NDA 220138

COMPLETE RESPONSE

Tris Pharma, Inc.
Attention: Rashmi Aravind
Senior Director of Regulatory Affairs
2033 Route 130
Suite #D
Monmouth Junction, NJ 08852

Dear Rashmi Aravind:

Please refer to your new drug application (NDA) dated and received August 20, 2025, and your amendments, submitted pursuant to [redacted] for oxybate for extended-release powder for oral suspension (oxybate ER OS).

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL/CLINICAL PHARMACOLOGY

The Agency finds that the scientific bridge between oxybate ER OS and the listed drugs (LDs), Xyrem and Xywav, is inadequate for the [redacted] Although the systemic exposures of the [redacted] of the proposed product are within the range of those observed for the LDs (Xyrem and Xywav), the shape of pharmacokinetic (PK) profiles is different from the LDs, as they are approved as twice-nightly regimens for the treatment of cataplexy or EDS in adults with narcolepsy. The exposure-response (E-R) analysis submitted by the Applicant relied on aggregated exposures (e.g., AUCinf, Cmax, and dose), assuming that the shape of PK profile has no effect on clinical response. However, this analysis itself does not demonstrate that differences in PK shape will not lead to different clinical outcomes. You have not submitted adequate and well-controlled clinical studies that support [redacted] of the LDs for [redacted]. In the absence of an adequate and well-controlled efficacy and safety study, the E-R analysis alone is insufficient to justify that the PK shape difference would not impact the efficacy or the safety of oxybate ER OS for [redacted]. Therefore, the proposed product, oxybate ER OS, cannot rely solely on the Agency's previous findings of effectiveness of the LDs for the treatment of cataplexy and EDS in narcolepsy.

Additional information will be necessary to resolve these deficiencies and support the safety and effectiveness of oxybate ER OS for (b) (4) (e.g., additional bridging studies to a product with similar PK shape and/or results from at least one adequate and well-controlled trial in patients with narcolepsy).

NONCLINICAL/PRODUCT QUALITY

(b) (4)

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling, other than the Additional Comments below, until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling, other than the Additional Comments below, until the application is otherwise adequate.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENT

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)].

We acknowledge receipt of your proposed REMS, included in your submission dated August 20, 2025, and amended on November 10, 2025, and January 30, 2026, which contains elements to assure safe use, an implementation system, and a timetable for

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for oxybate for extended-release oral suspension, if it is approved, to ensure that the benefits of the drug outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.[3] The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

For administrative purposes, designate all submissions related to the proposed REMS "**PROPOSED REMS for NDA 220138-AMENDMENT**."

To facilitate review of your submission, we request that you submit your proposed REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms or website screenshots, are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed modified REMS as described above, submit the REMS document in Structured Product Labeling (SPL) format as described 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 more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROPRIETARY NAME

The review of your proposed proprietary name has been terminated due to the deficiencies with the application as described in this letter. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter. If you do not have a conditionally acceptable proprietary name, you may submit a Request for Proprietary Name Review to your IND.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical

[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.

and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

    - Present tabulations of the new safety data combined with the original application data.

    - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Clinical

In any future submission of your Draft Label Text, you should include the relevant information from the LD prescribing information for cholestyramine (Questran), including safety information (e.g., contraindications and warnings and precautions) and safety monitoring (e.g., baseline laboratory assessments and medical evaluation prior to use; laboratory monitoring during treatment; and vitamin supplementation).

Human Factors

The results of the human factors (HF) validation study demonstrated several use errors, close calls, and use difficulties with critical tasks that may result in harm. We acknowledge you implemented additional post-validation risk controls to address some of the observed use issues; however, based on our review of the available participants' subjective feedback, root cause analysis, and proposed product user interface we identified additional risk controls to address the use issues. In this particular instance, we have determined these revisions can be implemented without additional HF data. Note that additional label and labeling comments may be forthcoming upon review of the future resubmission.

