CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214755Orig1s003

Trade Name:	LUMRYZ
Generic or Proper Name:	sodium oxybate
Sponsor:	Avadel CNS Pharmaceuticals, LLC
Approval Date:	October 31, 2023
Indication:	LUMRYZ is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy

CENTER FOR DRUG EVALUATION AND RESEARCH

214755Orig1s003

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	
REMS	**X**
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s003

APPROVAL LETTER

NDA 214755/S-3

SUPPLEMENT APPROVAL

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

Dear Ms. Scarola:

Please refer to your supplemental new drug application (sNDA) dated May 4, 2023, received, and your amendments, submitted under pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lumryz (sodium oxybate) for extended release oral suspension.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Lumryz risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

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

Your proposed modifications to the REMS consist of: updates to the REMS Document to align with the current Format and Content of a REMS Document Guidance for Industry and the REMS Document Technical Conformance Guide; changes to the reporting of the confirmation for prescriptions filled for Lumryz to the REMS; and changes to the Lumryz Prescription Form to comply with certain state requirements for paper prescriptions. Additionally, all REMS materials are aligned to the following changes to the REMS requirements:

- Prescribers are required to document and submit all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion; and report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the Risk Management Report.
- Pharmacies are required to obtain oxybate prescription information of last dispense date, days' supply, and prescriber's name by contacting all other REMS for oxybate products.

- Changes to the REMS Dispense Authorization (RDA) to include that the Patient Counseling Checklist is completed as required and the alerts and Risk Management Report history for the patient and their prescriber are reviewed by the pharmacist.
- The Applicant is required to ensure prescribers are able to access patient alerts and Risk Management Report histories.
- The Applicant is required to 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.

Your proposed modified REMS, submitted on May 4, 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 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 (i.e., 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 Pharmacies
   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. Wholesaler/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 product 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 deviation
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 Lumryz REMS 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 of 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's 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
    - Sedative hypnotic will not be taken at the same time as Lumryz
    - Sedative hypnotic will be taken at the same time as Lumryz
    - Sedative hypnotic will be taken as a sleep aid
    - Sedative hypnotic will be taken for different indication per medical need
    - Lumryz dose regimen changed
    - No rationale provided
    - 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
    - Benzodiazepine will not be taken at the same time as Lumryz
    - Benzodiazepine will be taken at the same time as Lumryz
    - Benzodiazepine will be taken as a sleep aid
    - Benzodiazepine will be taken for different indication per medical need
    - Lumryz dose regimen changed
    - No rationale provided
    - 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 patients 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 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 a RDA was provided
c. Number of prescriptions dispensed without a 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
   2. Intentional misuse
   3. Abuse
   4. Overdose
   5. 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, Healthcare Providers, and Pharmacists (to be submitted annually)

a. Assessment of patients', 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

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

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the 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 SPL format using the FDA automated drug registration and listing system (eLIST).
For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

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, call Ermias Zerislassie, Safety Regulatory Project Manager, at 301-796-2770.

Sincerely,

{See appended electronic signature page}

Marc Stone, M.D.
Deputy Director for Safety
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- 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/

MARC B STONE
10/31/2023 07:28:55 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s003

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: 10/2023

II. REMS Goal

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

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

III. REMS Requirements

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

1. Healthcare providers who prescribe LUMRYZ must:

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

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

2. Patients who are prescribed LUMRYZ:

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

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

3. Pharmacies that dispense LUMRYZ must:

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

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

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

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

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

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

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

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

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

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

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

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

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

1. Not stock LUMRYZ in retail pharmacies.

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

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

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

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

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

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

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

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

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

11. Ensure patients are able to change certified prescribers.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

IV. REMS Assessment Timetable

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

V. REMS Materials

The following materials are part of the LUMRYZ REMS:

Enrollment Forms:

Prescriber:

1. Prescriber Enrollment Form

Patient:

2. Patient Enrollment Form

Pharmacy:

3. Pharmacy Enrollment Form

Training and Educational Materials:

Prescriber:

4. Prescriber Brochure

Patient:

5. Patient Brochure

Pharmacy:

6. Certified Pharmacy Training Program

7. Pharmacy Staff Knowledge Assessment

8. Pharmacist Knowledge Assessment

Patient Care Forms:

9. Prescription Form
10. Patient Counseling Checklist

Communication Materials:

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

Other Materials:

14. Risk Management Report
15. REMS Program Website

VI. Statutory Elements

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

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

LUMRYZ™ REMS | Prescriber Enrollment Form

Lumryz
(sodium oxybate) for extended-release oral suspension

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

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

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

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

STEP 1: PRESCRIBER ATTESTATIONS

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

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

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

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

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

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

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

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

PRESCRIBER INFORMATION (*denotes required field)

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

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

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

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

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

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

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

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

_____ *Prescriber Signature

_____ *Date

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

Avadel

Reference ID: 5270348

LUMRYZ™ REMS | Patient 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.

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

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

PATIENT INFORMATION

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

REMS for Oxybate Products Participation

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

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

PRESCRIBER INFORMATION

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

PATIENT ATTESTATIONS:

Before I start treatment, I must:

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

During treatment

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

At all times

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

_____ *Pa ient/Guardian Signature

_____ *Date

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

* Guardian Email, if applicable: _____

PRESCRIBER:

By signing below, I acknowledge that:

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

_____ *Prescriber Signature

_____ *Date

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

Avadel

Reference ID: 5270348

LUMRYZ™ REMS | Pharmacy Enrollment Form

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

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

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

AUTHORIZED REPRESENTATIVE RESPONSIBILITIES

As the authorized representative, I must:

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

Before dispensing, all pharmacy staff must:

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

After dispensing, within 1 business day:

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

Before shipping, all pharmacy staff must:

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

CONTINUED >>

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

After shipping, all pharmacy staff must:

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

All pharmacy staff must:

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

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

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

PHARMACY INFORMATION

(*denotes required field)

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

AUTHORIZED REPRESENTATIVE INFORMATION

(All fields required)

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

_____ _____

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

Avadel

Reference ID: 5270348

LUMRYZ™ REMS

PRESCRIBER BROCHURE

Lumryz™

(sodium oxybate) for extended-release oral suspension Ⓒ

Reference ID: 5270348

Lumryz.

(sodium oxybate) for extended-release oral suspension

Dear Prescriber,

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

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

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

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

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

LUMRYZ is approved for the treatment of:

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

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

Sincerely,

Avadel CNS Pharmaceuticals, LLC

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

LUMRYZ is contraindicated for use in:

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

WARNINGS AND PRECAUTIONS

Central Nervous System Depression

- LUMRYZ is a central nervous system (CNS) depressant. Concurrent use of LUMRYZ with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating antiepileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.
  - If use of these CNS depressants in combination with LUMRYZ is required, dose reduction or discontinuation of one or more CNS depressants (including LUMRYZ) should be considered.
  - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with LUMRYZ should be considered.
- Patients who have sleep apnea or compromised respiratory function may be at a higher risk of developing respiratory depression, loss of consciousness, coma, and death with LUMRYZ use.
- Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that LUMRYZ does not affect them adversely (e.g., impaired judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking LUMRYZ.

Abuse and Misuse

- LUMRYZ is a Schedule III controlled substance.
- The active ingredient in LUMRYZ, sodium oxybate, is the sodium salt of gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. Illicit GHB has also been associated with drug-facilitated sexual assault.
- The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).
- You should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g., increase in size or frequency of dosing; reports of lost, stolen, or spilled medication; drug-seeking behavior; feigned cataplexy).

LUMRYZ REMS

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

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

Depression, Suicidality, and Other Behavioral / Psychiatric Adverse Reactions

- Depression, suicidal ideation and behavior, and other behavioral and psychiatric adverse reactions can occur in patients taking LUMRYZ.
- The emergence of depression in patients treated with LUMRYZ requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking LUMRYZ. Psychiatric reactions reported in adult clinical trials in patients with narcolepsy administered LUMRYZ included irritability, emotional disorder, panic attack, agitation, delirium, and obsessive thoughts. Patients should be instructed to call their healthcare provider if they experience any of these events.
- Anxiety can also occur in patients treated with LUMRYZ.

Use in Patients Sensitive to High Sodium Intake

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

Most Common Adverse Events

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

Adverse Reactions Leading to Treatment Discontinuation

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

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

Reference ID: 5270348

TABLE OF CONTENTS

PRESCRIBING LUMRYZ—A BRIEF GUIDE 5

RESPONSIBILITIES OF THE LUMRYZ REMS CERTIFIED PHARMACY 8

GUIDELINES FOR DOSING AND TITRATING LUMRYZ 9

ADDITIONAL INFORMATION ABOUT LUMRYZ 10

USE IN SPECIFIC POPULATIONS 11

PATIENT COUNSELING INFORMATION 12

Prescribing Information is also included.

PRESCRIBING LUMRYZ—A BRIEF GUIDE

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

PRESCRIBERS OF LUMRYZ

Prescribing LUMRYZ requires a one-time certification

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

SCREEN

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

COUNSEL

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

ENROLL

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

REPORT

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

Reference ID: 5270348

PATIENT ENROLLMENT

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

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

PRESCRIBING REQUIREMENTS

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

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

Verify that you have screened your patient for:

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

Verify that you have counseled the patient regarding:

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

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

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

Reference ID: 5270348

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

PATIENT EVALUATION

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

REFILL PRESCRIPTIONS

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

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

Certified Pharmacy

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

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

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

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

DOSING LUMRYZ

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

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

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

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

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

PATIENT DOSING INFORMATION

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

Additional Information About LUMRYZ

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

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

WHEN PRESCRIBING A CONTROLLED SUBSTANCE

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

DEPENDENCE AND TOLERANCE

Dependence

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

Tolerance

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

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

Use in Specific Populations

PREGNANCY

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

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

LABOR OR DELIVERY

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

LACTATION

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

PEDIATRIC USE

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

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

GERIATRIC USE

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

HEPATIC IMPAIRMENT

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

MALE AND FEMALE PATIENTS

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

RACIAL OR ETHNIC GROUPS

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

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

Patient Counseling Information

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

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

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

ALCOHOL OR SEDATIVE HYPNOTICS

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

SEDATION

Inform patients they are likely to fall asleep quickly after taking LUMRYZ (often within 5 minutes and usually within 15 minutes), but the time it takes to fall asleep can vary from night to night. The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls resulting in injuries, in some cases requiring hospitalization. Instruct patients to remain in bed following ingestion of LUMRYZ.

FOOD EFFECT

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

RESPIRATORY DEPRESSION

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

OPERATING HAZARDOUS MACHINERY

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

SUICIDALITY

Instruct patients to contact a healthcare provider immediately if the patient develops depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or suicidal ideation.

SLEEPWALKING

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

SODIUM INTAKE

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

SAFE USE, HANDLING, STORAGE, AND DISPOSAL

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

Reference ID: 5270348

Lumryz™

(sodium oxybate) for extended-release oral suspension CIII

Avadel™

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

MED-US-LUM-2100004
10/2023

LUMRYZ™ REMS

PATIENT BROCHURE

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

Lumryz™

(sodium oxybate) for extended-release oral suspension

Learn more scan to enroll.

Reference ID: 5270348

Lumryz.

(sodium oxybate) for extended-release oral suspension C

Dear Patient,

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

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

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

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

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

Sincerely,

Avadel CNS Pharmaceuticals, LLC

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

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

IMPORTANT INFORMATION ABOUT LUMRYZ INCLUDES THE FOLLOWING:

- When taking LUMRYZ, **do not** drink alcohol or take other medicines that slow your breathing or mental activity or make you sleepy. You could have serious side effects.
- LUMRYZ can cause serious side effects, including trouble breathing while asleep, confusion, unusual or disturbing thoughts, depression, and passing out, even at recommended doses. Tell your healthcare provider if you have any of these problems while taking LUMRYZ.
- Abuse of LUMRYZ can lead to dependence (a physical need to take the drug), craving for the medicine, and severe withdrawal symptoms (symptoms that start when the drug is stopped, especially when it is stopped suddenly).
- Each packet of LUMRYZ contains LUMRYZ powder, which will need to be mixed with water for once-nightly dosing prior to bedtime.
- Take 1 packet of LUMRYZ each day at bedtime.
- Mix and take LUMRYZ within 30 minutes. If not taken within 30 minutes of mixing, throw it away (dispose of it) and prepare a new dose.
- Avoid getting out of your bed after taking LUMRYZ. Some people fall asleep within 5 minutes of taking LUMRYZ and most will fall asleep within 15 minutes. The time it takes you to fall asleep might be different from night to night.
- **Do not** drive a car, use heavy machinery, fly an airplane, or do anything dangerous or that requires you to be alert for at least 6 hours after taking LUMRYZ. When you first start taking LUMRYZ, be careful until you know how LUMRYZ affects you.
- Keep LUMRYZ out of the reach of children and pets. Get emergency medical help right away if a child ingests LUMRYZ.
- Report all side effects to your healthcare provider.

WHAT WILL YOU FIND IN THIS BROCHURE?

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

WHAT IS THE LUMRYZ REMS?

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

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

Reference ID: 5270348

TABLE OF CONTENTS

ENROLLING IN THE LUMRYZ REMS 5

WHAT AM I REQUIRED TO DO IN THIS REMS? 5
DO I HAVE TO ENROLL IN THIS REMS? 5
WHY SHOULD I CONTACT THIS REMS? 5

FILLING YOUR LUMRYZ PRESCRIPTION 5

HOW IS MY PRESCRIPTION FILLED? 5
WHAT DOES A CERTIFIED PHARMACY DO? 5
WHAT WILL I GET WITH MY LUMRYZ PRESCRIPTION? 5
HOW DO I GET MY LUMRYZ REFILLS? 5
CAN MY LOCAL PHARMACY PROVIDE LUMRYZ? 5

INSURANCE COVERAGE 6

WILL INSURANCE PAY FOR MY LUMRYZ? 6
WHAT IS THE PHARMACY'S ROLE WITH MY INSURANCE? 6

HOW DO I TAKE MY LUMRYZ? 7

WHAT SHOULD I DO WHEN I GET MY LUMRYZ CARTON? 7
BEFORE EACH USE 7
MIX THE LUMRYZ SOLUTION AT YOUR BEDSIDE 8
TAKE THE LUMRYZ SOLUTION AT YOUR BEDSIDE 9
WHAT SHOULD I DO IF I MISS A DOSE? 10
HOW SOON WILL I SEE A CHANGE IN MY SYMPTOMS? 10
WHAT ARE THE SIDE EFFECTS OF LUMRYZ? 10
ARE THERE ANY PRECAUTIONS I SHOULD TAKE WHILE ON LUMRYZ? 10
HOW OFTEN SHOULD MY HEALTHCARE PROVIDER CHECK MY PROGRESS WITH LUMRYZ? 11

STORAGE AND SAFETY TIPS AT HOME 11

HOW DO I STORE LUMRYZ? 11
HOW DO I THROW AWAY (DISPOSE OF) LUMRYZ? 11
DRUG TAKEBACK PROGRAM 12
WHAT IF I HAVE CONCERNS ABOUT HAVING LUMRYZ IN MY HOME? 12

GETTING MORE INFORMATION 2

WHERE CAN I GET MORE INFORMATION ABOUT LUMRYZ? 12

Reference ID: 5270348

ENROLLING IN THE LUMRYZ REMS

WHAT AM I REQUIRED TO DO IN THIS REMS?

