

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214755Orig1s000

**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
Action Date	May 1, 2023
Nexus TTT #	2023-3984
Reviewer Name(s)	Timothy Bernheimer, PharmD Kate Oswell, MA Joseph Paradis, PharmD (DMAMES)
Team Leaders	Shelly Harris, ScD, MPH (DMAMES) Carolyn Tieu, PharmD, MPH
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Review Completion Date	April 27, 2023
Subject	Evaluation of the Proposed REMS
Established Name	Sodium Oxybate Extended-Release Oral Suspension
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals
Therapeutic Class	Central Nervous System Depressant
Formulation	Powder for extended-release oral suspension: packets of 4.5 g, 6 g, 7.5 g, and 9 g

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) and the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) is an addendum to the to the July 14, 2022, Risk Evaluation and Mitigation Strategy (REMS) review and evaluates the proposed REMS for Lumryz (sodium oxybate extended-release), New Drug Application (NDA) 214755, submitted by Avadel CNS Pharmaceuticals on March 10, 2023 and amended on March 30, 2023, April 11, 2023, April 14, 2023, April 25, 2023, and April 27, 2023.

The proposed indication for Lumryz is for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy. The application was granted a tentative approval (TA) on July 18, 2022, with a REMS to ensure that the benefits of the drug outweigh the risk of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.^a

The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The ETASU includes prescriber certification (ETASU A), pharmacy certification (ETASU B), and documentation of safe-use conditions (ETASU D).

DRM and DMAMES find the proposed REMS for Lumryz (sodium oxybate extended-release) as submitted on April 27, 2023 to be acceptable for approval.

1 Introduction

This is an addendum to the July 14, 2022¹ Risk Evaluation and Mitigation Strategy (REMS) review and evaluates the proposed REMS for Lumryz (sodium oxybate extended-release), New Drug Application (NDA) 214755, submitted by Avadel CNS Pharmaceuticals on March 10, 2023 and amended on March 30, 2023, April 11, 2023, April 14, 2023, April 25, 2023 and April 27, 2023.

2 Background

2.1 PRODUCT INFORMATION

Lumryz is a central nervous system depressant with the proposed indication for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.² Lumryz is proposed as granules for extended-release oral suspension in single dose packets of 4.5 g, 6 g, 7.5 g, and 9 g.

Lumryz NDA 214755, was granted a tentative approval (TA) on July 18, 2022, with a REMS to ensure that the benefits of the drug outweigh the risk of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.³ The REMS is comprised of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments report. The ETASU includes prescriber certification (ETASU A), pharmacy certification (ETASU B), and documentation of safe use conditions (ETASU D). For a full history of the product information and the rationale for the REMS, refer to the DRM July 14, 2022 review.¹

2.2 REGULATORY HISTORY

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

- 07/18/22: The NDA 214755 and the REMS received tentative approval
- 03/01/23: Applicant resubmitted NDA 214755; the submission did not include the REMS
- 03/10/23: Applicant submitted the complete REMS to NDA 214755
- 03/24/23: Interim comments issued to the Applicant based on DRM's review of proposed REMS⁴
- 03/30/23: Applicant submitted a REMS amendment
- 04/04/23: Interim comments issued to Applicant based on DRM's review of proposed REMS⁵
- 04/11/23: Applicant submitted a REMS amendment
- 04/13/23: Interim comments issued to Applicant based on DMAMES review of proposed Assessment Plan⁶
- 04/14/23: Applicant submitted a REMS amendment
- 04/25/23: Applicant submitted a REMS amendment to align the Prescriber Brochure and the Certified Pharmacy Training with proposed labeling
- 4/27/23: Applicant submitted a REMS amendment to align the Patient Brochure with changes made to the proposed Instructions For Use

3 Review of Proposed REMS

3.1 REMS GOALS

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

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

3.2 REMS REQUIREMENTS

3.2.1 Elements to Assure Safe Use (ETASU)

The Applicant proposed the following ETASU as part of the REMS requirements:

- ETASU A, Health care providers who prescribe Lumryz are specially certified under 505-1(f)(3)(A).
- ETASU B, Pharmacies that dispense Lumryz are specially certified under 505-1(f)(3)(B).
- ETASU D, Lumryz is dispensed to patients with evidence or other documentation of safe-use conditions under 505-1(f)(3)(D).

***Reviewer's Comment:** The Applicant's proposal for prescriber certification, pharmacy certification, and documentation of safe-use conditions is acceptable.*

3.2.2 REMS Participant Requirements and Materials

3.2.2.1 Healthcare Provider

The Applicant proposed prescriber certification. To become certified in the REMS, prescribers must enroll in the REMS by completing the **Prescriber Enrollment Form** and submitting it to the REMS. By signing the enrollment form, the prescriber agrees to review the prescribing information and **Prescriber Brochure**; assess the patient's health status to determine if Lumryz is medically appropriate by screening for a history of alcohol and drug abuse and other medical conditions and the concomitant use of sedative hypnotics, other CNS depressants or other potentially interacting agents; counsel the patient on the serious risks and safe use, handling, and storage of Lumryz; enroll the patient in the REMS and order the prescription using the **Prescription Form** before treatment initiation or treatment re-initiation for patients with a lapse of 6 months or longer; and report all potential serious adverse events including any cases of suspected abuse, misuse, or diversion to the Applicant. The following materials associated with healthcare provider certification: **Prescriber Enrollment Form and Prescription Form**.

***Reviewer's Comments:** We agree with the requirements for Health Care Providers as they align with the Xywav and Xyrem REMS and Sodium Oxybate REMS and mitigate the same risks. The **Prescriber Enrollment Form and Prescription Form** are acceptable.*

3.2.2.2 Patients

The Applicant proposed that Lumryz be dispensed with evidence or documentation of safe use conditions. The Lumryz REMS requires that Lumryz is only dispensed to patients (or patient-authorized adult designees) enrolled in the Lumryz REMS. By signing the **Patient Enrollment Form**, patients acknowledge that they have reviewed the **Patient Brochure**, that they have been counseled by the prescriber and agree to complete the **Patient Counseling Checklist** with the pharmacist; and to follow the safe use conditions explained by their doctor; and tell the Lumryz pharmacist and prescriber about any changes in the medicines they are taking and any changes in their medical history. Following enrollment, the patient remains enrolled in the Lumryz REMS unless they are disenrolled at the request

of a certified prescriber and/or pharmacy. A disenrolled patient may be re-enrolled in the Lumryz REMS if both the certified pharmacy and the certified prescriber agree to re-enroll the patient. The following material is associated with patient enrollment: **Patient Enrollment Form**.

Reviewer's Comments: Refer to our March 24, 2023⁴ and April 4, 2023⁵ reviews for DRM's rationale for changes that were needed. The Applicant has addressed our comments. We agree with the requirements for patients as they align with the Xywav and Xyrem REMS and Sodium Oxybate REMS and mitigate the same risks. The **Patient Enrollment Form** is acceptable.

3.2.2.3 Pharmacies that dispense

The Applicant proposed that the Lumryz REMS requires all pharmacies that dispense Lumryz to become certified. To become certified in the REMS, an authorized representative must be designated to complete and submit **the Pharmacy Enrollment Form** on behalf of the pharmacy and to oversee implementation and compliance with the REMS by ensuring that all pharmacy staff involved in the Lumryz REMS complete the **Certified Pharmacy Training Program**. Other certification requirements include: to use the **Patient Counseling Checklist** for new patients, existing patients who restart treatment after 6 months, and patients who report a change in their medication use or medical history; to provide 24/7 toll-free access to a 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 each shipment; to report each prescription filled for Lumryz to the other REMS for oxybate products and document this in the Lumryz REMS; to document and report all potential adverse events to the Applicant; to reconcile Lumryz inventory and provide dispensing, shipment and receipt dates to the REMS; to not distribute, transfer, loan or sell Lumryz; and to not stock Lumryz in retail pharmacies.

Additionally, the pharmacy must establish and carry out processes and procedures that address multiple safe use requirements of the REMS including the assessment of the patient's concomitant use of sedative hypnotics, CNS depressants, or other potentially interacting agents that either are unknown to the prescriber or pose a high risk of serious interaction; verify and document that the prescriber is certified and the patient is enrolled, that the patient has no other known active, overlapping prescriptions for sodium oxybate and other oxybate products, and that neither the prescriber or patient have been disenrolled from other oxybate product REMS for abuse, misuse, or diversion; and to assess the patient's potential for abuse, misuse, and diversion by reviewing **Risk Management Reports** in the patient's profile.

The Applicant proposed that inventory control at the pharmacies would be conducted with documentation being made available in the event of an audit.

The Lumryz REMS requires that the Lumryz certified pharmacies contact each REMS for oxybate products to obtain information about overlapping prescriptions for oxybate products and disenrollments from the other REMS for oxybate products in order to obtain authorization to dispense. Each Lumryz dispense must receive a pre-dispense authorization (PDA) from the REMS. The PDA verifies the pharmacy is certified, the prescriber is certified, the patient is enrolled, the patient has no active, overlapping prescriptions for oxybate products, and that the pharmacy made the required contact to each REMS for oxybate products.

The following materials are associated with pharmacy certification: **Pharmacy Enrollment Form, Patient Counseling Checklist, and Risk Management Reports**.

Reviewer's Comments: Refer to our July 14, 2022,¹ March 24, 2023⁴ and April 4, 2023⁵ reviews for DRM's rationale for changes that were needed. The Applicant has addressed our comments. The proposed requirements, **Pharmacy Enrollment Form, Patient Counseling Checklist and Risk Management Reports** are acceptable.

3.3 Wholesalers-distributors that distribute

Wholesalers, distributors, and other entities that distribute Lumryz must establish processes and procedures to ensure that Lumryz is distributed only to certified pharmacies, to train all relevant staff involved in distributing Lumryz on the REMS requirements, maintain records of all drug distributions, and comply with audits to ensure all processes and procedures are in place and are being followed. Lumryz will not be distributed to or stocked in retail pharmacies. Verification of the distribution of Lumryz to certified pharmacies will be part of the REMS Compliance Plan.

Reviewer's Comments: The proposed wholesaler-distributors requirements are acceptable.

3.3.1 REMS Applicant Requirements and Materials

3.3.1.1 Training

Healthcare providers who prescribe

The Applicant proposes training that must be available on the REMS website or delivered by the Applicant to the prescriber. The training includes the **Prescriber Brochure** which includes but is not limited to important safety information and a guide to safely prescribing Lumryz.

Pharmacies that dispense

The Applicant proposes training that must be available on the REMS website or delivered by the Applicant. The training includes the **Certified Pharmacy Training Program** – Pharmacy Staff module and Pharmacist module, **Pharmacy Staff Knowledge Assessment**, and **Pharmacist Knowledge Assessment**

Reviewer's Comment: Refer to our April 4, 2023⁵ review for DRM's rationale for changes that were needed. The Applicant has addressed our comments. The Applicant's proposed requirements and materials are acceptable.

3.3.1.2 Communication Materials

The Applicant proposed a detailed stakeholder outreach plan to address the risk of potential confusion due the existence of multiple REMS for oxybate products. The stakeholder outreach plan includes a **Dear Healthcare Provider (DHCP) Letter** with the Prescribing Information and a **REMS Fact Sheet** attached for healthcare providers who are likely to prescribe Lumryz, and a **Professional Society Letter** to target certain professional societies. The **DHCP Letter** will be provided via email within 14 calendar days of the date of first commercial distribution of Lumryz and 30 calendar days later. The following materials are associated with communication materials and dissemination plan: **Dear Healthcare Provider Letter, Fact Sheet, and Professional Society Letter.**

Reviewer's Comment: The proposed target audience, dissemination plan, and communication materials are acceptable.

3.3.1.3 Operations

The Applicant proposed to establish and maintain a REMS Call Center and **REMS Website** to support stakeholders who interface with the REMS, as well as a establish and maintain validated, secure, separate and distinct databases a database of all REMS participants, including a patient database, certified prescriber database, certified pharmacy database, and disenrolled prescriber database that will be queried independently through electronic verification. The **REMS Website** must include the capability to complete prescriber certification online, complete pharmacy staff and pharmacist knowledge assessments online, the capability to enroll and manage patients online, including the capability for pharmacies to obtain an authorization to dispense, complete **Risk Management Reports**, complete the **Patient Counseling Checklist**, and the option to print the Prescribing Information, Medication Guide, and REMS materials. To support REMS operations and as required in the REMS the Applicant will not stock Lumryz in retail pharmacies.

Reviewer's Comments: The proposed REMS operations are acceptable.

3.3.1.4 Compliance

To ensure REMS participants' compliance with the REMS requirements, the Applicant will verify annually that the authorized representative's name and contact information correspond to those of the current designated authorized representative for the healthcare setting or pharmacy. The Applicant will also ensure processes and procedures are in place to maintain adequate records to demonstrate that REMS requirements are being met, including, but not limited to: Lumryz distribution and dispensing; certification of prescribers and pharmacies; enrolled patients and audits of REMS participants.

The Applicant must audit the certified pharmacies and wholesalers-distributors and other entities that distribute Lumryz within 90 days after the pharmacy places its first order of Lumryz and 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.

Reviewer's Comments: The proposed compliance requirements as described in the REMS Document are acceptable.

If the NDA is approved, the Applicant should submit their audit plan and non-compliance plan methodologies within 60 days after product approval for Agency review.

3.4 REMS ASSESSMENT TIMETABLE

The Applicant proposed to submit REMS Assessments at 6 months, 12 months, and annually from the date of initial approval of the REMS.

Reviewer comments: The timetable for submission of assessment is acceptable.

4 Supporting Document

The REMS Supporting Document included the background and the Applicant's rationale for the REMS of the REMS currently under review.

In addition, the Applicant included REMS website portal screenshots as an appendix.

Reviewer's Comments: Refer to our April 4, 2023⁵ review for DRM's rationale for changes that were needed. The Applicant has addressed our comments. The Applicant's proposed Supporting Document is acceptable.

5 REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document. Refer to the Appendix for the final Assessment Plan.

Reviewer's Comments:

REMS Assessment Plan metrics were designed to evaluate whether the REMS is meeting its goal to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion, to evaluate if the REMS is functioning as designed, and to determine if stakeholders are compliant with REMS requirements.

The REMS Assessment Plan categories include Program Implementation and Operations, Enrollment and Certification, Utilization, Operation and Performance Data, REMS Compliance, Safe Use Behaviors, Health Outcomes and/or Surrogate of Health Outcomes, and Knowledge.

Updates to the assessment plan were made to align with the assessment plan for other REMS for oxybate products to include reporting of two previous, current and cumulative data for metrics where applicable, clarification to enrollment and certification metrics, addition of metrics to report reasons for rejected requests for Pre-Dispense Authorizations, clarification that only prescription sedative hypnotic be included in prescriber notifications, and elimination of safety surveillance metrics that are no longer required.

The Applicant accepted the additional revisions to the assessment plan as described in the April 4, 2023⁵ and April 13, 2023⁶ reviews. The REMS Assessment Plan is acceptable.

6 Discussion

Lumryz received tentative approval (TA) with a REMS on July 18, 2022.³ 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 ETASU employed in this REMS are prescriber certification (ETASU A), pharmacy certification (ETASU B), and documentation of safe use conditions (ETASU D). As part of prescriber certification, prescriber's attest that they will assess and screen the patient to determine that Lumryz is medically appropriate.

As part of pharmacy certification all pharmacy staff and pharmacists involved in dispensing Lumryz must complete training about the pharmacy's requirements in the REMS. Pharmacies are required to establish processes and procedures to complete the Patient Counseling Checklist for the required patients, report each prescription filled for Lumryz to the other REMS for oxybate products, report and document suspected misuse, abuse or diversion using the Risk Management Report, and to obtain authorization to dispense after safe use conditions are met (prescriber and pharmacy is certified, patient is enrolled, the patient has no active overlapping prescriptions for Lumryz, and the pharmacy verified that the patient has no other active, overlapping prescriptions for oxybate products that overlap with the current prescription for Lumryz and that the patient and prescriber have not been disenrolled from any other REMS for oxybate products for suspected abuse, misuse, or diversion by contacting each REMS for oxybate products).