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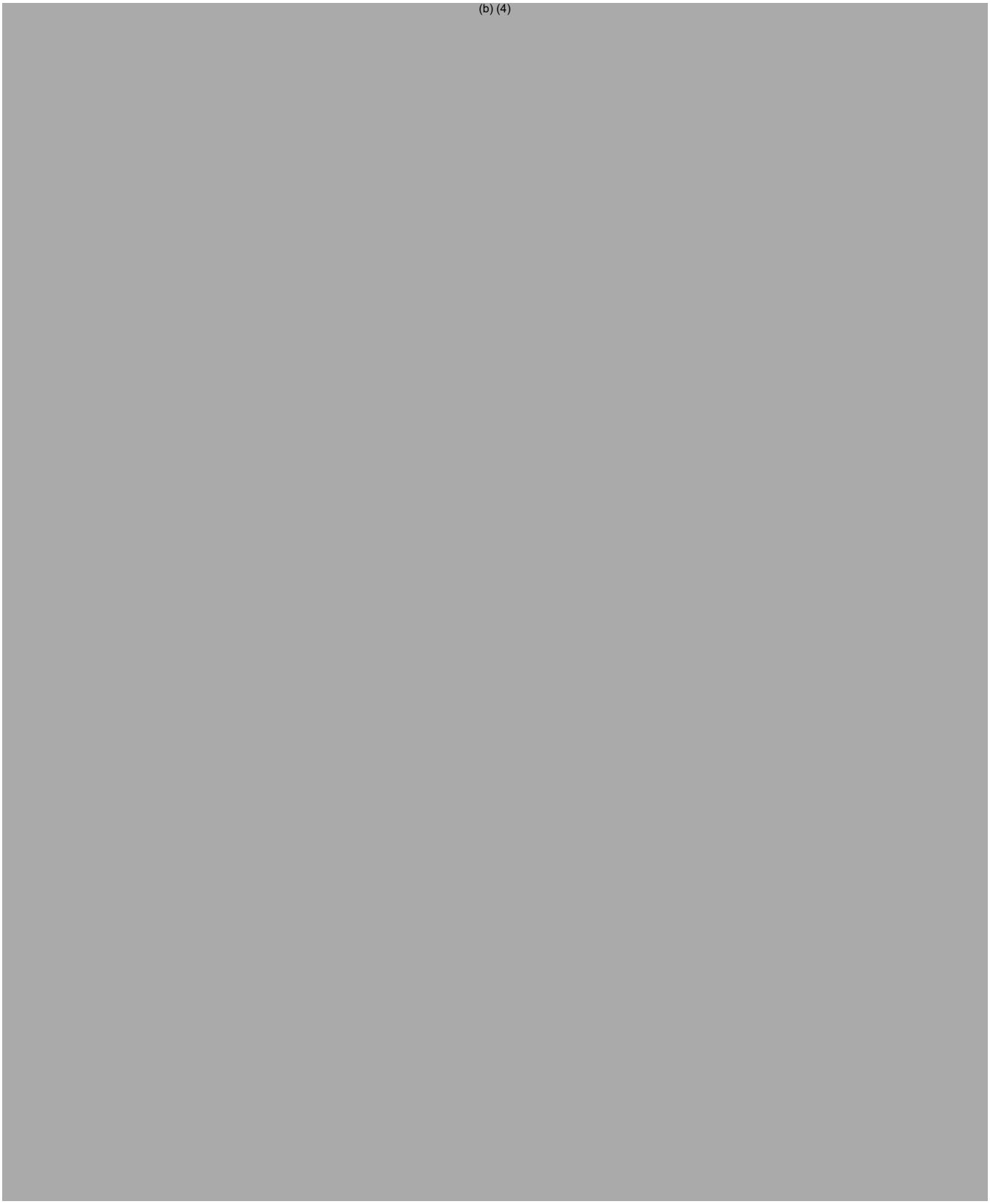

