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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.