Changes that needed to be made during this review cycle include alignment of the **Patient Brochure** with the Instructions For Use (IFU)⁴ to include the steps and graphics that are used to help patients take their medicine safely and removal of inappropriate options (e.g., (b) (4)

to generate PDA from the website portal and the **Certified Pharmacy Training Program**. These options are reasons to put a prescription on file at the pharmacy and not dispense until it is ensured under these situations the patient does not receive overlapping dispenses of an oxybate product.⁵

REMS Assessment Plan metrics were designed to evaluate whether the REMS is meeting its goal to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion, to evaluate if the REMS is functioning as designed, and to determine if stakeholders are compliant with REMS requirements. The Assessment Plan included in the July 18, 2022 Tentative Approval Letter was updated to align with metrics in the REMS Assessment Plan for other REMS for oxybate products.

7 Conclusions and Recommendations

DRM and DMAMES find the proposed REMS for Lumryz (sodium oxybate extended-release) as submitted on March 10, 2023 acceptable. DRM and DMAMES recommend approval of the REMS for Lumryz, received on December 15, 2020, and last amended on April 27, 2023, and appended to this review.

8 References

¹ Pratt, R. Evaluation of Needs for a REMS review for Lumryz (sodium oxybate extended-release) NDA 214755, DARRTED July 14, 2022 (available at: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80672e40>).

² Avadel. Proposed Prescribing Information for Lumryz (buprenorphine extended-release) March 1, 2023.

³Tentative Approval Letter for Lumryz (sodium oxybate extended-release) granules. NDA 214755. July 18, 2022 (available at: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80673821>).

⁴ Bernheimer, T. Review of Proposed REMS for Lumryz (sodium oxybate extended-release) NDA 214755, DARRTED March 24, 2023 (available at: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806bc91d>).

⁵ Paradis, J. Review of Proposed REMS for Lumryz (sodium oxybate extended-release) NDA 214755, DARRTED April 4, 2023 (available at: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806c0517>).

⁶ Paradis, J. Review of Proposed REMS for Lumryz (sodium oxybate extended-release) NDA 214755, DARRTED April 13, 2023 (available at: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806c314b>).

9 Appendix

REMS Assessment Plan

REMS Document

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
7. Pharmacy Staff Knowledge Assessment
8. Pharmacist Knowledge Assessment

Patient Care Forms

9. Prescription Form
10. Patient Counseling Checklist

Communication Materials

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

Other Materials

14. Risk Management Report
 15. REMS Website
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98 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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**Division of Mitigation Assessment and Error Prevention Surveillance (DMAMES)
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
Submission Type/Number	Original-1/60
TTT Number	2023-3984
Reviewers	Joseph Paradis, PharmD (DMAMES) Tim Bernheimer, PharmD (Division of Risk Management (DRM)
Team Leaders	Carolyn Tieu, PharmD, MPH (DRM) Shelly Harris, ScD, MPH (DMAMES)
Review Completion Date	April 13, 2023
Subject	Review of the Proposed Risk Evaluation and Mitigation Strategy (REMS)for Lumryz (sodium oxybate extended-release oral suspension)
Established Name	Sodium Oxybate Extended-Release Oral Suspension
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals, LLC
Therapeutic Class	Central Nervous System Depressant
Formulation(s)	Powder for extended-release oral suspension: nightly dose packets of 4.5 g, 6 g, 7.5 g, and 9 g
Submission Date	March 30, 2023

1. Introduction

This review evaluates the risk evaluation and mitigation strategy (REMS) for Lumryz (sodium oxybate) extended-release oral suspension, New Drug Application (NDA) 214755 submitted by Avadel CNS Pharmaceuticals LLC on March 30, 2023. The REMS assessment plan metrics that address Pre-Dispense Authorizations (PDA) is the subject of this review.

2. Background

The Applicant received tentative approval on July 18, 2022. On March 1, 2023, the Applicant submitted a request for full approval, and on March 10, 2023, submitted REMS materials. The Agency provided comments to the Applicant on March 24, 2023, and the Applicant responded on March 30, 2023.^a Additional comments were sent to the Applicant on April 4, 2023^b, and the Applicant responded via email on April 5, 2023, with a clarification for the PDA metrics included in the assessment plan.

3. 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

4. REMS Assessment Plan

On April 5, 2023, the Applicant responded via email with the following (the complete email is included):

“Metric 10 references “rejected PDAs;” however, a PDA is generated only if all REMS and safe use requirements are met. The Pharmacy REMS portal is

^a The March 30, 2023 submission for the Lumryz Full REMS is available at:

<\\CDSESUB1\EVSPROD\nda214755\0059\m1\us\116-risk-management\1162-rems\lumryz-rems-full.pdf>.

^b The April 4, 2023 Review and comments to Avadel is available at:

<https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806c0517>

specifically designed to have a hard stop in PDA generation if a pharmacy user provides any data that indicates the REMS and safe use requirements are not met. The screenshots on pages 82-87 of the REMS Supporting Document reflect the hard stop message a pharmacy user would see if he/she answered any PDA question that indicates a REMS or safe use requirement is not met. If this occurs, the pharmacy user is informed that a PDA cannot be generated. A PDA is intentionally not generated in these instances to ensure that a pharmacy user does not think he/she can proceed with the dispense of LUMRYZ without meeting all REMS and safe use requirements. This removes possible human error to help meet the REMS goal to ensure that pharmacy controls exist prior to filling prescriptions for LUMRYZ.

These hard stops are intentionally not tracked or saved in the Pharmacy REMS portal in case it was a data entry error, or the pharmacy user is doing a pre-check of the REMS verification requirements that are part of the PDA process. Pharmacies will provide prescription information to the LUMRYZ REMS for any delays or prescriptions they are unable to fill as required in metrics 9.a.i-vii with their dispense files.

Additional clarification is noted below on each of the metric 10 data points. Please confirm if additional discussion or clarification is requested. Avadel is available to have a call to discuss further.

10. Pre-Dispense Authorizations (PDAs)
 - a. Number of rejected PDAs and reasons for rejection
 - i. Avadel Response: PDAs are intentionally not generated if all REMS and safe use requirements are not met. This ensures the pharmacy user does not think he/she can proceed with dispensing LUMRYZ. Authorization to dispense is not approved so there is no Pre-Dispense Authorization Code.
 - b. Number of prescriptions dispensed where all REMS and safe use requirements were not met, but a PDA was provided
 - i. Avadel Response: A PDA would not be provided if all REMS and safe use requirements were not met.
 - c. Number of prescriptions dispensed without a PDA
 - i. Avadel Response: This metric will be provided.
 - d. Total number of PDA rejections, the number of these PDAs that were subsequently approved and the duration of time from rejection to approval
 - i. Avadel Response: A PDA is only generated if all REMS and safe use requirements are met. If these requirements are not met, a hard stop occurs. Thus, there are no metrics around new or updated requests submitted. The pharmacies will report to the LUMRYZ REMS any prescriptions that are delayed or unable to be filled with

their dispense files due to being unable to obtain information from other REMS for oxybate products. The LUMRYZ REMS will assess this information against the number of valid prescriptions reported to the REMS per metric 9.a.iv.”

Reviewer Comments:

- *Metric 10 of the assessment plan is required to document reasons that PDA requests were rejected. The metrics are reworded as below.*

10. Pre-Dispense Authorizations (PDAs)

- a. Number of ~~rejected~~ requested PDAs that were rejected and reasons for rejection
 - b. Number of prescriptions dispensed where all REMS and safe use requirements were not met, but a PDA was provided
 - c. Number of prescriptions dispensed without a PDA
 - d. ~~Total number of PDA rejections, the number of these rejected PDAs requests that were subsequently approved and the duration of time from rejection of the requests to approval~~
 - d. The number of requested PDAs that were rejected and were subsequently approved and the duration of time from rejection of the requests to approval
- *The Applicant indicates that these hard stops are intentionally not tracked or saved in the Pharmacy REMS portal. The reason for PDA request rejections is communicated to the pharmacy user based on screenshots on pages 82-87 in the REMS Supporting Document. It's necessary to capture the hard stop message that a pharmacy user would see to determine why PDAs are not issued (e.g., which specific safe use condition(s) are not met). Tracking this data is critical to allow monitoring and evaluation of the REMS in order for you to take reasonable steps to improve implementation of and compliance with the requirements of the REMS, as included in the REMS Document (To support REMS Program operations, Avadel CNS Pharmaceuticals, LLC must: Item 29).*
 - *Metric 10. b. will be maintained in the assessment plan. If no prescriptions meet this criterion, it should be reported in the assessments.*

5. Conclusions and Recommendations

The REMS Assessment Plan as included in the April 4, 2023, response to the March 30, 2023, comments, must be revised to ensure compliance with REMS requirements.

6. Comments to the Applicant

We have the following additional comments regarding the Pre-Dispense Authorization (PDA) metrics in the Lumryz Assessment Plan. Review of the proposed REMS is ongoing; these comments should not be considered final.

1. We do not agree with your April 5, 2023, response regarding the Pre-Dispense Authorization (PDA) metrics in the April 4, 2023 REMS Assessment Plan. See our response to your individual comments below:

a. Metric 10.a.: Number of rejected PDAs and reasons for rejection

Avadel Comment: PDAs are intentionally not generated if all REMS and safe use requirements are not met. This ensures the pharmacy user does not think he/she can proceed with dispensing Lumryz. Authorization to dispense is not approved so there is no Pre-Dispense Authorization Code.

Agency Response: We have revised the wording of Metric 10.a. to provide clarification that you should provide the number of requested PDAs that were rejected. The reason for PDA request rejections is communicated to the pharmacy user based on screenshots on pages 82-87 in the REMS Supporting Document^c. It's necessary to capture the hard stop message that a pharmacy user would see to determine why PDAs are not issued (e.g., which specific safe use condition(s) are not met). Tracking this data is critical to allow monitoring and evaluation of the REMS in order for you to take reasonable steps to improve implementation of and compliance with the requirements of the REMS, as included in the REMS Document (To support REMS Program operations, Avadel CNS Pharmaceuticals, LLC must: Item 29).

b. Metric 10.b: Number of prescriptions dispensed where all REMS and safe use requirements were not met, but a PDA was provided

Avadel Comment: A PDA would not be provided if all REMS and safe use requirements were not met.

Agency Response: Metric 10.b. should be maintained in the assessment plan. If no prescriptions meet this criterion, it should be reported as such in the REMS assessment report.

c. Metric 10.d.: Total number of PDA rejections, the number of these PDAs that were subsequently approved and the duration of time from rejection to approval

Avadel Comment: A PDA is only generated if all REMS and safe use requirements are met. If these requirements are not met, a hard stop occurs. Thus, there are no metrics around new or

^c The Supporting Document submitted on March 30, 2023 is available at:
<\\CDSESUB1\EVSPROD\nda214755\0059\m1\us\116-risk-management\1162-rem\2-rem-supporting-document.docx>.

updated requests submitted. The pharmacies will report to the Lumryz REMS any prescriptions that are delayed or unable to be filled with their dispense files due to being unable to obtain information from other REMS for oxybate products. The Lumryz REMS will assess this information against the number of valid prescriptions reported to the REMS per metric 9.a.iv.

Agency Response: We have revised the wording of Metric 10.d. to provide clarification that you should provide the number of rejected requests that were subsequently approved, and the time from rejection of the requests to approval.

As a reminder, reasons provided to the pharmacy for why a PDA was not issued include:

- Pharmacy is not certified
- Prescriber is not certified
- Patient is not enrolled
- Patient has an active, overlapping prescription for Lumryz
- Pharmacy did not confirm that a call was made to the other REMS for oxybate products to verify the patient has no active, overlapping prescriptions for oxybate products that overlaps with the current prescription for Lumryz, and that the patient and prescriber has not been disenrolled from any other REMS for oxybate products for suspected abuse, misuse, or diversion

For example, a pharmacy may receive the reason a PDA was not issued due to “prescriber is not certified.” After the pharmacy consults with the prescriber, the prescriber may certify in the REMS and ask the pharmacy to process the prescription again. Now that the prescriber is certified and this safe use condition is met, a PDA would be generated by the Lumryz REMS.

The PDA metrics are revised as follows:

10. Pre-Dispense Authorizations (PDAs)

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

Resubmission Instructions

Further changes are necessary for the REMS to be acceptable. Submit a REMS amendment by close of business April 17, 2023, that addresses these comments. Include the following:

- REMS Supporting Document, including the REMS Assessment Plan in clean Word, tracked Word, and clean PDF.
- One compiled PDF file that includes the REMS Document and all REMS materials (excluding the REMS Supporting Document) in their final format.

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**Division of Mitigation Assessment and Error Prevention Surveillance (DMAMES)
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
Submission Type/Number	Original-1/60
TTT Number	2023-3984
Reviewers	Joseph Paradis, PharmD (DMAMES) Tim Bernheimer, PharmD (Division of Risk Management (DRM)
Team Leaders	Carolyn Tieu, PharmD, MPH (DRM) Shelly Harris, ScD, MPH (DMAMES)
Review Completion Date	April 4, 2023
Subject	Review of the Proposed Risk Evaluation and Mitigation Strategy (REMS) for Lumryz (sodium oxybate extended-release oral suspension)
Established Name	Sodium Oxybate Extended-Release Oral Suspension
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals, LLC
Therapeutic Class	Central Nervous System Depressant
Formulation(s)	Powder for extended-release oral suspension: nightly dose packets of 4.5 g, 6 g, 7.5 g, and 9 g
Submission Date	March 30, 2023

1. Introduction

This review evaluates the risk evaluation and mitigation strategy (REMS) for Lumryz (sodium oxybate) extended-release oral suspension, New Drug Application (NDA) 214755 submitted by Avadel CNS Pharmaceuticals LLC on March 30, 2023. The REMS assessment plan, Certified Pharmacy Training Program and REMS Website portal screenshots are the subject of this review.

2. Background

The Applicant received tentative approval on July 18, 2022. On March 1, 2023, the Applicant submitted a request for full approval, and on March 10, 2023, submitted REMS materials. The Agency provided comments to the Applicant on March 24, 2023, and the Applicant responded on March 30, 2023.^a

3. 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

3. REMS Timetable of Submission of Assessments

The Applicant proposed to submit REMS Assessments at 6 months, 12 months, and annually from the date of initial approval of the REMS.

4. REMS Supporting Document

4.1 REMS Assessment Plan

After further review, the assessment plan requires additional revisions to those communicated to the Applicant on March 24, 2023. Metrics are required to be added to the assessment plan

^a The March 30, 2023 submission for the Lumryz Full REMS is available at:
<\\CDSESUB1\EVSPROD\nda214755\0059\m1\us\116-risk-management\1162-rems\lumryz-rems-full.pdf>.

to monitor the Pre-Dispense Authorization (PDA) process to ensure that the PDA process is working as intended to ensure compliance with REMS requirements. In addition, the Pharmacy Notification and Pharmacovigilance/Surveillance metrics are updated for clarification, and the two Knowledge, Attitude, and Behavior (KAB) Survey metrics are combined into one metric.

4.2 REMS Website Screenshots

The Applicant provided **REMS Website** screenshots of the portal for pharmacy staff as an Appendix to the REMS Supporting Document.^b After further review, the screenshots of the portal that depict the process for the PDA is not acceptable and requires additional clarification. Pharmacies should not obtain a PDA if the patient has an active overlapping oxybate prescription unless there is a valid reason for a dispense. Currently, in the PDA section of the portal, pharmacies can provide [REDACTED] (b) (4) as valid reasons to generate a PDA for active, overlapping prescriptions for oxybate product(s). These are not valid reasons for the pharmacy to obtain PDA and dispense sodium oxybate until the pharmacist ensures that under these situations a patient does not receive overlapping dispenses of sodium oxybate. The Applicant needs to remove these options from the website portal as PDAs generated for these reasons would not be appropriate.

5. REMS Materials

The Applicant revised the **Patient Brochure** to include the content and graphics from the Instructions For Use. With these changes, the **Patient Brochure** is acceptable.

As a result of the required revisions needed for the website portal, the Applicant needs to also revise the **Certified Pharmacy Training Program** to align with the above clarifications regarding the process to obtain a PDA.

We do not have additional comments on the other REMS materials and find them acceptable.

6. Conclusions and Recommendations

The REMS Assessment Plan as included in the March 30, 2023, response to the March 24, 2023, comments, must be revised to ensure compliance with REMS requirements, and align with other REMS for oxybate products.

Additionally, further changes to the **Certified Pharmacy Training Program** and the **REMS Website** portal screenshots are necessary for the REMS to be acceptable.

