U.S. FOOD & DRUG ADMINISTRATION

NDA 214755

TENTATIVE APPROVAL

Avadel CNS Pharmaceuticals, LLC
Attention: Marla E. Scarola
Vice President, Regulatory Program Management
The Weinberg Group
1129 Twentieth St, NW, Suite 600
Washington, DC 20036

Dear Ms. Scarola:

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

(b) (4)

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) and submitted labeling (cartons submitted November 15, 2021, and container labeling submitted November 4, 2021). This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of any new information that may come to our attention.

A listed drug(s) upon which your application relies is subject to a period of patent protection and your application contains a certification(s) to one or more patents under section 505(b)(2)(A)(iv) of the FD&C Act stating that the patent(s) is/are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("paragraph IV certification").[1]

Section 505(c)(3)(C) of the FD&C Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the FD&C Act that includes a paragraph IV

[1] This letter does not address whether any orphan drug exclusivity (ODE) recognized for Xyrem under NDA 021196 or for Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution under NDA 212690 affects the approvability of Avadel's application.

certification shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of a paragraph IV certification and for which patent information was submitted to FDA before the date on which you submitted your 505(b)(2) application. You notified us that you complied with the requirements of section 505(b)(3) of the FD&C Act.[2] However, the 45-day period described in section 505(c)(3)(C) of the FD&C Act has not yet expired, and your application is only eligible for a tentative approval at this time. If such a patent infringement action is brought prior to the expiration of 45 days from the later of the date the notice provided under section 505(b)(3) is received by the patent owner or approved application holder, your application would be subject to a 30-month stay of approval, unless other conditions are met.

To obtain final approval of this application, submit an amendment two or six months prior to the: (1) expiration of the patent(s) or (2) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL"**. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FD&C Act 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 FD&C Act, 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.

Your proposed REMS must also include the following:

[2] See NDA 214755, Notice of Paragraph IV Certification Amendment (Module 1.2) (June 7, 2022). In this correspondence, Avadel also states "[w]ith this amendment, Avadel requests tentative approval for the LUMRYZ NDA pursuant to 21 C.F.R. § 314.105(a)."

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[3] listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers that prescribe the drug 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, as amended is appended to this letter.

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

- Upon final approval, 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:

Program Implementation and Operations

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

    a. REMS Program implementation date

[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.

b. Date of first commercial distribution of Lumryz (sodium oxybate)

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 Statistics (per previous two reporting periods, current reporting period, and cumulatively)**

   a. Patients

      i. Number and percentage of newly enrolled patients stratified by age, geographic region (defined by US Census), and gender

      ii. Number and percentage of active patients enrolled (patients who received at least one shipment of Lumryz (sodium oxybate) during the current reporting period) stratified by age, geographic region (defined by US Census), and gender

      iii. Number and percentage of patients who have discontinued Lumryz (sodium oxybate) after receiving at least one shipment of Lumryz (sodium oxybate). Include demographics of discontinued patients and reasons for discontinuation

   b. Healthcare Providers

      i. 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)

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

iii. Number of active patients (patients who received at least one shipment of Lumryz (sodium oxybate) during the reporting period) by current enrolled prescriber

c. Certified Pharmacies

i. Number of newly certified pharmacies and total certified pharmacies

ii. Number of active pharmacies (e.g., dispensed one or more Lumryz (sodium oxybate) prescriptions)

3. Utilization Data (per previous two reporting periods, current reporting period, and cumulatively)

a. Number of shipments, including number of nightly dose packets, shipped by wholesalers, distributors, and other entities to pharmacies

b. Number and percentage of Lumryz (sodium oxybate) prescriptions (new and refill) dispensed by pharmacies to patients

c. Number and percentage of Lumryz (sodium oxybate) packets and shipments sent by pharmacies to patients stratified by dose strength

4. REMS Program Operation and Performance Data (per previous two reporting periods, current reporting period, and cumulatively)

a. REMS Program 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 (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 Program Compliance (per previous two reporting periods, current reporting period, and cumulatively)

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 (sodium oxybate)

ii. The number of audits expected, and the number of audits performed

iii. The number and type of deficiencies noted

iv. For those with deficiencies noted, report the status of corrective and preventative action (CAPA) proposed to address the deficiencies, including completion dates

v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken

vi. Provide details on deviations for the CAPA proposed, including timelines, and mitigating steps to address the deviations

vii. Confirm documentation of completion of training for relevant staff

viii. Review of cumulative findings to identify any trends of potential repeat issues, and steps to be taken to address these findings

ix. A summary report of the processes and procedures that are implemented to be in compliance with the REMS requirements

b. A summary report of noncompliance, associated corrective and preventive actions (CAPA) plans, and the status of CAPA plans including but not limited to:

i. A copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder, actions taken to address noncompliance for each event, and under what circumstances a

stakeholder would be suspended or decertified/disenrolled from the REMS

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

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

c. Healthcare Providers

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

ii. Number and percentage of Lumryz (sodium oxybate) prescriptions filled from a prescriber who was not certified

d. Certified Pharmacies

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

iii. Number and percentage of initial Lumryz (sodium oxybate) shipments sent to patients without completion of the Lumryz (sodium oxybate) 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 prescribed a daily dose of Lumryz (sodium oxybate) of >9 g

