NDA 021196/S-48
NDA 212690/S-19

SUPPLEMENT APPROVAL

Jazz Pharmaceuticals Ireland Limited
Attention: Arthur Merlin d'Estreux
Sr. Director, Regulatory Affairs Neurosciences
Jazz Pharmaceuticals
2005 Market Street, 21st Floor, Philadelphia, PA 19103

Dear Mr. d'Estreux:

Please refer to your supplemental new drug applications (sNDAs) dated and received May 23, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution 0.5 g/mL and Xyrem (sodium oxybate) oral solution 0.5 g/ml.

These "Changes Being Effected" sNDAs provide for proposed modifications to the approved Xywav and Xyrem Risk Evaluation and Mitigation Strategy (REMS).

We have completed our review of these supplemental applications, as amended. They are approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Xyrem was originally approved on February 27 2015. Xywav was approved on July 21, 2020, and joined the Xyrem REMS to form the Xywav and Xyrem REMS. The most recent REMS modification was approved on May 21, 2025. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS consists of updates to the XYWAV and XYREM REMS Website including a new design and removal of the Frequently Asked Questions. Your proposed modified REMS, submitted on May 23, 2025, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on August 12, 2021.

The REMS assessment plan has been revised to align with the modification.

The REMS Assessment Plan must include but is not limited to, the following information:

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

REMS Implementation and Operations

1. 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), indication, and sex
      iii. Number and percentage of active patients enrolled (patients who received at least one shipment of XYWAV or XYREM during the reporting period) stratified by age, geographic region (defined by US Census), and sex
      iv. Number and percentage of patients who have discontinued XYWAV or XYREM after receiving at least one shipment of XYWAV or XYREM Include demographics of discontinued patients and reasons for discontinuation.
      v. Number and percentage of patients who transitioned from XYREM to XYWAV
      vi. Number and percentage of patients who transitioned from XYWAV to XYREM
   b. Healthcare Providers:
      i. Total number of certified prescribers
      ii. Number and percentage of newly certified healthcare providers stratified by professional designation (i.e. MD, DO, PA, NP), medical specialty, and geographic region (defined by US Census)
      iii. Number and percentage of active certified healthcare providers (healthcare providers who have written at least one prescription for XYWAV or XYREM during the reporting period) stratified by professional designation (i.e. MD, DO, PA, NP), medical specialty, and geographic region (defined by US Census)
   c. Certified Pharmacy
      i. If the Certified Pharmacy was decertified during the reporting period and reasons for decertification.
2. Utilization Data
   a. Number and percentage of XYREM prescriptions (new and refills) dispensed
   b. Number and percentage of XYWAV prescriptions (new and refills) dispensed
   c. Number and percentage of XYREM bottles and shipments sent
   d. Number and percentage of XYWAV bottles and shipments sent

3. REMS Operation and Performance Data
   a. REMS Central Database Report

i. Summary of any REMS-related or system problems identified and a description of any corrective actions taken
ii. 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 or patient access issues

4. REMS Compliance
   a. Audits: Summary of audit activities including but not limited to:
      i. A copy of the audit plan for each audited stakeholder
      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. The status to include completion status
      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. Noncompliance: Summary of all noncompliance events, associated corrective and preventive actions (CAPA) plans, and the status of CAPA plans including but not limited to:
      i. A copy of the Noncompliance Action Plan inclusive of definitions of noncompliance events for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
      ii. Number of prescribers and pharmacy staff involved in more than one noncompliance event or repeated noncompliance events
      iii. Number of patients impacted by noncompliance events
      iv. For each noncompliance event type, report the following information:
         1. Number of occurrences
         2. Source of the noncompliance
         3. Root cause analysis
         4. Action(s) taken in response
         5. Description of any harm experienced by patients
      v. Number and percentage of noncompliance events associated with XYWAV only.
      vi. Number and percentage of noncompliance events associated with XYREM only.
   c. Healthcare Providers

i. Number and percentage of certified prescribers who were disenrolled during the reporting period and reasons for disenrollment. Include if any prescribers were re-certified.
ii. Number of disenrolled prescribers who were associated with a XYWAV or XYREM prescription and number of disenrolled prescribers associated with a XYREM or XYWAV shipment
iii. Number and percentage of XYWAV prescriptions filled from a prescriber who was not enrolled.
iv. Number and percentage of XYREM prescriptions filled from a prescriber who was not enrolled.

d. Certified Pharmacy
i. Number and percentage of XYWAV 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 XYREM prescriptions dispensed for more than a 30 days' supply (first fill) or more than a 90 days' supply (refills) and reasons.
iii. Number and percentage of XYWAV shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and Risk Management Reports (RMRs) completed
iv. Number and percentage of XYREM shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and Risk Management Reports (RMRs) completed.
v. Number and percentage of initial XYWAV shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist.
vi. Number and percentage of initial XYREM shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist.
vii. Number and percentage of XYWAV shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist as required when the patient notified the pharmacy of a new or change in concomitant medication or comorbidity.
viii. Number and percentage of XYREM shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist as required when the patient notified the pharmacy of a new or change in concomitant medication or comorbidity.
ix. Number and percentage of XYWAV shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist for patients that reinitiated therapy after lapse > 6 months.
x. Number and percentage of XYREM shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist for patients that reinitiated therapy after lapse > 6 months.