We recommend sending the following comments to the Applicant.

^b The March 30, 2023 submission for the Lumryz Supporting Document is available at: <\\CDSESUB1\EVSPROD\nda214755\0059\m1\us\116-risk-management\1162-rems\2-rems-supporting-document-redline.docx>.

7. Comments to the Applicant

We have the following additional comments regarding the of the proposed REMS assessment plan, Certified Pharmacy Training Program and REMS Website screenshots. Review of the proposed REMS is ongoing; these comments should not be considered final.

Assessment Plan

1. Minor editorial revisions are made to Pharmacy Notification Metrics 6.a.i.1 and 6.a.ii.1.
2. Metric 10 is added to capture the REMS Pre-Dispense Authorization (PDAs) process.
3. Metric 11.a.ii., Pharmacovigilance/Surveillance is revised for clarification.
4. The two Knowledge Attitudes and Behavior (KAB) survey metrics (Metric 12 and 13) are combined into one metric.

REMS Supporting Document

Refer to website screenshots of the portal for pharmacy on page 76 of the Supporting Document. Remove the following reasons from the PDA process:

-  (b) (4)
- 
- 

These are not valid reasons for the pharmacy to obtain PDA and dispense medication until it is ensured that under these situations a patient does not receive overlapping dispenses or shipments.

REMS Materials

Certified Pharmacy Training Program

Refer to page 11. We have made edits to clarify the point mentioned above. See attached redline document.

Resubmission Instructions

Further changes are necessary for the REMS to be acceptable. Submit a REMS amendment within five business days that addresses these comments. Include the following:

- Certified Pharmacy Training Program in clean Word, tracked Word, and clean PDF
- REMS Supporting Document, including the REMS Assessment Plan, and Website screenshots in clean Word, tracked Word, and clean PDF
- One compiled PDF file that includes the REMS Document and all REMS materials (excluding the REMS Supporting Document) in their final format

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

Application Type	NDA
Application Number	214755
PDUFA Goal Date	May 1, 2023
Nexus TTT #	2023-3984
Reviewer Name(s)	Timothy Bernheimer, PharmD Kate Oswell, MA Joseph Paradis, PharmD (DMAMES)
Team Leader(s)	Shelly Harris, ScD, MPH (DMAMES) Carolyn Tieu, PharmD, MPH
Associate Director	Jo Wyeth, PharmD (OMEPRM)
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	March 24, 2023
Subject	Evaluation of the Proposed REMS
Established Name	Sodium Oxybate Extended-Release Oral Suspension
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals
Therapeutic Class	Central Nervous System Depressant
Formulation	Powder for extended-release oral suspension: nightly dose packets of 4.5 g, 6 g, 7.5 g, and 9 g
Dosing Regimen	The recommended starting dosage is 4.5 g per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the effective dosage range of 6 g to 9 g per night orally

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1. Introduction

This review evaluates the Risk Evaluation and Mitigation Strategy (REMS) for Lumryz (sodium oxybate extended-release), New Drug Application (NDA) 214755, submitted by Avadel Pharmaceuticals CNS on March 10, 2023.

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

2. Regulatory History

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

- 07/18/22: The NDA 214755 and the REMS received tentative approval
- 03/01/23: Applicant resubmitted NDA 214755; the submission did not include the REMS
- 03/10/23: Applicant submitted the complete REMS to NDA 214755

3. Review of Proposed REMS

The following materials were reviewed and are acceptable:

- REMS Document
- Prescriber Enrollment Form
- Patient Enrollment Form
- Pharmacy Enrollment Form
- Prescriber Brochure
- Certified Pharmacy Training Program
- Pharmacy Staff Knowledge Assessment
- Pharmacist Knowledge Assessment
- Prescription Form
- Patient Counseling Checklist
- Dear Healthcare Provider Letter
- Dear Professional Society Letter
- REMS Fact Sheet
- Risk Management Report

The **Patient Brochure** is not acceptable and must be revised to align with the content and include the graphics from the Instructions For Use.

The public facing **REMS Website** screenshots are acceptable; however, only the public facing **REMS Website** screenshots are resubmitted. The Applicant needs to submit screenshots of the proposed **REMS Website** portal for pharmacy staff. These should be included as an Appendix to the REMS Supporting Document.

4. REMS Assessment Plan

The Lumryz REMS assessment plan included in the July 18, 2022, Tentative Approval Letter² requires revisions to align with assessment plans for other REMS for oxybate products.

Reviewer Comments:

- *Editorial changes have been made to clarify requirements for reporting of each metric for the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted.*
- *Metrics have been added to capture the total number of enrolled patients and the total number of certified healthcare providers and pharmacies.*
- *[REDACTED]* (b) (4)
- *Metrics have been added to capture data on authorized wholesalers/distributors.*
- *[REDACTED]* (b) (4)
- *For Metrics 6.a.i., and 8.a.i., only “prescription” sedative hypnotic agents are to be reported.*
- *The following revisions are required to be made to Metric 10, Health Outcomes and/or Surrogates of Health Outcomes: Pharmacovigilance/Safety Surveillance metrics to align with other REMS for oxybate products.*
 - *[REDACTED]* (b) (4)
 - *Revisions are required to clarify reporting requirements for serious adverse events to include an analysis of serious adverse events including a summary table for the number of reports of serious adverse events, including the following data; 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.*
 - *Metrics to report mortality rate calculations have been added.*
 - *A narrative summary is required to be included of each death case and each sexual abuse case.*
- *The following statement is required to be added to the REMS Supporting Document to align with other REMS for oxybate products, “The Lumryz REMS program will periodically monitor available safety databases for any information regarding serious adverse events associated with abuse, misuse, or diversion of Lumryz. Any relevant information will be included in the REMS assessments.”*

5. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on March 10, 2023. Review of the REMS proposal is ongoing; these comments should not be considered final.

Patient Brochure

Align the Patient Brochure with the content from the Instructions For Use, and include the steps and graphics that are used to help patients take their medicine safely.

REMS Website

You have proposed a REMS website portal for pharmacy staff to provide resources and ensure real-time access for pharmacies to verify safe use conditions. Submit screenshots as an Appendix in the Supporting Document showing the functionality for the website portal. For example, screenshots would show the verification process a pharmacy would walk through to complete the Patient Counseling Checklist and obtain a pre-dispense authorization.

REMS Supporting Document

Add the following statement to the REMS Supporting Document: “The Lumryz REMS will periodically monitor available safety databases for any information regarding serious adverse events associated with abuse, misuse, or diversion of Lumryz. Any relevant information will be included in the REMS assessments.”

REMS Assessment Plan

The Agency requires revisions to the assessment plan and the REMS Supporting Document to align with other REMS for oxybate products. The changes are summarized below, and a tracked changed version is attached with additions underlined and deletions in strikethrough.

1. Removed the timeframe for submission of each assessment metric from each individual metric and placed at the beginning of the assessment plan. All metrics are to be reported for the two previous, current, and cumulative reporting periods (where applicable), unless otherwise noted.
2. Editorial changes were made throughout to remove the generic name and to remove the word “program” from the REMS Assessment Plan.
3. Changed the heading of Metric 2 to REMS Enrollment and Certification Statistics.
4. Added REMS Enrollment and Certification Statistics metrics to capture the total number of enrolled patients and the total number of certified healthcare providers and pharmacies.
5.  (b) (4)
6. Added metrics to capture data on authorized wholesaler/distributors.
7.  (b) (4)
8. For Metrics 6.a.i., and 8.a.i., only “prescription” sedative hypnotic agents are to be reported as listed on the FDA website, <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sleep-disorder-sedative-hypnotic-drug-information>.
9. Revised Metric 9 to incorporate the language “other REMS for oxybate products.”
10. Revised Metric 10: Health Outcomes and/or Surrogates of Health Outcomes: Pharmacovigilance/Safety Surveillance metrics as follows:
 - Removed the following data fields:  (b) (4)
 - Added an analysis of serious adverse events to include the following additional metrics: 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.

- Added mortality rate calculation metrics.
- Added the requirement to include a narrative summary of each death and each sexual abuse case.

11. Added the following heading to Metric 14, "Overall Assessment of REMS Effectiveness."

Resubmission Instructions

Further changes are necessary for the REMS to be acceptable. Submit a REMS amendment within five business days that addresses these comments. Include the following:

- Patient Brochure in clean Word, tracked Word, and clean PDF
- REMS Supporting Document, including the REMS Assessment Plan, in clean Word, tracked Word, and clean PDF
- One compiled PDF file that includes the REMS Document and all REMS materials (excluding the REMS Supporting Document) in their final format.

6. References

¹Avadel CNS Pharmaceuticals. Proposed Prescribing Information for Lumryz (sodium oxybate extended-release) March 1, 2023.

²The July 18, 2022 Tentative Approval Letter is available at:

<https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80673821>.

7. Appendix

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Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEUROSCIENCE
DIVISION OF NEUROLOGY 1**

NDA/BLA #s: 214755
Products: Lumryz (sodium oxybate), extended-release oral suspension
APPLICANT: Avadel CNS Pharmaceuticals, LLC
FROM: Teresa Buracchio, MD
DATE: July 15, 2022

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use (ETASU) is necessary for Lumryz (sodium oxybate) to ensure that the benefits of the drug outweigh the risks of serious adverse outcomes resulting from inappropriate

prescribing, misuse, abuse, and diversion.¹ In reaching this determination, we considered the following:

- A. Lumryz (sodium oxybate) will be indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy. The prevalence of narcolepsy with cataplexy has been estimated to be between 25 and 50 per 100,000 people and the incidence of narcolepsy with cataplexy has been estimated to be 0.74 per 100,000 person years.²
- B. Narcolepsy is a clinical syndrome of daytime sleepiness with cataplexy, hypnagogic hallucinations, and sleep paralysis. It is the second most common cause of disabling daytime sleepiness after obstructive sleep apnea.^{3,4} Cataplexy is a chronic and life-long disorder that is disabling and may lead to serious injury. Excessive daytime sleepiness can impair performance over time, as measured by response latency, response variability, speed, accuracy, hand-eye coordination, decision-making, and memory. Of particular importance are the adverse consequences of such effects on driving and the increased risk of potentially fatal motor vehicle accidents.
- C. Adult patients on stable doses of Lumryz (sodium oxybate) had statistically significant improvement in the Maintenance of Wakefulness Test that measures latency to sleep onset and in Clinical Global Impression-Improvement, and fewer cataplexy attacks than did patients randomized to placebo.
- D. Lumryz (sodium oxybate) will be used on a chronic basis in patients with narcolepsy.
- E. The active moiety of Lumryz (sodium oxybate), oxybate (also known as gamma-hydroxybutyrate or GHB), is associated with the risks of central nervous system depression, respiratory depression, abuse, and misuse. Lumryz (sodium oxybate) is a central nervous system depressant, which may cause serious outcomes even at approved doses. Because of its effects on the central nervous system, Lumryz (sodium oxybate) may impair respiratory drive, especially in patients with compromised respiratory function. In clinical trials with sodium oxybate, clinically significant respiratory depression occurred in oxybate-treated patients even at doses currently recommended in labeling. When used with other central nervous system depressants, however, the risk of adverse outcomes including respiratory depression, hypotension, profound sedation, syncope, and

¹ 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 The epidemiology of narcolepsy. Longstreth WT Jr, Koepsell TD, Ton TG, Hendrickson AF, van Belle G. *Sleep*. 2007;30(1):13.

³ Narcolepsy and excessive daytime sleepiness. Zeman A, Britton T, Douglas N, Hansen A, Hicks J, Howard R, Meredith A, Smith I, Stores G, Wilson S, Zaiwalla Z. *BMJ*. 2004;329(7468):724.

⁴ The neurobiology, diagnosis, and treatment of narcolepsy. Scammell TE. *Ann Neurol*. 2003;53(2):154.

death increases. For this reason, the use of Lumryz (sodium oxybate) with alcohol and sedative-hypnotics is contraindicated.

Lumryz (sodium oxybate), is a Schedule III controlled substance. Other approved drugs with the same active moiety of oxybate, are associated with the risks of abuse and misuse. GHB, the active moiety of Lumryz (sodium oxybate), is a Schedule I controlled substance. Abuse of GHB either alone or in combination with other CNS depressants is associated with adverse reactions including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with amnesia, particularly when combined with alcohol, has proven to be dangerous for voluntary and involuntary users (e.g., assault victims).

Misuse and inappropriate prescribing of another sodium oxybate product (Xyrem) have also been demonstrated to occur. Misuse and inappropriate prescribing have the potential to cause serious outcomes primarily related to the risks of central nervous system and respiratory depression.

F. Lumryz (sodium oxybate) is not a new molecular entity.

The elements of the REMS will be: elements to assure safe use (including that healthcare providers who prescribe Lumryz (sodium oxybate) are specially certified, that Lumryz (sodium oxybate) will be dispensed only by pharmacies that are specially certified, and that Lumryz (sodium oxybate) will be dispensed and shipped only to patients who are enrolled in the Lumryz (sodium oxybate) REMS Program with documentation of safe use conditions), an implementation system, and a timetable for submission of assessments of the REMS.

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

Application Type	NDA
Application Number	214755
PDUFA Goal Date	October 15, 2021
OSE RCM #	2021-56
Reviewer Name(s)	Bob Pratt, Pharm.D. Anahita Tavakoli, M.A. Joseph Paradis, Pharm.D. Division of Mitigation Assessment and Medication Error Surveillance
Team Leader	Jacqueline Sheppard, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	July 14, 2022
Subject	Determination and Evaluation of the Proposed REMS
Established Name	Sodium Oxybate Extended-Release Oral Suspension
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals
Therapeutic Class	Central Nervous System Depressant
Formulation	Powder for extended-release oral suspension: nightly dose packets of 4.5 g, 6 g, 7.5 g, and 9 g
Dosing Regimen	The recommended starting dosage is 4.5 g per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the effective dosage range of 6 g to 9 g per night orally

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Lumryz (sodium oxybate extended-release) is necessary to ensure the benefits outweigh its risks. Avadel Pharmaceuticals CNS submitted a New Drug Application (NDA 214755) for Lumryz with the proposed indication for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy. The risks associated with Lumryz include serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.^a The Applicant's proposed REMS submitted on December 15, 2020, and amended on August 3, August 5, September 27, October 8, October 14, 2021, and June 15, 2022, consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

DRM and the Division of Neurology I (DNI) have determined that a REMS is needed to ensure the benefits of Lumryz outweigh its risks. If approved, Lumryz will become the third member of the oxybate class of drugs with a REMS to mitigate the risks of serious adverse outcomes resulting from improper prescribing, misuse, abuse, and diversion. The class currently includes two separate, approved REMS programs, the Xywav and Xyrem REMS and the shared system Sodium Oxybate REMS. The proposed Lumryz REMS includes the same goals and ETASU as the REMS for the other two drugs in its class. While there are operational differences in the REMS, we find the approach for Lumryz provides a level of product safety equal to that of the Xywav and Xyrem REMS.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Lumryz (sodium oxybate extended-release) is necessary to ensure the benefits outweigh its risks. Avadel Pharmaceuticals CNS (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 214755 for Lumryz with the proposed indication for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy. This application is under review in the Division of Neurology I (DNI). The Applicant's proposed REMS submitted on December 15, 2020, and amended on August 3, August 5, September 27, October 8, October 14, 2021, and June 15, 2022, consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Lumryz outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.

2. Background

2.1. Product Information

Lumryz (sodium oxybate extended-release) is a central nervous system depressant with the proposed indication for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with

^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.

narcolepsy. Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous compound and metabolite of the neurotransmitter GABA. Although the mechanism of action of sodium oxybate is unknown, it is believed the therapeutic effects are mediated by GABA_B actions at noradrenergic, dopaminergic, and thalamocortical neurons that increase dopamine levels in the brain, producing sedation.¹ Sodium oxybate is a controlled substance classified as schedule III for its approved use and as schedule I for illicit use (GHB is known as the "date rape drug").

