, and T4) were measured at Weeks 6, 12, and 24. No premature deaths or early terminations occurred. No test article related clinical signs were observed and no effects on body weights or food consumption were noted. No test article related changes in clinical pathology parameters, or macroscopic and microscopic findings were noted. In general, levels of thyroid hormones deceased over the 6-months of dosing across all groups including controls. TSH levels tended to be higher in high dose male animals compared to controls, however, due to the low magnitude, high individual variability in TSH levels in all groups—

particularly in the high dose male group—and in the absence of any correlating histologic changes in any organs or tissues, the effects on TSH levels were not considered adverse. The no observed adverse effect level (NOAEL) for (b) (4) in this study was the high dose of 1500 mg/kg/day. In conclusion, the provided study is considered an adequately conducted GLP compliant study with no (b) (4) related adverse findings.

Although the Applicant did not provide additional nonclinical safety information to support the maximum daily intake of excipient (b) (4) in the drug product for the proposed pediatric patient population, based on a weight of evidence assessment, additional developmental toxicity studies are not warranted for the use of (b) (4) in pediatric patients 7 years of age and older. (b) (4) is not a novel excipient. This excipient is present in a number of approved drug products including those used to treat pediatric conditions (b) (4) The intended pediatric age range is 7 years of age and older, with an additional weight cutoff of ≥45 kg. The safety profile for (b) (4) is not expected to be significantly different between the adult and pediatric patient populations as no adverse effects on developing organ systems are anticipated with this patient age range. In the submitted 6-month toxicity study, no adverse findings were noted up to a maximum dose of 1500 mg/kg/day, including no histopathological findings in the thyroid and no adverse effects on levels of thyroid hormones TSH, T3, or T4. The safety margin at the maximum daily amount of (b) (4) of (b) (4) in the drug product compared to the NOAEL of 1500 mg/kg/day is approximately (b) (4)-fold in pediatric patients based on body surface area (b) (4) Furthermore, due to the molecular size of (b) (4) (~ (b) (4) g/mol) and based on oral absorption data from a similar compound (b) (4) no appreciable absorption of the excipient is expected. With little to no oral absorption of (b) (4) no systemic toxicity is anticipated with exposure to this excipient. This is further supported by the results of the 6-month toxicity study with no adverse effects noted. Therefore, based on the totality of available information, the maximum amount of (b) (4) in the sodium oxybate extended-release powder for oral solution drug product does not pose a significant risk to the pediatric population ages 7 and older.

6 Clinical Pharmacology

6.1. Executive Summary

Lumryz is approved for the treatment of cataplexy or EDS in adults with narcolepsy. In this efficacy supplement, the Applicant is seeking approval of Lumryz for the treatment of cataplexy or EDS in children 7 years of age and older with narcolepsy.

There are no new clinical studies submitted in this pediatric efficacy supplement. However, the Applicant previously demonstrated a pharmacokinetic (PK) bridge between Lumryz and the LD (Xyrem, immediate release sodium oxybate; NDA 021196) as part of original NDA 214755. The LD is approved for the treatment of cataplexy or EDS in adults and children aged 7 years and older with narcolepsy. As the clinical pharmacology review of the original NDA 214755 concluded that the scientific bridge between Lumryz and the LD is adequate, the proposed drug product, Lumryz can rely on the Agency's previous findings of safety and effectiveness of the LD for the treatment of cataplexy or EDS in children 7 years of age and older with narcolepsy. See the previous clinical pharmacology review for NDA 214755 archived on October 14, 2021, for details.

Although the pharmacokinetic (PK) shape of once-nightly administration of sodium oxybate oral solution and twice-nightly administration of the LD is different, a double-blind, randomized, placebo-controlled, two-arm multi-center study (Study CLFT218-1501; ClinicalTrials.gov identifier NCT02720744) demonstrated that sodium oxybate oral solution is safe and effective for the treatment of cataplexy or EDS in adult patients with narcolepsy (see the previous clinical review for NDA 214755 archived on July 14, 2022, for details). This suggests that the difference in PK shape between sodium oxybate oral solution and the LD did not appear to have a significant impact on the effectiveness and safety of sodium oxybate oral solution for the treatment of cataplexy or EDS in adult patients with narcolepsy.

The systemic exposures and safety profiles of the LD in pediatric patients with narcolepsy were comparable to that of adult patients with narcolepsy. The LD demonstrated effectiveness over placebo for the treatment of cataplexy and EDS in pediatric patients 7 years of age and older (see the previous clinical and clinical pharmacology reviews archived on October 26, 2018, and October, 23, 2018, respectively, for additional information). Therefore, the systemic exposures and safety profiles of sodium oxybate oral solution are also expected to be similar between adults and pediatric patients with narcolepsy. Further, the effectiveness of sodium oxybate oral solution is anticipated to be similar to the LD in pediatric patients with narcolepsy.

The Office of Clinical Pharmacology (OCP) recommends approval of sodium oxybate oral solution for the treatment of cataplexy or EDS in pediatric patients 7 years of age or older with narcolepsy.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

See Section 8.1.

7.2. Review Strategy

Clinical studies of sodium oxybate extended-release in pediatric subjects with EDS in narcolepsy were not necessary because the pediatric indication is supported by pharmacokinetic (PK) bridging to sodium oxybate immediate-release, which is approved already in the pediatric population with EDS in narcolepsy ages 7 and older (via Study 13-005 originally conducted under a supplement to NDA 21196).

The Applicant established the scientific bridging between the two drugs via a comparative relative bioavailability study (Study PKFT218-1801 conducted under the original NDA 214755). The sodium oxybate extended-release dosage regimen to be administered to pediatric patients can be based on the sodium oxybate immediate-release dosage regimen.

Additional supplemental evidential support also comes from Study CLFT218-1501 for sodium oxybate extended-release for the approved indication in adults with cataplexy and EDS in narcolepsy (the studies for sodium oxybate extended-release also included some limited data in adolescents). No novel clinical data were submitted with this sNDA.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy and Safety

8.1.1. Study PKFT218-1801 (conducted by the Applicant)

Although there is some difference in the shape of the PK profile, the scientific bridge between sodium oxybate extended-release 6 g and sodium oxybate immediate-release 6 g was confirmed in Study PKFT218-1801, a single-dose, randomized, two-sequence, crossover PK study conducted in 28 healthy adult subjects (see the previous clinical review for NDA 214755 archived on July 14, 2022, for details).

8.1.2. Study CLFT218-1501 (conducted by the Applicant)

The efficacy and safety of sodium oxybate extended-release was confirmed in Study CLFT218-1501, a randomized, double-blind, placebo-controlled study in which 212 mostly adult subjects with EDS or cataplexy in narcolepsy received sodium oxybate extended-release up to 9 g nightly for 13 weeks. Of note, 11 adolescent subjects 16 to 18 yearsof age were enrolled in this study (sodium oxybate n=4, placebo n=7). The primary efficacy measures for EDS were the Maintenance of Wakefulness score and Clinical Global Impression and for cataplexy was mean number of cataplexy attacks over a 2-week period for each dose (9 g, 7.5 g, and 6 g daily). The primary efficacy analysis indicated that sodium oxybate extended-release demonstrated a statistically significant superiority over placebo (p-value <0.0001) on all three primary efficacy parameters and at all three doses. The safety profile was not significantly different from that of other oxybate products.

8.1.3. Study CLFT218-1901 (conducted by the Applicant)

The safety of sodium oxybate extended-release was also supported by Study CLFT218-1901, an open-label, uncontrolled, long-term (up to 2 years) safety study enrolling 180 mostly adult subjects with narcolepsy who completed Study CLFT218-1501 or were novel subjects currently receiving a stable dose of oxybate or who were naïve to oxybate therapy. Subjects received sodium oxybate extended-release titrated up to 9 g daily as tolerated to effect. No new safety findings were observed in this long-term safety study.

8.1.4. Study 13-005 (conducted by the Innovator)

The efficacy and safety of sodium oxybate immediate-release in the pediatric narcolepsy population was confirmed in Study 13-005, a randomized withdrawal study in which 104 subjects ages 7 to 16 years with narcolepsy received sodium oxybate immediate-release. The study comprised the following periods:

- A 3- to 10-week, open-label, dose titration (up to 9 g nightly) period (n=104)

- A 2- to 3-week, open-label, stable-dose period (n=99)
- A 2-week, randomized, double-blind, placebo-controlled, withdrawal period (n=63)
- An up to 3 years total-treatment, open-label, safety period (n=95)

The primary efficacy parameter was the change in weekly number of cataplexy attacks during the 2-week randomized, controlled, withdrawal period compared to the last 2 weeks of the stable-dose period. Key secondary efficacy parameters were the Clinical Global Impression of Change for cataplexy severity and change in the modified Epworth Sleepiness Scale score from the end of the stable-dose period to the end of the randomized withdrawal period.

A pre-specified interim efficacy analysis was conducted after 35 subjects completed or discontinued early from the randomized withdrawal period; the Data Safety Monitoring Board concluded that sodium oxybate immediate-release was superior to placebo in the treatment of cataplexy (p-value <0.005), so the randomized withdrawal period was terminated.

The PK data revealed a profile in the pediatric population that was similar to that in adults, although the $AUC_{0\text{-}4h}$ was supra-dose-proportional.

In sodium oxybate immediate-release labeling, pediatric data in the Warnings and Precautions section include central sleep apnea and oxygen desaturation during polysomnographic evaluation; depression and suicidal ideation (SI); neuropsychiatric reactions including acute psychosis, confusion, and anxiety; and sleepwalking. Pediatric adverse events (AE) leading to discontinuation included tactile hallucination, SI, weight decreased, sleep apnea syndrome, affect lability, anger, anxiety, depression, and headache. Common AEs (>5%) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%), and sleepwalking (6%). The overall AEs profile of sodium oxybate immediate-release in the pediatric clinical study was similar to that seen in the adult clinical studies with notable exceptions of higher pediatric rates of enuresis, headache, and dizziness, and notable weight decrease and decreased appetite.

8.1.5. Study Results

See the previous clinical review for NDA 214755 archived on July 14, 2022, for details.

8.1.6. Assessment of Efficacy Across Trials

See the previous clinical review for NDA 214755 archived on July 14, 2022, for details.

8.2. Review of Safety

There were no new study data submitted with this application, as the indication approval relies on establishment of an acceptable scientific bridge to an approved drug.

8.2.1. Safety Review Approach

Not applicable.

8.2.2. Review of the Safety Database

Not applicable.

Overall Exposure

Not applicable.

Adequacy of the Safety Database

Not applicable.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Not applicable.

Categorization of Adverse Events

Not applicable.

Routine Clinical Tests

Not applicable.

8.2.4. Safety Results

Deaths

Not applicable as there is no new data to review.

Serious Adverse Events

Not applicable as there is no new data to review.

Dropouts and/or Discontinuations Due to Adverse Effects

Not applicable as there is no new data to review.

Significant Adverse Events

Not applicable as there is no new data to review.

Treatment Emergent Adverse Events and Adverse Reactions

Not applicable as there is no new data to review.

Laboratory Findings

Not applicable as there is no new data to review.

Vital Signs

Not applicable as there is no new data to review.

Electrocardiograms (ECGs)

Not applicable as there is no new data to review.

QT

Not applicable as there is no new data to review.

Immunogenicity

Not applicable as there is no new data to review.

8.2.5. Analysis of Submission-Specific Safety Issues

Sodium oxybate extended-release contains 820 to 1640 mg of sodium with each nightly exposure. For context, dietary guideline recommendations for daily sodium intake in the pediatric population are:[4]

- Ages 5 to 8 years 1500 mg daily
- Ages 9 to 13 years 1800 mg daily
- Ages 14 to 18 years (as with adults) 2300 mg daily

However, the safety of sodium oxybate extended-release is not expected to differ from that of the LD, which has the same levels of sodium. See the consults to the Office of Orphan Products Development from the Division of Neurology 1, archived May 1, 2023, and from the Division of Psychiatry for this supplement for more information on the sodium content of sodium oxybate extended-release relative to other available therapy.

[4] U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2020-2025. 9th Edition. December 2020. Available at DietaryGuidelines.gov

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Not applicable as there is no new data to review.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable as there is no new data to review.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

Human Reproduction and Pregnancy

Not applicable.

Pediatrics and Assessment of Effects on Growth

No new data has been submitted regarding growth concerns.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable as there is no new data to review.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Sodium oxybate extended-release postmarketing experience includes the following adverse events (AE): arthralgia, decreased appetite, fall, fluid retention, “hangover,” headache, hypersensitivity, hypertension, memory impairment, nocturia, panic attack, vision blurred, and weight decreased.

Expectations on Safety in the Postmarket Setting

Sodium oxybate extended-release is expected to have the same safety in the post-market setting as the LD.

8.2.11. Integrated Assessment of Safety

The approval of sodium oxybate extended-release for pediatric patients 7 years of age and older is based on establishment of an adequate scientific bridge to the LD (including comparative bioavailability and a safety and efficacy study in adults). Sodium oxybate extended-release is expected to have the same safety as the LD.

8.3. Statistical Issues

Not applicable as no new data was submitted.

