NDA 214755

NDA APPROVAL

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

Dear Ms. Scarola:

Please refer to your new drug application (NDA) dated and received December 15, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lumryz (sodium oxybate) for extended-release oral suspension.

We acknowledge receipt of your amendment dated March 1, 2023, following our July 18, 2022, tentative approval letter.

This NDA provides for the use of Lumryz (sodium oxybate) for extended-release oral suspension for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.

APPROVAL & LABELING

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, Medication Guide, and REMS) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL*

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

Standard for Content of Labeling Technical Qs and As.[2]

The SPL will be accessible via publicly available labeling repositories.

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

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the container labels submitted on November 4, 2021, and carton labeling submitted on November 15, 2021, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214755**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Lumryz (sodium oxybate) extended-release oral suspension shall be 36-months from the date of manufacture when stored at 20°C to 25°C (68°F to 77° F).

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of systemic toxicity associated with the excipient (b) (4).

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4441-1 Conduct an oral absorption study of radiolabeled methacrylic acid copolymer, (b) (4) in rat. The methacrylic acid copolymer, (b) (4) should be the same as the excipient in the to-be-marketed product.

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

The timetable you submitted on April 26, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 07/2024
Study Completion: 09/2024
Final Report Submission: 12/2024

4441-2 Conduct a six-month oral toxicology study of methacrylic acid copolymer, (b) (4) in rat. The methacrylic acid copolymer, (b) (4) should be the same as the excipient in the to-be-marketed product. The study will only be needed if oral absorption is demonstrated in an adequately conducted study (PMR #4441-1).

The timetable you submitted on April 26, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2025
Study Completion: 02/2026
Final Report Submission: 08/2026

Submit clinical protocol(s) to your IND 126321 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the 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.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Lumryz (sodium oxybate) to ensure the benefits of the drug outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.[3]

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that Lumryz (sodium oxybate) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require: pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on December 15, 2020, amended, and appended to this letter, is approved.

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

[3] 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.

Your REMS must be fully operational before you introduce Lumryz (sodium oxybate) into interstate commerce.

The REMS assessment plan must include, but is not limited to, the following:

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

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

Program Implementation and Operations

1. **REMS Implementation (1st assessment after approval)**

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

2. **REMS Enrollment and Certification Statistics**

    a. Patients
        i. Total number of enrolled patients
        ii. Number and percentage of newly enrolled patients stratified by age, geographic region (defined by US Census), and gender
        iii. Number and percentage of active patients enrolled (i.e., patients who received at least one shipment of Lumryz during the reporting period) stratified by age, geographic region (defined by US Census), and gender
        iv. Number and percentage of patients who have discontinued Lumryz after receiving at least one shipment of Lumryz. Include demographics of discontinued patients and reasons for discontinuation

    b. Healthcare Providers
        i. Total number of certified healthcare providers
        ii. Number and percentage of newly certified healthcare providers stratified by professional designation (i.e., MD, DO,

PA, NP, Other), medical specialty, and geographic region (defined by US Census)

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

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

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

3. Utilization Data

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

4. REMS Operation and Performance Data

a. REMS Databases Report
   i. Number and percentage of contacts by stakeholder type (e.g., patients, healthcare providers, pharmacy, other)
   ii. Summary of reasons for contacts (e.g., enrollment questions) by reporter (e.g., authorized representative, patient, healthcare provider, other)
   iii. Summary of frequently asked questions by stakeholder type and topic

iv. Summary of any REMS-related problems identified, and a description of any corrective actions taken
v. If the summary reason for the calls indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden (e.g., pharmacy calls to other REMS for oxybate products) or patient access issues (e.g., patient's therapy delayed due to unwillingness of other REMS for oxybate products to provide necessary information)
vi. Summary of program or system problems and a description of any corrective actions taken

5. REMS Compliance

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

b. A summary report of noncompliance, associated corrective and preventive actions (CAPA) plans, and the status of CAPA plans including but not limited to:
   i. A copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder, actions taken to address noncompliance for each event, and under what

circumstances a stakeholder would be suspended or decertified/disenrolled from the REMS

ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:

1. The unique ID(s) of the stakeholder(s) associated with the noncompliance event to enable tracking over time
2. The source of the noncompliance data
3. The results of root cause analysis
4. What action(s) were taken in response

c. Healthcare Providers

i. Number and percentage of certified healthcare providers who were decertified and reasons for decertification. Include if any healthcare providers were re-certified

ii. Number and percentage of Lumryz prescriptions filled from a healthcare provider who was not certified

d. Certified Pharmacies

i. Number and percentage of Lumryz prescriptions dispensed for more than a 30 days supply (first fill) or more than a 90 days supply (refills) and reasons

ii. Number and percentage of Lumryz shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and *Risk Management Reports* completed

iii. Number and percentage of initial Lumryz shipments sent to patients without completion of the Lumryz REMS Patient Counseling Checklist

iv. Number and percentage of pharmacy decertifications and reasons for decertification. Include if any pharmacies were re-certified

e. Patients

i. Number and percentage of patients who were disenrolled from the program and reasons for disenrollment

ii. Number and percentage of patients who received prescriptions from more than one prescriber during their therapy

iii. Number and percentage of patients with overlapping Lumryz prescriptions (more than one active prescription shipped)

iv. Number of duplicate patients detected by certified pharmacies
v. Number and percentage of duplicate patients who were shipped Lumryz under more than one name or identifier
vi. Number and percentage of patients who were shipped Lumryz after being disenrolled

vii. Number of patients found to have active, overlapping prescriptions for Lumryz and any other oxybate product (e.g., Xywav, Xyrem, or generic sodium oxybate)
viii. Number and percentage of patients who requested an early refill of Lumryz and reason for the request

1. Number and percentage of requests approved
2. Number and percentage of requests denied by the prescriber
3. Number and percentage of requests denied by the certified pharmacy
4. Number and percentage of patients with multiple (i.e., more than 1) requests for early refills

Safe Use Behaviors

6. Pharmacy Notifications

a. A summary of the notifications by pharmacies to prescribers for Lumryz. Each of the following situations will include the number and percentage of notifications, number of unique patients, the outcome of the pharmacy notification (e.g., counseled patient, discussed with prescriber) and outcome of Lumryz prescription disposition (e.g., prescriber approved shipment, prescriber requested shipment hold, prescriber denied shipment, pharmacy approved shipment):
    i. Use with prescription sedative-hypnotics indicated for sleep (e.g., eszopiclone, zaleplon, zolpidem, temazepam, suvorexant, quazepam, estazolam, flurazepam, triazolam, tasimelteon, ramelteon). Indicate specific actions taken by the prescriber and the prescriber's rationale for continuing treatment in response to the notification including the following:
        1. Treatment with Lumryz will be discontinued
        2. Sedative hypnotic will be discontinued
        3. Dosage of sedative hypnotic has been/will be reduced
        4. Information unavailable

5. No action (continue sedative hypnotic with Lumryz)
6. Prescriber's rationale for continued use of sedative hypnotic with Lumryz
    - Sedative hypnotic will not be taken at the same time as Lumryz
    - Sedative hypnotic will be taken at the same time as Lumryz
    - Sedative hypnotic will be taken as a sleep aid
    - Sedative hypnotic will be taken for different indication per medical need
    - Lumryz dose regimen changed
    - No rationale provided

ii. Benzodiazepines (e.g., diazepam, alprazolam or any not listed in metric 6.a.i.). Indicate specific actions taken by the prescriber and the prescriber rationale for continuing treatment in response to the notification including the following:
    1. Treatment with Lumryz will be discontinued
    2. Benzodiazepine will be discontinued
    3. Dosage of benzodiazepine has been/will be reduced
    4. Information unavailable
    5. No action (continue benzodiazepine with Lumryz)
    6. Prescriber's rationale for continued use of benzodiazepine with Lumryz
        - Benzodiazepine will not be taken at the same time as Lumryz
        - Benzodiazepine will be taken at the same time as Lumryz
        - Benzodiazepine will be taken as a sleep aid
        - Benzodiazepine will be taken for different indication per medical need
        - Lumryz dose regimen changed
        - No rationale provided

