

## **XYREM REMS DOCUMENT**

### **NDA 21-196 XYREM<sup>®</sup> (SODIUM OXYBATE) ORAL SOLUTION**

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### **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

#### **I. GOAL:**

The goal of the XYREM REMS is to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of XYREM by:

- A. Informing prescribers, pharmacists, and patients of:
  - 1. The risk of significant CNS and respiratory depression associated with XYREM
  - 2. The contraindication of use of XYREM with sedative hypnotics and alcohol
  - 3. The potential for abuse, misuse, and overdose associated with XYREM
  - 4. The safe use, handling, and storage of XYREM
- B. Ensuring that pharmacy controls exist prior to filling prescriptions for XYREM that:
  - 1. Screen for concomitant use of sedative hypnotics and other potentially interacting agents
  - 2. Monitor for inappropriate prescribing, misuse, abuse, and diversion of XYREM
  - 3. Notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion.

#### **II. REMS ELEMENTS:**

##### **A. Medication Guide**

A Medication Guide will be dispensed with each XYREM prescription in accordance with 21 CFR 208.24.

[The XYREM Medication Guide](#) is part of the REMS and is appended.

## **B. Elements to Assure Safe Use**

### **1. Healthcare Providers who prescribe XYREM are specially certified.**

- a.** Jazz Pharmaceuticals will ensure that healthcare providers who prescribe XYREM are specially certified in the XYREM REMS Program. To become certified to prescribe XYREM, each prescriber must complete and submit to the XYREM REMS Program the [XYREM REMS Program Prescriber Enrollment Form](#), which includes the prescriber agreeing to:
  - i.** Review the [Prescribing Information \(PI\)](#) and the [XYREM REMS Program Prescriber Brochure](#).
  - ii.** Screen each patient for whom XYREM is prescribed for:
    - a. History of alcohol or substance abuse
    - b. History of sleep-related breathing disorders
    - c. History of compromised respiratory function
    - d. Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
    - e. History of depression or suicidality.
  - iii.** Counsel each patient prior to initiating therapy regarding the serious risks and safe use, handling, and storage of XYREM.
  - iv.** Enroll each patient in the XYREM REMS Program by completing and submitting the [XYREM REMS Program Patient Enrollment Form](#) to the XYREM REMS Program.
  - v.** Evaluate each patient within the first 3 months of starting XYREM therapy, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while on XYREM therapy.
    - a. Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
    - b. Serious adverse events
    - c. Signs of abuse and misuse, including:
      1. An increase in dose or frequency of dosing
      2. Reports of lost, stolen, or spilled medication

3. Drug-seeking behavior.

- vi. Report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death, and any cases of suspected abuse, misuse, or diversion to Jazz Pharmaceuticals.
- b. The prescriber will complete the [XYREM REMS Program Prescription Form](#) for each new prescription and submit the form to the XYREM REMS Program. By completing and signing this form, the prescriber acknowledges:
  - i. Having an understanding of:
    - a. The approved indications of XYREM:
      - 1. Treatment of cataplexy in narcolepsy
      - 2. Treatment of excessive daytime sleepiness in narcolepsy
    - b. The serious risks associated with XYREM
    - c. The Prescribing Information (PI) and the [XYREM REMS Program Prescriber Brochure](#).
  - ii. Having screened the patient for the following:
    - a. History of alcohol or substance abuse
    - b. History of sleep-related breathing disorders
    - c. History of compromised respiratory function
    - d. Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
    - e. History of depression or suicidality.
  - iii. Having counseled the patient on:
    - a. The serious risks associated with XYREM
    - b. Contraindications (alcohol and sedative hypnotics) and implications of concomitant use of XYREM with other potentially interacting agents
    - c. Preparation and dosing instructions for XYREM
    - d. Risk of abuse and misuse associated with XYREM
    - e. Risk of operating hazardous machinery, including automobiles or airplanes, for the first 6 hours after taking a dose of XYREM
    - f. Safe use, handling, and storage of XYREM.
  - iv. That XYREM is medically appropriate for the patient.