xi. Number of prescriptions dispensed without verification of current overlapping prescription or disenrollment from other REMS for oxybate products

e. Patients
   i. Number and percentage of patients who were disenrolled from the XYWAV and XYREM REMS and reasons for disenrollment
   ii. Number and percentage of patients associated with more than one prescriber during their therapy
   iii. Number and percentage of patients with overlapping XYWAV or XYREM prescriptions (i.e., more than one active prescription shipped)
   iv. Number and percentage of patients with concurrent XYWAV and XYREM prescriptions
   v. Number and percentage of patients with an overlapping prescription for XYWAV or XYREM and any other oxybate product
   vi. Number of duplicate patients detected by the Certified Pharmacy
   vii. Number and percentage of duplicate patients who were shipped XYWAV or XYREM under more than one name or identifier
   viii. Number and percentage of patients who were shipped or XYWAV or XYREM after being disenrolled
   ix. Number and percentage of patients who requested an early refill of XYWAV 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 requests for early refills.
   x. Number and percentage of patients who requested an early refill of XYREM and reason for 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 requests for early refills.

Safe Use Behaviors

5. Pharmacy Notifications (for both XYWAV and XYREM)
   a. A summary of the notifications by pharmacists to prescribers for both XYWAV and XYREM. For each of the following situations, 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

prescriber's designee) and outcome of XYWAV and XYREM 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 rationale for continuing treatment in response to the notification including the following:
    1. Treatment with XYWAV/XYREM 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 XYWAV or XYREM)
    6. Prescriber's rationale for continued use of sedative hypnotic with XYWAV or XYREM
        a) Sedative hypnotic will not be taken at the same time as XYWAV/XYREM
        b) Sedative hypnotic will be taken at the same time as XYWAV/XYREM
        c) Sedative hypnotic will be taken as a sleep aid
        d) Sedative hypnotic will be taken for different indication per medical need
        e) XYWAV/XYREM dose regimen changed
        f) No rationale provided

ii. Benzodiazepines (e.g., diazepam, alprazolam or any not listed in metric 5.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 XYWAV/XYREM 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 XYWAV or XYREM)
    6. Prescriber's rationale for continued use of benzodiazepine with XYWAV or XYREM
        a) Benzodiazepine will not be taken at the same time as XYWAV/XYREM
        b) Benzodiazepine will be taken at the same time as XYWAV/XYREM
        c) Benzodiazepine will be taken as a sleep aid
        d) Benzodiazepine will be taken for different indication per medical need

e) XYWAV/XYREM dose regimen changed
f) 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

6. Risk Management Reports (RMRs) (for both XYWAV and XYREM)
   a. Number and percentage of RMRs submitted
   b. Number and percentage of unique patients with a 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 (list reasons)
   g. Number and percentage of prescriber-related RMRs
   h. Number and percentage of RMRs that included an adverse event
7. XYWAV and XYREM REMS Patient Counseling Checklist (per reporting period and cumulatively, for both XYWAV and XYREM)
   a. Summary table for both XYWAV and XYREM 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 7.a.i.)
         2. Sedating antidepressants or antipsychotics, sedating anti-epileptics, and sedating antihistamines
         3. General anesthetics
         4. Muscle relaxants
         5. Opioid analgesics
         6. Divalproex sodium or other valproate drug (e.g., valproic acid)

7. Illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB])

b. Summary tables for both XYWAV and XYREM 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

Health Outcomes and/or Surrogates of Health Outcomes

8. Pharmacovigilance/surveillance (per reporting period)
   a. Analysis of serious adverse events and separate summary tables for XYWAV and XYREM of the number of reports of serious adverse events. The summary tables will include the following data fields:date, case report ID, age, sex, serious adverse event(s) reported, outcome (hospitalization or death), associated factor (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 XYWAV and XYREM. All tables should 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 associated with any reported deaths.
         2. Calculation of the overall, and age and sex-specific mortality rates.
         3. Calculation of the standardized mortality rates, adjusted for age and sex, 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.
         3. Intentional misuse
         4. Abuse
         5. Overdose
         6. Diversion
         7. 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

9. Knowledge, Attitude, and Behavior (KAB) Surveys of Patients, Caregivers, Pharmacists, and Healthcare Providers (to be submitted every other year beginning with the April 2023 assessment)

a. Assessment of patients'/caregivers', pharmacists', and healthcare providers' understanding of the following:
    i. The risk of significant CNS and respiratory depression associated with XYWAV and XYREM even at recommended doses
    ii. The contraindicated uses of XYWAV and XYREM
    iii. The potential for abuse, misuse, and overdose associated with XYWAV and XYREM
    iv. The safe use, handling, and storage of XYWAV and XYREM
    v. The XYWAV and XYREM REMS requirements.

10. 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. Provide a breakdown of scores within Module A and B
    b. Summary of the most frequently missed post-training knowledge assessment questions
    c. Summary of potential comprehension or perception issues identified with the post-training knowledge assessment by module
    d. Number of pharmacy staff who did not pass the knowledge assessments.

Overall Assessment of REMS Effectiveness

11. 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.

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) of the FDCA. 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 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 that 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 REMS modifications, 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 212690; NDA 021196 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

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 212690; NDA 021196 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 212690/S-000; NDA 021196/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 212690/S-000; NDA 021196/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 212690/S-000; NDA 021196/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 212690/S-000; NDA 021196/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 REVISIONS FOR NDA 212690; NDA 021196

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, 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

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 more information on submitting REMS in SPL format, please email

FDAREMSwebsite@fda.hhs.gov.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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, call Ermias Zerislassie, Associate Director for Postmarket Regulatory Science, at 301-796-2770.
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Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):
- REMS Document

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/

TIFFANY R FARCHIONE
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