Lumryz is supplied as granules for oral suspension in single dose packets of 4.5 g, 6 g, 7.5 g, and 9 g. The recommended starting dosage is 4.5 g self-administered by the patient once nightly at bedtime. The dosage may be increased by 1.5 g per night at weekly intervals to the effective dosage range of 6 g to 9 g per night as a chronic use medication.^b The Lumryz NDA is a 505(b)(2) application that relies, in part, on FDA's finding of safety and effectiveness for Xyrem (sodium oxybate) based on a comparative bioavailability study as the bridge to the listed drug.^c Lumryz is designated as an orphan product for the treatment of narcolepsy and is not currently approved in any jurisdiction. However, Lumryz is a member of the sodium oxybate class of drugs that have REMS to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion. The class currently includes two separate and approved REMS programs. Please see Table 1 in the Appendix for a comparison of the pharmacy operations of the approved REMS programs.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 214755 relevant to this review:

- 1/8/2018: Orphan drug designation granted for the treatment of narcolepsy
- 9/29/2020: The Agency issued a written response to the Applicant's meeting package submitted to IND 126321 on 8/18/2020 requesting discussion of the REMS for Lumryz. The Agency agreed with the Applicant's approach to submit a REMS that is separate from the other approved REMS for sodium oxybate products based on several differences with the approved products, such as the dose administration schedule, dose preparation, and the purported lack of a drug-drug interaction between Lumryz and divalproex sodium.
- 12/15/2020: NDA 214755 submission received by the Agency. The submission included a proposed REMS with ETASU, an implementation system, and a timetable for submission of assessments.
- 4/15/2021: Information Request (IR) sent to the Applicant requesting additional details related to the process to obtain pre-dispense authorization from the REMS and the use of a third-party logistics (3PL) provider to distribute Lumryz to certified pharmacies.
- 4/28/2021: REMS Correspondence received by the Agency in response to the 4/15/2021 IR. The Applicant indicated that (b) (4) will be the REMS Administrator and (b) (4) will be the 3PL provider. (b) (4) will use real-time reporting to provide the Applicant with access to current inventory information and analyses for inventory management. The 3PL provider will report

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

pharmacy distribution data to the REMS for verification and compliance monitoring. The 3PL provider will not enroll in the REMS and is not included in the REMS audit plan but will be audited per the Applicant's vendor management program.

- 7/20/2021: IR sent to the Applicant requesting the addition of a REMS Prescription Form to the REMS materials and to revise several REMS materials including the Enrollment Forms; and to explain several operational aspects of the program.
- 8/3/2021: The Applicant submitted a response to the 7/20/2021 IR that included redlined and clean versions of the REMS document, supporting document, and REMS materials. The response included a Prescription Form.
- 8/5/2021: The Applicant submitted a revised REMS supporting document containing a corrected certified pharmacy workflow diagram.
- 8/19/2021: IR sent to the Applicant requesting details related to the processes for disenrolling prescribers and patients and further revisions to the Prescription Form.
- 8/24/2021: The Applicant submitted a response to the 8/19/2021 IR as REMS Correspondence. The Applicant clarified the process for disenrolling a patient or prescriber. The Applicant also agreed that the Prescription Form must be used for initial prescriptions and for patients with a lapse in treatment of 6 months or longer, and that the form will include a pharmacy attestation statement.
- 9/3/2021: IR sent to the Applicant requesting details related to the identification of overlapping Lumryz prescriptions; the views provided by the secure pharmacy portal and secure prescriber portal to the users; confirmation that all oxybate products (Xyrem, Xywav and any ANDAs containing oxybate) meet the definition of sodium oxybate when identifying overlapping prescriptions; and the mechanism by which the reporting of Lumryz dispenses to other oxybate REMS programs will be documented in the Lumryz REMS.
- 9/8/2021: The Applicant submitted a response to the 9/3/2021 IR as REMS Correspondence. The Applicant clarified that the certified pharmacy verifies the patient has no known active, overlapping prescriptions for Lumryz during the pre-dispense authorization process. The response also described the information provided by the secure pharmacy portal and secure prescriber portal. Additionally, the Applicant requested confirmation that FDA will require the other programs to report dispensing to the Applicant.
- 9/13/2021: IR sent to the Applicant that provided the Agency's redlined versions of the REMS document, Patient Counseling Checklist, REMS Fact Sheet, Risk Management Report, and REMS Assessment Plan.
- 9/14/2021: The Agency emailed clean Word versions of revised attestation statements for the Prescriber Enrollment Form, Patient Enrollment Form, Pharmacy Enrollment Form, and Prescription Form, which were inadvertently omitted from the IR sent on 9/13/2021.
- 9/24/2021: Teleconference between the Agency and the Applicant to 1) clarify prescription processing, including telephone verification that the patient has no active, overlapping oxybate prescriptions and the patient/prescriber have not been disenrolled from other oxybate REMS

programs for potential abuse, misuse, or diversion in order to receive authorization to dispense; 2) clarify the process for documentation and outcome for a specific dispense if the pharmacy is unable to confirm the safe use conditions with the other oxybate product REMS programs and; 3) discuss the Agency's request that the Applicant submit Status Updates after product launch related to communication with the REMS for other oxybate products.

- 9/27/2021: The Applicant submitted a response to the 9/13/2021 and 9/14/2021 IR as a REMS Amendment that included redlined and clean versions of the REMS document, supporting document, and all REMS materials. In their response, the Applicant clarified that the secure pharmacy portal provides the certified pharmacy users access to the patient's comorbid conditions and concomitant medication history that has been reported to the REMS program on the Patient Counseling Checklist(s). The Applicant also requested clarification whether the Agency is able to provide notice when the Sodium Oxybate REMS program and/or any other REMS program for other oxybate products becomes fully active and operational in order for the Lumryz REMS to initiate additional contacts to newly active programs.
- 9/27/2021: The Applicant sent an email to the Agency that proposed an alternate dispensing process if the Lumryz certified pharmacy does not receive confirmation from the other oxybate product REMS program(s) that a patient or prescriber has not been disenrolled and that the patient does not have an active, overlapping oxybate prescription.
- 10/4/2021: IR sent to the Applicant that provided the Agency's redlined Word versions of the REMS document, REMS materials, and REMS supporting document. The Agency also provided comments about the Applicant's proposal (b) (4). The review team did not agree with the proposal, concluding it would be premature to include the process as an operational aspect or requirement of the REMS at this time.
- 10/8/2021: The Applicant submitted a response to the 10/4/21 IR as a REMS Amendment that included redlined and clean versions of the REMS document, supporting document, and all REMS materials.
- 10/12/2021: IR sent to the Applicant that provided the Agency's redlined pdf versions of the REMS materials. The Agency also provided comments about the title of the REMS program as listed in the REMS Document and REMS Supporting Document. The Agency subsequently sent an email to the Applicant the same day with redlined Word versions of the REMS Document and REMS Supporting Document to reflect the titling changes to the documents.
- 10/14/2021: The Applicant submitted a response to the 10/12/21 IR as a REMS Amendment that included redlined and clean versions of the REMS document, supporting document, and all REMS materials.
- 6/15/2022: The Applicant submitted redlined and clean versions of the REMS document, supporting document, and all REMS materials that align with the Prescribing Information submitted on June 6, 2022.

- 6/23/2022: The Agency sent email correspondence to the Applicant with additional comments and edits on the REMS Assessment Plan. The Applicant was instructed to wait on making additional REMS submissions, as the Agency may have additional comments on the REMS materials.
- 7/12/2022: The Applicant submitted REMS Correspondence with questions regarding the Assessment Plan.
- 7/13/2022: The Agency responded to questions regarding the Assessment Plan and sent a revised Assessment Plan to the Applicant by email.
- 7/14/2022: The Applicant submitted a revised Supporting Document and concurred with the Agency's changes to the Assessment Plan.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Narcolepsy is a clinical syndrome of disordered sleep-wake control in which elements of sleep intrude into wakefulness and elements of wakefulness intrude into sleep. The result is a combination of chronic daytime sleepiness with varying amounts of cataplexy, hypnagogic hallucinations, and sleep paralysis.^{2,d} The features of narcolepsy frequently worsen during the first few months to years and then persist for life. Nearly half of patients with narcolepsy report that sleepiness and cataplexy substantially interfere with their daily lives, including school, work, marriage, or social life.³ The syndrome is one of the most common causes of disabling daytime sleepiness after obstructive sleep apnea. Narcolepsy with cataplexy is estimated to have a prevalence of 25 to 50 per 100,000 people and an incidence of 0.74 per 100,000 person-years. Narcolepsy typically begins in the teens and early twenties, but occasionally occurs as early as five years of age or after 40 years of age.^{2,e}

3.2. Description of Current Treatment Options

All patients with narcolepsy have daytime sleepiness to some extent and most require medication that promotes wakefulness. FDA-approved drugs to treat narcolepsy with EDS include methylphenidate, modafinil, and solriamfetol. Around 30 percent of patients also have cataplexy that is substantial enough to warrant pharmacologic treatment. Treatment options for these patients include drugs such as venlafaxine, atomoxetine, and fluoxetine, which increase noradrenergic and serotonergic signaling to suppress REMS sleep and reduce cataplexy. Patients with an inadequate response to these agents may be treated with pitolisant, which is approved for the treatment of EDS or cataplexy in adults with narcolepsy and is an alternative to the oxybate salts.³

Sodium oxybate and other oxybate salts are used as a treatment for cataplexy and EDS associated with narcolepsy. Xyrem (sodium oxybate) was approved on July 17, 2002, for the treatment of cataplexy in

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

^e Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

patients with narcolepsy, and on November 18, 2005, for the treatment of excessive daytime sleepiness in patients with narcolepsy. FDA initially approved Xyrem (NDA 021196) under the restricted distribution provisions of 21 CFR 314 Subpart H, and Xyrem was approved with the Xyrem Risk Management Program to assure safe use of the product (also referred to at the time as the “Xyrem Success Program”). Section 505-1 of the FD&C Act establishes FDA’s risk evaluation and mitigation strategy (REMS) authority. A REMS is a required risk management strategy that includes one or more elements to ensure that the benefits of a drug outweigh its risks. When Congress passed the FDA Amendments Act (FDAAA) in 2007, which established Section 505-1, it set forth a comprehensive statutory framework that requires a careful balance between the need to evaluate and mitigate the risks of a drug to ensure that its benefits outweigh its risks, and the potential burdens of REMS elements on patient access and the health care delivery system. For drugs previously approved under Subpart H with restricted distribution, like Xyrem, FDAAA established that they were “deemed to have in effect an approved [REMS] under Section 505-1 of the [FD&C] Act,” and required the submission of a proposed REMS within 180 days for FDA’s review and approval. A REMS for Xyrem was approved by FDA on February 27, 2015. A generic sodium oxybate was approved with a shared system REMS on January 17, 2017. Xywav, a lower sodium, mixed salts oxybate formulation was approved and added to the existing Xyrem REMS on July 21, 2021.

4. Benefit Assessment

The clinical trial supporting the application (Study CLFT218-1501 [NCT02720744]) was a multicenter, prospective, randomized, double-blind, placebo-controlled Phase 3 study in 212 adult narcolepsy patients with cataplexy (n=162) and without cataplexy (n=50). Patients were randomized 1:1 to receive Lumryz doses (n=107) of 6.0 g, 7.5 g, and 9.0 g nightly using an upward titration over three treatment periods compared with placebo (n=105) for 13 weeks. The co-primary efficacy endpoints for evaluating EDS were the mean sleep latency on the Maintenance of Wakefulness Test (MWT)^{4,f} and the proportion of patients with a Clinician Global Impression-Improvement (CGI-I) sleepiness rating of 'much improved' or 'very much improved'.^{5,g} For the group of narcolepsy patients with cataplexy, the primary endpoint was measured by the mean number of weekly cataplexy attacks from the Sleep and Symptom Daily Diary.

Treatment with Lumryz demonstrated a significant improvement in the change from baseline for the primary endpoints that evaluated EDS. The MWT least squares mean change from baseline for patients receiving Lumryz was 8.1 minutes vs. 3.1 minutes for placebo ($p<0.0001$) at Week 3 (6.0 g dose); 9.6 minutes in the Lumryz group vs. 3.3 minutes in the placebo group ($p<0.0001$) at Week 8 (7.5 g dose); and 10.8 minutes in the Lumryz group vs. 4.7 minutes in the placebo group ($p<0.0001$) at Week 13 (9.0 g

^f The MWT measures the ability of an individual to remain awake for a defined period of time. The primary measure from the MWT is the mean sleep latency. Among healthy individuals who complete a four session, 40-minute protocol, the mean sleep latency is approximately 30 minutes, with greater than 97% of individuals having a mean sleep latency of eight minutes or greater. A mean sleep latency less than eight minutes is generally considered abnormal.

^g CGI-I is a scale of symptom improvement reported by clinicians that is evaluated on a 7-point scale, centered at 4 (no change) and ranging from 1 (very much improved) to 7 (very much worse).

dose). The mean CGI scores decreased (indicating improvement) a greater extent from baseline in the Lumryz group compared with the placebo group for all three doses. The proportion of patients who were much improved or very much improved was 40.2% in the Lumryz group vs. 5.7% in the placebo group at Week 3 (Odds Ratio [OR] 10.29 [p<0.0001]); 64.0% in the Lumryz group vs. 22.2% in the placebo group at Week 8 (OR 5.67 [p<0.0001]); and 72.5% in the Lumryz group vs. 31.7% in the placebo group at Week 13 (OR 5.56 [p<0.0001]).⁶

In the narcolepsy patients with cataplexy, Lumryz demonstrated a significant mean weekly reduction in the number of cataplexy attacks (NCA) compared with placebo. At baseline, the mean weekly NCA were approximately 19 in both patient groups. The NCA least squares mean difference from placebo for patients receiving Lumryz was -4.83 (p<0.0001) at Week 3; -6.27 (p<0.0001) at Week 8; and -6.65 (p<0.0001) at Week 13.⁶

The statistical reviewer concluded that Study CLFT218-1501 has provided sufficient evidence that Lumryz is effective as compared with placebo in the treatment of cataplexy attacks and daytime sleepiness in patients with narcolepsy.^{6,h}

5. Risk Assessment & Safe-Use Conditions

A total of 258 healthy volunteer subjects were treated in 10 Phase 1 pharmacology studies. One adverse event reported during these studies was classified as serious. The case involved a 54-year-old female who experienced a serious adverse event (SAE) of severe sedation characterized by loss of consciousness with associated vomiting that occurred two hours after treatment on Day-1 of the 9 g dose period. She was hospitalized in the intensive care unit in a coma (Glasgow Coma Scale 6), subsequently recovered, and was discharged home the following day. Pharmacokinetic testing results showed no evidence of product dose-dumping.⁷

Five SAEs that occurred in five patients treated with Lumryz were reported in the previously described Phase 3 Study CLFT218-1501. The SAEs included paresthesia; diabetes mellitus inadequate control; hypertension, perirectal abscess, and suicidal ideation. The serious event of suicidal ideation occurred in a 37-year-old female during the Lumryz 9 g dose period and was considered related to the study drug. Each SAE resulted in hospitalization of the patient and each event subsequently resolved. Two patients in the placebo group experienced one SAE each, which included drug hypersensitivity and pelvic inflammatory disease.⁸

The clinical reviewer concluded that the adverse event profile of Lumryz is not substantially different from that of the approved oxybate products, Xyrem, and that the other components of the safety profile of Lumryz do not reveal any data of significant clinical concern; thus, the main safety concerns with Lumryz are those of central nervous system depression and abuse and misuse.⁹ The draft prescribing information states that Lumryz is contraindicated in combination with alcohol and sedative hypnotics, and in patients with succinic semialdehyde dehydrogenase deficiency. Concurrent use of Lumryz with other CNS depressants may increase the risk of respiratory depression, hypotension, profound sedation,

^h Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

syncope, and death. Lumryz produces dose-dependent CNS effects, including hypnotic and positive subjective reinforcing effects. The onset of effect is rapid, enhancing its potential for abuse and misuse, and the rapid onset of sedation coupled with the amnestic features of the drug has proven dangerous for the voluntary and involuntary user. Depression, and suicidal ideation and behavior, can occur in patients treated with Lumryz, as well as other behavioral and psychiatric adverse reactions.¹⁰

Patients who are treated with Lumryz must be counseled by both the prescriber and pharmacist about the serious risks and safe use, handling, and storage of Lumryz, and that alcohol and sedative hypnotics should not be taken with Lumryz. Patients should also be monitored by the prescriber and the pharmacist for concomitant use of sedative hypnotics, other CNS depressants or other potentially interacting agents, adverse events, and signs of abuse and misuse.