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

DO I HAVE TO ENROLL IN THIS REMS?

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

WHY SHOULD I CONTACT THIS REMS?

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

FILLING YOUR LUMRYZ PRESCRIPTION

HOW IS MY PRESCRIPTION FILLED?

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

WHAT DOES A CERTIFIED PHARMACY DO?

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

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

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

WHAT WILL I GET WITH MY LUMRYZ PRESCRIPTION?

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

HOW DO I GET MY LUMRYZ REFILLS?

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

CAN MY LOCAL PHARMACY PROVIDE LUMRYZ?

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

Reference ID: 5270348

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.

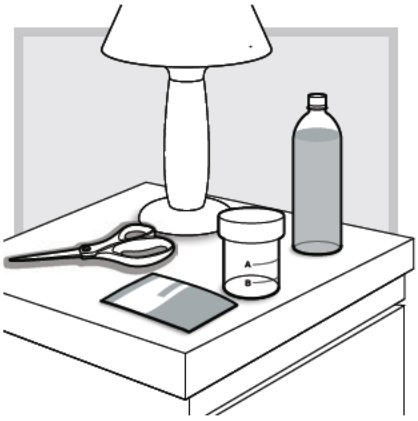
Open the LUMRYZ carton by tearing the tamper-evident seal with your hands or by using a pair of scissors.

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:



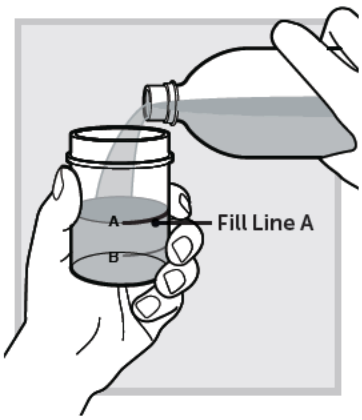
- 1 bottle or glass of water (1/3 cup). Do not use hot water.
- 1 LUMRYZ packet
- 1 clean mixing cup. - The cap is not child resistant.
- 1 pair of scissors (optional)

Reference ID: 5270348

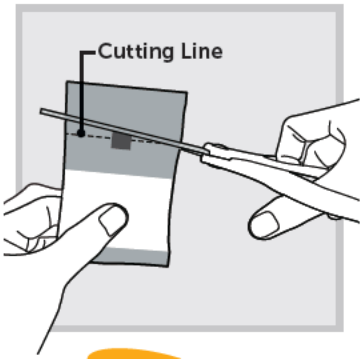
HOW DO I TAKE MY LUMRYZ?

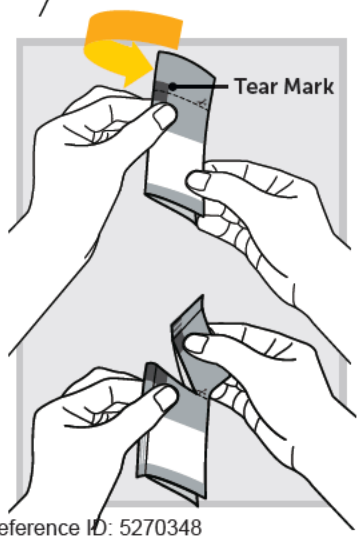
MIX THE LUMRYZ SOLUTION AT YOUR BEDSIDE

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.



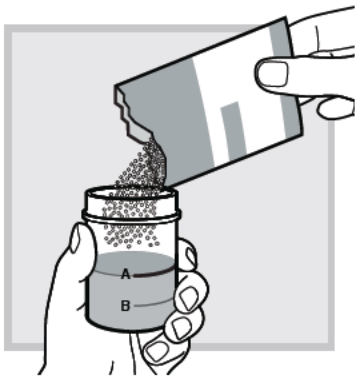


3. Open 1 packet:

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

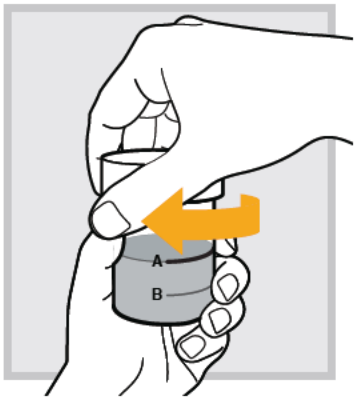
-or-

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

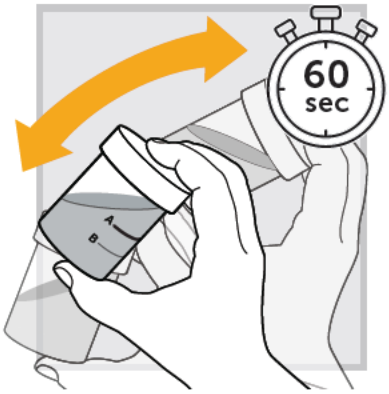


4. Pour the entire content from the packet into the water-filled mixing cup.

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.

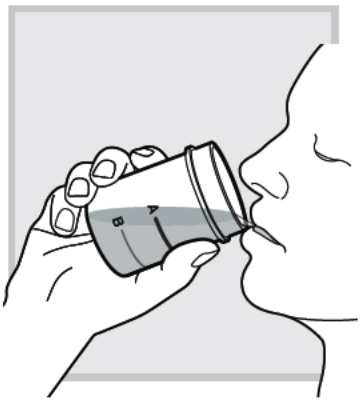
The mixing cup cap is not child resistant. If the mixed solution is not drank immediately, then do not remove the cap, and keep out of reach of children.

Reference ID: 5270348

HOW DO I TAKE MY LUMRYZ?

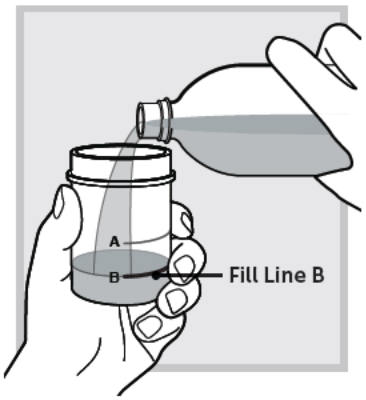
TAKE THE LUMRYZ SOLUTION AT YOUR BEDSIDE

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



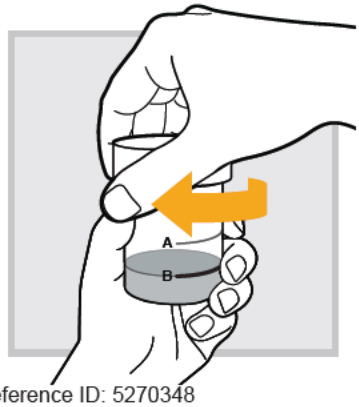
9 While sitting in bed drink the mixed solution within **30 minutes** of mixing.

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

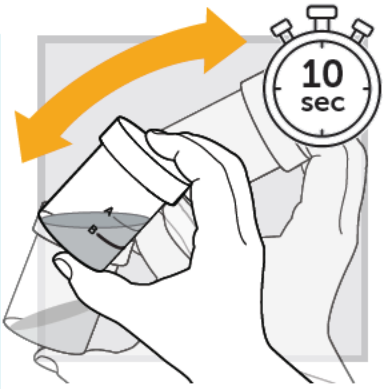


10 Immediately refill your mixing cup with water up to **Fill Line B** (lower line) to mix in any medicine left in the mixing cup.

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



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

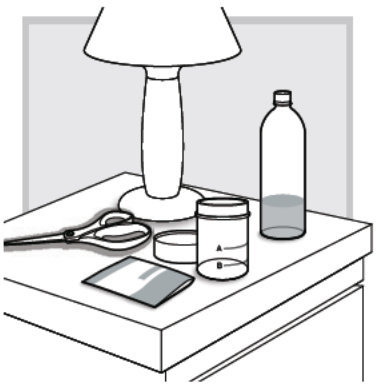


12 Shake well again for **10 seconds.**

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

14 Drink the mixed solution immediately after mixing.

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



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

Avoid getting out of your bed after taking your dose.

Reference ID: 5270348

WHAT SHOULD I DO IF I MISS A DOSE?

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

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

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

HOW SOON WILL I SEE A CHANGE IN MY SYMPTOMS?

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

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

WHAT ARE THE SIDE EFFECTS OF LUMRYZ?

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

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

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

ARE THERE ANY PRECAUTIONS I SHOULD TAKE WHILE ON LUMRYZ?

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

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

Reference ID: 5270348

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

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

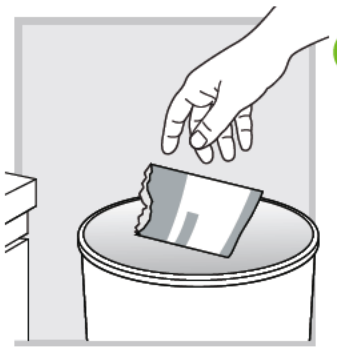
When you first start taking LUMRYZ, you may need to talk to your healthcare provider often until he/she determines the best dose for you. It is possible your dose may need to be adjusted. Your healthcare provider will evaluate you within the first 3 months of taking LUMRYZ and may reevaluate you every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

STORAGE AND SAFETY TIPS AT HOME

HOW DO I STORE LUMRYZ?

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

HOW DO I THROW AWAY (DISPOSE OF) LUMRYZ?



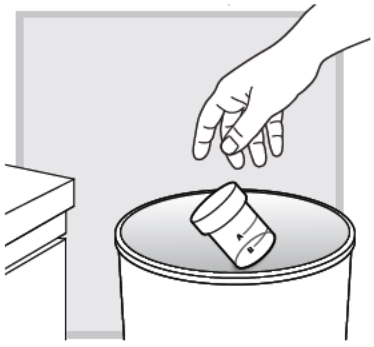
1 The next day, place the empty LUMRYZ packet in the trash.

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

2 Empty any unused LUMRYZ down the sink drain the next day.

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

After you finish all of the packets in your LUMRYZ carton



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

Reference ID: 5270348

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: 5270348

NOTES

KEEP THIS BOOKLET AS A HELPFUL REMINDER

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

Lumryz™

(sodium oxybate) for extended-release oral suspension CIII

Avadel™

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

MED-US-LUM-2100005
09/2023

LUMRYZ™ REMS

Certified Pharmacy Training — Pharmacy Staff and Pharmacists

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

Lumryz™

(sodium oxybate) for extended-release oral suspension Ⓒ

Reference ID: 5270348

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

Dear LUMRYZ REMS Certified Pharmacy Staff,

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

The LUMRYZ REMS

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

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

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

LUMRYZ is approved for:

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

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

Sincerely,

Avadel CNS Pharmaceuticals, LLC

TABLE OF CONTENTS

LUMRYZ REMS TRAINING: PHARMACY STAFF MODULE 4

IMPORTANT SAFETY INFORMATION 5

INDICATIONS AND USAGE 5

HOW SUPPLIED 5

CONTROLLED SUBSTANCE SCHEDULING 5

BOXED WARNING 5

CONTRAINDICATIONS 6

WARNINGS AND PRECAUTIONS 6

LUMRYZ REMS REQUIREMENTS 7

OVERVIEW OF CERTIFIED PHARMACY RESPONSIBILITIES 8

ENROLLMENT VERIFICATION 8

PRESCRIPTION PROCESSING 9

SHIPPING 10

MONITORING FOR INAPPROPRIATE PRESCRIBING, ABUSE, MISUSE, AND DIVERSION 10

ADVERSE EVENT REPORTING 11

ONGOING PATIENT EDUCATION 11

DRUG TAKEBACK PROGRAM 11

LUMRYZ REMS TRAINING: PHARMACIST MODULE 12

LUMRYZ REMS REQUIREMENTS 13

CERTIFIED PHARMACY RESPONSIBILITIES 14

PATIENT COUNSELING AND SCREENING 15

CLINICAL USE CLARIFICATIONS 15

PRESCRIPTION REFILLS 16

MONITORING AND ASSESSING FOR SIGNS OF ABUSE, MISUSE, AND DIVERSION 17

SHIPPING PROCEDURES 18

INVENTORY CONTROL 18

Reference ID: 5270348

CERTIFIED PHARMACY TRAINING — PHARMACY STAFF MODULE

LUMRYZ™ REMS

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

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

Lumryz™

(sodium oxybate) for extended-release oral suspension Ⓒ

Reference ID: 5270348

IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

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

HOW SUPPLIED

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

CONTROLLED SUBSTANCE SCHEDULING

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

BOXED WARNING

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

- **Central Nervous System Depression**

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

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

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

Reference ID: 5270348

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.

Reference ID: 5270348

LUMRYZ REMS REQUIREMENTS

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

Notable requirements of this REMS include:

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

Further information is available at www.LUMRYZREMS.com.

Reference ID: 5270348

OVERVIEW OF CERTIFIED PHARMACY RESPONSIBILITIES

PRESCRIPTION PROCESSING

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

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

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

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

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

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

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

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

SHIPPING

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

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

MONITORING FOR INAPPROPRIATE PRESCRIBING, ABUSE, MISUSE, AND DIVERSION

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

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

Reference ID: 5270348

ADVERSE EVENT REPORTING

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

ONGOING PATIENT EDUCATION

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

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

DRUG TAKEBACK PROGRAM

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

CERTIFIED PHARMACY TRAINING — PHARMACIST MODULE

LUMRYZ™ REMS

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

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

Lumryz™

(sodium oxybate) for extended-release oral suspension Ⓒ

Reference ID: 5270348

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

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

Pharmacist duties will include:

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

LUMRYZ REMS REQUIREMENTS

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

CERTIFIED PHARMACY RESPONSIBILITIES

Certified pharmacies will:

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

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

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

PATIENT COUNSELING AND SCREENING

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

CLINICAL USAGE CLARIFICATIONS

The pharmacist must:

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

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

PRESCRIPTION REFILLS

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

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

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

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

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

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

SHIPPING PROCEDURES

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

INVENTORY CONTROL

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

LUMRYZ™ REMS | Pharmacy Staff Knowledge Assessment

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

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

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

PHARMACY STAFF INFORMATION

(*denotes required field)

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

LUMRYZ REMS TRAINING: PHARMACY STAFF MODULE

SELECT THE BEST ANSWER FOR EACH OF THE FOLLOWING QUESTIONS.