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

v. Number of duplicate patients detected by certified pharmacies

vi. Number and percentage of duplicate patients who were shipped Lumryz (sodium oxybate) under more than one name or identifier

vii. Number and percentage of patients who were shipped Lumryz (sodium oxybate) after being disenrolled

viii. Number of patients found to have active, overlapping prescriptions for Lumryz (sodium oxybate) and any other oxybate product (e.g., Xywav, Xyrem, or generic Sodium Oxybate)

ix. Number and percentage of patients who requested an early refill of Lumryz (sodium oxybate) 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 (more than 1) requests for early refills

Safe Use Behaviors

6. Pharmacy Notifications (per previous two reporting periods, current reporting period, and cumulatively)

a. A summary of the notifications by pharmacies to prescribers for Lumryz (sodium oxybate). 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 (sodium oxybate) prescription disposition (e.g., prescriber approved shipment, prescriber requested shipment hold, prescriber denied shipment, pharmacy approved shipment):

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

      1. Treatment with Lumryz (sodium oxybate) will discontinue
      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 (sodium oxybate))
      6. Prescriber's rationale for continued use of sedative hypnotic with Lumryz (sodium oxybate)

         - Sedative hypnotic will not be taken at the same time as Lumryz (sodium oxybate)
         - Sedative hypnotic will be taken at the same time as Lumryz (sodium oxybate)
         - Sedative hypnotic will be taken as a sleep aid
         - Sedative hypnotic will be taken for different indication per medical need
         - Lumryz (sodium oxybate) 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 (sodium oxybate) will discontinue
      2. Benzodiazepine will be discontinued

3. Dosage of benzodiazepine has been/will be reduced
4. Information unavailable
5. No action (continue benzodiazepine with Lumryz (sodium oxybate))
6. Prescriber's rationale for continued use of benzodiazepine with Lumryz (sodium oxybate)
    - Benzodiazepine will not be taken at the same time as Lumryz (sodium oxybate)
    - Benzodiazepine will be taken at the same time as Lumryz (sodium oxybate)
    - Benzodiazepine will be taken as a sleep aid
    - Benzodiazepine will be taken for different indication per medical need
    - Lumryz (sodium oxybate) dose regimen changed
    - No rationale provided

iii. Use with other concomitant CNS-depressant medications (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)* (per previous two reporting periods, current reporting period, and cumulatively)

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 Program *Patient Counseling Checklist* (per previous two reporting periods, current reporting period, and cumulatively)

a. Summary table from REMS Program *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. 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 (sodium oxybate) from REMS Program *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 Oxybate REMS

a. Information on patients with active, overlapping prescription or disenrollment or deactivation for misuse, abuse, etc., in other Oxybate REMS and outcomes

i. For unsuccessful attempts or those that resulted in a treatment delay indicate the REMS program contacted

ii. Number and dates of unsuccessful contact attempts to other REMS, 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 Oxybate REMS

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, other Oxybate REMS 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 Oxybate REMS

Health Outcomes and/or Surrogates of Health Outcomes

10. Pharmacovigilance/surveillance (per reporting period)

a. Summary table for Lumryz (sodium oxybate) of the number of reports of serious adverse events, including the following data fields (CIOMS II line listings): date, report ID, report type, notifier, age, gender, start and stop date, dose, frequency, onset date, system organ class, outcome, and causality. Tables will include an overall narrative summary of the adverse events and data fields reported.

i. All cases of death

1. Number, percentage, and type of *RMRs*, notifications, and alerts within 6 months of the reported deaths

ii. 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 and alcohol by concomitant sedative hypnotics usage.
2. Intentional misuse
3. Abuse
4. Overdose
5. Medication error

iii. Cases of sexual abuse

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

Knowledge

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

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

i. The risk of significant CNS and respiratory depression associated with Lumryz (sodium oxybate) even at recommended doses

ii. The contraindicated uses of Lumryz (sodium oxybate) with sedative hypnotics and alcohol

iii. The potential for abuse, misuse, and overdose associated with Lumryz (sodium oxybate)

iv. The safe use, handling, and storage of Lumryz (sodium oxybate)

v. The Lumryz (sodium oxybate) REMS Program requirements

12. KAB Surveys of Pharmacists (to be submitted annually)

a. Assessment of pharmacists' understanding of the following:

i. The risk of significant CNS and respiratory depression associated with Lumryz (sodium oxybate) even at recommended doses

ii. The contraindicated uses of Lumryz (sodium oxybate) with sedative hypnotics and alcohol

iii. The potential for abuse, misuse, and overdose associated with Lumryz (sodium oxybate)

iv. The safe use, handling, and storage of Lumryz (sodium oxybate)

v. The Lumryz (sodium oxybate) REMS Program 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

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 1 or more such goals or such elements should be modified.

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

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.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing

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

NDA #214755 REMS ASSESSMENT METHODOLOGY

Upon final approval, 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 FD&C Act 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.

Upon final approval, 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.

If you have any questions, contact Teresa Wheelous, Regulatory Project Manager, at teresa.wheelous@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director
Division of Neurology 1
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

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

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

/s/

TERESA J BURACCHIO
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