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RESEARCH**

APPLICATION NUMBER:

214755Orig1s000

OTHER ACTION LETTERS



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.

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

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 diversion³ listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

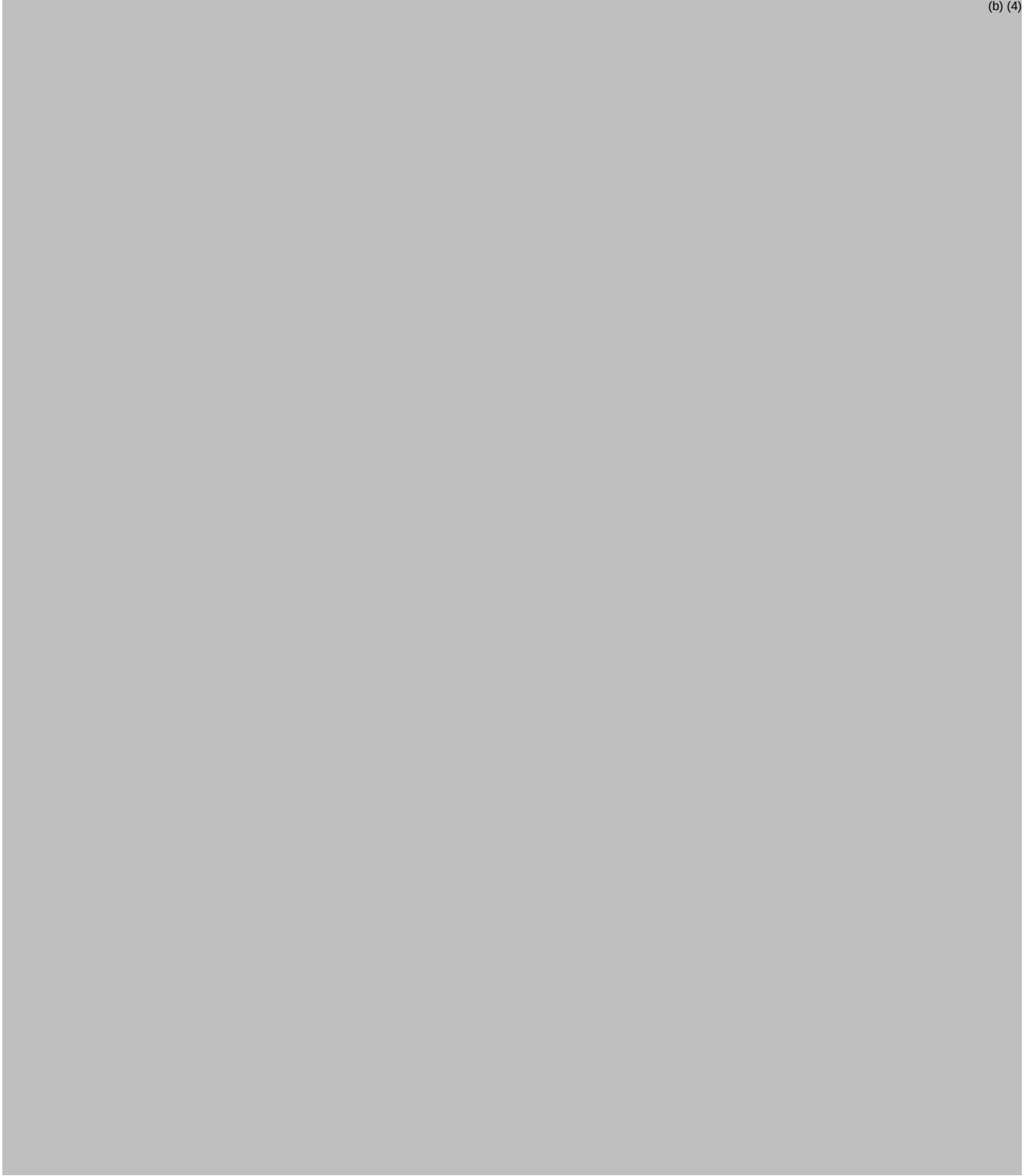


(b) (4)



(b) (4)

(b) (4)



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.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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
 - o Prescribing Information
 - o Medication Guide
 - o Instructions for Use
- REMS

124 Page(s) of Draft Labeling and Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

TERESA J BURACCHIO
07/18/2022 02:23:37 PM