NDA 021196/S-43
NDA 212690/S-12

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 application (sNDA) dated and received December 15, 2022, 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 0.5g/ml.

This Prior Approval sNDA provides for proposed modifications to the approved Xywav and Xyrem Risk Evaluation and Mitigation Strategy (REMS).

We have completed our review of this supplemental application, as amended. It is 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 February 9, 2022. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of adding electronic prescribing functionality to the REMS website to allow prescribers to register for the Drug Enforcement Administration (DEA) Electronic Prescribing for Controlled Substances (EPCS) and submit Xywav or Xyrem Prescription Forms electronically through the REMS website directly to the Certified Pharmacy. The following materials are affected by this proposed modification: REMS Document, Xywav Prescription Form, Xyrem Prescription Form, and Prescriber Brochure, and REMS Website. The pharmacy requirements were changed to verify and document the patient has no other active prescriptions for oxybate products before dispensing Xywav and Xyrem by reviewing the information received from other REMS for oxybate products. The Applicant requirements were changed to include reporting patient and prescriber disenrollment in the Xywav and Xyrem REMS due to suspected abuse, misuse, or diversion to all other REMS for oxybate products and to maintain a process to provide Xywav and Xyrem

prescription information to other pharmacies upon request to verify that the named patient has no other active, overlapping prescriptions for oxybate products and that the patient and prescriber have not been disenrolled from the Xywav and Xyrem REMS for suspected abuse, misuse, or diversion. Additionally, the REMS Document was revised to align with the current Format and Content of a REMS Document Guidance for Industry and the REMS Document Technical Conformance Guide. The Prescriber Enrollment and Patient Enrollment Forms were also revised to align with the changes to the REMS Document. The following materials were also revised to align with the Instructions For Use: Xyrem Brochure for Pediatric Patients and their Caregivers, Xyrem Patient Quick Start Guide, Xywav Brochure for Pediatric Patients and their Caregivers, and the Xywav Patient Quick Start Guide.

Your proposed modified REMS, submitted on December 15, 2022, 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 revised 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.

Program 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 gender
      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 gender
      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 Program Operation and Performance Data
   a. REMS Program Central Database 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. Call center report with number of calls received and a summary of reasons for calls by stakeholder type
      iv. Summary of frequently asked questions by stakeholder type and topic
      v. Summary of any REMS-related problems identified and a description of any corrective actions taken
      vi. 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
      vii. Summary of program or system problems and a description of any corrective actions taken.

4. REMS Program 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 accumulative 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 de-certified 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 or deviation 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 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 and Xyrem prescription and number of

disenrolled prescribers associated with a Xywav and Xyrem 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 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

vii. Number and percentage of Xywav shipments sent to patients without completion of the Xywav and Xyrem REMS Patient Counseling Checklist when the patient notified the pharmacy of a new medication or change in concomitant medication or comorbidity

viii. Number and percentage of initial Xyrem shipments sent to patients without completion of the Xywav and Xyrem REMS Patient Counseling Checklist.

ix. 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

x. Number and percentage of Xyrem shipments sent to patients without completion of the Xywav and Xyrem REMS Patient Counseling Checklist when the patient notified the

pharmacy of a new medication or change in concomitant medication or comorbidity

e. Patients
   i. Number and percentage of patients who were disenrolled from the program 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 prescriptions (more than one active prescription shipped)
   iv. Number and percentage of patients with concurrent Xywav and Xyrem prescriptions
   v. Number of duplicate patients detected by the Certified Pharmacy
   vi. Number and percentage of duplicate patients who were shipped Xywav or Xyrem under more than one name or identifier
   vii. Number and percentage of patients who were shipped Xywav or Xyrem after being disenrolled
   viii. 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.
   ix. 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 pharmacies 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:
   - Treatment with Xywav/Xyrem will be discontinued
   - Sedative hypnotic will be discontinued
   - Dosage of sedative hypnotic has been/will be reduced
   - Information unavailable
   - No action (continue sedative hypnotic with Xywav or Xyrem)
   - Prescriber's rationale for continued use of sedative hypnotic with Xywav or Xyrem
     - Sedative hypnotic will not be taken at the same time as Xywav/Xyrem
     - Sedative hypnotic will be taken at the same time as Xywav/Xyrem
     - Sedative hypnotic will be taken as a sleep aid
     - Sedative hypnotic will be taken for different indication per medical need
     - Xywav/Xyrem dose regimen changed
     - 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:
   - Treatment with Xywav/Xyrem will be discontinued
   - Benzodiazepine will be discontinued
   - Dosage of benzodiazepine has been/will be reduced
   - Information unavailable
   - No action (continue benzodiazepine with Xywav or Xyrem)
   - Prescriber's rationale for continued use of benzodiazepine with Xywav or Xyrem

- Benzodiazepine will not be taken at the same time as Xywav/Xyrem
- Benzodiazepine will be taken at the same time as Xywav/Xyrem
- Benzodiazepine will be taken as a sleep aid
- Benzodiazepine will be taken for different indication per medical need
- Xywav/Xyrem 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

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. REMS Program Patient Counseling Checklist for both Xywav and Xyrem
   a. Summary table for both Xywav and Xyrem 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. 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:

- Benzodiazepines (e.g., diazepam, alprazolam or any not listed in metric 7.a.i.)
- Sedating antidepressants or antipsychotics, sedating anti epileptics, and sedating antihistamines
- General anesthetics
- Muscle relaxants
- Opioid analgesics
- Divalproex sodium or other valproate drug (e.g.,valproic acid)
- Illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB]).

b. Summary tables for both Xywav and Xyrem 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:

c. Sleep apnea

d. 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, gender, 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 or 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 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 ~~and~~
    2) Use with alcohol.
    3) Intentional misuse
    4) Abuse
    5) Overdose
    6) 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 ~~Program~~ 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 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:

Submit your proposed audit plan and noncompliance plan for FDA review within 30 days of the date of this letter.

Prominently identify the submission 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- AUDIT PLAN and NONCOMPLIANCE PLAN.

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

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

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.

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, PharmD, Associate Director for Postmarket Regulatory Science, at 301-796-2770.

Sincerely,

{See appended electronic signature page}

Marc Stone, M.D.
Deputy Director for Safety
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- REMS documents and REMS materials

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/

MARC B STONE
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