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

Avadel

LUMRYZ™ REMS | Pharmacist Knowledge Assessment

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

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

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

PHARMACIST INFORMATION

(*denotes required field)

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

LUMRYZ REMS TRAINING: PHARMACISTS MODULE

SELECT THE BEST ANSWER FOR EACH OF THE FOLLOWING QUESTIONS.

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

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

Reference ID: 5270348

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 Prescription
The available strengths of LUMRYZ are 4.5g, 6g, 7.5g and 9g. LUMRYZ box quantities are 7 or 30 packets.

Titrated Dose					Maintenance Dose			
Medication	Frequency	Strength	Quantity	Refills	Medication	Strength	Quantity	Refills
	Week 1	_____ g	_____ box(es) of seven (7)	N/A			_____ box(es) of thirty (30)	
	Week 2	_____ g	_____ box(es) of seven (7)					
	Week 3	_____ g	_____ box(es) of seven (7)					
	Week 4	_____ g	_____ box(es) of seven (7)					

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

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

Special Instructions:

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

_____ *Prescriber Signature

_____ *Date

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

_____ *Prescriber Signature

_____ *Date

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

_____ Supervising Physician Signature

_____ Date

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

_____ *Pharmacist Signature

_____ *Date

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

PRESCRIBER ATTESTATIONS

I understand that:

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

Before treatment initiation (first dose), I must:

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

Before treatment re-initiation, I must:

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

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

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

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

At all times, I must:

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

PHARMACIST ATTESTATIONS

As the pharmacist, I must

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

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

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

PHARMACIST INFORMATION (All fields required)

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

PATIENT INFORMATION (All fields required)

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

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

STEP 1: PATIENT INFORMATION (Select One)

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

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

STEP 2: COUNSELING

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

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

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

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

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

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

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

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

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

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

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

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

STEP 3: SCREENING

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

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

☐ Yes ☐ No If Yes, ☐ Counseled Patient

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

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

☐ Yes ☐ No If Yes, ☐ Counseled Patient

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

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

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

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

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

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

☐ Yes ☐ No If Yes, ☐ Counseled Patient

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

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

☐ Yes ☐ No If Yes, ☐ Counseled Patient

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

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

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

Please list the question(s):	Question

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

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

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): _____

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

STEP 5: COMPLETION SUMMARY

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

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

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

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

_____

_____

My signature below signifies:

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

_____ _____

Pharmacist Signature **Date**

Avadel

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

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

FDA-REQUIRED REMS SAFETY INFORMATION

Dear Healthcare Provider:

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

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

Risks of LUMRYZ

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

LUMRYZ REMS Requirements

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

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

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

Adverse Event Reporting

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

Sincerely,

Avadel CNS Pharmaceuticals, LLC

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

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

FDA-REQUIRED REMS SAFETY INFORMATION

Dear Professional Society:

We request that you share the following with your members.

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

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

Risks of LUMRYZ

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

LUMRYZ REMS Requirements for Prescribers

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

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

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

Adverse Event Reporting

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

Sincerely,

Avadel CNS Pharmaceuticals, LLC

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

LUMRYZ™ REMS Fact Sheet

LUMRYZ REMS OVERVIEW

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

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

PRESCRIBERS must be certified in the LUMRYZ REMS

PHARMACIES must be certified in the LUMRYZ REMS

PATIENTS must be enrolled in the LUMRYZ REMS

Scan to access

WHAT IS THE RISK?

LUMRYZ:

- Is a central nervous system (CNS) depressant and can cause obtundation and clinically significant respiratory depression at recommended doses
- Has a known potential for abuse and misuse, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death

How Can Prescribers Manage the Risk?

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

How Can Pharmacies Manage the Risk?

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

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

Avadel

Reference ID: 5270348

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

WHAT ARE THE KEY REQUIREMENTS OF THE LUMRYZ REMS?

PRESCRIBERS

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

PHARMACIES

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

REPORTING ADVERSE EVENTS

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

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

MED-US-LUM-2100015
10/2023

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

Avadel

Reference ID: 5270348

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

INSTRUCTIONS

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

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

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

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

To complete an RMR:

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

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

ALL SECTIONS REQUIRED TO BE COMPLETED

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

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

PATIENT AND/OR PRESCRIBER BEING REPORTED

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

ALL SECTIONS REQUIRED TO BE COMPLETED

LUMRYZ REMS RISK MANAGEMENT REPORT

Addendum to an Existing RMR: ☐ Yes ☐ No

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

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

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

RMR Event (please provide detail):

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

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

Summary of investigation:

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

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

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

_____ Signature

_____ Date

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

Avadel

LUMRYZ™ REMS (Risk Evaluation and Mitigation Strategy)

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

Prescribers

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

Learn about Prescriber Certification

LEARN MORE

Patients

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

Learn about Patient Enrollment

LEARN MORE

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

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

INDICATION

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

Prescribers

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

To become certified in the LUMRYZ REMS, prescribers must:

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

To enroll a patient in the LUMRYZ REMS:

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

Administration Requirements:

Before treatment initiation, the prescriber will:

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

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

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

At all times, the prescriber will:

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

LUMRYZ™ REMS Prescriber Enrollment Form

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

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

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

STEP 1 PRESCRIBER ATTESTATIONS

I have:

- Reviewed the Prescribing Information.
- Reviewed the **Prescriber Brochure**.

I understand:

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

Before treatment initiation (first dose), I must:

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

Before treatment re-initiation, I must:

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

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

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

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

At all times, I must:

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

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

Prescriber Information (* *denotes required field*)

*NPI No.

CONTINUE

LUMRYZ™ REMS Prescriber Enrollment Form

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

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

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

STEP 1 PRESCRIBER ATTESTATIONS

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

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

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

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

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

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

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

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

Prescriber Information (* *denotes required field*)

*NPI No.
1234567890

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

Facility/Practice Name | *State License No.

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

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

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

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

*Phone | *Fax | *Email

*Preferred Method of Contact
☐ Email ☐ Fax

Office Contact Information

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

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

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

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

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

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

☐ *Prescriber Signature

CANCEL SUBMIT

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

LUMRYZ™ REMS Prescriber Enrollment Form

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

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

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

STEP 1 PRESCRIBER ATTESTATIONS

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

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

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

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

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

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

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

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

Prescriber Information (* *denotes required field*)

*NPI No.
1234567890

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

Facility/Practice Name | *State License No.

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

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

*Professional Designation Other: RN

*Medical Specialty Other: Internist

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

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

*Phone | *Fax | *Email

*Preferred Method of Contact: ☐ Email ☐ Fax

Office Contact Information

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

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

Office Contact Email

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

Office Contact Email

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

Office Contact Email

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

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

☐ *Prescriber Signature

CANCEL | SUBMIT

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

LUMRYZ REMS Prescriber Enrollment Successful

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

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

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

Patients

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

To become enrolled in the LUMRYZ REMS, patients must:

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

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

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

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

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

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

Resources

Resources for Prescribers

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

Resources for Pharmacies

- Certified Pharmacy Training Program
- Patient Counseling Checklist

Resources for Patients

- Patient Brochure
- Medication Guide
- Patient Enrollment Form

Contact Us

Phone: 1-877-453-1029

Fax: 1-877-206-3198

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

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

Pharmacy Staff Registration

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

Required fields are denoted by "*".

Pharmacy Staff User Information

* Pharmacy Identifier

CANCEL CONTINUE

Pharmacy Staff Registration

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

Required fields are denoted by "*".

Pharmacy Staff User Information

*Pharmacy Identifier

1111

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

ABC Pharmacy

*I am a Pharmacist

Yes No

*First Name

*Last Name

*Email Address

*Phone

CLEAR SUBMIT

Pharmacy Staff Registration

Your registration has been successfully submitted.

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

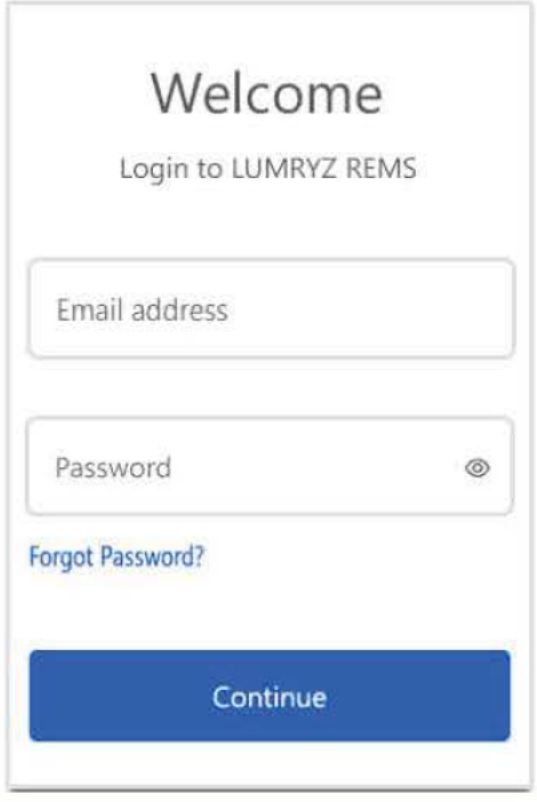
If you do not receive the email within the next few hours, or would like to update your information at any time, please contact the LUMRYZ REMS for assistance at 1-877-453-1029.

Lumryz

(sodium oxybate) for extended-release oral suspension 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:

214755Orig1s003

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 3 received May 4, 2023 (sequence 67), amended on May 24, 2023 (sequence 71), June 14, 2023 (sequence 78), June 21, 2023 (sequence 80), July 31, 2023 (sequence 88), September 11, 2023 (sequence 95), September 21, 2023 (sequence 97), October 25, 2023 (sequence 105), October 30, 2023 (sequence 106), and October 31, 2023 (sequence 107)
Action Date	October 31, 2023
Nexus TTT #	2023-4700
Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS (DRM) Kate Oswell, MA (DRM)
Acting Team Leader	Joseph Paradis, PharmD (OMEPRM) Timothy Bernheimer, PharmD (DRM)
Division Director	Cynthia LaCivita, PharmD (DRM)
Review Completion Date	October 31, 2023
Subject	Review of proposed Major REMS Modification
Established Name	Sodium Oxybate Extended-Release Oral Suspension
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 grams, 6 grams, 7.5 grams, and 9 grams

TABLE OF CONTENTS

EXECUTIVE SUMMARY 3

1. Introduction 4
2. Background 5
   - 2.1. PRODUCT INFORMATION 5
   - 2.2. Regulatory History 6
3. Review of Proposed REMS Modifications 7
   - 3.1. REMS Document 7
   - 3.2. REMS Requirements 7
     - 3.2.1. REMS Participant Requirements and Materials 7
       - 3.2.1.1. Healthcare Provider 7
       - 3.2.1.2. Patients 8
       - 3.2.1.3. Pharmacies that dispense 8
     - 3.2.2. REMS Applicant Requirements and Materials 9
       - 3.2.2.1. Training 9
       - 3.2.2.2. Communication 10
       - 3.2.2.3. Operations 10
       - 3.2.2.4. Compliance 11
   - 3.3. REMS Assessment Timetable 11
4. Supporting Document 11
5. REMS Assessment Plan 11
6. Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials 11
7. Discussion 12
8. Conclusions and Recommendations 13
9. References 13
10. Appendix 13

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 May 4, 2023 and was amended on May 24, 2023, June 14, 2023, June 21, 2023, July 31, 2023, September 11, 2023, September 21, 2023, October 25, 2023, October 30, 2023, and October 31, 2023.

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] of Lumryz. 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 are to update the requirement for prescribers to document and submit all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion to the REMS using the **Risk Management Report**; move the confirmation that each prescription filled for Lumryz was reported to each REMS for oxybate products from the dispense authorization; add guardian email as a required field to **Patient Enrollment Form**; provide editorial or grammatical changes to **Patient Counseling Checklist** and Supporting Document; provide changes to the **Prescriber Enrollment Form** to allow the prescriber to designate multiple office contacts to support administrative activities and communications with the REMS; and to update the **Prescription Form** to comply with certain state requirements for paper prescriptions. The following REMS materials are affected by this proposed modification:

- **REMS Document**
- **Prescriber Enrollment Form**
- **Patient Enrollment Form**
- **Prescriber Brochure**
- **Certified Pharmacy Training Program**
- **Prescription Form**
- **Patient Counseling Checklist**
- **REMS Fact Sheet**
- **REMS Website Screenshots**

In addition, during the review of this supplement we communicated to the Applicant that the following modifications were necessary:

- Prescribers are required to report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the **Risk Management Report**.
- Certified pharmacies are required to obtain oxybate prescription information of last dispense date, days' supply, and prescriber's name by contacting all other REMS for oxybate products.
- Changes to the dispense authorization requirement to include that the **Patient Counseling Checklist** is completed as required and the alerts and **Risk Management Report** histories for the patient and their prescriber are reviewed by the pharmacist.
- The Applicant is required to ensure certified pharmacies and prescribers are able to access patient alerts and **Risk Management Report** histories.

[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.

- The Applicant is required to 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.

DRM finds the proposed modifications to Lumryz REMS to be acceptable and recommends approval of the REMS Modifications. There are no changes to the timetable for submission of assessments of the REMS. There are changes to the Assessment Plan to include additional metrics to capture shipment made without completion of the **Patient Counseling Checklist**; to capture "other" reasons for the prescriber's rationale to continue interacting concomitant medications; and the Pre-dispense Authorization (PDA) was revised to REMS Dispense Authorization (RDA) to align with other REMS for oxybate products.

1. Introduction

This review evaluates the proposed major 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 May 4, 2023 and was amended on May 24, 2023, June 14, 2023, June 21, 2023, July 31, 2023, September 11, 2023, September 21, 2023, October 25, 2023, October 30, 2023, and October 31, 2023.