8.4. Conclusions and Recommendations

An expanded pediatric indication for sodium oxybate extended-release for the treatment of cataplexy and EDS in narcolepsy in patients 7 years of age and older is supported by establishing an adequate scientific bridge (via a comparative bioavailability study and a safety and efficacy study in adults) to the LD (sodium oxybate immediate-release), which is already approved in the same pediatric population. The sodium oxybate extended-release dosage regimen to be administered to pediatric patients can be based on the sodium oxybate immediate-release dosage regimen. Therefore, clinical studies of sodium oxybate extended-release in pediatric subjects with narcolepsy were not necessary.

The primary safety concerns for sodium oxybate extended-release (CNS depression, abuse and misuse, sodium content) remain pertinent to the pediatric population and are adequately described in and mitigated by labeling and with the appropriately modified REMS (i.e., pediatric-specific data and language). In totality, the expected benefit of sodium oxybate extended-release outweighs the safety risks in the pediatric patient population. The value of sodium oxybate extended-release as a once-nightly option for treatment of cataplexy and EDS associated with narcolepsy is justified, and the review team recommends an approval action.

9 Advisory Committee Meeting and Other External Consultations

Not applicable. An Advisory Committee meeting was not held because this drug is already approved for the same indication in the adult patient population and because the application did not raise scientific or technical matters that would benefit from advisory committee discussion.

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10 Pediatrics

Because sodium oxybate extended-release for the treatment of narcolepsy has an orphan drug designation, it is exempt from Pediatric Research Equity Act (PREA) requirements. A proposed pediatric study request (PPSR) was not submitted. However, this supplemental new drug application addresses treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy.

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11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information (PI)

- Indications and Usage: The Indications and Usage statement was revised to include pediatric patients 7 years of age and older.

- Dosage and Administration: Pediatric dosage recommendation were modified into two distinct sections for pediatric patients 7 years of age and older weighing 45 kg or more and for pediatric patients 7 years of age and older and weighing less than 45 kg who may be switching from immediate-release sodium oxybate. Further additions include maximum dosages based upon the LD for each pediatric group and a statement that there is insufficient information available to inform dosage recommendations for patients weighing less than 20 kg.

- Warnings and Precautions: Pediatric-specific clinical safety findings were added to the Respiratory Depression and Sleep-Disordered Breathing, Depression and Suicidality, Other Behavioral or Psychiatric Adverse Reactions, and Parasomnias sections.

- Adverse Reactions: Adverse reaction information from the pediatric study with immediate-release sodium oxybate was added to Section 6.1.

- Use in Specific Populations: Section 8.4 Pediatric Use was revised to include relevant information from the pediatric study with immediate-release sodium oxybate.

  A minor revision to the Juvenile Animal Toxicity Data section was made to better align with the LD.

- Clinical Pharmacology: Section 12.3 Pharmacokinetics was revised to include relevant PK measures that are important for the safe and effective use of sodium oxybate extended-release powder for oral solution, as per current labeling guidance.

- Clinical Studies: Information from the pediatric study with immediate-release sodium oxybate was added.

Patient Labeling

- Medication Guide (MG) and the Instructions for Use (IFU) were revised to align with the revisions to the PI.

12 Risk Evaluation and Mitigation Strategies (REMS)

All oxybate products, including Lumryz (sodium oxybate extended-release), are subject to a REMS to mitigate the risk of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion. As described in the Lumryz approval letter, 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.

The REMS for Lumryz was originally approved on May 1, 2023. The REMS consists of elements to assure safe use (ETASU), implementation system, and a timetable for submission of assessments. The ETASU include healthcare provider certification, pharmacies certification, and documentation of safe use conditions. In this sNDA submission, the Sponsor proposed modifications to the REMS to align with the expanded pediatric indication and associated dosage recommendations and clinical safety data, and language specific to pediatric patients and caregivers in the REMS materials. A new educational material for pediatric patients and caregivers was also added. The REMS goal and REMS elements remains the same as that approved on May 1, 2023. The Agency has determined that the proposed REMS is acceptable for the expanded pediatric indication.

See the Division of Risk Management Review of proposed REMS modification for further details.

13 Postmarketing Requirements and Commitment

There were no outstanding safety issues that would require issuing a postmarketing requirement. This sNDA provides pediatric information and because sodium oxybate extended-release for the treatment of narcolepsy has an orphan drug designation, it is exempt from Pediatric Research Equity Act (PREA) requirements (see Section 10). There are no outstanding efficacy issues that would necessitate negotiation of a postmarketing commitment.

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14 Division Director (Clinical) Comments

This review reflects my edits and feedback. I agree with the findings as described by the review team and concur with the approval decision.

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15 Appendices

15.1. References

None.

15.2. Financial Disclosure

Not applicable due to no clinical studies submitted with this sNDA.

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes ☐	No ☐ (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

Not applicable due to no new nonclinical data submitted with this NDA.

15.1. Clinical Pharmacology

Not applicable due to no new clinical pharmacology data submitted with this NDA.

15.2. Additional Clinical Outcome Assessment Analyses

Not applicable due to no COA analyses being necessary.

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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/

BERNARD A FISCHER
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s006

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 6 received November 7, 2023, (sequence 110) and amended May 7, 2024 (sequence 139), August 16, 2024 (sequence 153), October 7, 2024 (sequence 162), October 9, 2024 (0163), and October 11, 2024 (sequence 164)
Action Date	September 7, 2024
Nexus TTT #	2023-7129
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	October 15, 2024
Subject	Review of proposed Major 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

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EXECUTIVE SUMMARY

This is a review of 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 November 7, 2023 and amended on May 7, 2024, August 16, 2024, October 7, 2024 October 9, 2024, and October 11, 2024.

The REMS for Lumryz was originally approved on May 1, 2023, to mitigate the risk of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.[a] The most recent REMS modification was approved on September 26, 2024. The REMS consists of elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

The Applicant's proposed modifications to the REMS to align with the efficacy supplement to expand the indication to include pediatric patients 7 years of age and older. The REMS modifications include language specific to pediatric patients and caregivers, and a new REMS material, the **Pediatric Patients and their Caregivers Brochure**.

During the review of this REMS modification, we communicated to the Applicant that the **Dear Healthcare Provider Letter**, the **Dear Professional Society Letter**, and the **Fact Sheet** were no longer needed given that the dissemination plan of these materials has been completed.

DRM finds the proposed modifications to Lumryz REMS to be acceptable and recommends approval of the REMS modification. There are no changes to the timetable for submission of assessments of the REMS. There are changes to the REMS Assessment Plan to account for the additional surveyed population of caregivers for pediatric patients receiving Lumryz.

1 Introduction

This review evaluates the proposed modifications to the REMS for Lumryz (sodium oxybate extended-release), NDA 214755, submitted by Avadel CNS Pharmaceuticals (Applicant) on November 7, 2023 and amended on May 7, 2024, August 16, 2024, October 7, 2024, October 9, 2024, and October 11, 2024.

The Applicant's proposed modifications to the REMS to include language for pediatric patients and caregivers and to align with the proposed changes to labeling. The modification also includes the addition of a new REMS material, the **Pediatric Patients and their Caregivers Brochure**.

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 packets that contain a single dose 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.

[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.

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 modification to the Lumryz REMS was on September 26, 2024. The Lumryz REMS 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).

2.2 REGULATORY HISTORY

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

- **11/07/23:** Applicant submitted an efficacy supplement to expand the indication to include patients 7 years of age and older with narcolepsy. The submission included REMS modifications to include language for pediatric patients and caregivers and to align with the proposed changes to labeling.
- **04/23/24:** Interim Comments issued to the Applicant based on DRM's April 21, 2024 review of proposed REMS modifications.[3]
- **05/07/24:** Applicant submitted a REMS amendment in response to DRM's April 23, 2024 Interim Comments.
- **08/09/24:** Interim Comments issued to the Applicant based on DRM's review of proposed REMS modifications.[4]
- **08/16/24**: Applicant submitted a REMS amendment in response to DRM's August 9, 2024 Interim Comments.
- **10/04/24**: Interim Comments issued to the Applicant based on DRM's review of proposed REMS modifications.[5]
- **10/07/24**: Applicant submitted a REMS amendment in response to DRM's Interim Comments.
- **10/08/24**: Information Request sent to the Applicant on REMS website portal screenshots in the Supporting Document.[6]

- **10/09/24**: Applicant submitted an amendment containing REMS submission with edits in response to DRM's Information Request.
- **10/10/24**: Information Request sent to the Applicant to align the Prescriber Brochure and Patient Counseling Checklist with the applicable changes made to the prescribing information.[7]
- **10/11/24**: Applicant submitted an amendment containing REMS submission with edits in response to DRM's Information Request.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITIONS

Narcolepsy is a lifelong neurological condition characterized by disordered control of the sleep-wake cycle.[8] The overall prevalence of narcolepsy with cataplexy is estimated to be 25 to 50 per 100,000 people. Narcolepsy often begins in childhood, with an estimate of 33% of patients that develop symptoms before the age of 15 years, and up to 5% of patients before the age of 5 years.[9] The diagnostic criteria of narcolepsy in children are the same as adults, however diagnosis is often delayed in children.[9] Common symptoms of narcolepsy include excessive daytime sleepiness, hypnagogic hallucinations, sleep paralysis, and disrupted nighttime sleep. Cataplexy (sudden loss of muscle tone often triggered by strong emotions) is another common symptom of narcolepsy, however it can present differently in children and can sometimes be confused with atonic seizures.[9]

Narcolepsy in children is associated with several comorbidities, such as weight gain, precocious puberty, and neurological/psychiatric disorders (e.g., depression, anxiety disorder, and attention deficit hyperactivity disorder). Additionally, narcolepsy in children can have a negative impact on quality of life and is associated with learning problems, poor academic performance, and social isolation.[10]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment options for narcolepsy in children include lifestyle modifications (e.g., improved sleep hygiene) and pharmacotherapy for symptomatic management. The 2021 American Academy of Sleep Medicine clinical practice guideline suggests clinicians use sodium oxybate or modafinil for the treatment of narcolepsy in pediatric patients, however this was a conditional recommendation, and clinicians are expected to use their clinical knowledge on the best appropriate treatment for individual patients.[11]

Although modafinil has been used to treat narcolepsy in children, it is not FDA-approved for use in children with narcolepsy. Xyrem (sodium oxybate) and Xywav (calcium, magnesium, potassium, and sodium oxybates), both immediate-release oxybate products, are FDA-approved drugs for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy include.[12,13] Both Xywav and Xyrem are subject to a REMS to mitigate the risk of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.

Additionally, Wakix (pitolisant) was recently approved for the treatment of EDS in pediatric patient 6 years of age and older with narcolepsy on June 21, 2024, however use of Wakix for the treatment of cataplexy is only approved in adult patients.[14] Other drugs such as methylphenidate and dextroamphetamine are approved for the treatment of narcolepsy, and have been used in pediatric patients. Tricyclic antidepressants, and selective serotonin reuptake inhibitors have also been used, but evidence supporting the use of these drugs for children with cataplexy or EDS with narcolepsy is limited.

4 Benefit Assessment

The effectiveness of Lumryz for the treatment of cataplexy and excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy based upon data from a prior double-blind placebo-controlled, randomized-withdrawal study (Study 13-005) in patients treated with immediate-release sodium oxybate (Xyrem). Additional evidential support comes from previous efficacy data for Lumryz for the approved indication in adults with cataplexy and EDS in narcolepsy (Study CLFT218-1501); and previous findings from a prior single-dose, randomized, two-sequence, crossover, comparative bioavailability study (Study PKFT218-1801).

The clinical review team recommends approval for the expanded pediatric indication for Lumryz for the treatment of cataplexy and EDS in narcolepsy in patients 7 years of age and older. Refer to the Multi-Disciplinary Review and Evaluation for more information.[15]

5 Risk Assessment and Safe-Use Conditions

The safety profile for pediatric patients receiving immediate-release sodium oxybate was generally consistent with the safety profile for adults, with the main safety concerns being central nervous system depression, and abuse and misuse. Pediatric patients with narcolepsy also experienced suicidal ideation, depression, neuropsychiatric reactions (including psychosis, confusion, and anxiety), and parasomnias while taking immediate-release sodium oxybate.[16]

6 Expected Postmarket Use

In addition to the likely providers for Lumryz for adults (e.g. providers specializing in sleep medicine, neurology, and pulmonology), it is expected that providers specializing in pediatrics are likely given the proposed use in pediatric patients 7 years and older.

7 Review of Proposed REMS Modifications

The Applicant proposed to include information on the pediatric indication, pediatric dosing information, adverse reactions, and patient counseling information for pediatric patients and caregivers throughout REMS materials. There are no changes to the REMS goal, REMS Document, or REMS elements.

Reviewer's comments: *Changes to include prescribing and counseling information for pediatric patients to the REMS are acceptable.*

7.1 REMS REQUIREMENTS

7.1.1 REMS Participant Requirements and Materials

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

7.1.1.1 Healthcare Providers that prescribe

The Applicant proposed that healthcare providers counsel caregivers on the serious risks, safe use, handling, and storage of Lumryz by using a new patient educational material, the **Pediatric Patients and**

their Caregivers Brochure, when counseling pediatric patients. The **Prescriber Enrollment Form** and **Prescription Form** were modified with the updated indication to include patients 7 years of age and older.