6. Expected Postmarket Use

Lumryz will primarily be prescribed and dispensed for use in the home setting. The drug will be self-administered by the patient at bedtime. It is expected that many prescribers of Lumryz will be familiar with the use of oxybate products for the treatment of narcolepsy, including the serious risks and the requirement for a REMS, based on experience with Xywav and Xyrem. Based on REMS assessment findings from Xywav and Xyrem, the medical specialties that most frequently prescribe these drugs are internal medicine, neurology, pulmonology, and family medicine/general practice.¹¹ We expect the prescribing population to be similar for Lumryz.

7. Risk Management Activities Proposed by the Applicant

7.1. Review of Applicant's Proposed REMS

The Applicant submitted a REMS proposal on December 15, 2020, which was amended on August 3, August 5, September 27, October 8, October 14, 2021, and June 15, 2022. Our evaluation of the proposed Lumryz REMS takes into consideration what has been required of other oxybate product REMS programs to ensure that the different REMS for these products attain the same level of patient safety. The Lumryz REMS proposal includes ETASU consisting of prescriber certification; pharmacy certification; safe-use conditions (enrollment of patients and completion of the Patient Counseling Checklist by the pharmacist); an implementation system; and a timetable for submission of the assessment of the REMS. The Applicant accepted all Agency-proposed changes and the REMS as submitted on June 15, 2022, is acceptable.

7.1.1. REMS Goal

The Applicant's final submission included the following goal and objectives of the REMS:

The goal of the Lumryz REMS Program 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

Reviewer's Comments: *The Applicant's original proposal included the same goals and objectives of the other approved oxybate REMS with two minor exceptions noted below:*

Objective 2a. – The phrase "and other potentially interacting agents" in the Xywav/Xyrem and Sodium Oxybate REMS was replaced with "other CNS depressants". We disagreed with this change and determined that the objective should remain, "Screen for concomitant use of sedative hypnotics and other potentially interacting agents." ⁱ The broader language would ensure that if future drug products were approved that potentially have a drug-drug interaction with Lumryz, they would be included in the screening without having to modify the REMS.

[REDACTED] (b) (4)

The Applicant accepted the Agency's rationale for both Objective 2a [REDACTED] (b) (4). The goals and objectives submitted in the amendment submitted on June 15, 2022, are the same as in the currently approved Xywav and Xyrem REMS program and Sodium Oxybate REMS program are acceptable.

7.1.2. REMS Requirements

7.1.2.1. Healthcare Providers who prescribe Lumryz are specially certified

The Applicant proposed prescriber certification. To become certified in the REMS, prescribers must enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS Program. By signing the enrollment form, the prescriber agrees to review the prescribing information and prescriber brochure; assess the patient's health status to determine if Lumryz is medically appropriate by screening for a history of alcohol and drug abuse and other medical conditions and the concomitant use of sedative hypnotics, other CNS depressants or other potentially interacting agents; counsel the patient on the serious risks and safe use, handling, and storage of Lumryz; enroll the patient

ⁱ Personal email communication, R. Mani, Clinical Reviewer, DN I, August 23, 2021.

in the REMS and report all potential serious adverse events including any cases of suspected abuse, misuse, or diversion to the Applicant.

Reviewer's Comments: *We agree with the requirements for Health Care Professionals as they align with the Xywav and Xyrem and Sodium Oxybate REMS programs.*

7.1.2.2. Lumryz will be dispensed to patients with evidence or other documentation of safe-use conditions

The Applicant proposed that Lumryz be dispensed with evidence or documentation of safe use conditions. The Lumryz REMS requires that Lumryz is only dispensed to patients (or patient-authorized adult designees) enrolled in the Lumryz REMS. By signing the Patient Enrollment Form, patients acknowledge that they have been counseled by the prescriber and agree to complete the patient counseling checklist with the pharmacist; and to follow the safe use conditions explained by their doctor; and tell the Lumryz pharmacist and prescriber about any changes in the medicines they are taking and any changes in their medical history. Following enrollment, the patient remains enrolled in the Lumryz REMS Program unless they are disenrolled at the request of a certified prescriber and/or pharmacy. A disenrolled patient may be re-enrolled in the Lumryz REMS if both the certified pharmacy and the certified prescriber agree to re-enroll the patient.

Reviewer's Comments: *We agree with the requirements for patients as they align with the Xywav and Xyrem and Sodium Oxybate REMS programs.*

7.1.2.3. Pharmacies that dispense Lumryz are specially certified

The Applicant proposed that the Lumryz REMS requires all pharmacies that dispense Lumryz to become certified. To become certified in the REMS, an authorized representative must be designated to complete and submit the Pharmacy Enrollment Form on behalf of the pharmacy and to oversee implementation and compliance with the REMS by ensuring that all pharmacy staff involved in the Lumryz REMS complete the Certified Pharmacy Training Program. Other certification requirements include: to use the Patient Counseling Checklist for new patients, existing patients who restart treatment after 6 months, and patients who report a change in their medication use or medical history; to provide 24/7 toll-free access to a 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 each shipment; to report each prescription filled for Lumryz to the other REMS for oxybate products and document this in the Lumryz REMS Program; to document and report all potential adverse events to the Applicant; to reconcile Lumryz inventory and provide dispensing, shipment and receipt dates to the REMS program; to not distribute, transfer, loan or sell Lumryz; and to not stock Lumryz in retail pharmacies.

Additionally, the pharmacy must establish and carry out processes and procedures that address multiple safe use requirements of the REMS including the assessment of the patient's concomitant use of sedative hypnotics, CNS depressants, or other potentially interacting agents that either are unknown to

the prescriber or pose a high risk of serious interaction; verify and document that the prescriber is certified and the patient is enrolled, that the patient has no other known active, overlapping prescriptions for sodium oxybate and other oxybate products, and that neither the prescriber or patient have been disenrolled from other oxybate product REMS programs for abuse, misuse, or diversion; and to assess the patient's potential for abuse, misuse, and diversion by reviewing risk management reports in the patient's profile.

The Applicant proposed that inventory control reconciliation at the pharmacies would be conducted in accordance with state and federal regulations for Schedule III controlled substances with documentation being made available in the event of an audit. Federal regulations and state regulations do not require inventory reconciliation for schedule III drugs more often than annually or biennially (depending on the state).

The Lumryz REMS requires that the Lumryz certified pharmacies communicate by phone with pharmacies that are certified in other REMS programs for oxybate products to obtain information about overlapping prescriptions for oxybate products and disenrollments from the other programs in order to obtain authorization to dispense. Each Lumryz dispense must receive a pre-dispense authorization (PDA) from the REMS. The PDA verifies the pharmacy is certified, the prescriber is certified, the patient is enrolled, the patient has no active, overlapping prescriptions for Lumryz, and that the pharmacy made the required calls to Pharmacies in the other oxybate product REMS programs. Sharing information from other oxybate REMS programs should only be minimally burdensome, and it is in line with standard pharmacy practice.

Reviewer's Comments: *We agree with the requirements for pharmacies as they align with the Xywav and Xyrem and Sodium Oxybate REMS programs. Lumryz will use multiple certified pharmacies to dispense the drug. Due to the use of multiple pharmacies, the use of an authorized representative is necessary. We find this deviation from the Xywav and Xyrem REMS acceptable and do not find that the inclusion of multiple pharmacies constitutes a safety risk.*

We did not find the proposed inventory control reconciliation process acceptable. In considering that federal regulations and state regulations do not require inventory reconciliation for schedule III drugs more often than annually or biennially (depending on the state) the Lumryz REMS proposes a substantial difference from the other oxybate REMS programs, (b) (4)

We expressed our concerns to the Applicant, and they agreed to conduct inventory reconciliation bi-weekly, which is more in line with the Xywav and Xyrem REMS and Sodium Oxybate REMS.

7.1.2.4. Wholesalers, distributors, and other entities that distribute

Wholesalers, distributors, and other entities that distribute Lumryz must establish processes and procedures to ensure that Lumryz is distributed only to certified pharmacies, to train all relevant staff involved in distributing Lumryz on the program requirements, maintain records of all drug distributions, and comply with audits to ensure all processes and procedures are in place and are being followed.

The Applicant has selected a Third-Party Logistics (3PL) provider to distribute Lumryz. The 3PL provider is DEA registered as an importer, exporter, and distributor. The 3PL provider will not take title to Lumryz

and thus will not enroll in the REMS but will receive and store Lumryz from the Applicant and distribute the drug to the certified pharmacies. Lumryz will not be distributed to or stocked in retail pharmacies. The 3PL provider uses a warehouse management system and real-time reporting to provide a view of the status of all inventory. Prior to distribution of Lumryz by the 3PL provider, the Applicant will verify the pharmacy is certified in the Lumryz REMS by calling the REMS or accessing a report listing the certified pharmacies. Verification of the distribution of Lumryz to certified pharmacies will be part of the REMS Compliance Plan.

Reviewer comments: *The use of a 3PL provider for storage and distribution of Lumryz is different from the other oxybate REMS. The Applicant asserts that less frequent shipments with larger volumes of product from the 3PL provider to the certified pharmacies reduce the risk of diversion and theft, though it is unclear to this reviewer how well the magnitude of risk correlates with the shipping frequency and volume of product shipped. Regardless, we find that the distribution approach for Lumryz provides a level of product security that is no less than that of the other oxybate product REMS programs. We find the use of a 3PL distributor model acceptable.*

7.1.2.5. Implementation System

Stakeholder Outreach Plan

The Applicant proposed a detailed stakeholder outreach plan to address the risk of potential confusion due the existence of multiple REMS programs for sodium oxybate products. The stakeholder outreach plan includes a Dear Healthcare Provider (DHCP) Letter with the Prescribing Information and a REMS Fact Sheet attached for healthcare providers who are likely to prescribe Lumryz, and a Professional Society Letter for the following professional societies: 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. The DHCP letters will be provided via email within 14 calendar days of the date of first commercial distribution of Lumryz and 30 calendar days later.

REMS Database

The Applicant will establish and maintain validated, secure databases of all REMS participants enrolled, certified and/or disenrolled in the REMS Program. There will be three options for the certified pharmacies to obtain authorization to dispense: 1) electronic verification between the certified pharmacy and the secure REMS databases; 2) accessing a REMS verification portal through the Lumryz REMS website and 3) by calling the REMS Coordinating Center. Authorization is required for every fill and needs to be completed regardless of the patient's method of payment.

Completed enrollment forms, prescription data, as well as information related to dosing, concomitant medications, and behavior that raises suspicion of abuse, misuse, or diversion, including complete risk management report histories, will be contained in the appropriate REMS database. Certified prescribers will be able to access a secure prescriber portal on the Lumryz REMS website to enter patient enrollment information, which will then be stored in the patient database. The secure

prescriber portal will display pertinent REMS information related only to the certified prescriber's enrolled patients. Certified pharmacies will be able to access a secure pharmacy portal on the Lumryz REMS website to submit the patient counseling checklist and the risk management report form, which will then be stored in the appropriate database. Additionally, certified pharmacies will also be able to review the patient's concomitant medication and comorbid conditions and obtain a pre-dispense authorization (PDA) through the secure pharmacy portal.

The Lumryz REMS will report patient and prescriber disenrollment in the Lumryz REMS due to suspected abuse, misuse, or diversion to the other oxybate product REMS programs by phone. This reporting will be documented in the Lumryz REMS databases. The REMS will also ensure pharmacies are able to verify by phone that the patient has no other active, overlapping prescriptions for oxybate products and that the patient and prescriber have not been disenrolled from the other oxybate product REMS for suspected abuse, misuse, or diversion. The Lumryz REMS will monitor certified prescribers and pharmacies for timely reporting to the Applicant of all potential adverse events and any behavior by patients or prescribers enrolled in the Lumryz REMS program that raises suspicion of abuse, misuse, or diversion.

The Lumryz REMS must audit the certified pharmacies and wholesalers-distributors and other entities that distribute Lumryz within 90 days after the pharmacy places its first order of Lumryz and after Lumryz is first commercially distributed, and annually thereafter, to ensure all REMS processes and procedures are in place, functioning, and comply with REMS program requirements. Additionally, all certified pharmacies are required to provide daily dispensing data to the REMS program. All data files received by the REMS are reviewed and assessed for potential noncompliance and any potential non-compliance will be addressed and reviewed with the applicable certified pharmacy authorized representative. The REMS noncompliance plan will be finalized after approval and submitted within 60 days of approval of the REMS. The noncompliance plan will address the criteria for noncompliance for each stakeholder, actions to be taken in addressing noncompliance events, and the circumstances under which a stakeholder should be suspended or decertified from the REMS.

Reviewer comments: *We agree with the proposed implementation system. The proposed stakeholder outreach dissemination plans do not require the use of regular mail unless the provider's email address is not available, or the email is undeliverable, or if the first two emails sent are marked as unopened. Based on the most recent Xyrem and Xywav Assessment Reports, internal medicine and family medicine providers frequently prescribe oxybate products for narcolepsy, and the Applicant's target audience for dissemination appropriately includes these provider specialties. The proposed implementation system uses multiple, secured databases to maintain the requirements of the REMS program. We find this approach for Lumryz provides a level of product safety equal to those of the Xywav and Xyrem REMS and the Sodium Oxybate REMS.*

7.1.2.6. Timetable for Submission of Assessments of the REMS

The Applicant proposed to submit REMS Assessments at 6 months, 12 months, and annually from the date of initial approval of the REMS.

Reviewer comments: *The timetable for submission of assessment is acceptable.*

7.1.3. REMS Materials

The materials are aligned with the Xywav and Xyrem REMS and Sodium Oxybate REMS. Differences in the materials reflect the operations and labeling of Lumryz.

7.1.3.1. Prescriber Enrollment Form

By signing the Lumryz Prescriber Enrollment Form, the prescriber attests to understanding the indication, risks, and use of Lumryz; to have read the Prescribing Information and Prescriber Brochure; to screen, evaluate, counsel, and enroll each patient; and to report potential serious adverse events and cases of abuse, misuse, and diversion to the Applicant. In addition to the prescriber attestations, the form includes standard prescriber information including state license number, DEA number, NPI number, and facility or practice location. The attestations have been re-formatted to the Agency's current best practices, in which the attestations are aligned with the corresponding stakeholder requirements in the REMS document.

***Reviewer comments:** The new format for the attestations more clearly and comprehensively articulates the responsibilities of a certified prescriber as outlined in the REMS document. We find the revised prescriber enrollment form acceptable.*

7.1.3.2. Patient Enrollment Form

By signing the Patient Enrollment Form, patients acknowledge that they have reviewed the Patient Brochure; been counseled about the risks and the safe use, handling and storage of Lumryz; must enroll in the REMS; must complete the Patient Counseling Checklist with the pharmacist; must follow the safe use instructions from their doctor; must tell the pharmacist and their doctor about any changes in their medications and medical history; and that they have been notified that their personal identifiable information will be shared with the Lumryz REMS Program, other oxybate REMS programs, and the Applicant. The attestations have been re-formatted to the Agency's current best practices, in which the attestations are aligned with the corresponding stakeholder requirements in the REMS document. The Patient Enrollment Form also includes a question for the prescriber to indicate if the patient currently is or has ever been enrolled in another oxybate product REMS Program.

***Reviewer comments:** The attestation statements for the Patient Enrollment Form have been revised to articulate the responsibilities of the patient more clearly and comprehensively as outlined in the REMS document. We requested the inclusion of a question about the patient's enrollment history in other oxybate product REMS programs to increase the pharmacist's awareness to the potential for overlapping oxybate prescriptions and disenrollments from the other programs. The Applicant agreed with these changes and the form is acceptable.*

7.1.3.3. Pharmacy Enrollment Form

By signing the Pharmacy Enrollment form, the authorized representative attests they will establish multiple processes and procedures in the pharmacy that address the training of pharmacy staff and their successful completion of the required knowledge assessments; the assessment of the patient's concomitant medications; verification of the patient's prescription information; verification and

documentation that the patient does not have overlapping oxybate prescriptions and has not been disenrolled from other oxybate REMS programs for abuse, misuse, or diversion by contacting the other programs; obtaining authorization to dispense from the REMS program for each dispense of Lumryz; monitoring of the patient's potential for abuse, misuse, and diversion of Lumryz; following the REMS program dispensing limits and to ship, track, and verify receipt using an overnight service; to report each Lumryz prescription filled to the other oxybate REMS programs and document that reporting; reconcile Lumryz inventory; and to maintain all records. The enrollment form includes standard information related to the pharmacy's name, location, National Council for Prescription Drug Programs (NCPDP) number, DEA number, NPI number, and contact information for the authorized representative.