- v. Having listed all known prescription and nonprescription medications and doses on the XYREM REMS Program Prescription Form.
- c. Jazz Pharmaceuticals will:
- i. Ensure that the XYREM REMS Program Prescriber Enrollment Form can be completed via facsimile, mail, E-mail, or other means; that the XYREM REMS Program Patient Enrollment Form can be completed via facsimile, mail, or other means; and that the XYREM REMS Program Prescription Form can be completed via facsimile or mail.
  - ii. Ensure that materials appended to the XYREM REMS document will be made available through the XYREM REMS Program website ([www.XYREMREMS.com](http://www.XYREMREMS.com)) or by calling the XYREM REMS Program at 1-866-997-3688.
  - iii. Ensure that a prescriber is enrolled in the XYREM REMS Program only after verification that the XYREM REMS Program Prescriber Enrollment Form is complete and all enrollment requirements are met.
  - iv. Ensure that prescribers are notified when they are successfully enrolled in the XYREM REMS Program and are eligible to prescribe XYREM.
  - v. Maintain a secure and validated XYREM REMS Program Central Database containing information related to prescriber and patient enrollment, prescriptions, and concomitant medications (see [Section II.C.1.c.](#)).
  - vi. Ensure that enrolled prescribers continue to meet the requirements of the XYREM REMS Program and can disenroll non-compliant prescribers if the requirements are not met.
- d. The following are part of the XYREM REMS Program and are appended:
- i. [XYREM REMS Program Prescriber Enrollment Form](#)
  - ii. [XYREM REMS Program Prescriber Brochure](#)
  - iii. [XYREM REMS Program Patient Enrollment Form](#)
  - iv. [XYREM REMS Program Prescription Form](#)
  - v. [XYREM REMS Program Patient Quick Start Guide](#)
  - vi. [XYREM REMS Program website \(www.XYREMREMS.com\)](http://www.XYREMREMS.com).

**2. XYREM will be dispensed only by the central pharmacy that is specially certified.**

- a.** Jazz Pharmaceuticals will certify a central pharmacy that is contracted with Jazz Pharmaceuticals to distribute and dispense XYREM (the XYREM REMS Program Certified Pharmacy). XYREM will not be stocked in retail pharmacy outlets. To become certified in the XYREM REMS Program, the pharmacy must agree to:
- i.** Dispense XYREM only to patients enrolled in the XYREM REMS Program pursuant to a valid prescription written by a prescriber enrolled in the XYREM REMS Program (see Section II.B.1.b).
  - ii.** Ensure that all pharmacy staff involved in the XYREM REMS Program complete the [XYREM REMS Program Pharmacy Training Program](#).
  - iii.** Ensure that all XYREM REMS Program pharmacists also complete the pharmacist training in the XYREM REMS Program Pharmacy Training Program.
  - iv.** Utilize the secure and validated XYREM REMS Program Central Database.
  - v.** Provide 24-7 toll-free access to a XYREM REMS Program pharmacist.
  - vi.** Ship XYREM directly to each patient or a patient-authorized adult designee, and track and verify receipt of each shipment of XYREM.
  - vii.** Limit the first shipment to a one-month supply of XYREM, and subsequent shipments to no more than a three-month supply of XYREM.
  - viii.** Document and report all potential adverse events reported by all sources, including any CNS depression, respiratory depression, loss of consciousness, coma, and death, and any cases of suspected abuse, misuse, or diversion to Jazz Pharmaceuticals.
- b.** Prior to dispensing XYREM, the XYREM REMS Program Certified Pharmacy ensures that a XYREM REMS Program pharmacist will:
- i.** Ensure the completion of the [XYREM REMS Program Patient Counseling Checklist](#) and its requirements and the documentation of information received in the XYREM REMS Program Central Database.
  - ii.** Validate each XYREM REMS Program Prescription, by:

- a. Verifying in the XYREM REMS Program Central Database that both the prescriber and patient are enrolled in the XYREM REMS Program and that the patient has no other active XYREM prescription
- b. Confirming all prescription information, including patient name and two additional identifiers, prescriber name and information, dose, titration information (if applicable), number of refills, dosing directions, total quantity (days' supply), and concomitant medications.
- iii. Review the patient information contained in the XYREM REMS Program Central Database, including:
  - a. Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents that either are unknown to the prescriber or pose a high risk of serious interaction with XYREM
  - b. Alerts and [XYREM REMS Program Risk Management Reports](#) (RMRs) regarding potential abuse, misuse, or diversion.
- c. The XYREM REMS Program Certified Pharmacy will ship XYREM directly to each patient using an overnight service. In addition, the XYREM REMS Program Certified Pharmacy will verify that:
  - i. The shipment will be sent to a patient's confirmed shipping address
  - ii. The patient or patient-authorized adult designee will be available to receive the shipment
  - iii. The XYREM Medication Guide is included with each shipment, and a copy of the Patient Quick Start Guide is provided to a new patient who has not already received it from the prescriber
  - iv. Receipt of each shipment is confirmed and shipment and receipt dates are entered into the XYREM REMS Program Central Database.
- d. The XYREM REMS Program Certified Pharmacy will monitor and report to Jazz Pharmaceuticals all instances of patient or prescriber behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion of XYREM.
  - i. The XYREM REMS Program Certified Pharmacy will document these events, including all requests for early refills, in the XYREM REMS Program Central Database by completing an RMR.