Reviewer's comments: *The Applicant incorporated our comments provided on April 23, 2024 to the prescriber requirements,* ***Prescriber Enrollment Form****, and* ***Prescription Form****. The proposed changes prescriber requirements and materials are acceptable.*

7.1.1.2 Patients

The Applicant proposed including the **Pediatric Patients and their Caregivers Brochure** as part of the materials patients need to review before treatment initiation and during treatment.

The Applicant also proposed changes to the **Patient Enrollment Form** to include data fields for caregiver information and added the statement: "A parent or caregiver of a patient under the age 18 must also read and understand each item before signing this enrollment form."

The **Patient Brochure** was updated with the pediatric indication for patients 7 years of age and older and the updated steps on how to take Lumryz.

The **Pediatric Patients and their Caregivers Brochure** was developed to educate caregivers and pediatric patients and includes section with information and graphical images (like a storybook) directed towards pediatric patients, as well as section for caregivers to educate and involve their child in the safe use of Lumryz.

Reviewer's comments: *The Applicant incorporated our comments provided on April 23, 2024 to the* ***Patient Enrollment Form*** *and the* ***Pediatric Patients and their Caregivers Brochure****. The proposed changes to patient requirements and materials are acceptable.*

7.1.1.3 Pharmacies that dispense

The Applicant proposed that new patients be given the **Pediatric Patients and their Caregivers Brochure** with their first shipment. The proposed changes were applied to the **Pharmacy Enrollment Form**. Additionally, the **Patient Counseling Checklist** was edited to include: data fields for caregiver information; include information on "change of care responsibility" to step 1 and step 2; include "change in medication use or medical history" to the "scheduled refill" option in step 1; and counseling information for caregivers to align with pediatric and/or caregiver updates made to the prescribing information.

Reviewer's comments: *The Applicant incorporated our recommended edits and changes provided on April 23, 2024, August 9, 2024, and October 10, 2024 to the pharmacy requirements,* ***Pharmacy Enrollment Form,*** *and the* ***Patient Counseling Checklist****. Information on change of caregiver responsibility was added to ensure new caregivers for an already enrolled pediatric patients are educated. Additionally, the Applicant added "change in medication use and medical history" to the "scheduled refill" option to step 1 of the* ***Patient Counseling Checklist*** *given that certified pharmacies are required educate patients using the* ***Patient Counseling Checklist*** *if they report a change medication use or medical history. The proposed changes to pharmacy requirements,* ***Pharmacy Enrollment Form****, and* ***Patient Counseling Checklist*** *are acceptable.*

7.1.2 REMS Applicant Requirements and Materials

Only the affected Applicant requirements and their associated materials are reviewed below.

7.1.2.1 Training

The **Prescriber Brochure**, **Certified Pharmacy Training Program**, **Pharmacy Staff Knowledge Assessment**, and **Pharmacist Knowledge Assessment** were updated to align with the pediatric and/or caregiver updates that were made to the prescribing information. These changes include updating the indication to include pediatric patients 7 years of age and older; including caregivers when counseling or interacting with pediatric patients; and adding information on adverse reactions to the **Prescriber Brochure**. Pediatric dosing and counseling information was included in the **Prescriber Brochure** in the new Pediatric Patient Supplement section. Additionally, a statement regarding the need to counsel new caregivers of already enrolled pediatric patients on the risks and safe use of Lumryz was added to the **Certified Pharmacy Training Program.**

Reviewer's comments*: The Applicant addressed our comments which were provided on April 23, 2024, August 9, 2024, October 4, 2024, and October 10, 2024. The proposed changes to the* ***Prescriber Brochure****,* ***Certified Pharmacy Training Program****,* ***Pharmacy Staff Knowledge Assessment****, and* ***Pharmacist Knowledge Assessment*** *are acceptable****.***

7.1.2.2 Communication

The Applicant proposed to remove the **Fact Sheet**, **Dear Healthcare Provider Letter**, and the **Dear Professional Society Letter** from the REMS.

Reviewer's comments*: The dissemination plan for communication materials have been completed, and communication materials are no longer necessary in Lumryz REMS. The proposed changes to remove the communication materials are acceptable.*

7.1.2.3 Operations

The **REMS website** was updated with the proposed changes to the indication and REMS materials. A requirement was added to the REMS operation section of the REMS Document to ensure pediatric patients are able to change caregivers provided that the new caregiver has been counseled by a certified pharmacy on the serious risks and safe use of the drug and acknowledges that he/she had any questions about Lumryz answered before the drug product is dispensed and shipped.

Reviewer's comments*: The Applicant incorporated our comments provided on April 23, 2024. The proposed changes to the REMS website and the REMS operation requirements are acceptable.*

7.2 REMS ASSESSMENT TIMETABLE

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

8 Supporting Document

The REMS Supporting Document was updated to include the background of the REMS Modification currently under review. The website portal screenshots were also updated with the changes made to REMS materials.

Reviewer's comments*: The proposed changes to the REMS Supporting Document are acceptable.*

9 REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be addressed in the REMS Modification Approval letter.

The following revisions were made to metric 12 of the Assessment Plan as underlined below.

12. Knowledge, Attitude, and Behavior (KAB) Surveys of Patients/Caregivers, Healthcare Providers, and Pharmacists (to be submitted annually)
    a. Assessment of patients'/caregivers', healthcare providers' and pharmacists' understanding of the following:
        i. The risk of significant CNS and respiratory depression associated with Lumryz even at recommended doses
        ii. The contraindicated uses of Lumryz with sedative hypnotics and alcohol
        iii. The potential for abuse, misuse, and overdose associated with Lumryz
        iv. The safe use, handling, and storage of Lumryz
        v. The Lumryz REMS requirements

Reviewer's comments: *The assessment plan is acceptable.*

10 Discussion

The clinical reviewer recommends approval of Lumryz to expand the indication to include pediatric patients 7 years of age and older.

The safety profile for pediatric patients was generally consistent with the safety profile for adults, with the main safety concerns being central nervous system depression, and abuse and misuse. Because of the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion, a REMS is required to ensure the benefits outweigh the risks.

The Applicant's proposed REMS modification to the Lumryz REMS included language for pediatric patients and caregivers and to align with the proposed changes to labeling. The modification also included the addition of a new REMS material, the **Pediatric Patients and their Caregivers Brochure**. Additional changes during the course of the review included removing the **Fact Sheet**, **Dear Healthcare Provider Letter**, and **Dear Professional Society Letter** from the REMS.

Furthermore, the REMS Assessment Plan was revised to account for the additional surveyed population of caregivers for pediatric patients receiving Lumryz.

11 Conclusions and Recommendations

DRM finds the proposed REMS modification for Lumryz (sodium oxybate extended-release) as submitted received on November 7, 2023 and last amended on October 11, 2024 to be acceptable and we recommend approval.

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

The REMS Assessment Plan, as summarized in the REMS Supporting Document, has been revised to be consistent with the REMS Modification for Lumryz and will be included in the REMS Modification Approval letter.

12 References

1. Avadel CNS Pharmaceuticals, Inc. Lumryz (sodium oxybate extended-release). Prescribing Information. May 1, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214755Orig1s000lbl.pdf
2. Approval Letter for Lumryz (sodium oxybate extended-release). May 1, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/214755Orig1s000ltr.pdf
3. Olumba, S. Interim Review of Proposed Major REMS Modification for Lumryz. NDA 214755. April 21, 2024. DARRTS ID 5367008.
4. Olumba, S. Interim Review of Proposed Major REMS Modification for Lumryz. NDA 214755. August 9, 2024. DARRTS ID 5426911.
5. Olumba, S. Interim Review of Proposed Major REMS Modification for Lumryz. NDA 214755. October 4, 2024. DARRTS ID 5367008.
6. Information Request for Proposed Major REMS Modification for Lumryz. NDA 214755 October 8, 2024. DARRTS ID 5459737.
7. Information Request for Proposed Major REMS Modification for Lumryz. NDA 214755. October 10, 2024. DARRTS ID 5461320.
8. Center for Disease Control and Prevention. Heart Disease Facts. May 15, 2024. https://www.cdc.gov/heart-disease/data-research/facts-stats/index.html
9. Garber A. Stress testing for the diagnosis of obstructive coronary artery disease. Accessed August 7, 2024. https://www.uptodate.com/contents/stress-testing-for-the-diagnosis-of-obstructive-coronary-artery-disease?search=coronary%20computed%20tomographic%20angiography%20cad&source=search_result&selectedTitle=2%7E150&usage_type=default&display_rank=2#H1
10. Plazzi G, Clawges HM, Owens JA. Clinical Characteristics and Burden of Illness in Pediatric Patients with Narcolepsy. *Pediatr Neurol*. Aug 2018;85:21-32. doi:10.1016/j.pediatrneurol.2018.06.008
11. Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. Sep 1 2021;17(9):1881-1893. doi:10.5664/jcsm.9328
12. Jazz Pharmaceuticals. Xyrem (sodium oxybate). Prescribing Information. Last updated April 4, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021196s042lbl.pdf
13. Jazz Pharmaceuticals. Xywav (calcium, magneisum, potassium, and sodium oxybates). Prescribing Information. Last updated April 4, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212690s011lbl.pdf

14. Harmony. Wakix (pitolisant hydrochloride). Prescribing Information. June 21, 2024 https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/211150s005 (b) (4) pdf
15. Multi-Disciplinary Review and Evaluation: Lumryz (sodium oxybate extended-release). NDA 214511. Review in progress. Accessed October 3, 2024.
16. Proposed prescribing information for Lumryz (sodium oxybate extended-release) as currently edited by FDA. Accessed October 4, 2024.

13 Appendix

Assessment Plan

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
- Pediatric Patients and their Caregivers Brochure

Pharmacy:

- Certified Pharmacy Training Program
- Pharmacy Staff Knowledge Assessment
- Pharmacist Knowledge Assessment

Patient Care Forms

- Prescription Form
- Patient Counseling Checklist

Other Materials

- Risk Management Report
- REMS Program Website

Lumryz REMS Assessment Plan

For each metric, provide the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted

Program Implementation and Operations

1. **REMS Implementation (1st assessment after approval)**
    a. REMS implementation date
    b. Date of first commercial distribution of Lumryz
    c. Date when the Lumryz REMS call center became operational
    d. Date when the Lumryz REMS website became live and operational
    e. Date(s) when the Dear Healthcare Provider Letter and Dear Professional Society Letter were provided
        i. Number of letters sent by method of distribution (mail/email)
        ii. Number of letters returned/undeliverable and number of unopened emails for each mailing

2. **REMS Enrollment and Certification Statistics**
    a. Patients
        i. Total number of enrolled patients
        ii. Number and percentage of newly enrolled patients stratified by age, geographic region (defined by US Census), and gender
        iii. Number and percentage of active patients enrolled (i.e., patients who received at least one shipment of Lumryz during the reporting period) stratified by age, geographic region (defined by US Census), and gender
        iv. Number and percentage of patients who have discontinued Lumryz after receiving at least one shipment of Lumryz. Include demographics of discontinued patients and reasons for discontinuation
    b. Healthcare Providers
        i. Total number of certified healthcare providers
        ii. Number and percentage of newly certified healthcare providers stratified by professional designation (i.e., MD, DO, PA, NP, Other), medical specialty, and geographic region (defined by US Census)
        iii. Number and percentage of active certified healthcare providers (healthcare providers who have written at least one prescription for Lumryz during the reporting period) stratified by professional designation (i.e., MD, DO, PA, NP, Other), medical specialty, and geographic region (defined by US Census)
    c. Certified Pharmacy
        i. Total number of certified pharmacies
        ii. Number of newly certified pharmacies
        iii. Number of active pharmacies (e.g., dispensed one or more Lumryz prescriptions)
    d. Wholesalers/Distributors
        i. Total number of authorized wholesalers/distributors
        ii. Number and percentage of newly authorized wholesalers/distributors

iii. Number and percentage of active wholesalers/distributors (i.e., have shipped Lumryz at least once during the reporting period)

3. Utilization Data

a. Number of shipments, including number of Lumryz packets, shipped by wholesalers, distributors, and other entities to pharmacies.
b. Number and percentage of Lumryz prescriptions (new and refill) dispensed by pharmacies to patients.
c. Number and percentage of Lumryz packets and shipments sent by pharmacies to patients stratified by dose strength.