Reviewer comments: The use of a pharmacy enrollment form is necessary for the Lumryz REMS to ensure the certified pharmacies agree to adhere to all the requirements necessary to comply with the REMS. This differs from the Xywav and Xyrem REMS, which uses a single central pharmacy that also serves as the REMS Administrator. We find the level of patient safety with use of the Lumryz certified pharmacy enrollment process to be of the same standard as with the single central pharmacy for Xywav/Xyrem and the Sodium Oxybate REMS pharmacy enrollment form. The Pharmacy Enrollment form is acceptable.

7.1.3.4. Prescriber Brochure

The Prescriber Brochure provides an overview of Lumryz that includes important safety information; a guide to prescribing Lumryz, including the REMS requirements for prescriber enrollment and enrollment of patients; patient screening and counseling requirements; evaluation of patients while on therapy; responsibilities of the Lumryz certified pharmacy; information about dosing and titrating Lumryz; dependence and tolerance; and use in specific populations. Prescribers report serious adverse events and any cases of suspected abuse, misuse, or diversion to the Applicant.

Reviewer comments: The content provided in the Lumryz Prescriber Brochure is consistent with the content in the brochures for the other oxybate products. We find this material acceptable.

7.1.3.5. Patient Brochure

The Patient Brochure informs patients of what they are required to do in the Lumryz REMS, how to get their prescription filled, how to take the nightly dose, side effects and precautions, and storage and safety of Lumryz at home. Insurance-related information is also included as a matter of convenience, though the REMS does not require any activities related to insurance.

Reviewer comments: The content provided in the Lumryz Patient Brochure is consistent with the content in the Patient Brochures for the other oxybate programs. We find this material acceptable.

7.1.3.6. Certified Pharmacy Training Program

The Certified Pharmacy Training Program consists of two modules in one document. The two modules are: *Training for Pharmacy Staff involved in the Lumryz REMS* and *Training for Pharmacists involved in dispensing Lumryz*. All pharmacy staff and pharmacists involved in dispensing Lumryz must complete the Pharmacy Staff Module and the Pharmacy Staff Knowledge Assessment. The information is aligned

with the Lumryz labeling and REMS operations. Pharmacists must also complete the Pharmacist Module and the Pharmacist Knowledge Assessment.

Training for Staff involved in the Lumryz REMS

The Lumryz REMS pharmacy staff module contains information about the important safety information, indications and usage, how Lumryz is supplied, controlled substance scheduling, the boxed warning, contraindications, warnings and precautions, and prescription processing. The material specifically spells out the need for review of comorbid conditions and concomitant medications, the requirement to obtain a PDA to verify the safe use conditions for each dispense, which verifies the pharmacy is certified, the prescriber is certified, the patient is enrolled, the patient has no active, overlapping prescriptions for Lumryz, and that the pharmacy made the required calls to the other oxybate REMS programs; the requirement to make a call to the Xywav and Xyrem REMS and the Sodium Oxybate REMS to verify the patient has no active overlapping oxybate prescriptions and that the patient/prescriber has not been disenrolled for abuse, misuse, or diversion; and the need to complete the pharmacy counseling checklist for applicable patients.

Training for Pharmacists involved in the Dispensing of Lumryz

The pharmacist module provides additional training for REMS requirements related to patient counseling and screening, clinical use clarifications, prescription refills, monitoring and assessing for signs of abuse, misuse, and diversion, shipping procedures, and inventory control. The module specifically describes how new pharmacists will receive support from a pharmacist experienced in the program, use of the patient counseling checklist, duties related to detailed monitoring and completion of risk management reports, follow-up interactions with patients and prescribers, and documentation. Pharmacists will also be required to review the Lumryz prescribing information.

Reviewer Comments: *The content of the Training Materials is consistent with those of the other oxybate REMS programs. The differences in content relate to the indications and Instructions for Use in the drug labeling and the operational functions of the Lumryz REMS. We note that the Lumryz training program does not describe a reverse distribution takeback program for unused, leftover, or expired Lumryz. However, the Lumryz pharmacist module provides instruction for the pharmacist to counsel the patient on proper drug disposal of unused oxybate from a prior prescription. We find this approach appropriate, and the documents as submitted on June 15, 2022, are acceptable.*

7.1.3.7. Pharmacy Staff and Pharmacist Knowledge Assessments

Pharmacy staff and pharmacists are required to review the pertinent certified pharmacy training modules and to successfully complete the corresponding pharmacy staff and pharmacist knowledge assessment(s). The successful completion of the knowledge assessment(s), which is defined as achieving a score of 80% or greater, are required for the pharmacy authorized representative to enroll the pharmacy in the REMS for certification and for all staff and pharmacists involved in dispensing Lumryz.

Reviewer comments: *The content of the Lumryz pharmacy knowledge assessments is similar to that for the Xywav and Xyrem REMS and Sodium Oxybate REMS knowledge assessments. Differences in content are related to differences in operational aspects of the programs and the labeling. The definition of*

successful completion of the Lumryz assessments as 80% is consistent with other REMS programs. In a set of comments dated October 4, 2021, we requested that the knowledge assessments do not include the correct answers because the REMS materials are posted online at the REMS@FDA public website. The Applicant agreed and resubmitted the material on October 8, 2021, without keyed answers. We find this material acceptable.

7.1.3.8. Prescription Form

A Lumryz Prescription Form will be required for all initial prescriptions and for patients with a lapse in treatment of 6 months or longer. The prescription form may also be used for refills and renewals of Lumryz prescriptions.

By signing the Lumryz prescription form, the prescriber acknowledges that they have an understanding of and agree to the REMS requirements; understand the approved indications of Lumryz and important safety information and the requirements for patient screening and counseling; requirements for re-enrollment of patients and ongoing assessment of patients, and the reporting of serious adverse events and cases of abuse, misuse, and diversion to the Applicant. The form includes the prescriber's contact and licensing information; patient information including the patient's concomitant medications and comorbid conditions; the patient's fixed or titrated dosing schedule; dispensing instructions; and a pharmacy section to document that the other oxybate REMS programs have been contacted to confirm that the patient has no other active overlapping prescriptions for sodium oxybate, that the patient and prescriber have not been disenrolled in the REMS program for suspected abuse, misuse, or diversion, and to report that a prescription for Lumryz is being filled for the patient. The prescription form also notes that the form may not satisfy all legal requirements for prescribing Lumryz in all states and instructs prescribers to submit all prescriptions in accordance with applicable state laws.

***Reviewer comments:** The Applicant's original submission did not include a prescription form. After negotiations with the Applicant concerning the use of electronic prescriptions, the Applicant submitted a prescription form which included a section to document the interaction with the other REMS programs in the August 3, 2021, REMS Amendment. The prescriber attestation statements on the Lumryz form have been re-formatted to the Agency's current best practices. We find the Prescription Form acceptable.*

7.1.3.9. Patient Counseling Checklist

The patient counseling checklist is used by pharmacists to screen and counsel new patients and existing patients who are either restarting treatment after not receiving Lumryz for six months or longer or who report a new medication or new comorbid medical condition. For new patients and for patients who are restarting Lumryz treatment after not receiving it for 6 months or longer, the patient counseling checklist is completed in its entirety.

The pharmacist counsels the patient on therapy expectations, preparation and administration of the dose, necessary precautions, and potential side effects of Lumryz. The pharmacist also screens the patient for concomitant medications (including alcohol use) and medical conditions that may put the patient at risk for CNS or respiratory depression. If concomitant medications or comorbidities are discovered that the prescriber has not previously indicated awareness of, the pharmacist will consult the

prescriber and document the outcome on the checklist. For prescriber consults related to the use of concomitant sedative hypnotics or benzodiazepines, the checklist documents whether Lumryz is to be continued and any actions to be taken with the concomitant medication, as well as the prescriber's rationale for continuing the concomitant medication with Lumryz. In the case of prescription renewals and refills, pharmacy staff will transfer the patient to a pharmacist for counseling. The pharmacist will review patient-provided changes related to their medications or medical conditions and will complete the appropriate sections of the checklist.

The completed counseling checklist is submitted to the REMS, which verifies all required information has been provided and documents the information in the REMS patient database.

Reviewer comments: *The patient counseling checklist is acceptable.*

7.1.3.10. Communication Materials

The Lumryz stakeholder outreach plan includes a Dear Healthcare Provider Letter provided to healthcare providers who are likely to prescribe Lumryz and a Dear Professional Society Letter to professional societies for distribution to their members at their discretion. The prescribing information and a Lumryz REMS Fact Sheet will be attached to the letters. The letters inform the recipients about the risks of Lumryz, the requirement for a REMS, and the reporting of adverse events. The fact sheet provides information about the risks of Lumryz, how prescribers and pharmacies can manage the risks; reporting adverse events; and key requirements and responsibilities of the REMS for prescribers, pharmacies, and patients.

Reviewer comments: *The content and format of the communication materials for stakeholder outreach are acceptable.*

7.1.3.11. Risk Management Report

Risk Management Report (RMR) forms are completed by pharmacies 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, RMR forms can be completed by the pharmacist online or completed via paper and faxed to the REMS. The RMR history available in the secure pharmacy portal includes the ability to see all RMR forms submitted from all certified Lumryz pharmacies and allows for the review of prior events of suspected abuse, misuse, or diversion. Examples of events that would require completion of an RMR include patient requests for early refills and/or prescriber approval of early refill requests; the patient's loss/misuse of the product; the patient claiming they did not receive the product, but the delivery service shows receipt of delivery; the shipment was lost, stolen, or delivered to an incorrect address and was not returned; tampering with, counterfeiting or contamination of the product; or 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. Categories for suspicious activity include 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; and excess medication on hand.

The pharmacy can use the RMR form to request the REMS to disenroll a patient or prescriber for suspected abuse, misuse, or diversion based on the history.

Reviewer comments: The Applicant has provided a very detailed process for documenting suspicious activity related to the use and misuse of Lumryz. We find the RMR forms and associated activities acceptable.

7.1.3.12. REMS Program Website

The Lumryz REMS website contains pages with information for prescribers and patients, including enrollment and certification requirements as outlined in the REMS document and the ability to enroll online. Other pages include a 'Contact Us' page with contact information for the REMS program call center, a 'Resources' page for access to enrollment forms and REMS materials for prescribers, pharmacies, and patients, and registration and login pages for pharmacies and prescribers to access the secure pharmacy and prescriber portals.

Reviewer Comment: We find the content and operation of the REMS Website acceptable.

7.1.4. REMS Assessment Plan

The Assessment Plan is appended to the supporting document and can be found in section 10.2 of this review. The Applicant will evaluate the effectiveness of the program to determine if the REMS is meeting its goals to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion. The proposed REMS Assessment Plan includes metrics on implementation of the REMS program, enrollment statistics, utilization data, program operation and performance data, program compliance, safe use behaviors, Risk Management Reports, the Patient Counseling Checklist, pharmacovigilance and surveillance; knowledge, attitude, and behavior surveys of patients, healthcare providers, and pharmacists; and certified pharmacy knowledge assessments. REMS assessments will be submitted to the Agency at 6 months, one year, and annually thereafter from the date of approval of the REMS. Assessments will also include health outcomes and/or surrogates of health outcomes; utilization data; REMS compliance; safety surveillance; and knowledge, attitude, and behavior surveys of healthcare providers and patients. The REMS assessment plan is found in the section 10.2 of the Appendix.

Reviewer Comment: *The Lumryz REMS assessment plan submitted by the Applicant was based on the Xywav and Xyrem REMS assessment plan included in the approval letter for Xywav dated July 21, 2020. We have updated the plan to correspond with changes made to the Xywav and Xyrem plan as part of a REMS modification approved August 12, 2021. The content of the Lumryz assessment plan is the same as for Xywav and Xyrem with exceptions related to the metrics for the Lumryz stakeholder outreach plan, and information related to overlapping prescriptions or disenrollments in other oxybate REMS programs.*

(b) (4)

. However, we rejected the request because the Lumryz REMS is a new program. We find the Lumryz REMS assessment plan to be appropriate to determine whether the goals and objectives of the REMS are being met. Future REMS assessment plan revisions, however, may

further define the specific metrics, or Key Performance Indicators (KPIs) that will be used to determine if the goal and objectives are met, and include a threshold for success.

8. Discussion of Need for a REMS

Lumryz is an extended-release formulation of sodium oxybate proposed for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy. The approved oxybate class products currently include two separate, approved REMS programs, the Xywav and Xyrem REMS and the shared system Sodium Oxybate REMS. The Clinical Reviewer recommends approval of Lumryz based on the efficacy and safety information available and reviewed for this application. DRM and DN1 agree that Lumryz must be approved with a REMS to ensure the benefits of the drug outweigh the risks.¹² If approved, the Lumryz REMS will become the third member of the oxybate class of drugs with a separate (third) REMS to mitigate these risks. However, at this time, only the Xyrem and Xywav REMS is implemented as these are the only products that are marketed. The Applicant proposed a REMS for Lumryz that consists of ETASU (prescriber certification, pharmacy certification, and documentation of safe use conditions), an implementation system, and a timetable for submission of assessments, to ensure the benefits of Lumryz outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.

Health care providers who prescribe Lumryz must be specially certified and enroll in the REMS. The prescriber attests to understanding the indication, risks, and use of Lumryz; to have read the Prescribing Information and Prescriber Brochure; to screen, evaluate, counsel, and enroll each patient; and to report potential serious adverse events and cases of abuse, misuse, and diversion to the Applicant. Patients must enroll and acknowledge that they have reviewed the Patient Brochure; been counseled about the risks and the safe use, handling and storage of Lumryz; complete the Patient Counseling Checklist with the pharmacist; follow the safe use instructions from their doctor; and must tell the pharmacist and their doctor about any changes in their medications and medical history. The Lumryz REMS will use multiple certified pharmacies to dispense Lumryz. Due to the use of multiple pharmacies, an authorized representative for each pharmacy is necessary. All pharmacy staff and pharmacists involved in dispensing Lumryz must complete training about the pharmacy's requirements in the REMS. These requirements include assessment of the patient's concomitant use of sedative hypnotics, CNS depressants, or other potentially interacting agents using the patient database, Prescription Form, and Patient Counseling Checklist; to verify and document through the PDA process that the patient has no other known active, overlapping prescriptions for sodium oxybate and other oxybate products, and that neither the prescriber or patient have been disenrolled from other oxybate product REMS programs for abuse, misuse, or diversion; to verify all prescription information; and to assess the patient's potential for abuse, misuse, and diversion by reviewing Risk Management Reports in the patient's profile.

Because the Lumryz REMS will be the third oxybate REMS program, there is a need for communication between the programs to ensure that patients who have enrolled in more than one program do not receive duplicate, overlapping oxybate prescriptions from different programs. In addition, communication between the programs is needed to ensure that prescribers and patients who are disenrolled from one program for abuse, misuse, or diversion are not able to prescribe or receive an

oxybate product from a different program. These communications are required for the Lumryz pharmacy to receive authorization to dispense from the REMS, and the PDA will be maintained in the Lumryz patient database as documentation that the communications took place; documentation of the communications by the pharmacy is also required on the Prescription Form. A REMS Oversight Committee (ROC) meeting was held June 11, 2021, to discuss the sodium oxybate REMS programs and the approach needed for information-sharing between the proposed Lumryz REMS, the Xywav and Xyrem REMS, and Sodium Oxybate REMS such that the three programs will meet safe-use conditions. The ROC agreed with the planned approach to approve the Lumryz REMS with required communications with the other oxybate REMS programs.¹³

Prescription information is to be reported to the other oxybate REMS programs each time Lumryz is dispensed, and this reporting is documented by the REMS in the appropriate REMS databases. The rationale for this requirement is consistent with the approach used in the Sodium Oxybate REMS when it was approved in 2017 where the review team concluded that the Sodium Oxybate REMS certified pharmacy would be required to provide its prescription information to the Xyrem REMS program each time a generic prescription is dispensed.^j Sodium oxybate prescriptions are defined as overlapping by the Lumryz REMS and Sodium Oxybate REMS when more than one prescription for sodium oxybate is received for a patient from multiple prescribers within an overlapping timeframe. We expect the Xywav and Xyrem central pharmacy to identify and share information about overlapping prescriptions when contacted by other pharmacies, as information that relates to patient safety is typically shared in practice in the absence of a specific REMS requirement. Moreover, all three REMS programs require the pharmacist to assess the patient's concomitant medication use prior to dispensing.

