DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021196/S-015

SUPPLEMENT APPROVAL

Jazz Pharmaceuticals
Attention: Jennifer Ekelund
Vice President, US Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Ekelund:

Please refer to your Supplemental New Drug Application (sNDA) dated August 29, 2008, received September 2, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and in accordance with section 909(b)(1) of the Food and Drug Administration Amendments Act of 2007 (FDAAA) for Xyrem (sodium oxybate) 500 mg/ml oral solution. Under section 909(b)(1) of FDAAA, we identified Xyrem as a product deemed to have in effect an approved risk evaluation and mitigation strategy (REMS) because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 314.500 et seq. (Subpart H).

We also acknowledge receipt of your submissions dated November 13, 2008, August 25 and 31, and October 7, 2009, February 3 and August 26, 2011, January 31, April 13, November 21, and December 20, 2012, June 29, July 17, September 10, and October 8, 2013, and April 11 and 22, and November 7, 2014.

This "Prior Approval" supplemental new drug application provides for a REMS that includes a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In accordance with section 505-1 of the FD&C Act, we have determined that a REMS is necessary for Xyrem to ensure that the benefits of the drug outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of Xyrem.

In accordance with section 505-1 of the FD&C Act, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Xyrem poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Xyrem. FDA has determined that Xyrem is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the

risks could affect patients' decisions to use, or continue to use, Xyrem. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Xyrem.

Pursuant to 505-1(f)(1), we have also determined that elements necessary to assure safe use are required as part of a REMS to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Xyrem.[1] The elements to assure safe (ETASU) use will mitigate the aforementioned risks by ensuring that, prior to filling Xyrem prescriptions, pharmacy controls exist that screen for concomitant use of sedative-hypnotics and other potentially interacting agents, monitor for inappropriate prescribing, misuse, abuse, and diversion, and notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse or misuse. In addition, the ETASU will mitigate the risks by informing prescribers, pharmacists, and patients of the risk of significant central nervous system and respiratory depression associated with Xyrem, the contraindication of use of Xyrem with sedative-hypnotics and alcohol, the potential for abuse, misuse, and overdose associated with Xyrem, and the safe use, handling, and storage of Xyrem.

Your proposed REMS, submitted on November 7, 2014, and appended to this letter, is approved. The REMS consists of a Medication Guide, ETASU, an implementation system, and a timetable for submission of assessments of the REMS.

FDA initially approved Xyrem in July 2002 under the restricted distribution provisions in 21 CFR Part 314 Subpart H. Sodium oxybate, which is a Schedule III controlled substance under the Controlled Substances Act (CSA), is associated with the risks of abuse and misuse. Sodium oxybate, the active ingredient of Xyrem, is the sodium salt of gamma-hydroxybutyrate (GHB), which is a Schedule I controlled substance under the CSA. Abuse of GHB either alone or in combination with other CNS depressants is associated with adverse reactions including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with amnesia, particularly when combined with alcohol, has proven to be dangerous for voluntary and involuntary users (e.g., assault victims).

When Congress passed FDAAA in 2007, it set forth a comprehensive statutory framework that requires a careful balance between the need to evaluate and mitigate risk of a drug to ensure that its benefits outweigh its risks, and the potential burdens of REMS elements on patient access and the health care delivery system. In addition, Congress expressly prohibited the use of ETASU to "block or delay approval" of applications under sections 505(b)(2) and 505(j) of the FD&C Act.[2] For drugs previously approved under Subpart H with restricted distribution, like Xyrem, FDAAA established that they were "deemed to have in effect an approved [REMS] under Section 505-1

[1] The goal of mitigating diversion in this REMS refers to preventing the sale or transfer of the drug outside the framework of the REMS in order to mitigate the risks of central nervous system depression, respiratory depression, abuse, and misuse.