4. REMS Operation and Performance Data

a. REMS Databases Report
   i. Number and percentage of contacts by stakeholder type (e.g., patients, healthcare providers, pharmacy, other)
   ii. Summary of reasons for contacts (e.g., enrollment questions) by reporter (e.g., authorized representative, patient, healthcare provider, other)
   iii. Summary of frequently asked questions by stakeholder type and topic
   iv. Summary of any REMS-related problems identified and a description of any corrective actions taken
   v. If the summary reason for the calls indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden (e.g., pharmacy calls to other REMS for oxybate products) or patient access issues (e.g., patient's therapy delayed due to unwillingness of other REMS for oxybate products to provide necessary information)
   vi. Summary of program or system problems and a description of any corrective actions taken

5. REMS Compliance

a. Audits: Summary of audit activities including but not limited to:
   i. A copy of the audit plan for certified pharmacies and wholesalers, distributors, and other entities that distribute Lumryz
   ii. The number of audits expected, and the number of audits performed
   iii. The number and type of deficiencies noted
   iv. For those with deficiencies noted, report the status of corrective and preventative action (CAPA) proposed to address the deficiencies, including completion dates
   v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
   vi. Provide details on deviations for the CAPA proposed, including timelines, and mitigating steps to address the deviations
   vii. Confirm documentation of completion of training for relevant staff
   viii. Review of cumulative findings to identify any trends of potential repeat issues, and steps to be taken to address these findings
   ix. A summary report of the processes and procedures that are implemented to be in compliance with the REMS requirements
b. A summary report of noncompliance, associated corrective and preventive actions (CAPA) plans, and the status of CAPA plans including but not limited to:

i. A copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder, actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or decertified/disenrolled from the REMS
ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:
    1. The unique ID(s) of the stakeholder(s) associated with the noncompliance event to enable tracking over time
    2. The source of the noncompliance data
    3. The results of root cause analysis
    4. What action(s) were taken in response

c. Healthcare Providers
    i. Number and percentage of certified healthcare providers who were decertified and reasons for decertification. Include if any healthcare providers were re-certified.
    ii. Number and percentage of Lumryz prescriptions filled from a healthcare provider who was not certified
d. Certified Pharmacies
    i. Number and percentage of Lumryz prescriptions dispensed for more than a 30 days' supply (first fill) or more than a 90 days' supply (refills) and reasons
    ii. Number and percentage of Lumryz shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and *Risk Management Reports* completed
    iii. Number and percentage of initial Lumryz shipments sent to patients without completion of the Patient Counseling Checklist
    iv. Number and percentage of Lumryz shipments sent to patients without completion of the Patient Counseling Checklist for patients that reinitiated therapy after a lapse of > 6 months
    v. Number and percentage of Lumryz shipments sent to patients without completion of the Patient Counseling Checklist when the patient notified the pharmacy of a new or change in concomitant medication or comorbidity
    vi. Number and percentage of pharmacy decertifications and reasons for decertification. Include if any pharmacies were re-certified.
e. Patients
    i. Number and percentage of patients who were disenrolled from the program and reasons for disenrollment
    ii. Number and percentage of patients who received prescriptions from more than one prescriber during their therapy
    iii. Number and percentage of patients with overlapping Lumryz prescriptions (more than one active prescription shipped)
    iv. Number of duplicate patients detected by certified pharmacies
    v. Number and percentage of duplicate patients who were shipped Lumryz under more than one name or identifier
    vi. Number and percentage of patients who were shipped Lumryz after being disenrolled
    vii. Number of patients found to have active, overlapping prescriptions for Lumryz and any other oxybate product (e.g., Xywav, Xyrem, or generic Sodium Oxybate)

viii. Number and percentage of patients who requested an early refill of Lumryz and reason for the request
    1. Number and percentage of requests approved
    2. Number and percentage of requests denied by the prescriber
    3. Number and percentage of requests denied by the certified pharmacy
    4. Number and percentage of patients with multiple (i.e., more than 1) requests for early refills

Safe Use Behaviors

6. Pharmacy Notifications

a. A summary of the notifications by pharmacies to prescribers for Lumryz. Each of the following situations will include the number and percentage of notifications, number of unique patients, the outcome of the pharmacy notification (e.g., counseled patient, discussed with prescriber) and outcome of Lumryz prescription disposition (e.g., prescriber approved shipment, prescriber requested shipment hold, prescriber denied shipment, pharmacy approved shipment):
    i. Use with prescription sedative-hypnotics indicated for sleep (e.g., eszopiclone, zaleplon, zolpidem, temazepam, suvorexant, quazepam, estazolam, flurazepam, triazolam, tasimelteon, ramelteon). Indicate specific actions taken by the prescriber and the prescriber rationale for continuing treatment in response to the notification including the following:
        1. Treatment with Lumryz will be discontinued
        2. Sedative hypnotic will be discontinued
        3. Dosage of sedative hypnotic has been/will be reduced
        4. Information unavailable
        5. No action (continue sedative hypnotic with Lumryz)
        6. Prescriber's rationale for continued use of sedative hypnotic with Lumryz
            a. Sedative hypnotic will not be taken at the same time as Lumryz
            b. Sedative hypnotic will be taken at the same time as Lumryz
            c. Sedative hypnotic will be taken as a sleep aid
            d. Sedative hypnotic will be taken for different indication per medical need
            e. Lumryz dose regimen changed
            f. No rationale provided
            g. Other rationale provided
    ii. Benzodiazepines (e.g., diazepam, alprazolam or any not listed in metric 6.a.i.). Indicate specific actions taken by the prescriber and the prescriber rationale for continuing treatment in response to the notification including the following:
        1. Treatment with Lumryz will be discontinued
        2. Benzodiazepine will be discontinued
        3. Dosage of benzodiazepine has been/will be reduced
        4. Information unavailable
        5. No action (continue benzodiazepine with Lumryz)
        6. Prescriber's rationale for continued use of benzodiazepine with Lumryz
            a. Benzodiazepine will not be taken at the same time as Lumryz
            b. Benzodiazepine will be taken at the same time as Lumryz

c. Benzodiazepine will be taken as a sleep aid
d. Benzodiazepine will be taken for different indication per medical need
e. Lumryz dose regimen changed
f. No rationale provided
g. Other rationale provided

iii. Use with other concomitant CNS depressant medications (i.e., sedating antidepressants or antipsychotics, sedating anti-epileptics, sedating antihistamines, general anesthetics, muscle relaxants, opioid analgesics, or illicit CNS depressants)
iv. Patient report of alcohol use
v. Patient report of diagnosis of sleep apnea
vi. Patient report of diagnosis of asthma, COPD, or other conditions affecting breathing
vii. Suspected abuse, misuse, or diversion
viii. Alerts regarding potential abuse, misuse, or diversion on the patient profiles
ix. Prescription error
x. Early refill requests

7. Risk Management Reports (RMRs)

a. Number and percentage of RMRs submitted
b. Number and percentage of unique patients with an RMR
c. Number and percentage of unique patients with multiple RMRs
d. Number and percentage of alerts generated from RMRs
e. Number and percentage of RMRs generated from early refill requests
f. Number and percentage of RMRs generated for other reasons, stratified by reasons
g. Number and percentage of prescriber-related RMRs
h. Number and percentage of RMRs that included reporting of an adverse event.

8. REMS Patient Counseling Checklist

a. Summary table from REMS Patient Counseling Checklists of the number and percentage of patients taking the following concomitant medications and who subsequently received at least one shipment of drug:
   i. Prescription sedative hypnotics indicated for sleep (e.g., eszopiclone, zaleplon, zolpidem, temazepam, suvorexant, quazepam, estazolam, flurazepam, triazolam, tasimelteon, ramelteon)
   ii. Alcohol
   iii. Other potentially interacting agents:
      1. Benzodiazepines (e.g., diazepam, alprazolam, or any not listed in metric 8.a.i.)
      2. Sedating antidepressants or antipsychotics, sedating anti-epileptics, and sedating antihistamines
      3. General anesthetics
      4. Muscle relaxants
      5. Opioid analgesics
      6. Illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB])
b. Summary table for Lumryz from REMS Patient Counseling Checklists of the number and percentage of patients who have been diagnosed with the following conditions and who subsequently received at least one shipment of drug:
   i. Sleep apnea

ii. Asthma, COPD, or other conditions affecting the respiratory system

9. Verification of Disenrollment or Active Prescriptions in Other REMS for Oxybate Products (per reporting period)

a. Information on patient with active, overlapping prescription or disenrollment or deactivation for misuse, abuse, etc., in other REMS for oxybate products and outcomes
   i. For unsuccessful attempts or those that resulted in a treatment delay, indicate the REMS contacted
   ii. Number and dates of unsuccessful contact attempts to other REMS for oxybate products, including hold times per contact attempt
   iii. For contacts resulting in a delay, the total number of contact attempts, and time from receipt of prescription to successful contact with other REMS for oxybate products
   iv. The number of prescriptions delayed or unable to be filled divided by the number of valid prescriptions received.
   v. Reason not dispensed (e.g., active prescription in other REMS for oxybate products, other REMS for oxybate products unresponsive, patient disenrolled or discontinued due to abuse, misuse or diversion)
   vi. Reports of any negative outcomes due to any treatment delay
   vii. Number of prescriptions dispensed without verification of current overlapping prescription or disenrollment from other REMS for oxybate products

10. REMS Dispense Authorizations (RDAs)

a. Number of requested RDAs that were rejected and reasons for rejection
b. Number of prescriptions dispensed where all REMS and safe use requirements were not met, but an RDA was provided
c. Number of prescriptions dispensed without an RDA
d. The number of requested RDAs that were rejected and were subsequently approved and the duration of time from rejection of the requests to approval

Health Outcomes and/or Surrogates of Health Outcomes

11. Pharmacovigilance/surveillance (per reporting period)
   a. Analysis of serious adverse events and summary table for Lumryz of the number of reports of serious adverse events, including the following data fields: date, case report ID, age, gender, serious adverse event(s) outcome (hospitalization or death), associated factors (i.e., concurrent use with sedative hypnotics or alcohol, intentional misuse, abuse, overdose, diversion, or medication error) and if cases are considered related or not related to Lumryz. Tables will include an overall narrative summary and analysis of the adverse events and data fields reported.
      i. All cases of death – include narrative summary of each death
         1. Number, percentage, and type of RMRs, notifications, and alerts within 6 months of the reported deaths
         2. Calculation of the overall, and age- and gender-specific mortality rates.
         3. Calculation of the standardized mortality rates, adjusted for age and gender, using both the point estimates and the lower bounds of the 95% confidence intervals as the reference rates.

ii. Serious adverse events with all outcomes of death, emergency department visits (when admitted to hospital), or hospitalizations resulting from or associated with the following:
    1. Use with concurrent sedative hypnotics
    2. Use with alcohol
    3. Intentional misuse
    4. Abuse
    5. Overdose
    6. Medication error
iii. Cases of sexual abuse – include narrative summary of each case
iv. Proportion of discontinued patients who were associated with a report of a serious adverse event, including death

Knowledge

12. Knowledge, Attitude, and Behavior (KAB) Surveys of Patients/ Caregivers, and Healthcare Providers, and Pharmacists (to be submitted annually)
    a. Assessment of patients'/ caregivers', and healthcare providers' and pharmacists' understanding of the following:
        i. The risk of significant CNS and respiratory depression associated with Lumryz even at recommended doses
        ii. The contraindicated uses of Lumryz with sedative hypnotics and alcohol
        iii. The potential for abuse, misuse, and overdose associated with Lumryz
        iv. The safe use, handling, and storage of Lumryz
        v. The Lumryz REMS requirements

13. Certified Pharmacy Knowledge Assessments (per reporting period and cumulatively)
    a. Number of pharmacy staff who completed post-training Knowledge Assessments including method of completion and the number of attempts needed to complete
        i. Breakdown of scores within the Pharmacy Staff Knowledge Assessment and Pharmacist Knowledge Assessment
    b. Summary of the most frequently missed post-training Pharmacy Staff Knowledge Assessment questions
    c. Summary of the most frequently missed post-training Pharmacist Knowledge Assessment questions
    d. Summary of potential comprehension or perception issues identified with the post-training Knowledge Assessments
    e. Number of pharmacy staff and pharmacists who did not pass the Knowledge Assessments

Overall Assessment of REMS Effectiveness

14. The requirements for assessments of an approved REMS under section 505-1 (g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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/s/

STEPHANIE N OLUMBA
10/15/2024 02:02:39 PM

KATE H OSWELL
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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 6 received November 7, 2023, (sequence 110) and amended May 7, 2024 (sequence 139), and August 16, 2024 (sequence 153)
Action Date	September 7, 2024
Nexus TTT #	2023-7129
Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS
Team Leader	Carolyn Tieu, PharmD, MPH
Review Completion Date	October 4, 2024
Subject	Review of proposed Major 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 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 November 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]

This interim review discusses additional changes needed to the REMS materials to align with the Prescribing Information.

2 REGULATORY HISTORY

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

- **11/07/23:** Applicant submitted an efficacy supplement to expand the indication to include patients 7 years of age and older with narcolepsy. The submission included REMS modifications to include language for pediatric patients and caregivers and to align with the proposed changes to labeling.
- **04/23/24:** Interim Comments issued to the Applicant based on DRM's review of proposed REMS modifications.
- **05/07/24:** Applicant submitted a REMS amendment in response to DRM's April 23, 2024 Interim Comments.
- **08/09/24:** Interim Comments issued to the Applicant based on DRM's review of proposed REMS modifications.
- **08/16/24**: Applicant submitted a REMS amendment in response to DRM's August 9, 2024 Interim Comments.
- **09/26/24**: Lumryz REMS modification approved to update the **Prescription Form** to include the starter pack as a prescribing option.
- **10/03/24**: Labeling Comments issued to the Applicant.

3 Comments to the Applicant

We have the following comments on the proposed REMS modification submitted with the efficacy supplement on November 7, 2023, last amended August 16, 2024. Review of the proposed REMS modification is ongoing, and these comments should not be considered final. Refer to the summary of the comments below.

[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.

General Comment

- Update the REMS materials as needed to align with the changes made to the Prescribing Information sent on 10/3/24.

Prescriber Brochure

- Update the pediatric dosing information (located on page 18 in Guidelines for Dosing and Titrating Lumryz for Pediatric Patients) in the Prescriber Brochure to align with the changes made to the Prescribing Information sent on 10/3/24.

Prescription Form

- Align the Prescription Form with the REMS modification to include the starter pack as a prescribing option on the Prescription Form approved on September 26, 2024.