Because this is a safety issue, our expectation is that the Xywav and Xyrem REMS will share information about the disenrollments of patients and prescribers with the Lumryz or Sodium Oxybate REMS programs, once these REMS programs are implemented. The number of disenrollments of patients for abuse, misuse, and diversion identified in the Xywav/Xyrem REMS Assessment Reports has been low, with only seven since the REMS was implemented in August 2015, and very few prescribers (12 cumulatively) have been disenrolled for DEA or state license issues.¹¹ Based on our experience with the Xyrem/Xywav REMS, we believe the risk of dispensing Lumryz in these scenarios is low. Nevertheless, the requirement for the Lumryz REMS to verify this information before a Lumryz prescription can be dispensed is a necessary safe use condition.

Sharing information from other oxybate REMS programs should only be minimally burdensome and is in line with standard pharmacy practice. To assess burden, we have requested the Applicant to provide the Agency with Status Updates after product launch related to communications with the REMS for other oxybate products.

The Applicant has selected a 3PL provider to distribute Lumryz. This entity will receive and store Lumryz from the Applicant and distribute the drug to the certified pharmacies. Lumryz will not be distributed to or stocked in retail pharmacies. Prior to distribution of Lumryz by the 3PL provider, the Applicant will

^j The Sodium Oxybate REMS was responsible for contacting the Xyrem REMS to report instances of patient/prescriber disenrollment in the Sodium Oxybate REMS due to suspected abuse, misuse, or diversion.

verify the pharmacy is certified in the Lumryz REMS by calling the REMS or accessing a report listing the certified pharmacies. Verification of distribution of Lumryz to certified pharmacies will be part of the REMS Compliance Plan. The distribution approach for Lumryz provides a level of product security that is no less than that of the other oxybate product REMS programs.

The Lumryz REMS utilizes multiple certified pharmacies and multiple validated, secure, separate, and distinct databases to track the REMS requirements. Implementation and operation of the REMS will be carried out using a contracted REMS administrator. Completed enrollment forms, prescription data, as well as information related to dosing, concomitant medications, and behavior that raises suspicion of abuse, misuse, or diversion, including complete risk management report histories, will be contained in the appropriate REMS database. Certified prescribers will be able to access a secure prescriber portal on the Lumryz REMS website to enter patient enrollment information, which will then be stored in the patient database. The secure prescriber portal will display pertinent REMS information related only to the certified prescriber's enrolled patients. Certified pharmacies will be able to access a secure pharmacy portal on the Lumryz REMS website to submit the patient counseling checklist and the RMR form, which will then be stored in the appropriate database. Additionally, certified pharmacies will also be able to review the patient's concomitant medication and comorbid conditions and obtain a PDA through the secure pharmacy portal.

Finally, to assist in stakeholder outreach and communication, the Applicant will implement a stakeholder outreach plan. The Lumryz stakeholder outreach plan includes a Dear Healthcare Provider Letter sent to healthcare providers who are likely to prescribe Lumryz and a Dear Professional Society Letter to professional societies for distribution to their members at their discretion. The prescribing information and a Lumryz REMS Fact Sheet will be attached to the letters. The letters inform the recipients about the risks of Lumryz, the requirement for a REMS, and the reporting of adverse events. The fact sheet provides information about the risks of Lumryz, how prescribers and pharmacies can manage the risks, the reporting of adverse events, and key requirements and responsibilities of the REMS for prescribers, pharmacies, and patients.

9. Conclusion & Recommendations

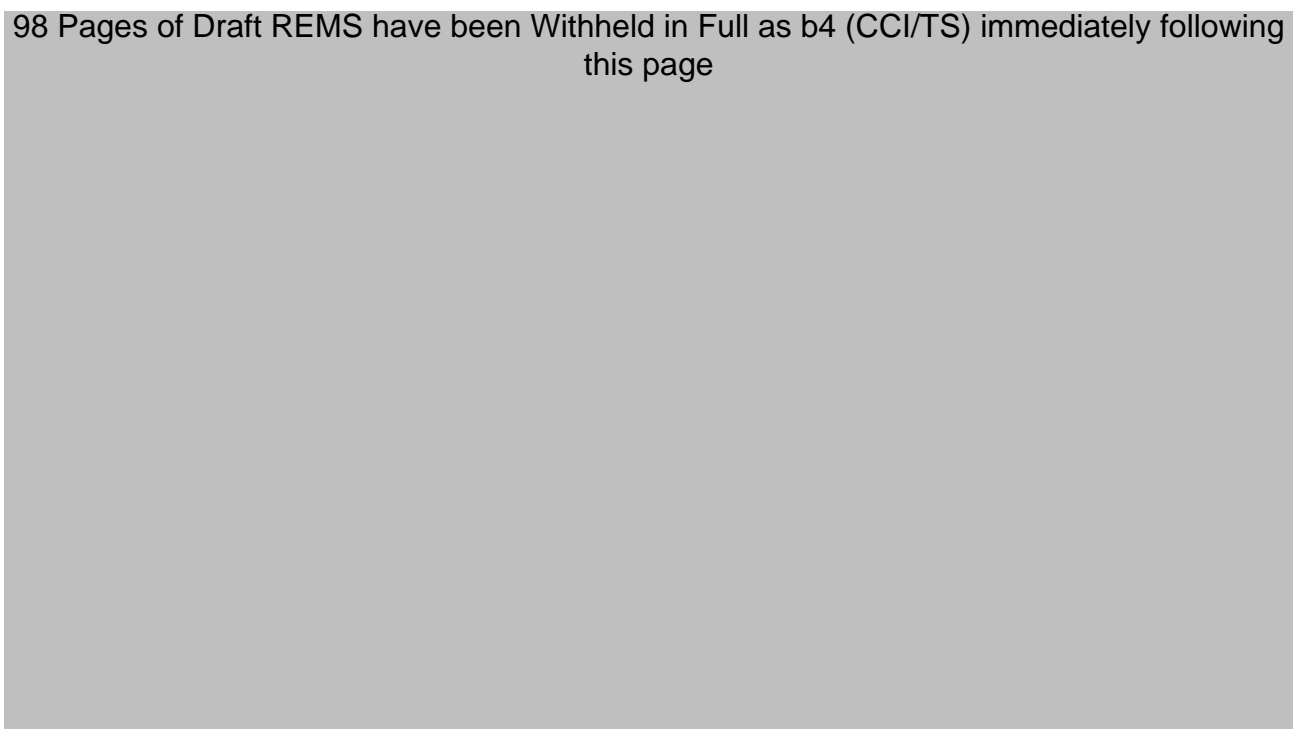
Based on the magnitude and severity of the risk of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion, we agree that requiring a REMS consisting of elements to assure safe use is necessary to ensure that the benefits of Lumryz outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion. DRM finds the proposed Lumryz REMS, and its appended materials as submitted on June 15, 2022, to be acceptable. DRM recommends approval of the Lumryz REMS, received on December 15, 2020, and last amended on June 15, 2022, appended to this review, and has determined it will offer the same level of safety as the other oxybate REMS programs.

10. Appendices

10.1. References

1. Avadel. Lumryz (sodium oxybate extended-release). NDA 214755. Module 2.5 - Clinical Overview. December 15, 2020.
2. Scammell T. Clinical features and diagnosis of narcolepsy in adults. In: Benca R, Eichler A, eds. *UpToDate*. Waltham, MA: UpToDate; 2021.
3. Scammell T. Treatment of narcolepsy in adults. In: Benca R, Eichler A, eds. *UpToDate*. Waltham, MA: UpToDate; 2021.
4. Freedman N. Quantifying sleepiness. In: Harding S, Eichler A, eds. *UpToDate*. Waltham, MA: UpToDate; 2021.
5. Avadel. Lumryz (sodium oxybate extended-release). NDA 214755. Module 5.3.5.1. Study CLFT218-1501 Study Body Report. December 15, 2020.
6. Yan S. Food and Drug Administration. Division of Biometrics I. Lumryz (sodium oxybate extended-release). NDA 214755. Statistical Review and Evaluation. September 24, 2021.
7. Avadel. Lumryz (sodium oxybate extended-release). NDA 214755. Module 5.3.3.4 - Study PKFT218-1601 - Study Report. December 15, 2020.
8. Avadel. Lumryz (sodium oxybate extended-release). NDA 214755. Module 2.7.4 - Summary of Clinical Safety. December 15, 2020.
9. Mani R. Food and Drug Administration. Division of Neurology I, Clinical Reviewer. Personal email communication. October 23, 2021.
10. Lumryz Prescribing Information. NDA 214755. June 6, 2022.
11. Jazz Pharmaceuticals. Xyrem (sodium oxybate) NDA 21196 and Xywav (calcium, magnesium, potassium, and sodium oxybates) NDA 212690. REMS Assessment Report No. 7 (72-Month Assessment). February 26, 2021.
12. Yasuda S. Food and Drug Administration. Division of Neurology I. Lumryz (sodium oxybate extended-release). NDA 214755. Draft REMS Memorandum. July 11, 2022.
13. Food and Drug Administration. Lumryz (sodium oxybate extended-release). NDA 214755. REMS Oversight Committee Meeting Minutes. June 11, 2021.

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/s/

ROBERT G PRATT
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07/14/2022 03:42:53 PM

JOSEPH P PARADIS
07/14/2022 03:53:42 PM

JACQUELINE E SHEPPARD
07/14/2022 03:54:51 PM

CYNTHIA L LACIVITA
07/14/2022 04:08:33 PM
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Division of Risk Management (DRISK)
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
PDUFA Goal Date	October 15, 2021
OSE RCM #	2021-56
Reviewer Name(s)	Bob Pratt, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	September 13, 2021
Subject	Interim Comments for the Proposed REMS for Lumryz
Established Name	Sodium Oxybate for Extended-Release Oral Suspension
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals
Therapeutic Class	CNS Depressant
Formulation(s)	Powder for extended-release oral suspension: nightly dose packets of 4.5 g, 6 g, 7.5 g, and 9 g
Dosing Regimen	The recommended starting dosage is 4.5 g per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the effective dosage range of 6 g to 9 g per night orally.

1 Introduction

The following comments are based on the Agency's review of the proposed REMS for Lumryz (sodium oxybate extended-release), submitted with New Drug Application (NDA) 214755 by Avadel CNS Pharmaceuticals (Avadel) on December 15, 2020. The proposed indication is for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy. This application is under review in the Division of Neurology I (DNI). The Agency agreed to Avadel's request to submit a REMS separate from the REMS approved for Xywav (calcium, magnesium, potassium, and sodium oxybates)/Xyrem (sodium oxybate) and the Sodium Oxybate Shared System REMS based on differences in drug administration; the drug's formulation; the lack of a drug-drug interaction with divalproex sodium; and the drug distribution plan. The proposed REMS for Lumryz consists of elements to assure safe use (ETASU), a communication plan, an implementation system, and a timetable for submission of assessments to ensure the benefits of Lumryz outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.

2 Comments to the Applicant

The following comments are based on the Agency's review of the proposed REMS for Lumryz, submitted with NDA 214755 on December 15, 2020 and amended August 3, 2021 and August 5, 2021. We also refer to REMS Correspondence that you submitted on April 28, August 3, August 5, August 24, and September 8, 2021. To facilitate further review, we request that you submit your response as a REMS Amendment with cover letter by the close of business on September 27, 2021. The REMS Amendment should include clean and redlined Word versions of the:

- REMS document
- All REMS materials
- REMS supporting document

The amendment should also include a clean PDF version of the REMS website, if available.

Review of the REMS document, supporting document, and REMS materials is ongoing. Therefore, these comments should not be considered as final.

General Comments

1. We remind you that the labeling, REMS document, REMS materials, and REMS supporting document must all be aligned. If, after receipt of this Information Request, the Agency communicates changes to you regarding the labeling, the REMS must be aligned with those changes and the final FDA-approved version of the label.
2. The REMS materials and REMS supporting document must be aligned with the REMS document included with this Information Request as well as all other changes that you have acknowledged in previous REMS Correspondence sent to us. Additional comments about the REMS document, specific REMS materials, and the REMS assessment are found below.
3. Please clarify if the secure pharmacy portal provides access to the patient's comorbid conditions and concomitant medication history.

REMS Document

4. We have attached the Agency's redlined Word version of the REMS document, which has received clearance from the FDA Office of Chief Counsel. Our redlined version is with reference to the clean REMS document that you submitted in the August 3, 2021 REMS Amendment. We have the following general comments about the REMS document:
- a. We have used comment balloons to identify issues that remain under review by the NDA review team; the language currently found in the REMS document related to these issues is subject to change. We have also used comment balloons to provide the rationale for changes that may require further explanation.
 - b. Many of the editorial changes made to the REMS document are related to standardizing the description, format, or terminology of the content to align with the Agency's REMS document template and support Structured Product Labeling.
 - c. In the REMS Correspondence that we received September 8, 2021, you responded to our request to propose a process to report prescriptions filled for Lumryz to other oxybate salt REMS programs, which must be documented in the appropriate Lumryz REMS Program databases. You stated that this data is electronically entered by the certified pharmacy during the Lumryz REMS verification pre-dispense authorization process in the secure Lumryz REMS pharmacy portal when the certified pharmacy must:
 1. Verify that the patient has no other active prescriptions for sodium oxybate that overlap with the current Lumryz prescription, and
 2. Verify the patient/prescriber have not been disenrolled in the other oxybate salt REMS programs for suspected abuse, misuse, or diversion (as required by FDA, and assuming the anticipated agreement of the Xywav and Xyrem REMS Program and the Sodium Oxybate REMS program, if operational).Additionally, you noted that the certified pharmacies provide all Lumryz dispense data to the Lumryz REMS Program inclusive of these data points via secure data transmission.

Although you did not explicitly state that the process of documenting the reporting of Lumryz prescriptions filled to other oxybate product REMS programs will occur at the time of the certified pharmacy's phone calls regarding overlapping prescriptions and disenrollment issues, we accept that the other REMS programs will understand the call is for the purpose of dispensing Lumryz, and that providing Lumryz dispense data to the Lumryz REMS program is acceptable documentation of that reporting. However, we have determined the Lumryz REMS must report disenrollments of patients and prescribers from the Lumryz REMS to the other oxybate product REMS programs for suspected abuse, misuse, or diversion. This requirement has been added to the implementation system of the REMS document. We note that as part of your response, you proposed a process similar to the pre-dispense authorization process where the pharmacies of the other oxybate product REMS programs utilize phone calls to the Lumryz REMS Program for information regarding potential overlapping prescriptions and disenrollment issues. You noted that if Avadel is required to report to the other programs at an appropriate interval, you request confirmation that FDA will require the other programs to report the same information on the same interval for their respective program to Avadel. We are unable to provide this confirmation or disclose information to you regarding other oxybate product applications and REMS programs.

Prescriber Enrollment Form; Patient Enrollment Form; Pharmacy Enrollment Form; Prescription Form

5. We have attached the Agency's clean Word versions of revised attestation statements for the Prescriber Enrollment Form, Patient Enrollment Form, Pharmacy Enrollment Form, and Prescription Form, which have received clearance from the FDA Office of Chief Counsel. The attestations have been re-formatted to the Agency's current best practices, in which the attestations are aligned with the corresponding stakeholder requirements in the REMS document; additional attestations of understanding are also included. Please replace the attestations in the enrollment forms and prescription form that you submitted August 3, 2021 with the corresponding revised attestations.

Certified Pharmacy Training Program

6. The Inventory Control section of the pharmacy training program states, "Lumryz inventory must be (b) (4) documentation must be made available in the event of an audit."

You previously stated that you are currently evaluating several pharmacies for potential certification in the REMS. With reference to the States where these pharmacies are located, please clarify the frequency in which inventory reconciliation is required for Schedule III controlled substances for pharmacies in these States.

Patient Counseling Checklist

7. We have attached the Agency's redlined Word version of the Patient Counseling Checklist. Our redlined version is with reference to the clean Patient Counseling Checklist that you submitted in the August 3, 2021 REMS Amendment.