The proposed modifications to the REMS are to update the requirement for prescribers to document and submit all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion to the REMS using the **Risk Management Report**; move the confirmation that each prescription filled for Lumryz was reported to each REMS for oxybate products from the dispense authorization; add guardian email as a required field to **Patient Enrollment Form**; provide editorial or grammatical changes to **Patient Counseling Checklist** and Supporting Document; provide changes to the **Prescriber Enrollment Form** to allow the prescriber to designate multiple office contacts to support administrative activities and communications with the REMS; and to update the **Prescription Form** to comply with certain state requirements for paper prescriptions. The following REMS materials are affected by this proposed modification:

- **REMS Document**
- **Prescriber Enrollment Form**
- **Patient Enrollment Form**
- **Prescriber Brochure**
- **Certified Pharmacy Training Program**
- **Prescription Form**
- **Patient Counseling Checklist**
- **REMS Fact Sheet**
- **REMS Website Screenshots**

In addition, during the review of this supplement we communicated to the Applicant that the following modifications were necessary:

- Prescribers are required to report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the **Risk Management Report**.
- Certified pharmacies are required to obtain oxybate prescription information of last dispense date, days' supply, and prescriber's name by contacting all other REMS for oxybate products.

- Changes to the authorization requirement to include that the **Patient Counseling Checklist** is completed as required and the alerts and **Risk Management Report** histories for the patient and their prescriber are reviewed by the pharmacist.
- The Applicant is required to ensure certified pharmacies and prescribers are able to access patient alerts and **Risk Management Report** histories.
- The Applicant is required to 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.

2. Background

2.1. PRODUCT INFORMATION

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

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

[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.

2.2. Regulatory History

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

- **05/01/23:** Lumryz approved with REMS for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.
- **05/04/23:** Applicant submitted a minor REMS modification. The following changes were included amongst others: (b) (4) and (b) (4) (b) (4)
- **05/24/23:** Applicant submitted REMS amendment to correct typographical error in PDF layout version of the **Prescriber Enrollment Form.**
- **06/08/23:** Information Request sent to the Applicant to submit video storyboard with transcript and complete video file of the Lumryz REMS Overview Video on the REMS Website.
- **06/14/23:** Information Request response received from the Applicant to provide video storyboard with transcript and complete video file of the Lumryz REMS Overview Video on the REMS Website.
- **06/15/23:** Information Request sent to the Applicant to submit the complete REMS with all REMS materials.
- **06/21/23:** A Prior Approval Supplement Acknowledgment letter was sent to Applicant informing them that the proposed changes are considered to be a major REMS modification.
- **06/21/23:** Information Request response received from Applicant. Applicant submitted complete REMS with all REMS materials as requested by the Agency.
- **07/31/23:** Applicant submitted a REMS amendment to provide changes to the **Prescriber Enrollment Form** to allow the prescriber to designate multiple office contacts to support administrative activities and communications with the REMS.
- **09/11/23:** Applicant submitted a REMS amendment to provide changes to the **Prescription Form** to comply with certain state requirements for paper prescriptions.
- **09/14/23:** Interim comments issued to the Applicant based on DRM's review of proposed Major REMS modification. DRM conveyed to the Applicant that we do not agree (b) (4) (b) (4)
- **09/21/23:** Applicant submitted a REMS amendment in response to DRM's September 14, 2023 review.
- **10/18/23:** Interim comments issued to the Applicant based on DRM's review of proposed Major REMS modification.
- **10/25/23:** Applicant submitted a REMS amendment in response to DRM's October 18, 2023 review.
- **10/27/23:** Information Request sent to the Applicant with comments on REMS website portal screenshots.

- **10/30/23:** Applicant submitted an amendment containing REMS submission with edits in response to DRM's review.
- **10/31/23**: Information Request sent to the Applicant with comments on **Prescriber Brochure**.
- **10/31/23**: Applicant submitted an amendment containing REMS submission with edits in response to DRM's review.

3. Review of Proposed REMS Modifications

3.1. REMS Document

The proposed changes to the format of the REMS Document include:

- In Section I. Administrative Information, the addition of "Risk: serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion" above the application number to align with the REMS Document Technical Conformance Guide. [3,4]
- The addition of Section VI. "Statutory Elements" to align with the REMS Document Technical Conformance Guide which includes, ETASU, implementation systems, and timetable for submission of assessments.

Reviewer's Comments: *The REMS Document is acceptable.*

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 Provider

In the currently approved Lumryz REMS, prescribers are required to report any cases of suspected abuse, misuse, or diversion to Avadel CNS Pharmaceuticals, LLC; and to report requests to disenroll a patient to a certified pharmacy. This modification will require prescribers to assess the patient's potential for abuse, misuse, and diversion; and to 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 and Management Report**; and to report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the **Risk Management Report**. The REMS Document, **Prescriber Enrollment Form,** and **Prescription Form** were aligned with the addition of this requirement. Additionally, as a result of this change, the format of the **Risk Management Report** was modified to allow both pharmacists and prescribers to utilize the material.

The Applicant made changes to the **Prescription Form** to comply with certain state requirements for paper prescriptions. Furthermore, in the current **Prescriber Enrollment Form**, there are data fields for office contact name and phone number. The Applicant added to the **Prescriber Enrollment Form** multiple fields to designate multiple office contacts to support administrative activities and communications with the REMS.

Reviewer's Comments: *The prescriber requirements,* ***Prescriber Enrollment Form****,* ***Prescription Form****, and* ***Risk Management Report*** *are acceptable. The requirements for prescribers to use the* ***Risk Management Report*** *to report requests to disenroll a patient due to these behaviors will relieve burden*

*on certified pharmacies and prescribers by using the REMS as a single point of contact. In the currently approved Lumryz REMS, healthcare providers are required to report any cases of suspected abuse, misuse, or diversion to Avadel CNS Pharmaceuticals, LLC and to report requests to disenroll a patient to a certified pharmacy. They are not required to use the **Risk Management Report** to report and request these things. The requirement for prescribers using the **Risk Management Report** to report to the REMS suspicious abuse, misuse, or diversion harmonizes this activity across multiple oxybate REMS which will lessen stakeholder burden and confusion.*

3.2.1.2. Patients

The Applicant updated the attestations on the **Patient Enrollment Form** with the REMS Document. The Applicant also made changes to the **Patient Enrollment Form** to add a required field for the Guardian's email address to allow for a guardian to receive an email link for signature if not present in the office for patient enrollment. The prescriber information section in the **Patient Enrollment Form** was also changed to include additional data fields for DEA number, Prescriber's address, and fax number.

Additionally, the **Patient Brochure** was updated with editorial changes to clarify that a pharmacist at a certified pharmacy will review important information about Lumryz with the patient; and to add additional information regarding how patients can obtain information on a drug takeback program to return any unused, leftover or expired drug product.

Reviewer's Comments: *The **Patient Enrollment Form** and **Patient Brochure** are acceptable.*

3.2.1.3. Pharmacies that dispense

The Applicant's proposed modifications to the pharmacy requirements in the REMS Document include:

- In the approved REMS, certified pharmacies are required to obtain authorizations to dispense Lumryz by contacting the REMS to verify the pharmacy is certified, the prescriber is certified, the patient is enrolled, and the patient has no active, overlapping prescriptions. With this modification, the authorization to dispense was updated to include completion of the **Patient Counseling Checklist** as required and that alerts and **Risk Management Report** histories for the patient and their prescriber are reviewed by the pharmacist.
- The requirements regarding certified pharmacies contact to all other oxybate REMS to verify the patient has no other active prescription for oxybate products that overlap with the current prescription for Lumryz were updated to include specific prescription information (i.e., last date dispensed, days' supply, and prescriber name) that the certified pharmacy must obtain during the required contact to all other oxybate REMS.
- A requirement was added for certified pharmacies to verify in the Lumryz REMS that the patient has no other active Lumryz prescriptions through processes and procedures established as a requirement of the REMS.
- References regarding contacting "the" other REMS for oxybate products were updated to "all" other REMS for oxybate products throughout the REMS Document.
- A section on "to maintain certification to dispense" was added to the pharmacy requirements of the REMS Document to specify the requirements if the authorized representative is different from the previously designated authorized representative.
- A requirement was added for certified pharmacies to report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the **Risk Management Report**. This requirement was previously only described in the **Certified Pharmacy Training Program**.

- In the section "To become certified to dispense", the pharmacy requirement to establish processes and procedures to verify the patient and prescriber are enrolled, the patient has no other active Lumryz prescriptions. This corresponds and aligns with an existing pharmacy requirement.
- The requirement for pharmacies to report each prescription filled for Lumryz to all REMS for oxybate products was edited to specify that this requirement must be completed within 1 business day of dispensing.

The Applicant also updated the pharmacy attestations on the **Pharmacy Enrollment Form** to align with the updated REMS Document. Additionally, the Applicant removed the NCPDP data field from the **Pharmacy Enrollment Form**.

Additionally, the Applicant proposed to update the **Patient Counseling Checklist** to change (b) (4) in question #3 (b) (4) and to add the option "none"; and to add "None of the Above" as an option in Step 4 for Concomitant Medication Type and Medical Condition summaries. Also, the Applicant added to Step 4 an "other (specify)" option to the "Prescriber's rationale for continuing concomitant medication with Lumryz" question.

Reviewer's Comments: *The pharmacy requirements,* ***Pharmacy Enrollment Form,*** *and* ***Patient Counseling Checklist*** *are acceptable. The additions to the authorization to dispense requirement described above will ensure that safe use conditions are met and support compliance with pharmacy requirements that must be completed prior to dispensing Lumryz. Additionally, changes made to the pharmacy requirements will improve communication between REMS for oxybate products.*

3.2.2. REMS Applicant Requirements and Materials

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

3.2.2.1. Training

The Applicant updated the **Prescriber Brochure** to include the changes to the healthcare provider requirements as described in section 3.2.1.1; the Applicant also updated the **Prescriber Brochure** to include a statement that clarifies that there is no reciprocity for patient enrollment and prescriber certification across oxybate REMS. Although certified prescribers are not required to review patient alerts and **Risk Management Report** histories in Lumryz REMS, the Applicant will provide prescribers access to alerts and Risk Management Report histories for review as needed; and a description of this process was added to the **Prescriber Brochure.**

The Applicant also proposed changes to the **Certified Pharmacy Training Program** by moving the confirmation that each prescription filled for Lumryz was reported to each REMS for oxybate products from the authorization to dispense. This confirmation was moved to be included in the nightly data exchange of prescription information to the REMS. The Applicant edited the training to state that certified pharmacies must provide confirmation of receipt of each prescription filled and shipment received of Lumryz to the REMS electronically instead of accessing the REMS website or by calling the REMS. Additionally, the Applicant provided edits to the **Certified Pharmacy Training Program** to align with the changes made to the pharmacy requirements in the REMS Document. The section entitled "Enrollment Verification" under "Overview of Certified Pharmacy Responsibilities was removed from the **Certified Pharmacy Training Program** and moved to the Supporting Document; and the pre-dispense authorization was renamed the REMS Dispense Authorization (RDA). Additionally, in circumstances where the patient has changed pharmacies, the Applicant added a process in the **Certified Pharmacy**

Training Program for a new certified pharmacy to contact the Lumryz REMS certified pharmacy that filled the previous prescription to obtain the most recent **Prescription Form**.

The Applicant also provided edits to the **Pharmacy Staff Knowledge Assessment** to align with the updated pharmacy requirements and the RDA; and added additional questions to both the **Pharmacy Staff Knowledge Assessment** and the **Pharmacist Knowledge Assessment.**

Reviewer's Comments*: The* ***Prescriber Brochure, Certified Pharmacy Training Program, Pharmacy Staff Knowledge Assessment****, and* ***Pharmacist Knowledge Assessment*** *are acceptable. Changes made to training materials were necessary to align with changes made to prescriber and pharmacy requirements; and to align with the training materials with the materials for other REMS for oxybate products. Given that Lumryz REMS is a separate REMS from other REMS for oxybate products, it is important that the* ***Prescriber Brochure*** *informs prescribers that certification in any other REMS for oxybate products is not reciprocal with the Lumryz REMS.*

3.2.2.2. Communication

The Applicant made changes to the **Fact Sheet** to align with the changes made to the healthcare provider requirements as described above in section 3.2.1.1. Additionally, the Applicant edited the **Fact Sheet** to make the overview of key requirements of the REMS more concise.

Reviewer's Comments: *The* ***Fact Sheet*** *is acceptable.*

3.2.2.3. Operations

The Applicant modified the REMS website to align with changes made to healthcare provider requirements as described above in section 3.2.1.1. Additionally, the Applicant removed the REMS overview video from the REMS website.

The Applicant also updated the REMS Operation section of the REMS Document to align the Applicant's requirements with the updated REMS participants requirements and operations. With this modification, the Applicant must now authorize dispensing for each patient after verifying the pharmacy is certified, the prescriber 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 prescribers are reviewed by the pharmacist, and the patient has no active, overlapping prescriptions for oxybate products. In the approved REMS, the authorization requirements did not include verification of the **Patient Counseling Checklist** is completed as required, and that the alerts and **Risk Management Report** history for the patient and their prescribers are reviewed by the pharmacist. The Applicant must also ensure certified pharmacies and prescribers are able to access alerts and **Risk Management Report** histories; and 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.

Reviewer's Comments: *The REMS website and the proposed changes to the operations are acceptable. Additions to the Applicant's authorization requirement (the verification of the* ***Patient Counseling Checklist*** *is completed as required, and that the alerts and* ***Risk Management Report*** *history for the patient and their prescribers are reviewed by the pharmacist) were necessary to support changes to the pharmacy requirements as described in section 3.2.1.3. In addition, the process to provide Lumryz prescription information to other pharmacies will support communication between all REMS for oxybate products.*

3.2.2.4. Compliance

The Applicant made changes to a compliance requirement to add wholesalers-distributors as a REMS participant that the Applicant is required to monitor on an ongoing basis to ensure the requirement of the REMS are being met.

Reviewer's Comments: *The proposed changes to ensure stakeholder's compliance are acceptable.*

3.3. REMS Assessment Timetable

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

4. Supporting Document

The Applicant made changes to the REMS Supporting Document to include the background of the REMS Modification currently under review. The Applicant appended versions of the knowledge assessments with answers; included prescriber portal screenshots that displayed patient alerts and **Risk Management Report** histories; updated pharmacy portal screenshots to include screenshots of prescriber alerts and **Risk Management Report** histories and screenshots of the updated RDA functionality. Additionally, the Applicant added the sample call script that are used by certified pharmacies when contacting other REMS for oxybate products to the Supporting Document.

Reviewer's Comments*: The Supporting Document is acceptable.*

5. REMS Assessment Plan

The assessment plan was revised to include metrics to capture the number of Lumryz shipments sent to patients without completion of the **Patient Counseling Checklist** for patients that notified the pharmacy of a new or change in concomitant medication or comorbidity and for those with lapse in therapy for greater than six months. An additional metric was added to capture "other" reasons for the prescriber's rationale to continue interacting concomitant medications. Also, Pre-dispense Authorization (PDA) was revised to REMS Dispense Authorization (RDA) to align with other REMS for oxybate products.

