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

1.c. Pharmacovigilance/surveillance (totals for the current REMS assessment reporting period and cumulative totals from start of program, if feasible)

Jazz Pharmaceuticals will provide to FDA the following:

- Summary tables of the number of reports of serious adverse events to include all outcomes of death, emergency department visits (when admitted to hospital), or hospitalizations resulting from or associated with the following:
  - Use with concurrent sedative hypnotics and alcohol
  - Intentional misuse
  - Abuse
  - Overdose
  - Medication error
- Cases of Sexual Abuse.

The summary tables will include the following data fields (CIOMS II line listings): date, report ID, report type, notifier, age, gender, start and stop date, dose, frequency, onset date, system organ class, outcome, and causality.

1.d. Program infrastructure and performance surveillance (information for the current REMS assessment reporting period)

Jazz Pharmaceuticals will provide to FDA the following:

- Call center report with number of calls received
- Summary of frequently asked questions
- Summary of any REMS-related problems identified
- Summary of program or system problems and a description of any corrective actions taken

1.e. A report on periodic assessments of the dispensing of the Medication Guide in accordance with 21 CFR 208.24

Jazz Pharmaceuticals will report to FDA on the dispensing of the Medication Guide as part of the REMS assessments.

1.f. With respect to REMS goals, an assessment of the extent to which the Elements to Assure Safe Use are meeting the goals or whether the goals or such elements should be modified

Jazz Pharmaceuticals will institute a system of oversight and review to evaluate whether the REMS is meeting its goals. If Jazz Pharmaceuticals determines, based on the results of the assessments, surveillance, and knowledge assessments, that modifications to the XYREM REMS program are needed (or that an element is no longer needed) to continue to ensure that the benefits of XYREM outweigh the risks and that the REMS is not unduly burdensome to

patient access or the healthcare system the company will submit a prior approval supplement to FDA proposing a revised REMS prior to implementing any changes to the approved REMS.

For the 12-month assessment after approval of the finalized REMS and all subsequent REMS assessments submitted thereafter:

1.g. Assessment of patients'and prescribers' understanding of the following:

- The risk of significant CNS and respiratory depression associated with XYREM even at recommended doses
- The contraindicated uses of XYREM
- The potential for abuse, misuse, and overdose associated with XYREM
- The safe use, handling, and storage of XYREM
- The XYREM REMS Program requirements.

Patient and prescriber knowledge assessments are described in Sections 5.j and 5.k and provided in Appendix 2 of the REMS supporting document.

1.h. Certified Pharmacy knowledge assessments

- Assessment of the understanding of all Certified Pharmacy staff involved in the XYREM REMS Program of the following:
  - The approved indications for XYREM
  - The abuse potential of XYREM
  - The contraindication of use of XYREM with sedative hypnotics and alcohol
  - The risk of significant CNS and respiratory depression associated with XYREM even at recommended doses
  - The XYREM REMS Program requirements
  - The types of information in the Central Database
  - Monitoring patients for signs of inappropriate prescribing, abuse, misuse, and diversion
  - The requirement to report all potential adverse events
- Assessment of pharmacists' understanding of the following:
  - Requirements for limiting the first prescription to a one-month supply and subsequent prescriptions to no more than a three-month supply
  - Prescriber notification requirements
  - Requirements for validating the prescriber's and patient's enrollment
  - The ability to disenroll a prescriber or patient for noncompliance with the XYREM REMS Program
  - Requirements for validating a XYREM prescription
  - Requirement for completing the XYREM REMS Program Patient Counseling Checklist

- Actions taken if the patient is using a contraindicated medication or other potentially interacting agent
- Patient counseling information
- Requirements to consult with the prescriber when clarification is needed for a prescription and/or for an early refill request
- Requirements for completing XYREM REMS Program RMRs
- Requirements for shipment of XYREM to the patient

The XYREM REMS Program Certified Pharmacy Knowledge Assessments are described in Section 5.l and provided in Appendix 1 of the REMS supporting document.

1.i. A summary report of audits of the Certified Pharmacy conducted during the assessment period

Jazz Pharmaceuticals will provide a summary of the audits of the Certified Pharmacy that were conducted during the assessment period, including the topics covered during the audit and the number of significant observations.

1.j. Patient knowledge survey

A representative sample of patients will be surveyed using a structured questionnaire annually following the first formal XYREM REMS Program assessment. The objective is to assess their knowledge of the key risk information and REMS requirements, including the serious risks associated with XYREM. The knowledge survey will be conducted according to industry standards and will assess patients and caregivers of pediatric patients who have received XYREM for at least one month.