[2] FD&C Act Section 505-1(f)(8).

of the [FD&C] Act," and required the submission of a proposed REMS within 180 days for FDA's review and approval.[3]

FDA is mindful of the statutory requirement under the FD&C Act that ETASU be "commensurate with the specific serious risk[s] listed in the labeling" of the drug, that ETASU "not be unduly burdensome on patient access to the drug," and "to the extent practicable," that ETASU be structured "so as to minimize their burden on the health care delivery system."[4] We also note that it is part of FDA's statutory mandate to approve generic drugs that meet the standard for approval.[5]

Pursuant to these statutory provisions, FDA has sought to finalize and approve the REMS for Xyrem since 2008. In doing so, we have faced repeated, lengthy delays. The REMS you submitted on November 7, 2014, which we are now approving, contains a requirement that Xyrem be distributed only by a single pharmacy. Jazz's position that a single pharmacy is critical to the safe use of Xyrem has not been a consistent one. In 2009, Jazz submitted a supplemental NDA for a new indication for Xyrem for treatment of fibromyalgia in which it proposed to include multiple certified pharmacies.[6]

However, by early 2011, after FDA declined to approve the fibromyalgia indication, Jazz changed its position. By that time, Jazz had been granted several patents related to its single pharmacy distribution system. In its 2013 SEC filings, Jazz noted that it expected FDA modifications to the Xyrem REMS and stated that, "depending on the extent to which certain provisions of our Xyrem deemed REMS which are currently protected by our method of use patents covering the distribution of Xyrem are changed as part of updating our REMS documents, the ability of our existing patents to protect our Xyrem distribution system from generic competitors may be reduced."[7] This statement, in conjunction with Jazz's change in position regarding the necessity of the single pharmacy requirement, suggests Jazz's awareness that the Xyrem REMS could have the effect of blocking or delaying approval of generic versions of Xyrem. Such an outcome would reflect the use of REMS to block or delay generic competition in a manner inconsistent with section 505-1(f)(8). It would also place an unjustified burden on patient access and on the healthcare delivery system.

FDA is approving the REMS Jazz submitted on November 7, 2014, closing a chapter on a REMS that has been pending for 7 years -- far longer than could have been reasonably anticipated when FDAAA was enacted. Our action approving the REMS submitted by Jazz should not be construed or understood as agreement with Jazz that limiting dispensing to a single pharmacy is

[3] FDAAA Section 909(b)(1).
[4] FD&C Act Section 505-1(f)(2)(A), (C), and (D).
[5] FD&C Act Section 505(j).
[6] Transcript of the Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee (Aug. 20, 2010) at 99 ("NDA 22-531, sodium oxybate for fibromyalgia indication, was submitted to the agency on December 11, 2009") available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM225445.pdf.
[7] Form 10-Q, September 30, 2013, at 54.

the only way to ensure that the benefits of Xyrem outweigh the risks under section 505-1 of the FD&C Act. We continue to be concerned that limiting the distribution of Xyrem to one pharmacy imposes burdens on patient access and the healthcare delivery system. No other currently approved REMS requires a sponsor to limit dispensing to a single pharmacy.

At this time, FDA finds that the REMS approved today meets the applicable statutory standards. As with all REMS, FDA intends to evaluate the Xyrem REMS, including the burdens it imposes, on an ongoing basis and will require modifications as appropriate.

The REMS assessment plan should include, but is not limited to, the following:

For the 6-month assessment and all subsequent REMS assessments submitted thereafter:

1. 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.

2. 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 >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 Risk Management Reports 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 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])
- 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.

3. 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.

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.

4. 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.

5. 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.

6. 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:

7. 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.

8. 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 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 Risk Management Reports
        - Requirements for shipment of XYREM to the patient

9. 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 numbers of significant observations.

10. 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 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 and the XYREM REMS Program Patient Quick Start Guide.

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 and the survey instrument are provided in Appendix 2 of the 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.

11. 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 and the survey instrument are provided in Appendix 2 of the 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.

12. 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 Supporting Document.

13. Surveillance and monitoring

Jazz Pharmaceuticals will periodically monitor available safety databases, such as those established by the Drug Abuse Warning Network (DAWN), 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 Society for Forensic Toxicologists (SOFT) for any information regarding abuse, misuse, or diversion of sodium oxybate. Any relevant information will be included in the REMS assessments.

In addition to the assessments submitted according to the timetable included in the approved REMS, 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 FD&C Act.

Under section 505-1(g)(2)(C), FDA may require the submission of a REMS assessment if FDA determines that that an assessment is needed to evaluate whether the approved strategy should be modified to ensure the benefits of the drug outweigh the risks of the drug or minimize the burden on the health care delivery system of complying with the strategy.

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 021196 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - 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.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021196 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021196
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021196
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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 (301) 796-4193.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
02/27/2015