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

6. Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on June 21, 2023 to provide feedback on the content of the REMS Overview Video on the REMS website. The OPDP review was completed by Koung Lee on July 12, 2023.[5] The OPDP review recommendations and DRM comments are summarized in our September 14, 2023[6] review and comments were communicated to the Applicant.

Reviewer's Comments: *The Applicant removed the REMS Overview Video from the REMS website in the September 21, 2023 response. We agree with this change.*

7. Discussion

The REMS modifications were necessary to ensure efficient reporting by prescribers for suspected abuse, misuse, and diversion to the REMS; to support compliance with pharmacy requirements that must be completed prior to dispensing; to harmonize activities across REMS for oxybate products; and to improve communication between all REMS for oxybate products.

The changes to allow prescribers to use the **Risk Management Report** as described above are intended to minimize delays, errors, or lost reports of a patient's potential for abuse, misuse, or diversion. Having prescribers document these instances with the **Risk Management Report** will ensure safe use and reduce burden on certified pharmacies and prescribers by using the REMS as a single point of contact. Additionally, there are multiple REMS for oxybate products and the changes were also made to harmonize activities across REMS, when possible, to reduce stakeholder confusion.

In addition, DRM communicated several changes that were necessary during the review of this supplement to support compliance with pharmacy requirements that must be completed before dispensing, as well as to align with other REMS for oxybate products that utilize multiple pharmacies and a separate REMS administrator. For instance, the authorization to dispense was updated to include completion of the **Patient Counseling Checklist** as required and that alerts and **Risk Management Report** histories for the patient and their prescriber are reviewed by the pharmacist. Additionally, the requirement for pharmacies to report each prescription filled for Lumryz to all REMS for oxybate products was changed to specify that this requirement must be completed within 1 business day of dispensing to improve communication and timely reporting to other REMS for oxybate products.

Additionally, the Applicant moved the confirmation that each prescription filled for Lumryz was reported to each REMS for oxybate products from the PDA, as described in the **Certified Pharmacy Training Program**. This was necessary because the confirmation can only occur until after the prescription is dispensed which is after the PDA generation.

As result of the changes to participant requirements and their affected materials, several changes were needed to the Applicant requirements to support operations. DRM provided comments to the Applicant to 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. This requirement will improve communications between REMS for oxybate products.

The assessment plan was updated to include metrics to capture shipments that may be sent to patients without completion of a **Patient Counseling Checklist** for patients that notified the pharmacy of a new or change in concomitant medication or comorbidity and for those with lapse in therapy for greater than six months. This aligns with the assessment plan for other REMS for oxybate products. An additional metric was added to capture "other" reasons for the prescriber's rationale to continue interacting concomitant medications and PDA was revised to REMS Dispense Authorization (RDA) to align with other REMS for oxybate products. No changes were made to the timetable for assessments.

Furthermore, modifications to the Lumryz REMS still align with the safety requirements for the Xywav and Xyrem REMS, another REMS for oxybate products. The REMS goals and elements remains the same for both REMS.

8. Conclusions and Recommendations

DRM finds the proposed REMS modifications for Lumryz (sodium oxybate extended-release) as submitted on May 4, 2023, amended on May 24, 2023, June 14, 2023, June 21, 2023, July 31, 2023, September 11, 2023, September 21, 2023, October 25, 2023, October 30, 2023, and October 31, 2023 acceptable. The REMS materials were amended to be consistent with the revised REMS document. DRM recommends approval of the REMS Modification for Lumryz, received on May 4, 2023 and last amended on October 31, 2023, and appended to this review.

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.

9. 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. DARRTS May 01, 2023(accessed at https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806c8270)

[3] U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) January 2023; *Format and Content of a REMS Document Guidance for Industry*; accessed at https://www.fda.gov/media/77846/download

[4] U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) January 2023; *REMS Document Technical Conformance Guide*; accessed at https://www.fda.gov/media/164344/download

[5] Lee, K. Office of Prescription Drug Promotion (OPDP) Comments on Draft Risk Evaluation and Mitigation Strategies (REMS) Material for Lumryz REMS NDA 214755, DARRTS July 12, 2023 (accessed at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806de8fc).

[6] Olumba, S. Interim Review of Proposed Major REMS Modification for Lumryz. NDA 214755. DARRTED September 14, 2023 (available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806f41a4)

10. 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

Pharmacy:

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

Patient Care Forms

- Prescription Form
- Patient Counseling Checklist

Communication Materials

- Dear Healthcare Provider Letter
- Dear Professional Society Letter
- REMS Fact Sheet

Other Materials

- Risk Management Report
- REMS Program Website

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

/s/

STEPHANIE N OLUMBA
10/31/2023 05:25:27 PM

KATE H OSWELL
10/31/2023 05:31:23 PM

JOSEPH P PARADIS
10/31/2023 05:32:46 PM

TIMOTHY J BERNHEIMER
10/31/2023 05:35:31 PM

CYNTHIA L LACIVITA
10/31/2023 05:41:54 PM

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

Application Type	NDA
Application Number	214755
Supplement Number, Date Received	Supplement 3 received May 4, 2023 (sequence 67), amended on May 24, 2023 (sequence 71), June 14, 2023 (sequence 78), June 21, 2023 (sequence 80), July 31, 2023 (sequence 88), September 11, 2023 (sequence 95), and September 21, 2023 (sequence 97)
Action Date	October 31, 2023
Nexus TTT #	2023-4700
Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS Kate Oswell, MA
Acting Team Leader	Timothy Bernheimer, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	October 18, 2023
Subject	Review of proposed Major REMS Modification
Established Name	Sodium Oxybate Extended-Release Oral Suspension
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals
Therapeutic Class	Central Nervous System Depressant
Formulation(s)	Powder for extended-release oral suspension: packets of 4.5 g, 6 g, 7.5 g, and 9 g

TABLE OF CONTENTS

1. Introduction 3
2. Regulatory History 3
3. Review of Proposed REMS Modifications 3
   3.1. REMS Goals 3
   3.2. REMS Requirements 3
      3.2.1. REMS Participant Requirements and Materials 3
         3.2.1.1. Healthcare Provider 3
         3.2.1.2. Patients 4
         3.2.1.3. Pharmacies that dispense 4
      3.2.2. REMS Applicant Requirements and Materials 5
         3.2.2.1. Training 5
         3.2.2.2. Communication 6
         3.2.2.3. Operations 6
   3.3. REMS Assessment Timetable 7
4. Supporting Document 7
   4.1. REMS Assessment Plan 7
5. Conclusions and Recommendations 7
6. Comments to the Applicant 7
7. References 10
8. Appendix 10

1. Introduction

This review evaluates the proposed major 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 May 4, 2023 and was amended on May 24, 2023, June 14, 2023, June 21, 2023, July 31, 2023, September 11, 2023, and September 21, 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 increased risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion[a] of Lumryz.[2]

2. Regulatory History

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

- 09/14/23: Interim comments issued to the Applicant based on DRM's review of proposed Major REMS modification.[3]
- 09/21/23: Applicant submitted an amendment, subject of this review.

3. Review of Proposed REMS Modifications

3.1. REMS Goals

The Applicant proposed modifications to the REMS goals by (b) (4) from the following objective (strikethrough: deletion): (b) (4) (b) (4)

Reviewer's Comments: *We do not agree with the Applicant's edits to the REMS goal. The Applicant stated* (b) (4) *However,* (b) (4) *must remain in the REMS goal because it aligns with the REMS goals for all other approved REMS for oxybates products.*

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 Provider

The Applicant did not accept the changes the Agency conveyed on September 14, 2023[3] to add the requirements for prescribers to use the **Risk Management Report** (**RMR**) to document and submit

[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.

patient behavior suspicious of abuse, misuse, or diversion and to report requests to disenroll a patient due to these behaviors.

[redacted] This change was made to the REMS Document, **Prescriber Enrollment Form,** and **Prescription Form**. As a result of this change, the Applicant did not make the changes the Agency conveyed to edit the **RMR** to include prescribers as a type of reporter.

Reviewer's Comments: *We do not agree with the Applicant's proposal* [redacted] *Use of the **RMR** by prescribers in the Lumryz REMS is intended to ensure safe use and reduce burden on certified pharmacies and prescribers by using the REMS as a single point of contact.* [redacted] *and similar changes by the Agency have been applied to REMS. We will send comments to the Applicant* [redacted] *for prescribers to use the **RMR** to document and submit patient behavior suspicious of abuse, misuse, or diversion and to report requests to disenroll a patient due to these behaviors.*

*We will also ask the Applicant to apply the changes made to the REMS Document to the **Prescriber Enrollment Form** and **Prescription Form.** Additionally, we will ask the Applicant to edit the **RMR** as conveyed in our September 14, 2023 comments to include prescribers as a type of reporter for the **RMR.***

*Additionally, some of the data fields on the **Prescription Form** are too small and may cause errors when completing the form. The font size of the data fields and the attestations in the **Prescription Form** will need to be increased to minimize errors and improve readability.*

3.2.1.2. Patients

The Applicant made the changes the Agency conveyed on September 14, 2023[3] to the patient requirements in the REMS Document, **Patient Enrollment Form**, and the **Patient Brochure**. The Applicant clarified that the email link for the signature will link to the online version of the **Patient Enrollment Form**. Furthermore, the Applicant provided edits to the information in the **Patient Brochure** regarding the drug takeback program, and now states "Lumryz patients can return any unused, leftover or expired drug product through a drug takeback program. To [redacted] obtain information, please contact the Lumryz REMS" (underline: additions; and strikethrough: deletions).

Reviewer's Comments: *The patient requirements in the REMS Document, the **Patient Enrollment Form**, and **Patient Brochure** are acceptable.*

3.2.1.3. Pharmacies that dispense

The Applicant made some of the changes the Agency conveyed on September 14, 2023[3] to the pharmacy requirements in the REMS Document, **Pharmacy Enrollment Form**, the **RMR**, and **Patient Counseling Checklist.** The Applicant provided edits to the pharmacy requirements: (underline: additions; and strikethrough: deletions) "verify the patient has no other active prescriptions for oxybate products

that overlap with the current prescription for LUMRYZ (by ~~obtaining~~ [redacted] oxybate prescription information of last dispense date, days' supply, and prescriber's name)". The Applicant applied the changes they made to the pharmacy requirements in the REMS Document to the **Pharmacy Enrollment Form.** Furthermore, the Applicant removed the NCPDP data field from the **Pharmacy Enrollment Form.**

Reviewer's Comments: *The **Patient Counseling Checklist** is acceptable. We do not agree with the Applicant's proposed changes to the pharmacy requirements. The Applicant states* [redacted] *The pharmacy must obtain information by contacting all oxybate REMS that there are no active, overlapping prescriptions.* [redacted] *We have provided edits to the REMS Document to change* [redacted] *to "obtaining".*

*We have also provided additional edits to the pharmacy requirements in the REMS Document. Under, the section, " To become certified to dispense", we have added a pharmacy requirement to establish processes and procedures to verify the patient and prescriber are enrolled, the patient has no other active Lumryz prescriptions. This corresponds and aligns with an existing pharmacy requirement. Additionally, we have made edits to the requirement for pharmacies to report each prescription filled for Lumryz to all REMS for oxybate products to specify that this requirement must be completed after dispensing, within 1 business day. This will ensure timely reporting to other REMS for oxybate products. These changes will also need to be applied to the **Pharmacy Enrollment Form**. We will ask the Applicant to apply the edits made to the pharmacy requirements in the REMS Document to the **Pharmacy Enrollment Form**.*

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 Applicant made some of the changes the Agency conveyed on September 14, 2023[3] to the **Prescriber Brochure**, **Certified Pharmacy Training**, **Pharmacy Staff Knowledge Assessment**, and **Pharmacist Knowledge Assessment.** [redacted] Also, the Applicant moved the information regarding product information (i.e., date or fill, days' supply, quantity, and NDC) outside of the REMS Dispense Authorization section in the **Certified Pharmacy Training Program.** Additionally, the Applicant provided edits to the **Pharmacy Staff Knowledge Assessments**: a response in question 12 was edited to align with how it is presented in the **Certified Pharmacy Training.**

Reviewer's Comments: The ***Pharmacy Staff Knowledge Assessment*** *and the **Pharmacist Knowledge Assessment** are acceptable. As mentioned above in section 3.2.1.1, we do not agree with Applicant's proposals* [redacted] *We will provide comments to the Applicant to edit the **Prescriber Brochure** to include the updated prescriber requirements as explained in section 3.2.1.1. To align with the prescriber requirements, we have*

(b) (4)

*In circumstances where the patient has changed pharmacies, we have added to the **Certified Pharmacy Training Program** a process for the new pharmacy to contact the Lumryz REMS certified pharmacy that filled the previous prescription to obtain the most recent **Prescription Form**. During the review, it has come to our attention that the **Prescription Form** is not uploaded to the patient account information functionality of the REMS Website. As a result, a pharmacy that is different from the pharmacy that filled the previous prescription and is processing a refill (e.g., transferred prescription) or a renewal (e.g., prescription sent from a prescriber) for an existing Lumryz REMS enrolled patient must contact the pharmacy that filled the previous prescription for which the most recent **Prescription Form** was received. This form is needed by the dispensing pharmacy because it contains the list of medications and comorbidities sourced from the prescriber; and the Lumryz REMS does not appear to capture or retain information on the **Prescription Form** so it is accessible for all certified pharmacies. We acknowledge that the **Prescription Form** is required for treatment initiation, treatment re-initiation after a lapse in treatment for 6 months or longer and that the **Patient Counseling Checklist** is also required in these instances. However, the **Prescription Form** may be used by prescribers for existing patients for refills and renewals. Therefore, there may be instances where a pharmacy receives a **Prescription Form** but is not required to complete the **Patient Counseling Checklist**. The **Prescription Form** is a tool that the prescriber may use, at any time, to indicate their awareness of the patient's concomitant medications and comorbid conditions. This means the last completed **Patient Counseling Checklist** may not capture all pertinent information available about the patient's comorbid conditions and relevant concomitant medication use. As described in the pharmacy training, a certified pharmacy must validate all prescriptions prior to dispensing Lumryz. Before a prescription for Lumryz can be dispensed to a patient, the pharmacy must review the **Prescription Form** for medications and comorbidities. If a patient changes pharmacies, the new pharmacy cannot rely on the **Patient Counseling Checklist** alone to meet the REMS requirement to assess the patient's concomitant use of sedative hypnotics, other CNS depressants or other potentially interacting agents that may be unknown to the prescriber.*

3.2.2.2. Communication

The Applicant made some of the changes the Agency conveyed on September 14, 2023[3] to the **Fact Sheet.** The Applicant edited the **Fact Sheet** (b) (4) (b) (4)

Reviewer's Comments: *We will send comments to the Applicant to align the **Fact Sheet** with the changes to the healthcare provider requirements explained above in section 3.2.1.1.*

3.2.2.3. Operations

The Applicant made some of the changes the Agency conveyed on September 14, 2023[3] to the **REMS website.** The Applicant edited the **REMS website** (b) (4) (b) (4) Additionally, the Applicant states (b) (4) (b) (4)

Reviewer's Comments: *We will send comments to the Applicant to align the **REMS website** with the changes to the healthcare provider requirements as explained above in section 3.2.1.1. The Applicant's response* (b) (4)

(b) (4)

3.3. REMS Assessment Timetable

The Applicant did not propose any changes to the timetable for submission of assessment of REMS.