The protocol includes details on the sample size and associated confidence intervals for various response rates: selection criteria for defining the sample, the expected number of patients or caregivers to be surveyed, recruitment strategies, how and when the surveys will be administered, an explanation of controls used to minimize bias, an explanation of the controls used to compensate for the limitations associated with the methodology, the survey instruments (questionnaires and/or moderator's guide), and any available background information on testing of survey questions and correlation to the information of the Medication Guide, the XYREM REMS Program Patient Quick Start Guide, and the XYREM REMS Program Brochure for Pediatric Patient and Their Caregivers.

Survey data collection will be completed approximately 10 months after implementation of the REMS, thus enabling XYREM knowledge assessments to be submitted to the FDA at the 12-month REMS assessment, at all subsequent REMS assessments, and as needed following substantive changes to the REMS-related educational materials. The protocol for the patient survey is provided in Appendix 2 of the REMS supporting document.

Data from the patient survey will be reported as descriptive statistics for the survey administration, study population, and survey questions. Results will include numbers of patients, patient contacts by the Certified Pharmacy, patient demographics, and response data showing level of patient understanding of the risks associated with XYREM use.

1.k. Prescriber knowledge survey

A representative sample of prescribers will be surveyed annually following the first formal XYREM REMS Program assessment. The objective is to assess their knowledge of the XYREM REMS key risk information and program requirements. The goal of this survey initiative will be to determine whether the XYREM REMS Elements to Assure Safe Use are effective in educating prescribers about the key risk information and the procedures to be followed in the XYREM REMS. The survey will be conducted according to industry standards and will assess prescribers who have prescribed XYREM.

The protocol includes details on the sample size and the associated confidence intervals for response rates, selection criteria for defining the sample, the expected number of prescribers to be surveyed, recruitment strategies, how and when the surveys will be administered, an explanation of the controls used to minimize bias, an explanation of the controls used to compensate for the limitations associated with the methodology, the survey instruments (questionnaires and/or moderator's guide), and any available background information on testing of survey questions and correlation to the messages of the prescribing information and XYREM REMS Program Prescriber Brochure.

Survey data collection will be completed approximately 10 months following implementation of the REMS, thus enabling XYREM knowledge assessments to be submitted to the FDA at the 12-month REMS assessment, at all subsequent assessments, and as needed following substantive changes to the REMS-related educational materials. The protocol for the prescriber survey is provided in Appendix 2 of the REMS supporting document. Results will include numbers of prescribers, prescriber contacts by the Certified Pharmacy, prescriber demographics, and response data showing level of prescriber understanding of safe use of XYREM, including approved indications; contraindications; risk of severe CNS/respiratory depression; abuse, misuse, and diversion; and death.

1.l. Certified Pharmacy training knowledge assessments

All Certified Pharmacy staff involved in the XYREM REMS Program will be required to complete Module A of the XYREM REMS Program Certified Pharmacy Training at least annually. In addition, all pharmacists involved in dispensing XYREM under the XYREM REMS Program will be required to complete Module B of the XYREM REMS Program Certified Pharmacy Training at least annually. A knowledge assessment must be successfully completed for each module as part of the training requirement. Successful completion of the knowledge assessments requires an 80% accuracy level. The Module A and Module B Knowledge Assessments are provided in Appendix 1 of the REMS supporting document.

The following metrics will assess the post-training knowledge assessment:

A. Number of completed post-training knowledge assessments including method of completion and number of attempts to complete by module
B. Summary of the most frequently missed post-training knowledge assessment questions by module
C. A summary of potential comprehension or perception issues identified with the post-training knowledge assessment by module

1.m. Surveillance and monitoring

Jazz Pharmaceuticals will periodically monitor available safety databases, such as those established by), the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS), the National Forensic Laboratory Information System, the National Drug Threat Assessment, and the for any information regarding abuse, misuse, or diversion of sodium oxybate. Any relevant information will be included in the REMS assessments.

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 1 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 21196 REMS ASSESSMENT METHODOLOGY

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 21196 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 21196/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 21196/S-000 PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 21196/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 21196/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 21196

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

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the 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 SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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 Vandna Kishore, Regulatory Project Manager, at Vandna.Kishore@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- REMS

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/

NICHOLAS A KOZAUER on behalf of ERIC P BASTINGS
10/26/2018