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