4. Supporting Document

The Applicant made some of the changes the Agency conveyed on September 14, 2023[3] to the REMS Supporting Document. The Applicant did not append prescriber portal screenshots and the updated pharmacy portal screenshots. The Applicant states they will provide the screenshots in a subsequent submission.

Reviewer's Comments*: We will ask the Applicant again to provide prescriber portal screenshots and to provide updated pharmacy portal screenshots that include the changes that were made to the REMS Document and REMS materials. Specifically, the prescriber portal screenshot should display* ***RMR*** *history and patient alerts. For pharmacy portal screenshots, we will send a comment to the Applicant to submit screenshots of the prescriber alerts and* ***RMR*** *histories for review by a pharmacist. The Applicant will also need to provide screenshots of the updated RDA functionality that verify the* ***Patient Counseling Checklist*** *is completed as required, and the alerts and* ***RMR*** *history for the patient and their prescriber are reviewed by the pharmacist. And we will ask the Applicant to add the sample call script used by certified pharmacies when contacting other REMS for oxybate products to the Supporting Document.*

4.1. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document.

Reviewer's Comments: *DRM has consulted DMAMES to review the Assessment Plan. The Assessment Plan is currently under review. Refer to DRM September 14, 2023[3] review for DMAMES review on the Assessment Plan.*

5. Conclusions and Recommendations

DRM does not find the proposed REMS modifications for Lumryz (sodium oxybate extended-release) as submitted on May 4, 2023 and last amended on September 21, 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 5 business days.

6. Comments to the Applicant

We have the following comments on the proposed REMS modification, submitted on May 4, 2023 and last amended September 21, 2023. Review of the REMS proposal is ongoing; these comments should not be considered final. See a summary of the comments below and attached reline documents.

REMS Document

- We have provided edits in the REMS Document. Please apply these edits to REMS materials and Supporting Document.
- (b) (4)
- Apply the changes made to the prescriber requirements in REMS Document to the Prescriber Enrollment Form, Prescription Form, Prescriber Brochure, Fact Sheet, REMS website, and Supporting Document.
- We do not agree with the proposal to change “obtaining” to (b) (4) in the pharmacy requirement for oxybate prescription information of last dispense date, days’ supply, and prescriber’s name. With your proposal, (b) (4) (b) (4) The pharmacy must obtain information by contacting all oxybate REMS that there are no active, overlapping prescriptions. (b) (4) We have provided edits to the REMS Document to change (b) (4) to “obtaining".
- We have additional edits to the pharmacy requirements in the REMS Document. Under, the section, *To become certified to dispense*, we have added a pharmacy requirement to establish processes and procedures to verify the patient and prescriber are enrolled, the patient has no other active Lumryz prescriptions. This corresponds and aligns with an existing pharmacy requirement.
- We have edits to the requirement for pharmacies to report each prescription filled for Lumryz to all REMS for oxybate product to specify that this requirement must be completed after dispensing, within 1 business day. This will ensure timely reporting to other REMS for oxybate products.
- As you know, there are multiple oxybate products that are subject to a REMS and we are trying to harmonize activities across REMS when possible, to reduce stakeholder confusion.
- Apply the changes made to the pharmacy requirements in REMS Document to the Pharmacy Enrollment Form and Supporting Document.
- See redlined REMS Document for additional comments.

Certified Pharmacy Training Program

- (b) (4)
- In circumstances where the patient has changed pharmacies, we have added to the Certified Pharmacy Training Program a process for the new pharmacy to contact the Lumryz REMS certified pharmacy that filled the previous prescription to obtain the most recent Prescription Form. During the review, it has come to our attention that the Prescription Form is not uploaded to the patient information functionality on the REMS Website. As a result, a pharmacy that is different from the pharmacy that filled the previous prescription and is processing a refill (e.g., transferred prescription) or a renewal (e.g., prescription sent from a prescriber) for an existing Lumryz REMS enrolled patient must contact the pharmacy that filled the previous prescription for which the most recent Prescription Form was received. This form is needed by the dispensing pharmacy because it contains the list of medications and comorbidities provided by the prescriber; and the Lumryz REMS does not appear to capture or retain information on the

Prescription Form so it is accessible for all certified pharmacies. Your REMS needs to capture or retain information on the Prescription Form so it can be shared if needed with another pharmacy. We acknowledge that the Prescription Form is required for treatment initiation, treatment re-initiation after a lapse in treatment for 6 months or longer and that the Patient Counseling Checklist is also required in these instances. However, the Prescription Form may be used by prescribers for existing patients for refills and renewals. Therefore, there may be instances where a pharmacy receives a Prescription Form but is not required to complete the Patient Counseling Checklist. The last completed Patient Counseling Checklist may not capture all pertinent information available about the patient's comorbid conditions and relevant concomitant medication use. The Prescription Form is a tool that the prescriber may use, at any time, to indicate their awareness of the patient's concomitant medications and comorbid conditions. As described in the pharmacy training, a certified pharmacy must validate all prescriptions prior to dispensing Lumryz. Before a prescription for Lumryz can be dispensed to a patient, the pharmacy must review the Prescription Form for medications and comorbidities. If a patient changes pharmacies, the new pharmacy cannot rely on the Patient Counseling Checklist alone to meet the REMS requirement to assess the patient's concomitant use of sedative hypnotics, other CNS depressants or other potentially interacting agents that are unknown to the prescriber.

- See redlined Certified Pharmacy Training Program.

Prescription Form

- Some of the data fields on the Prescription Form are too small and may cause errors when completing the form. Increase font size of the data fields and the attestations in the Prescription Form to minimize errors and improve readability.

Risk Management Report (RMR)

- See our comments sent September 14, 2023. We are (b) (4) trying to align to our best ability to reduce stakeholder confusion, and therefore our edits should be retained. Edit the RMR as conveyed on September 14, 2023 to include prescribers as a type of reporter for the RMR.

REMS Website

- We acknowledge your proposal (b) (4)

REMS Supporting Document

- Align the Supporting Document with changes made to the REMS Document.
- Provide prescriber portal screenshots that display RMR history and patient alerts.
- Provide pharmacy portal screenshots that display:
    - Screenshots of the prescriber alerts and Risk Management Report histories for review by a pharmacist.
    - Screenshot of the updated RDA functionality that include the Patient Counseling Checklist is completed as required, and the alerts and Risk Management Report history for the patient and their prescriber are reviewed by the pharmacist.
- Add the sample call script used by certified pharmacies when contacting other REMS for oxybate products to the Supporting Document.

Resubmission Instructions

The following material contains revisions. If you find this acceptable, update the material with the revisions and hold of resubmitting the materials until the next complete submission.

- Certified Pharmacy Training Program

Submit the following revised REMS materials within 5 business days that addresses these comments. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous). The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following documents:

- REMS Document
- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Prescriber Brochure
- Prescription Form
- Fact Sheet
- Risk Management Report
- REMS Website
- 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.

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. DARRTS May 01, 2023(accessed at https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806c8270)

[3] Olumba, S. Interim Review of Proposed Major REMS Modification for Lumryz. NDA 214755. DARRTED September 14, 2023 (available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806f41a4)

8. Appendix

- REMS Document
- Certified Pharmacy Training Program

32 Page(s) of Draft REMS has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

STEPHANIE N OLUMBA
10/18/2023 11:50:10 AM

KATE H OSWELL
10/18/2023 11:51:37 AM

TIMOTHY J BERNHEIMER
10/18/2023 11:55:58 AM

LAURA A ZENDEL on behalf of CYNTHIA L LACIVITA
10/18/2023 12:53:49 PM

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

Application Type	NDA
Application Number	214755
Supplement Number, Date Received	Supplement 3 received May 4, 2023 (sequence 67), amended on May 24, 2023 (sequence 71), June 14, 2023 (sequence 78), June 21, 2023 (sequence 80), and July 31, 2023 (sequence 88)
Action Date	October 31, 2023
Nexus TTT #	2023-4700
Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS Kate Oswell, MA Joseph Paradis, PharmD (OMEPRM)
Secondary Reviewer	Timothy Bernheimer, PharmD
Associate Director	Jo Wyeth, PharmD (OMEPRM)
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	September 14, 2023
Subject	Review of proposed Major REMS Modification
Established Name	Sodium Oxybate Extended-Release Oral Suspension
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals
Therapeutic Class	Central Nervous System Depressant
Formulation(s)	Powder for extended-release oral suspension: packets of 4.5 g, 6 g, 7.5 g, and 9 g

TABLE OF CONTENTS

1. Introduction 3
2. Regulatory History 3
3. Review of Proposed REMS Modifications 4
   3.1. REMS Document 4
   3.2. REMS Requirements 4
      3.2.1. REMS Participant Requirements and Materials 4
         3.2.1.1. Healthcare Provider 4
         3.2.1.2. Patients 5
         3.2.1.3. Pharmacies that dispense 6
      3.2.2. REMS Applicant Requirements and Materials 7
         3.2.2.1. Training 7
         3.2.2.2. Communication 8
         3.2.2.3. Operations 9
         3.2.2.4. Compliance 9
   3.3. REMS Assessment Timetable 10
4. Supporting Document 10
   4.1. REMS Assessment Plan 10
5. Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials 10
6. Conclusions and Recommendations 11
7. Comments to the Applicant 11
8. References 16
9. Appendix 16

1. Introduction

This review evaluates the proposed major 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 May 4, 2023 and was amended on May 24, 2023, June 14, 2023, June 21, 2023, and July 31, 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 increased risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion[a] of Lumryz.[2]

The Applicant proposed modifications to the REMS (b) (4) remove confirmation that each prescription filled for Lumryz was reported to each REMS for oxybate products from the pre-dispense authorization; add guardian email as a required field to **Patient Enrollment Form**; provide editorial or grammatical changes to **Patient Counseling Checklist** and Supporting Document; (b) (4) (b) (4) and to provide changes to the **Prescriber Enrollment Form** to allow the prescriber to designate multiple office contacts to support administrative activities and communications with the REMS. The following REMS materials are affected by this modification:

- **REMS Document**
- **Prescriber Enrollment Form**
- **Patient Enrollment Form**
- **Prescriber Brochure**
- **Certified Pharmacy Training Program**
- **Prescription Form**
- **Patient Counseling Checklist**
- **REMS Fact Sheet**
- **REMS Website Screenshots**

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.
- 05/04/23: Applicant submitted a minor REMS modification.
- 05/24/23: Applicant submitted REMS amendment to correct typographical error in PDF layout version of the **Prescriber Enrollment Form.**
- 06/08/23: Information Request sent to the Applicant to submit video storyboard with transcript and complete video file of the Lumryz REMS Overview Video on the REMS Website.

[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.

- 06/14/23: Information Request response received from the Applicant to provide video storyboard with transcript and complete video file of the Lumryz REMS Overview Video on the REMS Website.
- 06/15/23: Information Request sent to the Applicant to submit the complete REMS with all REMS materials.
- 06/21/23: A Prior Approval Supplement Acknowledgment letter was sent to Applicant informing them that the proposed changes are considered to be a major REMS modification.
- 06/21/23: Applicant submits complete REMS with all REMS materials as requested by the Agency.
- 07/31/23: Applicant submitted REMS amendment to provide changes to the **Prescriber Enrollment Form** to allow the prescriber to designate multiple office contacts to support administrative activities and communications with the REMS.

3. Review of Proposed REMS Modifications

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

3.1. REMS Document

The Applicant did not propose any changes to the format of the REMS Document.

Reviewer's Comments: *We made changes to the REMS Document to align with the current Format and Content of a REMS Document Guidance for Industry 2023 and the REMS Document Technical Conformance Guide 2023.[3,4] Changes we made include: added a statement regarding the risk the REMS is designed to address to section I; removed the word "program" throughout the REMS Document; and added section VI. "Statutory Elements" which lists the elements to assure safe use.*

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 Provider

The Applicant proposed changes (b) (4) (b) (4) (b) (4) Additionally, the Applicant updated the **Prescription Form** by adding more space to the Medications and Comorbidities data fields to allow prescribers more space to enter the information on the form. Furthermore, the Applicant proposed changes to the **Prescriber Enrollment Form** to add multiple office contact information.

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

(b) (4)

(b) (4) *Additionally, we have added the requirement for prescribers to assess the patient's potential for abuse, misuse, and diversion; and to 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* ***RMR.*** *This will ensure that reporting to the REMS occurs in an efficient manner that avoids potential delays, errors, or lost reports to the REMS.*

Currently, healthcare providers are required to report requests to disenroll a patient to a certified pharmacy. The Lumryz REMS uses a REMS administrator to support REMS operations and accommodates dispensing from more than one pharmacy. (b) (4) *prescribers making these requests to the pharmacy instead of directly to the REMS could potentially cause delays in disenrolling patients who are suspected of abuse or misuse from the Lumryz REMS, and this may result in this information not being shared with prescribers and pharmacies certified in the Lumryz REMS, and other REMS for oxybate products in a timely manner. For these reasons, we have revised the requirement to have healthcare providers report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the* ***RMR.*** (b) (4) *. Furthermore, we have edited the instructions on the* ***RMR*** *to include prescribers as a type of reporter and reviewer of* ***RMR*** *histories. Prescribers' assessment of misuse, abuse, and diversion can be improved if prescribers have access to the alerts and* ***RMR*** *histories in the REMS Database before prescribing an oxybate product. This would allow prescribers to review prior events of suspected abuse, misuse, or diversion and gives prescribers a more complete picture of the patient's history, including if patients were previously prescribed an oxybate product by another prescriber. The Applicant needs to provide prescribers access to patient alerts and* ***RMR*** *histories, similar to how this information is accessed by certified pharmacies. We have added text to the* ***Prescriber Brochure*** *to explain that prescribers may review patient alerts and RMR histories by accessing the REMS website or by calling the REMS.*

We agree with the Applicants edits to the ***Prescription Form****; however, we will send the Applicant a comment to align the prescriber attestations on the* ***Prescription Form*** *and the* ***Prescriber Enrollment Form*** *with the REMS Document. Furthermore, we agree with the Applicants proposed changes to the* ***Prescriber Enrollment Form*** *to add additional office contact information and email.*

3.2.1.2. Patients

The **Patient Enrollment Form** was updated to add a required field for the Guardian's email address to allow for a guardian to receive an email link for signature if not present in the office for patient enrollment.