iii. Use with other concomitant CNS-depressant medications (i.e., sedating antidepressants or antipsychotics, sedating anti-epileptics, sedating antihistamines, general anesthetics, muscle relaxants, opioid analgesics, or illicit CNS depressants)

iv. Patient report of alcohol use

v. Patient report of diagnosis of sleep apnea

vi. Patient report of diagnosis of asthma, COPD, or other conditions affecting breathing

vii. Suspected abuse, misuse, or diversion
viii. Alerts regarding potential abuse, misuse, or diversion on the patient profiles
ix. Prescription error
x. Early refill requests

7. *Risk Management Reports (RMRs)*

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

8. REMS *Patient Counseling Checklist*

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

been diagnosed with the following conditions and who subsequently received at least one shipment of drug:

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

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

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

10. Pre-Dispense Authorizations (PDAs)

1. Number of requested PDAs that were rejected and reasons for rejection
2. Number of prescriptions dispensed where all REMS and safe use requirements were not met, but a PDA was provided
3. Number of prescriptions dispensed without a PDA
4. The number of requested PDAs that were rejected and were subsequently approved and the duration of time from rejection of the requests to approval

Health Outcomes and/or Surrogates of Health Outcomes

11. Pharmacovigilance/surveillance (per reporting period)

a. Analysis of serious adverse events and summary table for Lumryz of the number of reports of serious adverse events, including the following data fields; date, case report ID, age, gender, serious adverse event(s) outcome (hospitalization or death), associated factors (i.e., concurrent use with sedative hypnotics or alcohol, intentional misuse, abuse, overdose, diversion, or medication error) and if cases are considered related or not related to Lumryz. Tables will include an overall narrative summary and analysis of the adverse events and data fields reported.

i. All cases of death - include narrative summary of each death
    1. Number, percentage, and type of *RMRs*, notifications, and alerts within 6 months of the reported deaths
    2. Calculation of the overall, and age- and gender-specific mortality rates.
    3. Calculation of the standardized mortality rates, adjusted for age and gender, using both the point estimates and the lower bounds of the 95% confidence intervals as the reference rates.

ii. Serious adverse events with all outcomes of death, emergency department visits (when admitted to hospital), or hospitalizations resulting from or associated with the following:
    1. Use with concurrent sedative hypnotics
    2. Use with alcohol
    2. Intentional misuse
    3. Abuse
    4. Overdose
    5. Medication error

iii. Cases of sexual abuse – include narrative summary of each case

iv. Proportion of discontinued patients who were associated with a report of a serious adverse event, including death

Knowledge

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

a. Assessment of patients', healthcare providers' and pharmacists' understanding of the following:

i. The risk of significant CNS and respiratory depression associated with Lumryz even at recommended doses
ii. The contraindicated uses of Lumryz with sedative hypnotics and alcohol
iii. The potential for abuse, misuse, and overdose associated with Lumryz
iv. The safe use, handling, and storage of Lumryz
v. The Lumryz REMS requirements

13. Certified Pharmacy Knowledge Assessments (per reporting period and cumulatively)

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

Overall Assessment of REMS Effectiveness

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

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

i. Submit your proposed audit plan **and** non-compliance plan for FDA review within 60 days of this letter.

ii. Submit your proposed protocol for the knowledge survey(s) for FDA review within 90 days of this letter.

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

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

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

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

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

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

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

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

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

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support*

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

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

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

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

NDA 214755 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 214755/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 214755/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 214755/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

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

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

REMS REVISION FOR NDA 214755

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

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

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

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

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication,

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

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

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

If you have any questions, contact Jack Dan, Regulatory Project Manager, at Jack.Dan@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director (Acting) & Deputy Director
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

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

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

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

/s/

TERESA J BURACCHIO
05/01/2023 11:05:33 AM