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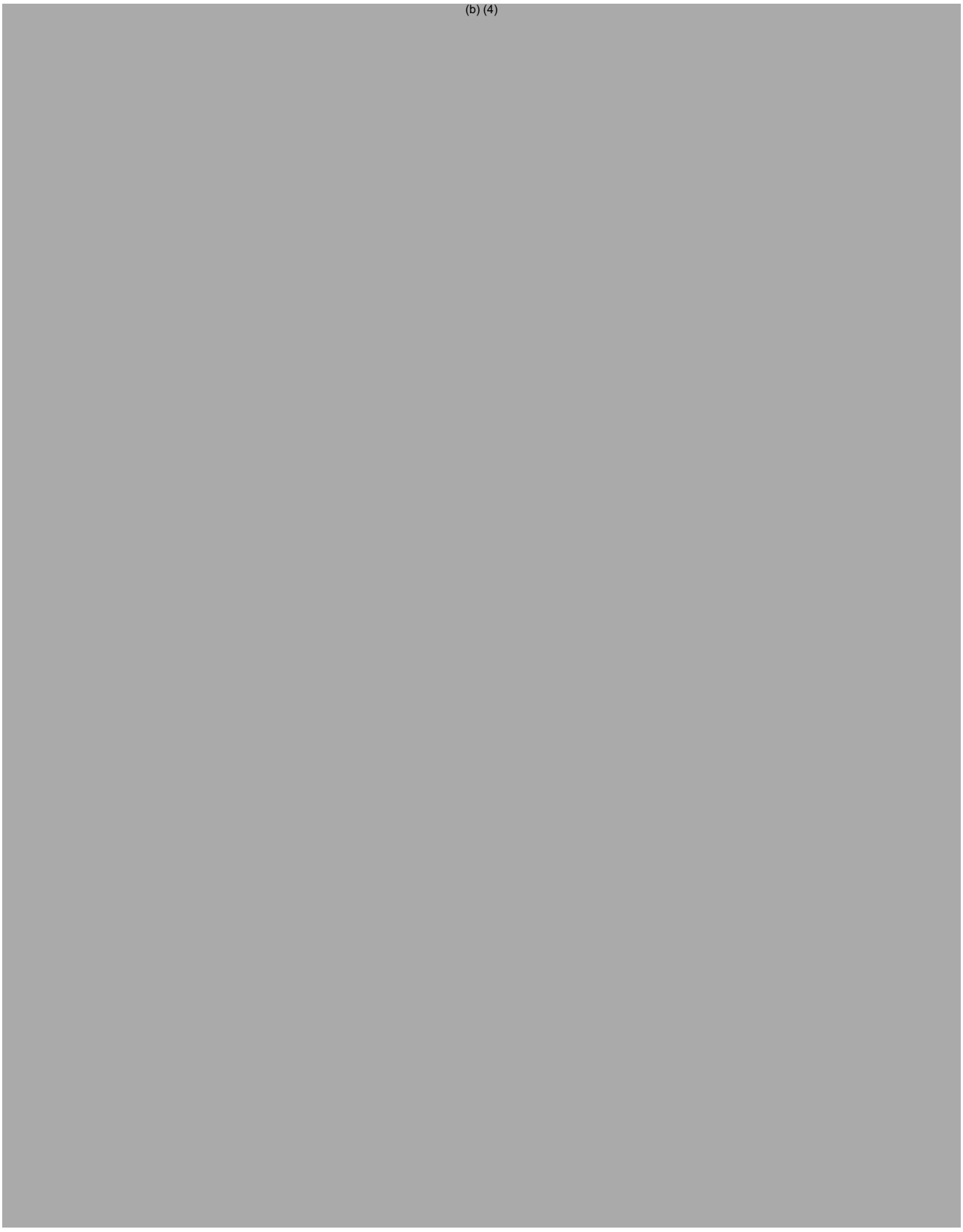

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OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

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

If you have any questions, contact (b) (4) .

Sincerely,

{See appended electronic signature page}

(b) (4)

Center for Drug Evaluation and Research

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/

(b) (4)

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