Reviewer's Comments: *Changes to the* ***Patient Enrollment Form*** *are acceptable. Comments will be sent to the applicant to ask if the email link for the signature will link to the online version of the* ***Patient Enrollment Form.***

Additionally, we updated the patient requirement in the REMS Document regarding monitoring 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 to specify that this will be done "by your prescriber." We will send a comment to the Applicant to align the patient attestations on the ***Patient Enrollment Form*** *with the updated patient requirements in the REMS Document.*

Currently there is a question in the Patient information section of the ***Patient Enrollment Form*** *that asks: is patient currently or has patient ever been enrolled in an oxybate product REMS. However, that question should be revised into two separate questions to capture current or previous enrollment in other REMS for oxybate products:*

- *Is the patient currently enrolled in other REMS for oxybate products? Yes or no.*
- *Was the patient previously enrolled in other REMS for oxybate products? Yes or no.*

Additionally, the Prescriber Information section should be expanded to include data fields for DEA number, Prescriber's address, and fax number. All should be considered required fields. This change aligns with the Patient Enrollment Forms for other REMS for oxybate products.

During this review, we made editorial changes to the ***Patient Brochure*** *to improve the flow and clarity of the content. We will also send the Applicant a comment to bold names of REMS materials and remove italics throughout all REMS materials because this will improve readability, and to apply this change across all materials. Furthermore, we will send the Applicant a comment to add additional information regarding a drug takeback program, as this will align with other REMS for oxybate products. A drug takeback program will give patients an additional option to dispose any unused medications to facilitate safe disposal.*

3.2.1.3. Pharmacies that dispense

The **Patient Counseling Checklist** was updated to change (b) (4) in question #3 in "Step 3: Screening" (b) (4) and add an option of "None". Additionally, the Applicant added "None of the Above" as an option in Step 4 for Concomitant Medication Type and Medical Condition summaries.

Reviewer's Comments: *The proposed changes to the* ***Patient Counseling Checklist*** *are acceptable. Additionally, we added to Step 4 an "other (specify)" option to the "Prescriber's rationale for continuing concomitant medication with Lumryz" question. This will allow for other rationales for continuing treatment not specified on the* ***Patient Counseling Checklist*** *to be captured and reported.*

Additionally, we made changes to pharmacy requirements in the REMS Document. The requirement to obtain authorization was updated to include completion of the ***Patient Counseling Checklist*** *as required and the review of the alerts and* ***RMR*** *histories for the patient and their prescriber. This change was made* (b) (4) *to support compliance with pharmacist completion of these steps prior to receiving authorization to dispense the drug. To clarify what information the certified pharmacy must obtain from all other REMS to verify the patient has no other active prescriptions that overlap with the current prescription for the patient, we added that pharmacies must obtain last date dispensed, days' supply, and prescriber name. To confirm that the patient has no other active overlapping Lumryz prescriptions, we have added the requirement to verify in the REMS that the patient has no other active Lumryz prescriptions through processes and procedures established as a requirement of the REMS. Additionally, references regarding contacting "the" other REMS for oxybate products were updated to "all" other REMS for oxybate products throughout the REMS Document. We revised this for clarity because there is more than one approved REMS for oxybate products. Additionally, we have provided edits to the pharmacy attestation on the* ***Prescription Form*** *to*

reflect this change. A comment will be sent to the Applicant to replace "the" in "the other REMS for oxybate products" with "all" where applicable throughout all REMS materials.

Furthermore, a section on "to maintain certification to dispense" was added to the pharmacy requirements of the REMS Document. The new section (b) (4) *will ensure compliance of pharmacy re-certification if the authorized representative is different from the previously designated authorized representative. Furthermore, we added the requirement to report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the* ***RMR.*** *This requirement was described in the* ***Certified Pharmacy Training*** *but was not stated in the REMS Document. This requirement differs from Xywav and Xyrem (X/X) REMS because in that REMS there is a single certified pharmacy that is also the REMS administrator which is able to disenroll patients. This new requirement for Lumryz* (b) (4) *allows dispensing from multiple pharmacies and utilize a separate REMS administrator. The REMS administrator or the Applicant will determine if the patient should be disenrolled, and thus the pharmacies will have to report requests of disenrollment to the REMS.*

As a result of the changes to the pharmacy requirements in the REMS Document, the pharmacy attestations on the ***Pharmacy Enrollment Form*** *will need to align with the updated REMS Document. Additionally, the* ***Pharmacy Enrollment Form*** *contains a data field that captures NCPDP, however this field may be unnecessary since the switch system has been removed. We will send comments to the Applicant to provide a rationale for collecting NCPDP or remove the NCPDP field from all REMS materials if the field was in reference to the switch. We will also ask the Applicant to include additional data fields to capture the authorized representative's job title/role and credentials;* (b) (4)

Furthermore, we have provided edits to the ***RMR.*** *We added the example "prescribers whose DEA and/or state license numbers cannot be validated and the prescriber is submitting a Prescription Form and/or LUMRYZ prescription" as an example of events that would require completion of an* ***RMR****. This is an example of an event that could indicate a reasonable suspicion of abuse, misuse, or diversion.* (b) (4) (b) (4)

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** was updated to include the Applicant proposed changes (b) (4) (b) (4) The Applicant proposed changes to the **Certified Pharmacy Training Program** by removing confirmation that each prescription filled for Lumryz was reported to each REMS for oxybate products from the pre-dispense authorization; additionally, the **Certified Pharmacy Training Program** was edited to state that certified pharmacies must provide confirmation of receipt of each prescription filled and shipment received of Lumryz to the REMS electronically instead of accessing the REMS website or by calling the REMS.

Reviewer's Comments*: As mentioned above in section 3.2.1.1, we do not agree with the proposal* (b) (4) (b) (4)

[redacted] *We updated the* ***Prescriber Brochure*** *to align with the revised prescriber requirements in the REMS Document; and we have provided edits clarifying that there is no reciprocity for patients and prescribers across oxybate REMS to the* ***Prescriber Brochure.*** *Given that Lumryz REMS is a separate REMS from other REMS for oxybate products, it important for prescribers to understand that certification in any other REMS for oxybate products is not reciprocal with the Lumryz REMS.*

Currently, pharmacies are required to document and submit confirmation that each prescription filled for Lumryz was reported to each REMS for oxybate products. As explained in the ***Certified Pharmacy Training Program,*** *this confirmation was part of the pre-dispense authorization. A pharmacy cannot confirm a Lumryz dispense to other REMS for oxybate products until that prescription is dispensed which has to occur after the pre-dispense authorization generation and therefore the confirmation should be moved from the pre-dispense authorization. The Applicant provided a comment stating that pharmacies will now confirm they reported each prescription filled for Lumryz to each REMS for oxybate products via the data exchange. We agree with the Applicant, however, the Applicant* [redacted] *We added information regarding this requirement* [redacted] *and will ask the Applicant to explain in the Certified Training that the confirmation of receipt of each prescription filled and shipment received of Lumryz by a patient to be reported to the Lumryz REMS electronically through the data exchange.*

Additionally, we have provided edits to the ***Certified Pharmacy Training Program*** *to align with the changes made to the pharmacy requirements in the REMS Document. We have also made changes to improve clarity, reduce redundancy,* [redacted] *For example, the pre-dispense authorization was renamed the REMS Dispense Authorization (RDA) because this aligns with* [redacted] *other REMS; and is the Agency's preferred term. We removed the section entitled "Enrollment Verification" under "Overview of Certified Pharmacy Responsibilities," because this is a responsibility of the REMS and not certified pharmacies. We will send a comment to the Applicant to retain and incorporate this information in the Supporting Document. Additionally, for reasons explained above in section 3.2.1.2, we will send comments to the Applicant to add information regarding a drug takeback program to the* ***Certified Pharmacy Training Program****.*

We have provided edits to the ***Pharmacy Staff Knowledge Assessment*** *to align with the updated pharmacy requirements and the RDA. We replaced a question that described REMS requirements other than pharmacy requirements. Additionally, we have added additional questions to both the* ***Pharmacy Staff Knowledge Assessment*** *and the* ***Pharmacist Knowledge Assessment*** *to be more comparable with the number of questions in X/X REMS and SOX REMS Knowledge Assessments. Furthermore, the Applicant will be asked to append a version of each knowledge assessment with answers to the REMS Supporting Document.*

3.2.2.2. Communication

The **Fact Sheet** was updated to include the Applicant proposed changes [redacted]

Reviewer's Comments: *We aligned the* ***Fact Sheet*** *with the changes to the healthcare provider requirements explained above in section 3.2.1.1. Additionally, we provided edits to the* ***Fact Sheet*** *to improve the clarity of the content and to provide an overview of key requirements of the REMS.*

3.2.2.3. Operations

The REMS website was updated to include the Applicant proposed changes (b) (4) (b) (4) (b) (4) Additionally, the

Reviewer's Comments: *As mentioned above in section 3.2.1.1, we do not agree with the proposal* (b) (4) (b) (4) *Comments will be sent to the Applicant to align the* ***REMS website*** *with the edits and comments provided on the REMS Document and materials.*

We also do not agree with (b) (4) (b) (4)

Additionally, the Applicant provided a complete video file and transcript to the REMS Overview Video that is on the ***REMS website****. We have provided the video file and transcripts to the Office of Prescription Drug Promotion (OPDP) for review. See Section 5 below for additional details.*

Additionally, the Applicant will need to provide a contingency plan for answering calls outside of the operating hours of the REMS Call Center. Certified pharmacies may contact the Call Center during this time to obtain an RDA or to review alerts and RMR histories; and other REMS for oxybate products may call during this time to obtain the information necessary to verify that there are no active, overlapping oxybate prescriptions and that the patient or their prescriber have been disenrolled for abuse, misuse, or diversion.

Furthermore, we have provided several edits to the REMS Operation section of the REMS Document to align the Applicant's requirements with the REMS participants requirements and operations. As explained in section 3.2.1.1, we believe prescribers should have access to the alerts and ***RMR*** *histories, therefore we will ask the Applicant to provide a mechanism for certified prescribers to access this information (e.g., REMS website or REMS call center).*

3.2.2.4. Compliance

The Applicant did not propose any changes to the requirements to ensure REMS participant compliance with the REMS.

Reviewer's Comments: *Wholesalers-distributors are REMS participants of Lumryz REMS and should be routinely monitored; corrective actions should also occur if noncompliance is identified.*

Therefore, we have revised a compliance requirement to add wholesalers-distributors as a REMS participant that the Applicant is required to monitor on an ongoing basis to ensure the requirement of the REMS are being met.

3.3. REMS Assessment Timetable

The Applicant did not propose any changes to the timetable for submission of assessment of REMS.

4. Supporting Document

The REMS Supporting Document was changed to include the background of the REMS Modification currently under review. In addition, the Applicant provided minor grammatical changes.

***Reviewer's Comments**: The Applicant will be asked to align the Supporting Document, including pharmacy portal screenshots, with changes made to the REMS Document and REMS materials. During this review, we noticed that the Supporting Document* (b) (4) *includes Elements to Assure Safe Use, an Implementation System, and a Timetable for Submission of assessments.* (b) (4) *the Applicant is required to disseminate REMS communication materials to inform healthcare providers about the risks and safe use of Lumryz. Comments will be sent to the Applicant to rename* (b) (4) *section to "Communication Materials and Dissemination", and to move this section below the Elements to Assure Safe Use section. As stated in section 3.2.2.3, healthcare providers must be provided access to review patient alerts and **RMR** histories to assess the patient's potential for abuse, misuse, or diversion, and thus the prescribers will need access to alerts and **RMR** histories. Comments will be sent to the Applicant to add a mechanism for prescribers to obtain access. If online access is provided for prescribers, we will ask them to provide website portal screenshots of the prescriber access to alerts and **RMR** histories; and to append these screenshots as an Appendix in the Supporting Document.*

4.1. REMS Assessment Plan

The Applicant did not propose any changes to the REMS Assessment Plan. Revisions to the assessment plan are required to include metrics to capture the number of Lumryz shipments sent to patients without completion of the **Patient Counseling Checklist** for patients that notified the pharmacy of a new or change in concomitant medication or comorbidity and for those with lapse in therapy for greater than six months. An additional metric is required to capture "other" reasons for the prescriber's rationale to continue concomitant medication. Also, Pre-dispense Authorization (PDA) is revised to REMS Dispense Authorization (RDA) to align with other REMS for oxybate products.

See redlined version of assessment plan (attached) for specific changes.

5. Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on June 21, 2023 to provide feedback on the content of the REMS Overview Video on the REMS website. The OPDP review was completed by Koung Lee on July 12, 2023.[5] The OPDP recommendations are summarized below.

The video includes promotional statements throughout and minimizes the risks of the REMS by presenting incomplete risk information. Specific promotional and risk minimization claims from the video include the following:

(b) (4)

Reviewer's Comments: *We agree with the OPDP's recommendations and we will convey them to the Applicant. We find the video to contain promotional statements throughout, as well as minimization of the risks of the REMS by presenting incomplete risk information.*

6. Conclusions and Recommendations

DRM does not find the proposed REMS modifications for Lumryz (sodium oxybate extended-release) as submitted on May 4, 2023 and last amended on July 31, 2023, to be acceptable, as described in this review. Please send the comments in Section 7 to the Applicant in an Information Request and instruct the Applicant to submit a REMS amendment within 5 business days.

7. Comments to the Applicant

We have the following comments on the proposed REMS modification, submitted on May 4, 2023 and amended on May 24, 2023, June 14, 2023, June 21, 2023, and July 31, 2023. Review of the REMS proposal is ongoing; these comments should not be considered final. See a summary of the comments below and attached reline documents.

General Comment

- Align the Prescriber Enrollment Form, Patient Enrollment Form, Pharmacy Enrollment Form and Prescription Form with the REMS Document and the provided attestations.