Resubmission Instructions

Submit a REMS amendment by 10/7/24 that addresses these comments. The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following document:

- Prescriber Brochure
- Prescription Form

Additionally, include the Supporting Document and one compiled PDF file that includes the REMS Document and all REMS materials (excluding the Supporting Document) in their final format.

4 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

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/s/

CAROLYN N TIEU on behalf of STEPHANIE N OLUMBA
10/04/2024 04:32:57 PM

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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 6 received November 7, 2023 (sequence 110) and amended May 7, 2024 (sequence 139)
Action Date	September 7, 2024
Nexus TTT #	2023-7129
Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	August 8, 2024
Subject	Review of proposed Major 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 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 November 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]

This interim review discusses additional changes needed to the REMS: to align REMS materials with changes to the prescribing information; to provide editorial changes to the **Pharmacist Knowledge Assessment** and **Patient Counseling Checklist**; and to include the process of the REMS Dispense Authorization being valid for only 3 calendar days after it is generated in the Supporting Document.

2. Regulatory History

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

- **04/23/24:** Interim Comments issued to the Applicant based on DRM's review of proposed REMS modifications.
- **05/07/24:** Applicant submitted a REMS amendment in response to DRM's April 23, 2024 Interim Comments.

3. Comments to the Applicant

We have the following comments on the proposed REMS modification submitted with the efficacy supplement on November 7, 2023, last amended May 7, 2024. Review of the proposed REMS modification is ongoing, and these comments should not be considered final. Refer to the summary of the comments below.

General Comment

- Update the REMS materials as needed to align with the changes made to the Prescribing Information.

Prescriber Brochure

- Update the pediatric dosing information (located page 18 in Guidelines for Dosing and Titrating Lumryz for Pediatric Patients) and the Pediatric Use section (located on page 14) in the Prescriber Brochure to align with the changes made to the Prescribing Information.

Pharmacist Knowledge Assessment

- Rename the (b) (4) to Pediatric Patients and their Caregivers Brochure for question 9; and ensure that it is renamed across all REMS materials.

Patient Counseling Checklist

[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.

- Refer to the proposed change on the Patient Counseling Checklist to include “change in medication use or medical history” as an option to step 1. To reduce redundancy, combine that option with “scheduled refill” option. The option should state: “Scheduled refill (change in medication use or medical history)”.

Supporting Document

- Update the Supporting Document to align with changes made to the REMS materials (e.g., portal screenshots).
- Refer to the REMS Correspondence received on June 28, 2024 where it stated an “RDA generated in the Lumryz REMS is valid for only 3 calendar days before dispensing Lumryz. If a Lumryz dispense is delayed or does not occur within 3 calendar days of the RDA generation, then the pharmacist must verify all Lumryz REMS elements again prior to dispensing Lumryz and generate a new RDA to authorize the dispense.” This process in not described in the REMS supporting document. Add the process regarding the RDA is valid for only 3 calendar days to the REMS Supporting Document, in the RDA section on page 24 after number 6.

Resubmission Instructions

Submit a REMS amendment within 5 business days that addresses these comments. The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following documents:

- Prescriber Brochure
- Pharmacist Knowledge Assessment
- Patient Counseling Checklist
- REMS Supporting Document

Additionally, include one compiled PDF file that includes the REMS Document and all REMS materials (excluding the Supporting Document) in their final format.

4. 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

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/s/

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08/08/2024 12:58:53 PM

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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 6 received November 7, 2023 (sequence 110)
Action Date	September 7, 2024
Nexus TTT #	2023-7129
Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS Kate Oswell, MA Kathryn Marwitz, PharmD, MPH (DMAMES[a])
Team Leader	Carolyn Tieu, PharmD, MPH
Associate Director (DMAMES Designee)	Joseph Paradis, PharmD (OMEPRM)
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	April 18, 2024
Subject	Review of proposed Major 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

[a] DMAMES: Division of Mitigation Assessment and Medication Errors Surveillance

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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 November 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[b] of Lumryz.[2]

The Applicant submitted an efficacy supplement on November 7, 2023 to expand the indication of Lumryz to include pediatric patients 7 years of age and older with narcolepsy. As part of this supplement, the Applicant proposed REMS modifications to include language specific to pediatric patients and caregivers to align with the proposed changes to labeling. The supplement also includes the addition of a new REMS material, the (b) (4). These changes affect the REMS Document, REMS materials, and REMS Supporting Document.

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.
- **11/07/23:** Applicant submitted an efficacy supplement to expand the indication to include patients 7 years of age and older with narcolepsy.

3. Review of Proposed REMS Modifications

The Applicant proposed to include information on the pediatric indication, pediatric dosing information, adverse reactions, and patient counseling information for pediatric patients and caregivers throughout the REMS Document and REMS materials. The proposed changes will have to align with the final agreed upon prescribing information.

3.1. REMS Goal

The Applicant proposed (b) (4).

Reviewer's Comments: *We do not agree with the proposal* (b) (4)

[b] 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.

[redacted] *. We have removed* [redacted] *the REMS goal will remain as currently approved.*

3.2. REMS Requirements

3.2.1. REMS Participant Requirements and Materials

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

3.2.1.1. Healthcare Providers that prescribe

The Applicant proposed [redacted] s. The **Prescriber Enrollment Form** and **Prescription Form** were modified to align with the proposed changes and to include pediatric patients 7 years of age and older in the indication.

Reviewer's Comments: *As stated* [redacted] *. We have removed language* [redacted] *from the REMS Document,* ***Prescriber Enrollment Form****, and* ***Prescription Form.***

[redacted] *The Applicant needs to develop a section that provides specific information, including graphical images (like a storybook), directed towards pediatric patients. The Applicant should also develop a section for caregivers on important information your child must know about taking Lumryz and a section on including your child in his or her care. The Applicant should refer to the FDA-approved Xyrem Brochure for Pediatric Patients and their Caregivers on REMS@FDA as an example of this type of information. Since this brochure will include information directed towards pediatric patients, it should be renamed the "Pediatric Patients and their Caregivers Brochure." This change aligns with the pediatric patient educational materials in the Xywav and Xyrem REMS. We will inform the Applicant to rename the brochure throughout all REMS materials.*

3.2.1.2. Patients

The Applicant proposed including the [redacted] as part of the materials patients need to review before treatment initiation and during treatment.

The Applicant also proposed to change to the **Patient Enrollment Form** to include data fields for caregiver information and changes to the patient attestations adding [redacted] throughout the patient attestations.

The **Patient Brochure** was updated to reflect the pediatric indication and the updated steps on how to take Lumryz.

Reviewer's Comments: We agree with the inclusion of the [redacted] *(to be renamed the "Pediatric Patients and their Caregivers Brochure") as a patient material, but additional changes are necessary as described in section 3.2.1.1. Changes to the* ***Patient Brochure*** *are acceptable.*

It is not necessary to rename the patient attestations to [redacted] *" in the* ***Patient Enrollment Form*** [redacted] *. Adding data fields for caregiver*

*information to the **Patient Enrollment Form** is acceptable. To improve readability and clarity of the **Patient Enrollment Form**, we have removed the use of [redacted] (b) (4) " throughout the attestations and added a statement that reads: "A parent or caregiver of a patient under the age 18 must also read and understand each item before signing this enrollment form." Similar statements are included in other patient enrollment forms for other products with approved REMS used in pediatric patients (e.g., Zulresso REMS and iPLEDGE REMS).*

3.2.1.3. Pharmacies that dispense

The Applicant proposed that pharmacies counsel caregivers using the **Patient Counseling Checklist** for new patients, existing patients who restart treatment after not receiving Lumryz for 6 months or longer, and for patients who report a change in their medication use or medical history. The Applicant also proposed that caregivers be given a [redacted] (b) (4) with their first shipment. The proposed changes were made to the **Pharmacy Enrollment Form.** Additionally, the **Patient Counseling Checklist** was edited to include data fields for caregiver information, counseling information for caregivers, and to align with the pediatric and/or caregiver updates that were made to the prescribing information, Information For Use, and the Medication Guide.

Reviewer's Comments:** As explained in section 3.1, [redacted] (b) (4) We have removed the language [redacted] (b) (4) However, including information to counsel caregivers in the **Patient Counseling Checklist** is acceptable because it provides prompts for prescribers and pharmacies to counsel caregivers. In case there is a new caregiver for an already enrolled pediatric patients, the new caregiver will need to be educated. We've added this information on "change of care responsibility" to step 1 and step 2 in the **Patient Counseling Checklist.

3.2.2. REMS Applicant Requirements and Materials

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

3.2.2.1. Training

The **Prescriber Brochure**, **Certified Pharmacy Training Program**, **Pharmacy Staff Knowledge Assessment**, and **Pharmacist Knowledge Assessment** were updated to align with the pediatric and/or caregiver updates that were made to the prescribing information. These changes include updating the indication to include pediatric patients 7 years of age and older with narcolepsy; including caregivers when counseling or interacting with pediatric patients; and adding information on adverse reactions and dosing guidelines for pediatric patients in the **Prescriber Brochure.** The **Certified Pharmacy Training Program** includes the proposed REMS goal.

***Reviewer's Comments**: The Applicant's proposed changes to include information on counseling caregivers in the **Prescriber Brochure**, **Certified Pharmacy Training Program**, **Pharmacy Staff Knowledge Assessment,** and **Pharmacist Knowledge Assessment** are acceptable. Including information on counseling caregivers in the training materials will provide prompts for prescribers and pharmacies to counsel caregivers.*

*We have provided edits to the **Prescriber Brochure** to align with the Prescriber Brochure for other approved REMS for oxybate products; specifically, the pediatric dosing information was moved to a new*

section called the "Pediatric Patient Supplement." Additional information regarding counseling caregivers for pediatric patients was also added to Pediatric Patient Supplement section.

*We have aligned the REMS goal by reverting back to the currently approved REMS goal in the **Certified Pharmacy Training Program** as explained in section 3.1. We also added a statement regarding the need to counsel new caregivers of already enrolled pediatric patients on the risks and safe use of Lumryz, and this change aligns with the changes made to the **Patient Counseling Checklist**.*

3.2.2.2. Communication

The Applicant proposed (b) (4) The Applicant did not propose any changes to the **Dear Healthcare Provider Letter** and the **Dear Professional Society Letter**.

***Reviewer's Comments:** When Lumryz was first approved in 2023, the Applicant was required to disseminate communication materials to inform healthcare providers about the REMS and risks and safe use of Lumryz. The dissemination plans for the **Fact Sheet, Dear Healthcare Provider Letter,** and the **Dear Professional Society Letter** have been completed, and the communication materials are no longer necessary and can be removed. If the pediatric indication is approved, the Applicant can send letters to prescribers notifying them of the new indication outside of the REMS.*

3.2.2.3. Operations

The REMS website was updated to align with the pediatric updates made to the prescribing information and REMS materials.

***Reviewer's Comments:** We have added a requirement to the REMS operation section of the REMS Document to ensure pediatric patients are able to change caregivers provided that the new caregiver has been counseled by a certified pharmacy on the serious risks and safe use of the drug and acknowledges that he/she had any questions about Lumryz answered before the drug product is dispensed and shipped. The REMS website will need to align with changes made to the REMS Document and REMS materials described in this review.*

4. Supporting Document

The REMS Supporting Document was changed to include the background of the REMS Modification currently under review.

***Reviewer's Comments**: The Applicant will need to align the Supporting Document with changes made to the REMS Document and REMS materials.*

4.1. REMS Assessment Plan

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

***Reviewer's Comments:** DMAMES reviewed the Applicant's Assessment Plan for alignment with the Applicant's submitted efficacy supplement. We request that the Applicant revise metric 12 of their Assessment Plan to account for the additional surveyed population of caregivers for pediatric patients receiving Lumryz. The Applicant proposes surveying caregivers of pediatric patients in their Quantitative Testing of Patient Knowledge, Attitudes, and Behavior about Lumryz Patient KAB Protocol and Survey*

Version 2.0 dated September 6, 2023. Metric 12 of the Assessment Plan will need to be revised as underlined below.

12. Knowledge, Attitude, and Behavior (KAB) Surveys of Patients/Caregivers, Healthcare Providers, and Pharmacists (to be submitted annually)

- *a. Assessment of patients'/caregivers', healthcare providers' and pharmacists' understanding of the following:*
  - *i. The risk of significant CNS and respiratory depression associated with Lumryz even at recommended doses*
  - *ii. The contraindicated uses of Lumryz with sedative hypnotics and alcohol*
  - *iii. The potential for abuse, misuse, and overdose associated with Lumryz*
  - *iv. The safe use, handling, and storage of Lumryz*
  - *v. The Lumryz REMS requirements*

5. Conclusions and Recommendations

DRM does not find the proposed REMS modifications for Lumryz (sodium oxybate extended-release) as submitted on November 7, 2023 to be acceptable, as described in this review. Please send the comments in Section 6 to the Applicant in an Information Request and instruct the Applicant to submit a REMS amendment within 10 business days.

6. Comments to the Applicant

We have the following comments on the proposed REMS modification, submitted on November 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. See a summary of the comments below and attached relined documents.