- ii. Prior to granting an early refill request or if abuse, misuse, or diversion is suspected, the pharmacist will review the patient's RMR history and any alerts, and ensure the request or concern has been discussed with the prescriber prior to shipping XYREM.
  - iii. All reports of lost, stolen, destroyed, or spilled drug will be documented in the XYREM REMS Program Central Database by completing an RMR.
  - iv. Repeated reports of lost, stolen, destroyed, or spilled drug may be documented as an alert to the patient profile stored in the XYREM REMS Program Central Database.
  - v. The XYREM REMS Program Certified Pharmacy and/or prescriber may disenroll a patient from the XYREM REMS Program after review of incidents suggestive of abuse, misuse, or diversion.
- e. The following materials are part of the REMS and are appended:
- i. [XYREM REMS Program Certified Pharmacy Training Program](#)
  - ii. [XYREM REMS Program Patient Counseling Checklist](#)
  - iii. [XYREM Medication Guide](#)
  - iv. [XYREM REMS Program Risk Management Report Form.](#)

**3. XYREM will be dispensed and shipped only to patients who are enrolled in the XYREM REMS Program with documentation of safe use conditions.**

- a. Jazz Pharmaceuticals will ensure that XYREM is dispensed only by the XYREM REMS Program Certified Pharmacy, by direct shipment, to patients enrolled in the XYREM REMS Program.
- b. Jazz Pharmaceuticals will ensure that patients are enrolled in the XYREM REMS Program only if a prescriber enrolled in the XYREM REMS Program completes the XYREM REMS Patient Enrollment Form and submits the form to the XYREM REMS Program.
- c. Jazz Pharmaceuticals will ensure that XYREM is dispensed and shipped only to patients who have signed the prescriber-completed XYREM REMS Program Patient Enrollment Form and acknowledged that:
  - i. He/she has been counseled on the serious risks and safe use of XYREM
  - ii. He/she has asked the prescriber any questions about XYREM.

- d. Following enrollment, the patient remains in the XYREM REMS Program unless Jazz Pharmaceuticals, the XYREM REMS Program Certified Pharmacy, and/or prescriber determines the patient should be disenrolled. Reasons for disenrollment include: multiple suspicious early refill requests or other information that indicates possible abuse, misuse, or diversion.
- e. A disenrolled patient may be re-enrolled in the XYREM REMS Program. In order to re-enroll a patient who had been previously disenrolled for suspicions of abuse, misuse, or diversion, the XYREM REMS Program Certified Pharmacy must consult with the prescriber seeking to re-enroll the patient and communicate all relevant patient history to the prescriber, and both the pharmacist and the requesting prescriber must agree to re-enroll the patient.
- f. A patient may change prescribers provided that the new prescriber is also enrolled in the XYREM REMS Program and that the new prescription does not overlap with another active prescription for XYREM.

### **C. Implementation System**

- 1. The Implementation System for the XYREM REMS includes the following:**
  - a. Jazz Pharmaceuticals will ensure that XYREM is dispensed only by the XYREM REMS Program Certified Pharmacy.
  - b. XYREM will be shipped only to patients enrolled in the XYREM REMS Program pursuant to a valid prescription written by a prescriber enrolled in the XYREM REMS Program that does not overlap with another active prescription for XYREM.
  - c. Jazz Pharmaceuticals will ensure that a secure and validated XYREM REMS Program Central Database is maintained. The XYREM REMS Program Central Database will contain patient and prescriber enrollment status, all completed data forms, prescription and shipment data, as well as information related to dosing, concomitant medications, and behavior that raises suspicion of abuse, misuse, or diversion, including complete Risk Management Report histories.
  - d. Jazz Pharmaceuticals will ensure that a Medication Guide is included with each shipment of XYREM.

- e. Jazz Pharmaceuticals will monitor the XYREM REMS Program Certified Pharmacy for timely reporting to Jazz Pharmaceuticals of any behavior by patients or prescribers enrolled in the XYREM REMS Program that raises suspicion of abuse, misuse, or diversion.
- f. Jazz Pharmaceuticals will monitor the XYREM REMS Program Central Database to ensure compliance with the XYREM REMS Program and to evaluate the implementation of the elements under [Section II.B](#). Jazz Pharmaceuticals will ensure that appropriate corrective actions are implemented to address compliance concerns.
- g. Jazz Pharmaceuticals will audit the XYREM REMS Program Certified Pharmacy after approval of the XYREM REMS to ensure that it implements the XYREM REMS Program as directed. Thereafter, Jazz Pharmaceuticals will audit the XYREM REMS Program Certified Pharmacy at least annually, identify all issues of noncompliance, and institute appropriate corrective actions, potentially including pharmacy decertification.
- h. Jazz Pharmaceuticals will monitor the XYREM REMS Program Certified Pharmacy for timely reporting to Jazz Pharmaceuticals of all potential adverse events.
- i. Jazz Pharmaceuticals will monitor and evaluate the implementation of the Elements to Assure Safe Use and take reasonable steps to work to improve implementation of these elements.

#### **D. Timetable for Submission of Assessments**

Jazz Pharmaceuticals will submit the REMS assessments every 6 months from the date of the REMS approval (02/2015) for the first year, and then annually thereafter.

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each annual assessment will conclude no earlier than 60 days before the submission date for that assessment. The XYREM submissions will be submitted so that they are received by FDA on or before the due date.