- The pharmacy requirement to obtain authorization was updated to include the completion of the Patient Counseling Checklist as required and the review of the alerts and RMR histories for the patient and their prescriber.
- We recommend the Pre-Dispense Authorization (PDA) be renamed to REMS Dispense Authorization (RDA). In general, this aligns with the Agency's current thinking and will reduce confusion across the REMS for oxybate products. Rename the PDA to RDA across all REMS materials.
- To improve readability, bold names of REMS materials and remove italics throughout all REMS materials.
- Given there is more than one approved REMS for oxybate products, replace "the" in "the other REMS for oxybate products" with "all" where applicable throughout all REMS materials.

REMS Document

- The REMS Document is currently undergoing FDA clearance; however, we have attached a draft redline REMS Document with additional comments.
- The REMS Document have been edited to align closely with the *Format and Content of a REMS Document Guidance for Industry 2023 and the REMS Document Technical Conformance Guide 2023*.
- We do not agree with the proposal (b) (4)
  (b) (4)
- We have added a requirement for prescribers to assess the patient's potential for abuse, misuse, and diversion; and to 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 RMR.
- For similar reasons listed above, we have the requirement for prescribers to report requests to disenroll a patient for suspected abuse, misuse, or diversion to the REMS using the RMR.
- To clarify what information the certified pharmacy must obtain from all other REMS to verify the patient has no other active prescriptions that overlap with the current prescription for the patient, we added that pharmacies must obtain last date dispensed, days' supply, and prescriber name.
- See redlined REMS Document for additional comments.

Patient Enrollment Form

- We acknowledge the addition of the Guardian email link on the form. Clarify if the email link for the signature will link to the online version of the Patient Enrollment Form.
- A new data field section titled "REMS for Oxybate Products Participation" should be added. Currently there is a question in the Patient information section that asks: is patient currently or has patient ever been enrolled in an oxybate product REMS. However, that question be revised to two separate questions to capture current or previous enrollment in other REMS for oxybate products:
  - Is the patient currently enrolled in other REMS for oxybate products? Yes or no.
  - Was the patient previously enrolled in other REMS for oxybate products? Yes or no.
- Expand the Prescriber Information section to include data fields for DEA number, Prescriber's address, and fax number; and mark all as required fields.

- See redlined Patient Enrollment Form for comments.

Pharmacy Enrollment Form

- The form contains a data field that captures NCPDP, however this field may be unnecessary since the switch system has been removed. Provide a rationale for collecting NCPDP or remove the NCPDP field from all REMS materials if the field was in reference to the switch.
- Include additional data fields to capture the authorized representative's job title/role and credentials.

Prescriber Brochure

- We provided edits to the Prescriber Brochure to align with the revised prescriber requirements in the REMS Document.
- Prescribers' assessment of misuse, abuse, and diversion can be improved if prescribers have access to the alerts and RMR histories. This would allow prescribers to review prior events of suspected abuse, misuse, or diversion and give prescribers a more complete picture of the patient's history, including if patients were previously prescribed an oxybate product by another prescriber. Prescribers will need access to patient alerts and RMR histories, like the access provided for pharmacies. Provide a mechanism for certified prescribers to access this information (e.g., REMS website or REMS call center).
- See redlined Prescriber Brochure for additional comments.

Patient Brochure

- Propose a drug takeback program, as this will align with other oxybate REMS. A drug takeback program will give patients an option to safely dispose any unused medications. Add this information to the Patient Brochure and the Certified Pharmacy Training Program.
- See redlined Patient Brochure for additional comments.

Certified Pharmacy Training Program

- We removed the section entitled "Enrollment Verification" under "Overview of Certified Pharmacy Responsibilities," because this is a responsibility of the REMS and not of the certified pharmacy. Retain and incorporate this information in the Supporting Document.
- Explain in the Certified Training that certified pharmacies provide confirmation that each Lumryz prescription filled was reported to all REMS for oxybate products by submitting the confirmation electronically to the Lumryz REMS (e.g., with the shipment receipt reporting).
- See redlined Certified Pharmacy Training for additional comments.

Pharmacy Staff and Pharmacist Knowledge Assessments

- We have provided edits to the Knowledge Assessments to align with updated pharmacy requirements from the REMS Document as well as added additional questions to align closer with the number of questions in the other oxybate REMS.
- Include versions of the knowledge assessments with answers in the REMS Supporting Document as an Appendix.
- See redlined Knowledge Assessments for additional comments**.**

Patient Counseling Checklist

- We added to Step 4 an "other (specify)" option to the "Prescriber's rationale for continuing concomitant medication with Lumryz" question. This will allow for other rationales for continuing treatment not specified on the Patient Counseling Checklist to be captured and reported.

REMS Fact Sheet

- We provided edits to the Fact Sheet to improve the clarity of the content and to provide an overview of key requirements of the REMS.

Risk Management Report (RMR)

- The instructions on the RMR were edited to include prescribers as a type of reporter and reviewer of RMR histories.
- See redlined Risk Management Report for additional comments.

REMS Website

- We do not agree with (b) (4)
- Provide a contingency plan for answering calls outside of the operating hours of REMS Call Center. Certified pharmacies may call the Call Center during this time to obtain an RDA or to review alerts and RMR histories; and other REMS for oxybate products may call during this time to obtain the information necessary to verify that there are no active, overlapping oxybate prescriptions and that the patient or their prescriber have been disenrolled for abuse, misuse, or diversion.

The video on the REMS website has been reviewed by the FDA's Office of Prescription Drug Promotion (OPDP). The video includes promotional statements throughout and minimizes the risks of the REMS by presenting incomplete risk information. Specific promotional and risk minimization claims from the video include the following:

(b) (4)

The video must be revised to address the above comments or removed from the Lumryz REMS website.

REMS Supporting Document

- Align the Supporting Document with changes made to the REMS Document and REMS materials.
- Rename [redacted] section to "Communication Materials and Dissemination", and to move this section below the Elements to Assure Safe Use section. [redacted] the Applicant is required to disseminate REMS communication materials to inform healthcare providers about the risks and safe use of Lumryz.
- Add the mechanism for prescribers to obtain access to alerts and RMR histories. If online access is provided for prescribers, provide website portal screenshots and include these screenshots as an Appendix in the Supporting Document.
- Provide updated pharmacy portal screenshots that reflect changes made to REMS Document and materials (e.g., updated REMS dispense authorization screenshots).

REMS Assessment Plan

- Revisions to the assessment plan are required to include metrics to capture the number of Lumryz shipments sent to patients without completion of the Patient Counseling Checklist for patients that notified the pharmacy of a new or change in concomitant medication or comorbidity and for those with lapse in therapy for greater than six months.
- An additional metric is required to capture "other" reasons for the prescriber's rationale to continue concomitant medication.
- Pre-dispense authorization (PDA) is revised to REMS Dispense Authorization to align with other REMS for oxybate products.
- See redlined version of assessment plan (attached) for specific changes

Resubmission Instructions

The following materials contains revisions. Please update the materials with the revisions and hold off resubmitting these materials until the next complete submission.

- REMS Document
- Pharmacy Staff Knowledge Assessment
- Pharmacist Knowledge Assessment
- Patient Counseling Checklist
- REMS Fact Sheet

Submit the following revised REMS materials within 10 business days that addresses these comments. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous). The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following documents:

- Prescriber Enrollment Form
- Patient Enrollment Form
- Pharmacy Enrollment Form
- Prescriber Brochure
- Patient Brochure
- Certified Pharmacy Training Program
- Prescription Form
- Risk Management Report
- REMS Website
- 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.

8. 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. DARRTS May 01, 2023(accessed at https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806c8270)

[3] U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) January 2023; *Format and Content of a REMS Document Guidance for Industry*; accessed at https://www.fda.gov/media/77846/download

[4] U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) January 2023; *REMS Document Technical Conformance Guide*; accessed at https://www.fda.gov/media/164344/download

[5] Lee, K. Office of Prescription Drug Promotion (OPDP) Comments on Draft Risk Evaluation and Mitigation Strategies (REMS) Material for Lumryz REMS NDA 214755, DARRTS July 12, 2023 (accessed at:https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806de8fc).

9. Appendix

Assessment Plan

REMS Document

Enrollment Forms
Patient:

- Patient Enrollment Form

Training and Educational Materials
Prescriber:

- Prescriber Brochure

Patient:

- Patient Brochure

Pharmacy

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

Patient Care Forms

- Patient Counseling Checklist

Communication Materials

- REMS Fact Sheet

Other Materials

- Risk Management Report
- REMS Program Website

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

/s/

STEPHANIE N OLUMBA
09/14/2023 12:28:43 PM

KATE H OSWELL
09/14/2023 12:36:38 PM

JOSEPH P PARADIS
09/14/2023 12:38:33 PM

TIMOTHY J BERNHEIMER
09/14/2023 12:44:48 PM

JO H WYETH
09/14/2023 01:49:53 PM

LAURA A ZENDEL on behalf of CYNTHIA L LACIVITA
09/14/2023 02:23:46 PM

Office of Prescription Drug Promotion

Internal Consult

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

Please Note: The following review is for DRM only and should not be used to provide comments to the sponsor.

To: Kate Heinrich Oswell, Health Communications Analyst
Division of Risk Management (DRM)
Office of Surveillance and Epidemiology (OSE)

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Deputy Director, OPDP
Rachael Conklin, Team Leader, OPDP
Aline Moukhtara, Team Leader, OPDP
Ermias Zerislassie, Safety Regulatory Project Manager, OSE
Carolyn Tieu, Team Leader, DRM
Timothy Bernheimer, Risk Management Analyst, DRM
Cynthia LaCivita, Division Director, DRM
Jina Kwak, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: July 12, 2023

Re: NDA 214755
LUMRYZ™ (sodium oxybate) for extended-release oral suspension, CIII (Lumryz)

Comments on Draft Risk Evaluation and Mitigation Strategies (REMS) Material

---

Materials Reviewed

OPDP has reviewed the following proposed REMS material for Lumryz:

- REMS Video

The version of the draft REMS material used in this review were sent from DRM (Kate Heinrich Oswell) via email on July 7, 2023. The draft REMS material is attached to the end of this review memorandum.

OPDP offers the following comments on this draft REMS material for Lumryz.

General Comment

Please remind Avadel Pharmaceuticals (Avadel) that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the website, www.LUMRYZREMS.com, and dedicated phone number, 1-877-453-1029. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, Avadel should be reminded that the REMS specific website should not be the sole source of approved REMS materials.

REMS Materials

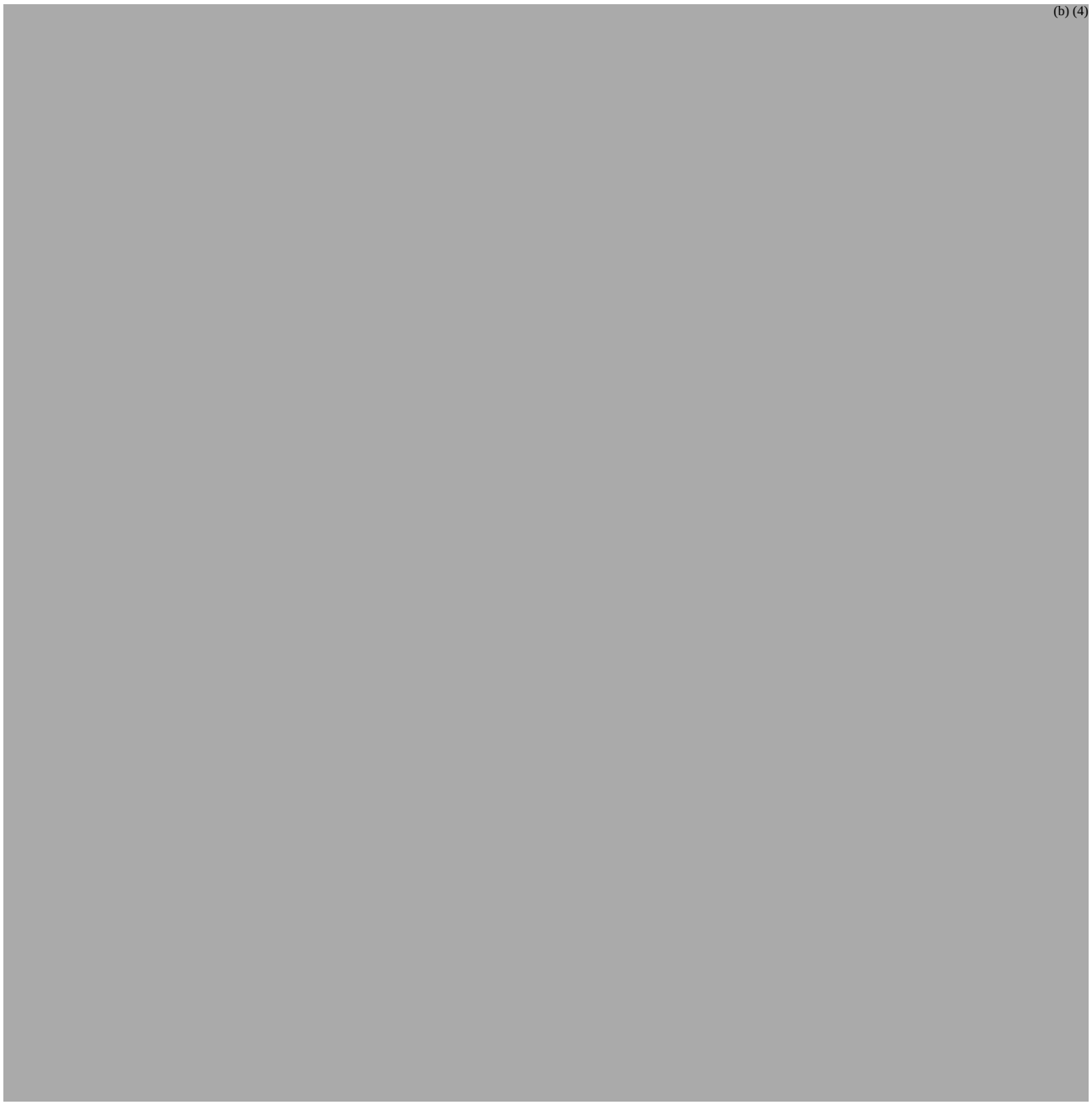
OPDP does not object to including the following material in the REMS program (please see "Specific Comments" below):

- REMS Video

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising them:

(b) (4)



We have no additional comments on this proposed REMS material at this time.

Thank you for your consult.

9 Page(s) of Draft REMS has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

KOUNG U LEE
07/12/2023 11:45:14 AM