General Comment

- It is not necessary to include [redacted (b) (4)]. Refer to our edits to the REMS Document and corresponding edits to the Prescriber Enrollment Form, Patient Enrollment Form, Pharmacy Enrollment Form, and Prescription Form.
- Information on counseling caregivers in other materials (e.g., patient counseling checklist and training materials) is appropriate and provides prompts for prescribers and pharmacies to counsel caregivers.
- Rename the [redacted (b) (4)] to be "Pediatric Patients and their Caregivers Brochure." Apply this change to the REMS Document, all REMS materials, and the Supporting Document.
- The dissemination plans for the Fact Sheet, Dear Healthcare Provider Letter, and the Dear Professional Society Letter have been completed, and the communication materials are no longer necessary. Remove references to these materials from other REMS materials and the Supporting Document. If the pediatric indication is approved, letters to prescribers notifying them of the new indication can be sent outside of the REMS.

REMS Document

- The REMS goal will remain the same as currently approved.

- We have added a requirement to the REMS operation section of the REMS Document to ensure pediatric patients are able to change caregivers provided that the new caregiver has been counseled by a certified pharmacy on the serious risks and safe use of the drug and acknowledges that he/she had any questions about Lumryz answered before the drug product is dispensed and shipped.

Patient Enrollment Form

- To improve readability, we have removed the use of [redacted] (b) (4) throughout the attestations and added a statement that reads: "A parent or caregiver of a patient under the age 18 must also read and understand each item before signing this enrollment form."

Prescriber Brochure

- The pediatric dosing information was moved to a new section called the "Pediatric Patient Supplement." Additional information regarding counseling caregivers for pediatric patients was added to Pediatric Patient Supplement.

Pediatric Patients and their Caregivers Brochure (previously [redacted] (b) (4))

- Develop a section that provides specific information, including graphical images (like a storybook), directed towards pediatric patients. For caregivers, develop a section on important information your child must know about taking Lumryz and a section on including your child in their care. By way of example, please refer to the following FDA-approved REMS material in the public domain (found at REMS@FDA): Xyrem Brochure for Pediatric Patients and their Caregivers.

Certified Pharmacy Training Program

- We have rejected the edits to the REMS goal; the REMS goal will remain the same as currently approved.
- A statement was added regarding the need to counsel new caregivers of already enrolled pediatric patients on the risks and safe use of Lumryz.
- We have identified editorial errors during this review; refer to the word document in track changes.

Patient Counseling Checklist

- We have added information on change of care responsibility to step 1 and step 2 in the Patient Counseling Checklist for a certified pharmacy to educate new caregivers for an already enrolled pediatric patient.

REMS Website

- Update the REMS website with the changes made to the REMS Document and REMS materials.

Supporting Document

- Align the Supporting Document with changes made to the REMS Document and REMS materials.

REMS Assessment Plan

- Revise Metric 12 of your Assessment Plan. This revision is requested because of the additional surveyed stakeholder you describe in your Quantitative Testing of Patient Knowledge, Attitudes, and Behavior about Lumryz Patient KAB Protocol and Survey Version 2.0 dated September 6, 2023. The two requested additions are underlined.

  12. Knowledge, Attitude, and Behavior (KAB) Surveys of Patients/Caregivers, Healthcare Providers, and Pharmacists (to be submitted annually)

a. Assessment of patients'/caregivers', healthcare providers' and pharmacists' understanding of the following:
    i. The risk of significant CNS and respiratory depression associated with Lumryz even at recommended doses
    ii. The contraindicated uses of Lumryz with sedative hypnotics and alcohol `q1`
    iii. The potential for abuse, misuse, and overdose associated with Lumryz
    iv. The safe use, handling, and storage of Lumryz
    v. The Lumryz REMS requirements

Resubmission Instructions

Submit the following revised REMS materials that address our comments within 10 business days. 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 feature the setting in which the author of comments and revisions can be identified (not anonymous). The next submission to the Gateway should include clean Word and tracked Word versions of the following documents:

- REMS Document
- Prescriber Enrollment Form
- Patient Enrollment Form
- Pharmacy Enrollment Form
- Prescriber Brochure
- Certified Pharmacy Training Program
- Pharmacy Staff Knowledge Assessment
- Pharmacist Knowledge Assessment
- Prescription Form
- Patient Counseling Checklist
- Pediatric Patients and their Caregivers Brochure
- REMS Website
- Supporting Document, including the assessment plan

Additionally, include one compiled PDF file that includes the REMS Document and all REMS materials (excluding the Supporting Document) in their final format. Submit a separate PDF file of the Supporting Document.

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)

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

Pharmacy

- Certified Pharmacy Training Program

Patient Care Forms

- Prescription Form
- Patient Counseling Checklist

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KATE H OSWELL
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KATHRYN K MARWITZ
04/18/2024 05:01:50 PM

CAROLYN N TIEU
04/19/2024 08:04:55 AM

JOSEPH P PARADIS
04/19/2024 08:15:18 AM

CYNTHIA L LACIVITA
04/21/2024 08:05:26 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s006

OTHER REVIEW(S)

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

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

Memorandum

Date: August 23, 2024

To: C. Eugene Lee, Regulatory Project Manager, Division of Psychiatry (DP)

David Millis, Medical Reviewer, DP

Kimberly Updegraff, Associate Director for Labeling, DP

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

CC: Susannah O'Donnell, Team Leader, OPDP

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

NDA: 214755, S-006

Background:
In response to DP's consult request dated November 15, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide/Instructions for Use (IFU), for supplement 006 for Lumryz. This was an efficacy supplement (S-006) to expand the indication of Lumryz to include pediatric patients 7 years of age and older with narcolepsy.

PI/Medication Guide/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 13, 2024, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide/IFU, and comments were sent under separate cover on August 20, 2024.

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.

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/s/

RACHAEL O OYEWOLE
08/23/2024 12:56:46 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 16, 2024
To:	C. Eugene Lee, PharmD Regulatory Project Manager **Division of Psychiatry (DP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Barbara Fuller, RN, MSN, WOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Rachael Oyewole, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	LUMRYZ (sodium oxybate)
Dosage Form and Route:	for extended-release oral suspension, CIII
Application Type/Number:	NDA 214755
Supplement Number:	S-006
Applicant:	Avadel CNS Pharmaceuticals, LLC

1 INTRODUCTION

On November 7, 2023, Avadel CNS Pharmaceuticals, LLC submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 214755/S-006 for LUMRYZ (sodium oxybate) for extended-release oral suspension. The Reference Listed Drug is XYREM (sodium oxybate) oral solution NDA 021196. With this submission, the Applicant proposes to expand the indication to include pediatric patients 7 years of age or older with narcolepsyThis collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry (DP) on November 15, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for LUMRYZ (sodium oxybate) for extended-release oral suspension.

2 MATERIAL REVIEWED

- Draft LUMRYZ (sodium oxybate) for extended-release oral suspension MG and IFU received on November 7, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 14, 2024.
- Draft LUMRYZ (sodium oxybate) for extended-release oral suspension Prescribing Information (PI) received on November 7, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 14, 2024.
- Approved LUMRYZ (sodium oxybate) for extended-release oral suspension labeling dated May 1, 2023.
- Approved XYREM (sodium oxybate) comparator labeling dated April 4, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria specified in the FDA's Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
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DMPP-OPDP review of sodium oxybate (LUMRYZ) NDA 214755/S-006 MG and IFU

RACHAEL O OYEWOLE
08/20/2024 07:44:34 AM

BARBARA A FULLER
08/20/2024 07:47:37 AM

LABELING 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:	July 29, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 214755/S-006
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
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Avadel CNS Pharmaceuticals, LLC
FDA Received Date:	November 7, 2023
TTT ID #:	2023-7128
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 INTRODUCTION

Avadel CNS Pharmaceuticals, LLC submitted an Efficacy Supplement for Lumryz (sodium oxybate) for extended-release oral suspension to expand the indication of Lumryz to include pediatric patients 7 years of age or older with narcolepsy. Subsequently, the Division of Psychiatry (DP) requested that we review the proposed Lumryz Prescribing Information (PI), Medication Guide (MG), and Instructions for Use (IFU) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 214755/S-006.

Table 1. Materials Considered for this Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

Our evaluation of the proposed Lumryz Prescribing Information (PI)[a], Medication Guide (MG), and Instructions for Use (IFU) did not identify areas of vulnerability that may lead to medication errors. Additionally, we note that the revisions made to the aforementioned labeling do not warrant any subsequent changes to the currently marketed container labels and carton labeling. Thus, we have no recommendations at this time.

[a] We also reviewed the proposed PI received on November 7, 2023 and revised (working document) by the Division of Psychiatry as of July 24, 2024.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Lumryz received on November 7, 2023 from Avadel CNS Pharmaceuticals, LLC.

Table 2. Relevant Product Information for Lumryz (proposed changes are in bold text)	
Initial Approval Date	05/01/2023
Active Ingredient	sodium oxybate
Indication	Lumryz is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in **patients 7 years of age and older** with narcolepsy.
Dosage Form	for extended-release oral suspension
Strength	4.5 g, 6 g, 7.5 g, and 9 g per packet
Route of Administration	Oral
Dose and Frequency	**Adult** 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. **Pediatric Dosing Information** **The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight.** [redacted] [redacted] **The dosage may be gradually titrated based on efficacy and tolerability.**

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Lumryz (proposed changes are in bold text)</th></tr>
<tr><td>How Supplied</td><td>Lumryz is a blend of white to off-white granules for extended-release oral suspension in water. Each carton contains either 7 or 30 packets of Lumryz, 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, 7.5 g, or 9 g doses.
<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>
</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).
Suspensions should be consumed within 30 minutes.</td></tr>
</table>

APPENDIX B. LABELING

B.1 List of Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Lumryz labeling submitted by Avadel CNS Pharmaceuticals, LLC. on November 7, 2023, available from: \\Cdsesub1\evsprod\NDA214755\0110\m1\us\114-labeling\114a-draft-label.

- Prescribing Information
- Medication Guide
- Instructions for Use

APPEARS THIS WAY ON ORIGINAL

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

APPENDIX C. PREVIOUS DMEPA REVIEWS

On July 24, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 214755. Our search identified one previous review[c] since the date of our last search on May 20, 2024, and we considered our previous recommendations to see if they are applicable for this current review.

APPEARS THIS WAY ON ORIGINAL

[c] Holmes, L. Label Labeling Packaging URRA Review for Lumryz (NDA 214755/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 May 31. TTT ID No.: 2024-7721.

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/s/

LORETTA HOLMES
07/29/2024 04:26:55 PM

YEVGENIYA M KOGAN
07/30/2024 11:03:00 AM

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 20, 2023

To: Tiffany Farchione, MD, Director, Division of Psychiatry

Through: Dominic Chiapperino, PhD, Director, Controlled Substance Staff (CSS)
Joshua Lloyd, MD, Medical Officer Team Leader, CSS

From: Renée Petit-Scott, MD, Medical Officer, CSS

Subject: **NDA 214755;** Lumryz (sodium oxybate); Prior Approval Supplement for pediatric indication
Indication: For the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy
Approved dosage form and strengths: Granules for extended-release oral suspension in water; 4.5 g, 6 g, 7.5 g, and 9 g
Applicant: Avadel CNS Pharmaceuticals, LLC
PDUFA goal date: September 7, 2024

Materials Reviewed:

Applicant Submission:

- Prior Approval Supplement 006 (Supporting Document Number [SDN] 173, received November 7, 2023

Prior Correspondence (under IND 126321):

- Type B Pre-NDA Meeting Minutes, November 10, 2022
- Inadequate (Pediatric) Study Request letter, August 17, 2021

I. Background

This memorandum is in response to a consult request dated November 28, 2023, from the Division of Psychiatry (DP) pertaining to a Prior Approval Supplement (PAS) for NDA 214755 for Lumryz (sodium oxybate) for extended-release oral suspension proposing to expand the indication to include pediatric patients seven years of age and older with narcolepsy. Lumryz was approved on May 1, 2023, for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy and is available only through the Lumryz Risk Evaluation and Mitigation Strategies (REMS).

Avadel CNS Pharmaceuticals, LLC (Avadel, the Applicant) was granted orphan drug designation on January 8, 2018, for sodium oxybate for the treatment of narcolepsy, and, as such, an Agreed initial Pediatric Study Plan (iPSP) was not required. In response to a Proposed Pediatric Study Request (submitted to support a Written Request), the Division of Neurology I (DNI, administrative division prior to transfer of the IND to the Division of Psychiatry, May 9, 2023) issued an Inadequate Study Request letter dated August 17, 2021, which stated that clinical studies of Lumryz in pediatric patients with narcolepsy may not be needed. The letter further stated that currently available safety and efficacy data in adults with narcolepsy, in combination with pharmacokinetic bridging data demonstrating bioequivalence between the listed drug Xyrem and Lumryz, have the potential to support a pediatric indication in patients seven years of age and older. Information needed to support a supplemental NDA submission to expand the indication into the pediatric population was further discussed during a Type B Pre-NDA meeting on October 12, 2022, and conveyed in the meeting minutes dated November 10, 2022. This PAS (S-006) submission appears to include the requested supportive information.