REMS Fact Sheet

8. We have attached the Agency's redlined Word version of the REMS Fact Sheet. Our redlined version is with reference to the clean REMS Fact Sheet that you submitted in the August 3, 2021 REMS Amendment.

Risk Management Report

9. We have attached the Agency's redlined Word version of the Risk Management Report. Our redlined version is with reference to the clean Risk Management Report that you submitted December 15, 2020.

REMS Assessment Plan

10. We have attached the Agency's redlined Word version of the REMS Assessment Plan. Our redlined version is with reference to the assessment plan provided in the clean REMS supporting document that you submitted in the August 5, 2021 REMS Amendment.

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Division of Risk Management (DRISK)
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
PDUFA Goal Date	October 15, 2021
OSE RCM #	2021-56
Reviewer Name(s)	Bob Pratt, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	August 19, 2021
Subject	Interim Comments for the Proposed REMS for Lumryz
Established Name	Sodium Oxybate for Extended-Release Oral Suspension
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals
Therapeutic Class	CNS Depressant
Formulation(s)	Powder for extended-release oral suspension: nightly dose packets of 4.5 g, 6 g, 7.5 g, and 9 g
Dosing Regimen	The recommended starting dosage is 4.5 g per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the effective dosage range of 6 g to 9 g per night orally.

1 Introduction

The following comments are based on the Agency's review of the proposed REMS for Lumryz (sodium oxybate extended-release), submitted with New Drug Application (NDA) 214755 by Avadel CNS Pharmaceuticals (Avadel) on December 15, 2020. The proposed indication is for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy. This application is under review in the Division of Neurology I (DNI). The Agency agreed to Avadel's request to submit a REMS separate from the REMS approved for Xywav (calcium, magnesium, potassium, and sodium oxybates)/Xyrem (sodium oxybate) and the Sodium Oxybate Shared System REMS based on differences in drug administration; the drug's formulation; the lack of a drug-drug interaction with divalproex sodium; and the drug distribution plan. The proposed REMS for Lumryz consists of elements to assure safe use (ETASU), a communication plan, an implementation system, and a timetable for submission of assessments to ensure the benefits of Lumryz outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.

2 Comments to the Applicant

The following comments are based on the Agency's review of the proposed REMS for Lumryz, submitted with NDA 214755 on December 15, 2020 and amended August 3, 2021. To facilitate further review, we request that you submit your response as REMS Correspondence within 5 business days. In your response, please acknowledge the required changes to the Lumryz Prescription Form described below; however, it is not necessary to submit redlined and clean versions of the Lumryz Prescription Form at this time.

Review of the REMS document, supporting document, and appended materials is ongoing. Therefore, these comments should not be considered as final. Prior to approval of the REMS, we will instruct you to submit a complete REMS Amendment that includes clean Word versions of the REMS document, each REMS material, and the REMS supporting document; a clean PDF version of the REMS website; and a clean PDF version of the full REMS comprised of the REMS document compiled with all REMS materials in a single file.

General Comments

- 1) We remind you that the labeling, REMS document, appended REMS materials, and REMS supporting document must all be aligned. If, after receipt of this Information Request, the Agency communicates changes to you regarding the labeling, the REMS must be aligned with those changes and the final FDA-approved version of the label.
- 2) The REMS document remains under review and we will send you an Agency-redlined version of the REMS document in a separate Information Request.
- 3) Please clarify the process for disenrollments of prescribers and patients for suspected abuse, misuse or diversion as far as whether the REMS is responsible for the final decision to disenroll. In addition, clarify the process prescribers use to request disenrollment of a patient for suspected abuse, misuse, or diversion.

Lumryz Prescription Form

- 4) The Agency requires that the Lumryz Prescription Form must be used for initial prescriptions and for patients with a lapse in treatment of 6 months or longer. The Prescription Form may also be used for refills and renewals of Lumryz prescriptions.
- 5) The Lumryz Prescription Form must include a pharmacist attestation at the bottom of the form that states the pharmacist has contacted the other REMS programs for oxybate salt products to:
 - a) Verify that the patient has no other active prescriptions for sodium oxybate that overlap with the current Lumryz prescription.
 - b) Verify the patient/prescriber have not been disenrolled in the other oxybate salts REMS programs for suspected abuse, misuse, or diversion.
 - c) Report this prescription filled for Lumryz.
- 6) You propose that the use of the Lumryz Prescription Form by prescribers is optional because many states and institutions require prescribers to submit prescriptions electronically, even more so when prescribing controlled substances.
 - a) You indicated that you are currently evaluating several pharmacies for potential certification in the REMS. With reference to the States where these pharmacies are located, please identify any States that do not provide an exception or waiver from electronic prescribing for a drug that the Agency requires the prescription to contain certain elements that are not able to be prescribed with electronic prescribing.
 - b) Please clarify the institutions you refer to in your statement that many states and institutions require electronic prescribing and describe the nature of any exemptions from electronic prescribing requirements at these institutions.
- 7) Please clarify the pre-dispense authorization process for prescription renewals and refills that do not involve use of the Lumryz Prescription Form, and whether this process requires confirmation that a call was made to the other oxybate salts REMS programs to verify that:
 - a) the patient has no other active prescriptions for sodium oxybate that overlap with the current Lumryz prescription
 - b) the patient/prescriber have not been disenrolled in the other oxybate salts REMS programs for suspected abuse, misuse, or diversion.
- 8) Please clarify the process of how information from the Lumryz Prescription Form is entered into the patient database.

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/s/

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Division of Risk Management (DRISK)
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
PDUFA Goal Date	October 15, 2021
OSE RCM #	2021-56
Reviewer Name(s)	Bob Pratt, Pharm.D.
Team Leader	Jackie Sheppard, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	July 20, 2021
Subject	Interim Comments for the Proposed REMS for Lumryz
Established Name	Sodium Oxybate for Extended-Release Oral Suspension
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals
Therapeutic Class	CNS Depressant
Formulation(s)	Powder for extended-release oral suspension: nightly dose packets of 4.5 g, 6 g, 7.5 g, and 9 g
Dosing Regimen	The recommended starting dosage is 4.5 g per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the effective dosage range of 6 g to 9 g per night orally.

1 Introduction

The following comments are based on the Agency's review of the proposed REMS for Lumryz (sodium oxybate extended-release), submitted with New Drug Application (NDA) 214755 by Avadel CNS Pharmaceuticals (Avadel) on December 15, 2020. The proposed indication is for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy. This application is under review in the Division of Neurology I (DNI). The Agency agreed to Avadel's request to submit a REMS separate from the REMS approved for Xywav (calcium, magnesium, potassium, and sodium oxybates)/Xyrem (sodium oxybate) and the Sodium Oxybate Shared System REMS based on differences in drug administration; the drug's formulation; the lack of a drug-drug interaction with divalproex sodium; and the drug distribution plan. The proposed REMS for Lumryz consists of elements to assure safe use (ETASU), a communication plan, an implementation system, and a timetable for submission of assessments to ensure the benefits of Lumryz outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.

2 Comments to the Applicant

The following comments are based on the Agency's review of the proposed REMS for Lumryz, submitted with NDA 214755 on December 15, 2020. To facilitate further review, we request that you submit your response as a REMS Amendment with cover letter within 10 business days. The REMS Amendment should include the following:

- Prescriber Enrollment Form (redlined and clean Word versions)
- Patient Enrollment Form (redlined and clean Word versions)
- Prescriber Brochure (redlined and clean Word versions)
- Certified Pharmacy Training Program (redlined and clean Word versions)
- Pharmacy Staff Knowledge Assessment (redlined and clean Word versions)
- Lumryz Prescription Form (Word version)
- REMS supporting document (redlined and clean Word versions)

Review of the REMS document, supporting document, and appended materials is ongoing. Therefore, these comments should not be considered as final. Prior to approval of the REMS, we will instruct you to submit a complete REMS Amendment that includes clean Word versions of the REMS document, each REMS material, and the REMS supporting document; a clean PDF version of the REMS website; and a clean PDF version of the full REMS comprised of the REMS document compiled with all REMS materials in a single file.

General Comments

1. We remind you that the labeling, REMS document, appended REMS materials, and REMS supporting document must all be aligned. If, after receipt of this Information Request, the Agency communicates changes to you regarding the labeling, the REMS must be aligned with those changes and the final FDA-approved version of the label.
2. Please identify the names and locations of the pharmacies that you intend to contract with and certify in the REMS. You may provide this information in the submission cover letter.

REMS Document

3. The REMS document remains under review and we will send you an Agency-redlined version of the REMS document in a separate Information Request. We currently have the following general comments about the REMS document:
 - a. Your REMS proposal does not include the use of a Lumryz Prescription Form by the prescriber. A Lumryz Prescription Form is required because it provides certain necessary documentation for safe use of the drug. We request that you submit a Lumryz Prescription Form that includes information similar to the prescription forms found in other currently approved sodium oxybate REMS programs, including prescriber information, patient information, the patient's current medications, dosing and dispensing instructions, prescriber attestation statements, and the prescriber's verification and signature.
 - b. Revise Section III.1. and the implementation system under Section 3 to incorporate the use of a Lumryz Prescription Form.
 - c. Revise Section III.3. to reflect the required use of a Pharmacy Enrollment Form and the responsibilities required of the pharmacy's authorized representative for pharmacies to become certified to dispense.
 - d. Under Section III.3., explain how you established a stock level (b) (4) inventory to be kept at a certified pharmacy, and how the stock level is determined relative to ongoing dispensing. Your explanation may be provided in the submission cover letter.
 - e. Under Section III. *To ensure REMS participants' compliance with the REMS Program, Avadel must: 22.*, explain how Avadel will monitor and evaluate the processes and procedures used by multiple certified pharmacies for placing patient monitoring alerts and patient disenrollment requests for potential abuse, misuse, or diversion. Your explanation may be provided in the submission cover letter.

Prescriber Enrollment Form

4. Add language to the attestation section noting that the prescriber will confirm with all patients if they are or have been part of the Xywav and Xyrem REMS Program and/or the Sodium Oxybate REMS Program.

Patient Enrollment Form

5. Add a question regarding whether the patient has enrolled in the Xywav and Xyrem REMS Program and/or the Sodium Oxybate REMS Program.

Prescriber Brochure

6. Include and describe the prescriber requirements related to the use of a Lumryz Prescription Form.

Certified Pharmacy Training Program

7. Include and describe the pharmacy requirements related to the use of a Lumryz Prescription Form.

Pharmacy Staff Knowledge Assessment

8. Revise Question 7 to clarify the use of a Lumryz Prescription Form.

Lumryz Prescription Form

9. Please see above (REMS document, bullet 3a) for details about a REMS Prescription form.

REMS supporting document

10. With reference to the REMS correspondence submission received by the Agency on April 28, 2021, please update Section I.C. Proposed Risk Mitigation Approach, and Section III.C. Implementation System, with the information that was provided in the REMS correspondence submission.
11. Please provide a schematic diagram of all steps in the certified pharmacy workflow to be used for dispensing Lumryz. At minimum, the steps diagrammed should include receipt of the prescription, obtaining pre-dispense authorization, processing of the insurance claim, the review of information in the REMS patient database and the type of information reviewed, consultation with external pharmacy databases and use of the Prescription Drug Monitoring Program, consultation with the Lumryz prescriber, counseling of the patient, communication with the Xywav and Xyrem REMS Program, communication with the Sodium Oxybate REMS Program if operational, communication with the Lumryz prescriber and prescribers of Xywav/Xyrem/Sodium Oxybate in the event overlapping sodium oxybate prescriptions are identified, shipment of Lumryz to the patient. The diagram may be submitted as an Appendix to the REMS supporting document.

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/s/

ROBERT G PRATT
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JACQUELINE E SHEPPARD
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Division of Risk Management (DRISK)
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
PDUFA Goal Date	October 15, 2021
OSE RCM #	2021-56
Reviewer Name(s)	Bob Pratt, Pharm.D.
Team Leader	Jackie Sheppard, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	April 13, 2021
Subject	Interim Comments for the Proposed REMS for Lumryz
Established Name	Sodium Oxybate for Extended-Release Oral Suspension
Trade Name	Lumryz
Name of Applicant	Avadel CNS Pharmaceuticals
Therapeutic Class	CNS Depressant
Formulation(s)	Powder for extended-release oral suspension: nightly dose packets of 4.5 g, 6 g, 7.5 g, and 9 g
Dosing Regimen	The recommended starting dosage is 4.5 g per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the effective dosage range of 6 g to 9 g per night orally.

1 Introduction

The following comments are based on the Agency's review of the proposed REMS for Lumryz (sodium oxybate extended-release), submitted with New Drug Application (NDA) 214755 by Avadel CNS Pharmaceuticals (Avadel) on December 15, 2020. The proposed indication is for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy. This application is under review in the Division of Neurology I (DNI). The Agency agreed to Avadel's request to submit a REMS separate from the REMS approved for Xywav (calcium, magnesium, potassium, and sodium oxybates)/Xyrem (sodium oxybate) and the Sodium Oxybate Shared System REMS based on differences in drug administration; the drug's formulation; the lack of a drug-drug interaction with divalproex sodium; and the drug distribution plan. The proposed REMS for Lumryz consists of elements to assure safe use (ETASU), a communication plan, an implementation system, and a timetable for submission of assessments to ensure the benefits of Lumryz outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.

2 Comments to the Applicant

The following comments are based on the Agency's review of the proposed REMS for Lumryz, submitted with NDA 214755 on December 15, 2020. To facilitate further review, we ask that you submit your response as REMS Correspondence within 15 business days. Review of the REMS document, supporting document, and appended materials is ongoing. Therefore, these comments should not be considered as final.

REMS supporting document

1. Under Section I. C. Proposed Risk Mitigation Approach, the REMS supporting document states that pharmacies are required to process all Lumryz prescriptions through their Pharmacy Management System and must obtain a Pre-Dispense Authorization using electronic verification from the Lumryz REMS, by requesting that the Lumryz REMS independently query the secure, validated, separate, and distinct Lumryz databases (patient database, specially certified prescriber database, specially certified pharmacy database, and disenrolled prescriber database).

FDA comments

- a. Identify the vendor selected to provide electronic verification services for the REMS. In addition, describe your processes to ensure all prescriptions, including cash claims, for Lumryz are not routed to commercial insurance payers without first being evaluated by the REMS safe-use rules.
- b. Describe in detail whether certified prescribers and certified pharmacies will access the secure, validated, separate, and distinct Lumryz databases, or if this access is only by the Lumryz REMS.
- c. Describe in detail the backup or manual Pre-Dispense Authorization processes the REMS will use in the event of an outage related to the Pharmacy Management System.

2. Under Section III. C. Implementation System, the REMS supporting document notes that Avadel will contract with a third-party logistics (3PL) provider to ship Lumryz to certified pharmacies based on Avadel's direction. Avadel will retain title to Lumryz and will never transfer title to the 3PL provider. In addition:
 - The 3PL provider will store and handle Lumryz in accordance with state and federal laws and regulations for Schedule III controlled substances and will ship Lumryz to certified pharmacies as directed by Avadel.
 - Prior to the 3PL provider distributing Lumryz, Avadel will verify the pharmacy is certified in the Lumryz REMS by calling the Lumryz REMS or accessing a report listing the certified pharmacies.
 - Distribution data will be provided to the Lumryz REMS for verification and compliance monitoring.

FDA comments

- a. Describe the selection criteria that Avadel is using to contract with a 3PL provider(s) to support distribution of Lumryz.
- b. Describe the supply chain integrity monitoring processes that Avadel will use to:
 - Monitor shipments of Lumryz into the 3PL provider warehouse from the Lumryz packaging site
 - Monitor current Lumryz inventory on hand at the 3PL provider warehouse
 - Monitor shipments of Lumryz from the 3PL provider warehouse to the certified pharmacies
- c. Describe the 3PL provider's reporting requirements and reporting schedule to the Lumryz REMS related to the monitoring of Lumryz inventory control and shipment tracking into and out of the 3PL provider warehouse.
- d. Describe the Lumryz REMS audit and compliance plan for the 3PL provider related to Lumryz inventory, storage, and shipments received from the Lumryz packaging site and shipments sent to the certified pharmacies.

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/

ROBERT G PRATT
04/13/2021 01:03:31 PM

JACQUELINE E SHEPPARD
04/13/2021 01:27:57 PM

DORIS A AUTH
04/14/2021 05:35:00 PM