DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021196/S-030

SUPPLEMENT APPROVAL

Jazz Pharmaceuticals
Attention: Wheatley Spence, MS
Associate Director, Regulatory Affairs
1818 Market Street, Suite 2350
Philadelphia, PA 19103

Dear Ms. Spence:

Please refer to your Supplemental New Drug Application (sNDA) dated April 27, 2018, received April 27, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xyrem® (sodium oxybate) oral solution, 500 mg/mL.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated May 18, 2018.

This Prior Approval supplemental new drug application proposes to expand the use of Xyrem for the treatment of cataplexy or excessive daytime sleepiness to pediatric patients 7 years of age and older with narcolepsy, and proposes modifications to the approved Xyrem risk evaluation and mitigation strategy (REMS).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your April 27, 2018, submission includes final printed labeling (FPL) for your Prescribing Information, Instructions for Use, and Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this FPL is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Xyrem was originally approved on February 27, 2015, and the most recent modification was approved on July 15, 2015. The REMS consists of a Medication Guide, 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 primarily of modifications to the REMS document and appended materials to align with labeling changes related to the new pediatric indication.

In accordance with section 505-1 of the FDCA, we have determined that the following additional REMS modifications are necessary to minimize burden on the healthcare delivery system of complying with the REMS:

Medication Guide: We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication

Guide as an element of the approved REMS to ensure that the benefits of Xyrem outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on April 27, 2018, amended and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on February 27, 2015.

The revised XYREM REMS Assessment Plan will include, but is not limited to, the following information:

For the 6-month assessment after approval of the finalized REMS and all subsequent REMS assessments submitted thereafter:

1.a. Program statistics (totals for the current REMS assessment reporting period and cumulative totals from approval of the finalized REMS, if feasible)

Jazz Pharmaceuticals will report to FDA the following:

- **Patients:**
  - Number of patients enrolled
  - Number of patients enrolled who received at least one shipment of XYREM
  - Number of duplicate patients detected by the Certified Pharmacy
  - Number of patients associated with more than one prescriber during their therapy
  - Number of patients who were disenrolled from the program and reasons for disenrollment
  - Number of patients who have discontinued XYREM after receiving at least one shipment of XYREM
    - Proportion of discontinued patients who were associated with a report of a serious adverse event, including death
  - Age and gender of enrolled patients.
- **Prescribers:**
  - Number of prescribers certified
  - Number of certified prescribers who have written at least one prescription for XYREM
  - Number of certified prescribers by specialty
  - Number of certified prescribers who were disenrolled during the reporting period and reasons for disenrollment

- Number of disenrolled prescribers who were associated with a XYREM prescription and number of disenrolled prescribers associated with a XYREM shipment
- Number of patients by current enrolled prescriber.

- **Certified Pharmacy**
  - If the Certified Pharmacy was decertified during the reporting period and reasons for decertification.

1.b. Dispensing and compliance data (totals for the current REMS assessment reporting period and cumulative totals from approval of the finalized REMS)

Jazz Pharmaceuticals will monitor and track shipping and handling of XYREM and report to FDA the following:

- Total number of prescriptions
- Total number of bottles and shipments sent
- Total number of first-time fills and refills
- Number of shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and RMRs completed
- Number of patients prescribed a daily dose greater than 9 g
- Number of prescriptions filled from a prescriber who was not enrolled
- Number of prescriptions for more than a 30 days' supply (first fill) or more than a 90 days' supply (refills) and reasons
- Number of RMRs submitted to the sponsor
  - Number of patients with an RMR
  - Number of patients with multiple RMRs
  - Number of alerts generated from RMRs
  - Number of RMRs generated from early refill requests
  - Number of RMRs generated for other reasons (list reasons)
  - Number of prescriber-related RMRs
- Number of patients with overlapping prescriptions (more than one active prescription)
- Number of duplicate patients who were shipped XYREM under more than one name or identifier
- Number of patients who were shipped XYREM after being disenrolled
- Number of patients who requested an early refill and reason for the request
  - Number of requests approved
  - Number of requests denied by the prescriber

  - Number of requests denied by the Certified Pharmacy
  - Number of patients with multiple requests for early refills
- Number of initial shipments sent to patients without completion of the XYREM REMS Program Patient Counseling Checklist
- Summary table from XYREM REMS Program Patient Counseling Checklists of the number of patients taking the following concomitant medications and who subsequently received at least one shipment of XYREM:
  - Sedative hypnotics
  - Alcohol
  - Other potentially interacting agents:
    - Sedating antidepressants, antipsychotics, or anti-epileptics
    - General anesthetic
    - Muscle relaxants
    - Opioid analgesics
    - Divalproex sodium or other valproate drug (e.g., valproic acid)
    - Illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB])
- Summary table from XYREM REMS Program Patient Counseling Checklists of the number of patients who have been diagnosed with the following conditions and who subsequently received at least one shipment of XYREM:
  - Sleep apnea
  - Asthma, COPD, or other conditions affecting the respiratory system
- Number of notifications by pharmacists to prescribers for the following situations and the outcome of the notification (dispensed XYREM, counseled patient, and summary of other actions):
  - Use with contraindicated medications (concomitant sedative hypnotics)
  - Use with other concomitant CNS-depressant medications (sedating antidepressants or antipsychotics, sedating anti-epileptics, general anesthetics, muscle relaxants, opioid analgesics, or illicit CNS depressants)
  - Patient report of alcohol use
  - Patient report of diagnosis of sleep apnea
  - Patient report of diagnosis of asthma, COPD, or other conditions affecting breathing
  - Suspected abuse, misuse, or diversion
  - Alerts regarding potential abuse, misuse, or diversion on the patient profiles
  - Prescription error
  - Early refill requests

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