II. Conclusions

- Sodium oxybate that is not contained in an approved drug product is a Schedule I controlled substance under the Controlled Substances Act (CSA).
- Lumryz (and other sodium oxybate products approved for medical use) is controlled under Schedule III of the CSA and is available only through the Lumryz REMS.
- No new clinical studies were conducted in support of this PAS, and this submission did not include a request for Lumryz rescheduling under the CSA. The information submitted to support the safe and effective use of Lumryz in pediatric patients seven years of age and older does not suggest that a change in scheduling status is required.
- Based on information conveyed in the Inadequate Study Request Letter (dated August 17, 2021) and the Type B Pre-NDA Meeting Minutes (dated November 10, 2022), the Applicant has submitted the following information to support expanding the indication to include pediatric patients seven years of age and older (briefly summarized):
    - Reliance on the established safety and efficacy profiles for sodium oxybate in pediatric patients seven years of age and older with narcolepsy (data from clinical studies of Xyrem, the listed drug).
    - The safety and efficacy data from the previously completed Phase 3 study, CLFT218-1501, of Lumryz in adults with narcolepsy.
    - Data from the previously completed pharmacokinetic bridging study, Study PKFT218-1501, which demonstrated the following:
        - Bioequivalence between Xyrem 6 g (3 g twice, total nightly dose), and Lumryz 6 g (single nightly dose)
        - Systemic exposure following administration of Lumryz 9 g once nightly (the highest recommended dose) is no higher than that observed following administration of Xyrem 4.5 g twice nightly.

  - The safe and effective pediatric (age seven years and older) dose for Lumryz is proposed to be calculated based on the approved pediatric (age seven years and older) dosing information for Xyrem.

- Based on the information included in this PAS, no edits are required for Section 9 of the most recently approved Lumryz label (approved with the NDA on May 1, 2023).

III. Recommendations

Because there are no new clinical abuse potential-related data to review, and the Applicant is not proposing Lumryz rescheduling or edits to Section 9 of the label, further CSS input is not needed during review of this PAS and a filing checklist for this NDA from CSS will not be completed.

Should there be any revisions to Section 9 of the label proposed during the PAS review cycle, the Division should reconsult CSS.

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/

RENEE L PETIT-SCOTT
12/20/2023 02:00:56 PM

JOSHUA M LLOYD
12/20/2023 06:12:46 PM

DOMINIC CHIAPPERINO
01/03/2024 12:55:41 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s006

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

NDA 214755/S-006

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Avadel CNS Pharmaceuticals, LLC
c/o ProPharma Group
Attention: Marla E. Scarola
Senior Vice President, Regulatory Process Management
1129 Twentieth St NW, Ste 600
Washington, DC 20036

Dear Marla Scarola:

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

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 7, 2024. We are reviewing your application according to the processes described in the draft guidance for industry, *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications*.[1] Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (i.e., filing, planning, mid-cycle, team, and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling by August 7, 2024, and, if necessary, we plan to communicate any anticipated postmarketing requirements and anticipated postmarketing commitments by August 7, 2024.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[2] and Pregnancy and Lactation Labeling Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights of Prescribing Information and Contents
- The Selected Requirements for Prescribing Information (SRPI)—a checklist of important format items from labeling regulations and guidances
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading
- Other prescription drug labeling resources for the Prescribing Information, patient labeling, and carton and container labeling

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

NATIONAL DRUG CODE(s)

Prior to the action date of your sNDA, we recommend you:

- Review the regulations that describe the requirements for national drug code (NDC(s)) including the requirements for obtaining new NDC(s) and restrictions regarding the use of NDC(s) [see 21 CFR 207.33 and 21 CFR 207.35, respectively].

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[2] Prescription Drug Labeling Resources website: https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[3] Pregnancy and Lactation Labeling Rule website: https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

- Ensure that NDC(s) that appear on prescription drug labeling (e.g., Prescribing Information, outer packaging, carton labeling, container labeling) are assigned correctly per the above. CDER does not typically review the accuracy of NDC(s) on prescription drug labeling prior to approval.

- Optionally, reserve new NDC(s) by referring to the Drug Registration and Listing website[4] or contacting eDRLS@fda.hhs.gov. Include the required additional data elements when converting the NDC reservation submission to a drug registration and listing submission when a drug is approved.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed Prescribing Information (PI) and Medication Guide (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry, *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

Do not submit launch materials until you have received our proposed revisions to the Prescribing Information (PI) and Medication Guide (as applicable), and you believe the labeling is close to the final version.

[4] https://www.fda.gov/drugs/guidance-compliance-regulatory-information/electronic-drug-registration-and-listing-system-edrls
[5] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

For more information regarding OPDP submissions, please see FDA.gov.[6] If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA; 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

If you have any questions, contact Eugene Lee, Senior Regulatory Project Manager, at C.Eugene.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

[6] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-prescription-drug-promotion-opdp

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/s/

TIFFANY R FARCHIONE
01/11/2024 10:34:10 AM

From: Lee, C. Eugene
Sent: Fri 04 Oct 2024 05:02:15 PM -0400 UTC
To: Marla Scarola
Subject: NDA 214755/S-006 (Lumryz): REMS IR
Categories: IR/Advice;REMS

Good afternoon Marla,

We have the following comments on the proposed REMS modification submitted with the efficacy supplement on 11/07/23, last amended 08/16/24. Review of the proposed REMS modification is ongoing, and these comments should not be considered final. Refer to the summary of the comments below.

General Comment

- Update the REMS materials as needed to align with the changes made to the Prescribing Information sent on 10/3/24.

Prescriber Brochure

- Update the pediatric dosing information (located on page 18 in Guidelines for Dosing and Titrating Lumryz for Pediatric Patients) in the Prescriber Brochure to align with the changes made to the Prescribing Information sent on 10/3/24.

Prescription Form

- Align the Prescription Form with the REMS modification to include the starter pack as a prescribing option on the Prescription Form approved on 09/26/24.

Resubmission Instructions

Submit a REMS amendment by 10/7/24 that addresses these comments. The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following document:

- Prescriber Brochure
- Prescription Form

Additionally, include the Supporting Document and one compiled PDF file that includes the REMS Document and all REMS materials (excluding the Supporting Document) in their final format.

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


FDA
U.S. FOOD & DRUG
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/s/

CHRISTOPHER E LEE
10/04/2024 05:12:36 PM

From: Lee, C. Eugene
To: Marla Scarola
Subject: NDA 214755/S-006 (Lumryz): Labeling Negotiations - Round 4
Date: Thursday, October 3, 2024 3:04:00 PM
Attachments: image001.png
image002.jpg
image003.jpg
image004.jpg
image005.jpg
image006.jpg
NDA 214755 S-006 - MG (tracked a) - Round 4 - 100324.docx
NDA 214755 S-006 - IFU (tracked a) - Round 4 - 100324.docx
NDA 214755 S-006 - USPI (tracked a) - Round 4 - 100324.docx

Good afternoon Marla,

We have reviewed your proposed labeling submitted on 11/07/23 and 08/15/24. Additional requested changes are tracked and/or enclosed in comments.

Accept all tracked changes agreed upon, delete comments that have previously been addressed, and use this as the base document. Make sure your new comments aren't anonymized, or they show proper date to show they're new. Track all proposed edits and respond to our comments as "Accept" or provide an explanation for proposing new text or not accepting our request. Please have all edits completed and label returned no later than COB Monday, 10/07/24.

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

44 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
10/03/2024 03:33:35 PM

From: Lee, C. Eugene
Sent: Fri 06 Sep 2024 05:02:09 PM -0400 UTC
To: Marla Scarola
Subject: RE: [EXTERNAL EMAIL] RE: [EXTERNAL] NDA 214755/S-006 update

Good afternoon Marla,

We acknowledge that the goal date for your pending application is September 7, 2024. However, your application remains under review and action will be delayed. At this time, we are unable to provide a specific update regarding an anticipated action date. If we require any additional information from Avadel to assist in our review of the application, we will contact you with any such requests. Additionally, we anticipate having further labeling comments and will provide these comments in the coming weeks.

Thanks so much,

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: Friday, September 6, 2024 3:17 PM
To: Lee, C. Eugene <C.Eugene.Lee@fda.hhs.gov>
Cc: Chang, ShinYe <ShinYe.Chang@fda.hhs.gov>
Subject: RE: [EXTERNAL EMAIL] RE: [EXTERNAL] NDA 214755/S-006 update

Hi, Eugene – Are you able to tell me whether the target action date of September 7 for S-006 will be missed?

Best,

Marla

MARLA SCAROLA
Senior Vice President Regulatory and Quality

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

From: Marla Scarola
Sent: Thursday, September 5, 2024 8:50 AM
To: Lee, C. Eugene <C.Eugene.Lee@fda.hhs.gov>
Cc: Chang, ShinYe <ShinYe.Chang@fda.hhs.gov>
Subject: RE: [EXTERNAL EMAIL] RE: [EXTERNAL] NDA 214755/S-006 update

Hi Eugene – Would you please provide me with an update on NDA 214755/S-006? We're still awaiting another round of labeling comments and the target action date of Sep 7 is fast approaching.

Best,
Marla

MARLA SCAROLA
Senior Vice President Regulatory and Quality

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

From: Marla Scarola <mscarola@avadel.com>
Sent: Tuesday, September 3, 2024 12:08 PM
To: Lee, C. Eugene <C.Eugene.Lee@fda.hhs.gov>
Subject: RE: [EXTERNAL EMAIL] RE: [EXTERNAL] NDA 214755/S-006 update

Hi Eugene,

Are you able to provide me with any update on the status of NDA214755/S-006 review? With a target action date of Saturday Sept 7, can we anticipate action on Friday Sept 6?

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: Tuesday, August 27, 2024 9:37 AM
To: Marla Scarola <mscarola@avadel.com>
Subject: RE: [EXTERNAL EMAIL] RE: [EXTERNAL] NDA 214755/S-006 update

Good morning Marla,

The team is still reviewing and discussing your labels. I will have to give you an update when I know more.

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

U.S. FOOD & DRUG ADMINISTRATION

From: Marla Scarola <mscarola@avadel.com>
Sent: Monday, August 26, 2024 10:13 AM
To: Lee, C. Eugene <C.Eugene.Lee@fda.hhs.gov>
Subject: RE: [EXTERNAL EMAIL] RE: [EXTERNAL] NDA 214755/S-006 update

Hi Eugene,

I hope you had a nice weekend! Even though the days are still hot, I'm starting to get a welcome glimpse of the cool fall air in the mornings and evenings. I wanted to touch base with you regarding anticipated timing for additional comments on the PI, MG, and IFU. Are you able to provide any insight?

Thanks,
Marla

MARLA SCAROLA
Senior Vice President Regulatory and Quality

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

From: Marla Scarola <mscarola@avadel.com>
Sent: Monday, August 19, 2024 3:30 PM
To: Lee, C. Eugene <C.Eugene.Lee@fda.hhs.gov>
Subject: RE: [EXTERNAL EMAIL] RE: [EXTERNAL] NDA 214755/S-006 update

Thanks, Eugene!

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: Monday, August 19, 2024 3:23 PM
To: Marla Scarola <mscarola@avadel.com>
Subject: [EXTERNAL EMAIL] RE: [EXTERNAL] NDA 214755/S-006 update

Thank you, Marla. The team is going over the USPI this week and we're meeting on Friday to discuss.

Best,

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: Friday, August 16, 2024 9:11 AM
To: Lee, C. Eugene <C.Eugene.Lee@fda.hhs.gov>
Subject: [EXTERNAL] NDA 214755/S-006 update

Happy Friday, Eugene! As you're likely aware, we returned the USPI yesterday. The response to the REMS IR is scheduled for submission today and the revised patent statement will go in

on Monday. We noted that two sections of the USPI were marked as still being under review. Do you have an anticipated timeline for providing comments on the remaining USPI sections as well as the MG and IFU?

Also, I saw your request for a courtesy copy of the patent statement; please find it attached.

Best,
Marla

MARLA SCAROLA
Senior Vice President Regulatory and Quality

avadel.com
16640 Chesterfield Grove Road, Suite 200
Chesterfield, MO 63005
Office: +1 636-237-7091
Mobile: (b) (6)

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/s/

CHRISTOPHER E LEE
09/06/2024 05:10:40 PM

From: Lee, C. Eugene
Sent: Tue 13 Aug 2024 11:31:05 AM -0400 UTC
To: Marla Scarola
Subject: NDA 214755/S-006 (Lumryz): Patent Information Amendment
Categories: IR/Advice;505(b)(2)

Good morning Marla,

With regard to NDA 214755, please refer to your supplemental new drug application (sNDA), S-006, dated and recevied 11/07/23, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Lumryz (sodium oxybate) ER suspension. We have the following comments/questions and request your response as soon as possible but no later than 08/20/24.

> *Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug or that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug. Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 021196 for Xyrem (sodium oxybate) solution but does not contain a patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely. After you submitted your 505(b)(2) application, the NDA holder for Xyrem (sodium oxybate) solution, timely filed information on U.S. Patent No. 11,986,446 ('446 patent) for listing in the Orange Book. Submit an appropriate patent certification or statement with respect to the '446 patent.*
>
> *If you elect to provide a paragraph IV certification (21 CFR 314.50(i)(1)(i)(A) (4)) with respect to the '446 patent, the certification is to be accompanied by a statement that you will comply with the requirements under 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under 314.52(c) with respect to the content of the notice. In addition, you must amend your application to provide proof of notification as required by 21 C.F.R. §314.52(e). We note that the 45-day period provided for in section 505(c)(3)(C) of the FD&C Act does not apply.*

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


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/s/

CHRISTOPHER E LEE
08/13/2024 11:38:20 AM

From: Lee, C. Eugene
To: Marla Scarola
Subject: NDA 214755/S-006 (Lumryz): Labeling Negotiations
Date: Friday, August 9, 2024 4:57:00 PM
Attachments: NDA 214755 S-006 - USPI (tracked a) - Round 2 - 080924.docx
image001.png

Good afternoon Marla,

We have reviewed your proposed Prescriber Information label submitted on 11/07/23. Additional requested changes are tracked and/or enclosed in comments.

Accept all tracked changes agreed upon, delete comments that have previously been addressed, and use this as the base document. Make sure your new comments aren't anonymized, or they show proper date to show they're new. Track all proposed edits and respond to our comments as "Accept" or provide an explanation for proposing new text or not accepting our request. Please have all edits completed and label returned no later than COB 08/15/24.

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

28 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
08/09/2024 05:01:09 PM

From: Lee, C. Eugene
Sent: Thu 18 Jul 2024 12:40:36 PM -0400 UTC
To: 'mscarola@avadel.com'
Subject: NDA 214755/S-006 (Lumryz): PREA Requirement/Orphan Drug Designation

Good afternoon Marla,

With regard to NDA 214755 (Lumryz) and the Supplement-006 submission received on 11/07/23, we noticed there was no statement submitted addressing the Pediatric Research Equity Act (PREA) requirements and your orphan drug designation. Please include a statement addressing the Pediatric Research Equity Act (PREA) requirement as part of the pediatric section (1.9 for eCTD submissions) of your supplemental new drug application. The Division would like this submitted by COB 07/25/24.

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

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/s/

CHRISTOPHER E LEE
07/18/2024 12:43:39 PM

From: Lee, C. Eugene
To: Marla Scarola
Subject: NDA 214755/S-006 (Lumryz): REMS Information Request
Date: Tuesday, April 23, 2024 11:54:00 AM
Attachments: 1-rems-document_Applicant.docx
3-rems-prescriber-enrollment-form.docx
4-rems-prescriber-brochure.docx
6-rems-certified-pharmacy-training-modules.docx
7-rems-patient-enrollment-form.docx
8-rems-pharmacy-enrollment-form.docx
9-rems-patient-counseling-checklist.docx
17-rems-prescription-form.docx
image001.png

Good morning Marla,

With regard to NDA 214755/S-006, please refer to your 11/07/23, new supplement submission with REMS modifications for Lumryz. We have the following comments/questions and request your response as soon as possible but no later than COB on 05/07/24.

REMS:

General Comment

- *It is not necessary to* [redacted (b) (4)] *. Refer to our edits to the REMS Document and corresponding edits to the Prescriber Enrollment Form, Patient Enrollment Form, Pharmacy Enrollment Form, and Prescription Form.*
- *Information on counseling caregivers in other materials (e.g., patient counseling checklist and training materials) is appropriate and provides prompts for prescribers and pharmacies to counsel caregivers.*
- *Rename the* [redacted (b) (4)] *to be "Pediatric Patients and their Caregivers Brochure." Apply this change to the REMS Document, all REMS materials, and the Supporting Document.*
- *The dissemination plans for the Fact Sheet, Dear Healthcare Provider Letter, and the Dear Professional Society Letter have been completed, and the communication materials are no longer necessary. Remove references to these materials from other REMS materials and the Supporting Document. If the pediatric indication is approved, letters to prescribers notifying them of the new indication can be sent outside of the REMS.*

REMS Document

- *The REMS goal will remain the same as currently approved.*
- *We have added a requirement to the REMS operation section of the REMS Document to ensure pediatric patients are able to change caregivers provided that the new caregiver has been counseled by a certified pharmacy on the serious risks and safe use of the drug and acknowledges that he/she had any questions about Lumryz answered before the drug product is dispensed and shipped.*

Patient Enrollment Form

- *To improve readability, we have removed the use of* [redacted (b) (4)] *" throughout the*

attestations and added a statement that reads: "A parent or caregiver of a patient under the age 18 must also read and understand each item before signing this enrollment form."

Prescriber Brochure

- *The pediatric dosing information was moved to a new section called the "Pediatric Patient Supplement." Additional information regarding counseling caregivers for pediatric patients was added to Pediatric Patient Supplement.*

Pediatric Patients and their Caregivers Brochure (previously Caregiver Brochure)

- *Develop a section that provides specific information, including graphical images (like a storybook), directed towards pediatric patients. For caregivers, develop a section on important information your child must know about taking Lumryz and a section on including your child in their care. By way of example, please refer to the following FDA-approved REMS material in the public domain (found at REMS@FDA): Xyrem Brochure for Pediatric Patients and their Caregivers.*

Certified Pharmacy Training Program

- *We have rejected the edits to the REMS goal; the REMS goal will remain the same as currently approved.*
- *A statement was added regarding the need to counsel new caregivers of already enrolled pediatric patients on the risks and safe use of Lumryz.*
- *We have identified editorial errors during this review; refer to the word document in track changes.*

Patient Counseling Checklist

- *We have added information on change of care responsibility to step 1 and step 2 in the Patient Counseling Checklist for a certified pharmacy to educate new caregivers for an already enrolled pediatric patient.*

REMS Website

- *Update the REMS website with the changes made to the REMS Document and REMS materials.*

Supporting Document

- *Align the Supporting Document with changes made to the REMS Document and REMS materials.*

REMS Assessment Plan

- *Revise Metric 12 of your Assessment Plan. This revision is requested because of the additional surveyed stakeholder you describe in your Quantitative Testing of Patient Knowledge, Attitudes, and Behavior about Lumryz Patient KAB Protocol and Survey Version 2.0 dated September 6, 2023. The two requested additions are underlined.*

  12. Knowledge, Attitude, and Behavior (KAB) Surveys of Patients/Caregivers, Healthcare Providers, and Pharmacists (to be submitted annually)

a. *Assessment of patients'/caregivers', healthcare providers' and pharmacists' understanding of the following:*
    i. *The risk of significant CNS and respiratory depression associated with Lumryz even at recommended doses*
    ii. *The contraindicated uses of Lumryz with sedative hypnotics and alcohol `q1`*
    iii. *The potential for abuse, misuse, and overdose associated with Lumryz*
    iv. *The safe use, handling, and storage of Lumryz*
    v. *The Lumryz REMS requirements*

Resubmission Instructions

Submit the following revised REMS materials that address our comments within 10 business days. 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 feature the setting in which the author of comments and revisions can be identified (not anonymous). The next submission to the Gateway should include clean Word and tracked Word versions of the following documents:

- *REMS Document*
- *Prescriber Enrollment Form*
- *Patient Enrollment Form*
- *Pharmacy Enrollment Form*
- *Prescriber Brochure*
- *Certified Pharmacy Training Program*
- *Pharmacy Staff Knowledge Assessment*
- *Pharmacist Knowledge Assessment*
- *Prescription Form*
- *Patient Counseling Checklist*
- *Pediatric Patients and their Caregivers Brochure*
- *REMS Website*
- *Supporting Document, including the assessment plan*

Additionally, include one compiled PDF file that includes the REMS Document and all REMS materials (excluding the Supporting Document) in their final format. Submit a separate PDF file of the Supporting Document.

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

69 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
04/24/2024 01:57:42 PM

From: Lee, C. Eugene
Sent: Mon, 05 Feb 2024 04:43:47 PM
To: 'Marla Scarola'
Subject: RE: [EXTERNAL] RE: NDA 214755/S-006 (Lumryz): Study May Proceed
Categories: Gen F/U

Good afternoon Marla,

The Agency agrees to waive the requirement for a 120-day safety update for NDA 214755/S-006, because there are no ongoing clinical studies.

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 <marla.scarola@propharmagroup.com>
Sent: Friday, February 2, 2024 11:25 AM
To: Lee, C. Eugene <C.Eugene.Lee@fda.hhs.gov>
Subject: [EXTERNAL] RE: NDA 214755/S-006 (Lumryz): Study May Proceed

Hi, Eugene,

Happy Friday! Given that there are no ongoing clinical studies in support of the pediatric indication supplement, does the Agency agree to waive the requirement for a 120-day safety update for the NDA 214755/S-006?

Best,
Marla

Marla Scarola
SENIOR VICE PRESIDENT, REGULATORY PROCESS MANAGEMENT

Office: +1 202-730-4129
Mobile: (b) (6)
www.propharmagroup.com

From: Lee, C. Eugene <C.Eugene.Lee@fda.hhs.gov>
Sent: Wednesday, January 17, 2024 2:08 PM
To: Marla Scarola <marla.scarola@propharmagroup.com>
Subject: NDA 214755/S-006 (Lumryz): Study May Proceed

Good afternoon Marla,

With regard to NDA 214755/S-006 (Lumryz), We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 7, 2024. The signed official letter is attached. The review team had no further comments or recommendations to share at this time.

Please reach out with any questions.

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

FDA U.S. FOOD & DRUG ADMINISTRATION

APPEARS THIS WAY ON ORIGINAL

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/s/

CHRISTOPHER E LEE
02/05/2024 04:49:52 PM

From: Lee, C. Eugene
Sent: Wed, 20 Dec 2023 11:21:01 AM
To: Marla Scarola
Subject: NDA 214755/S-006 (Lumryz): CMC Information Request
Categories: IR/Advice

Good morning Marla,

With regard to NDA 214755/S-006, please refer to your 11/07/23, prior approval supplement submission for Lumryz. We have the following request and would like your response as soon as possible but no later than 01/03/24.

CMC:

Provide a claim for categorical exclusion or an environmental assessment in Section 1.12.14, per 21 CFR 25.31 (b) or (c)

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

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/s/

CHRISTOPHER E LEE
12/20/2023 11:27:20 AM

NDA 214755/S-006

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Avadel CNS Pharmaceuticals, LLC
c/o ProPharma Group
Attention: Marla E. Scarola
Senior Vice President, Regulatory Process Management
1129 Twentieth St NW, Ste 600
Washington, DC 20036

Dear Marla Scarola:

We have received your supplemental new drug application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

We have received your REMS Revision submission for the following:

NDA NUMBER: 214755

SUPPLEMENT NUMBER: 006

PRODUCT NAME: Lumryz (sodium oxybate) extended-release oral suspension

DATE OF SUBMISSION: November 7, 2023

DATE OF RECEIPT: November 7, 2023

This supplemental application proposes the following modifications to the approved risk evaluation and mitigation strategy (REMS) for Lumryz:

- Added language to REMS, REMS supporting document, and REMS materials to indicate patient and/or caregiver to align with adding a pediatric supplement

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 6, 2024, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

FDA.gov.[1] Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

RESPONSIBILITIES UNDER TITLE VIII OF FDAAA AND 42 CFR PART 11

You are also responsible for complying with the applicable provisions of section 402(j) of the Public Health Service Act (PHS Act) [42 U.S.C. § 282(j)], including its implementing regulations in 42 CFR part 11. Section 402(j) of the PHS Act was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Unless you have delegated your responsibilities to another entity, you are the "responsible party" and are required to submit registration and results information for each "applicable clinical trial" to the ClinicalTrials.gov data bank, as provided by section 402(j) of the PHS Act and 42 CFR part 11.

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current data bank known as ClinicalTrials.gov to include mandatory registration and reporting of results information for applicable clinical trials of human drug products (including biological products) and device products. HHS issued a final rule, codified at 42 CFR part 11, implementing requirements for submitting clinical trial registration and results information to the ClinicalTrials.gov data bank.

In addition to the registration and results information submission requirements described above, FDAAA requires that, at the time of submission to FDA of an application under section 505/351 of the FDCA/PHS Act, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not submit such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 USC § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," to comply with the certification requirement. The form may be found at FDA.gov.[2]

In completing Form FDA 3674, you should review 42 USC § 282(j), including its implementing regulations in 42 CFR part 11, to determine whether the requirements of FDAAA apply to any clinical trial(s) for which data are included, relied upon, or otherwise referred to in the application that the certification accompanies. Refer to the following FDA guidance for industry *Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration*

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] https://www.fda.gov/media/134964/download.

Amendments Act of 2007,[3] which describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at FDA.gov.[4] Additional information regarding Title VIII of FDAAA, including its implementing regulations in 42 CFR part 11, is available at NIH.gov.[5] Additional information for registering your clinical trials is available at the Protocol Registration System website.[6]

We note that the failure to submit a certification required under section 402(j)(5)(B) of the PHS Act [42 USC § 282(j)(5)(B)], or knowingly submitting a false certification under such section, is a prohibited act under section 301(jj)(1) of the FD&C Act [21 USC § 331(jj)(1)].

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days after the date of this letter. In the cover letter accompanying the certification submission, clearly identify that it pertains to **NDA 214755/S-006** submitted on November 7, 2023, and that it contains the FDA Form 3674 that was required to accompany that application.

If you have already submitted the certification for this application, disregard the above.

If you have questions, contact me at C.Eugene.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

C. Eugene Lee, PharmD
Senior Regulatory Health Project Manager
Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

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[3] We update guidance documents periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/form-fda-3674-certifications-accompany-drug-biological-product-and-device-applicationssubmissions.
[4] https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/fdas-role-clinicaltrialsgov-information.
[5] http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html.
[6] http://prsinfo.clinicaltrials.gov/.

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/s/

CHRISTOPHER E LEE
11/22/2023 12:23:49 PM

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