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. 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 initial prescription and for patients who are reinitiating XYREM after a lapse in therapy of 6 months or longer 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
      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) 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 Brochure for Pediatric Patients and their Caregivers

vii. XYREM REMS Program website (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 and Pharmacy Knowledge Assessment Module A.

iii. Ensure that all XYREM REMS Program pharmacists also complete the pharmacist training in the XYREM REMS Program Pharmacy Training Program, Pharmacy Knowledge Assessment Module A, and Pharmacy Knowledge Assessment Module B.

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 first shipment will include a copy of the Patient Quick Start Guide (for adult patients) or the Brochure for Pediatric Patients and Their Caregivers (for pediatric patients).

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 Pharmacy Knowledge Assessment Module A
   iii. XYREM REMS Pharmacy Knowledge Assessment Module B
   iv. XYREM REMS Program Patient Counseling Checklist
   v. 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 to patients only after the patient has 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.

g. If a pediatric patient's caregiver changes, the new caregiver must be counseled by the Certified Pharmacy on the serious risks and safe use of XYREM and acknowledge that he/she has asked any questions about XYREM before XYREM is dispensed and shipped.

B. 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 or the enrolled patient-authorized adult designee, 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 RMR histories.
d. 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.

e. 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.

f. 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.

g. Jazz Pharmaceuticals will monitor the XYREM REMS Program Certified Pharmacy for timely reporting to Jazz Pharmaceuticals of all potential adverse events.

h. 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.
XYREM® (sodium oxybate) oral solution 0.5 g/mL

Complete and submit form online at www.XYREMREMS.com, OR scan and e-mail to XYREMPrescribers@express-scripts.com, OR fax to XYREM REMS Program at 1-866-470-1744 (toll free), OR mail to XYREM REMS Program, PO Box 66589, St. Louis, MO 63166-6589.
For more information, please call the XYREM REMS Program at 1-866-997-3688 (toll free).

**Step 1: ALL BOXES BELOW MUST BE CHECKED (√) IN ORDER FOR THE ENROLLMENT PROCESS TO BE COMPLETE AND BEFORE YOU CAN ENROLL PATIENTS AND PRESCRIBE XYREM.**

☐ I understand that XYREM is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

☐ I have read the Prescribing Information (PI) and the XYREM REMS Program Prescriber Brochure and understand that:
  - XYREM is a Schedule III CNS depressant and can cause obtundation and clinically significant respiratory depression at recommended doses
  - Alcohol and sedative hypnotics are contraindicated in patients who are using XYREM
  - Concurrent use of XYREM with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptics, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death
  - Patients who have sleep apnea or compromised respiratory function (e.g., asthma, COPD, etc.) may be at higher risk of developing respiratory depression, loss of consciousness, coma, and death with XYREM use

☐ I agree to:
  - Enroll each patient in the XYREM REMS Program
  - Screen each patient for history of alcohol or substance abuse, sleep-related breathing disorders, compromised respiratory function, depression, suicidality, and concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
  - Counsel each patient and/or caregiver prior to initiating therapy on the serious risks and safe use, handling, and storage of XYREM
  - Evaluate patients within the first 3 months of starting XYREM. It is recommended that patients be re-evaluated every 3 months thereafter while taking XYREM
  - 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

**Step 2: To help expedite the enrollment process, please PRINT clearly (*denotes required field).**

<table>
<thead>
<tr>
<th>Prescriber Information</th>
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<tbody>
<tr>
<td>*First Name: ___________________ M.I.: _____ *Last Name: ___________________ Prof. Designation (MD, DO, PA, NP): ________</td>
</tr>
<tr>
<td>*DEA No.: _________________ *State License No.: ___________________ *NPI No.: ___________________</td>
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<tr>
<td>Facility/Practice Name: ___________________________________________</td>
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<tr>
<td>*Street Address: ___________________________________________</td>
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<td>*City: ___________________ *State: ___________________ *Zip Code: ___________________</td>
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<tr>
<td>*Phone: ___________________ *Fax: ___________________ E-mail: ___________________</td>
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<tr>
<td>Office Contact: ___________________________________________ Office Contact Phone: ___________________</td>
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Additional office locations and contacts can be entered online at XYREMREMS.com.

**Step 3: Prescriber signature is required below for enrollment in the XYREM REMS Program.**

By signing below, I acknowledge the above attestations, and I understand that my personally identifiable information provided above will be shared with Jazz Pharmaceuticals, Inc., its agents, contractors, and affiliates and entered into a prescriber database for the XYREM REMS Program. I agree that I may be contacted in the future by mail, e-mail, fax, and/or telephone concerning XYREM, the XYREM REMS Program, and other XYREM programs and services.

*Prescriber Signature: ___________________ *Date: ___________________

Report SERIOUS ADVERSE EVENTS by contacting Jazz Pharmaceuticals at 1-800-520-5568 or jazzsafety@jazzpharma.com.
Dear Prescriber,

Welcome to the XYREM REMS Program, which was developed in collaboration with the Food and Drug Administration (FDA) as a Risk Evaluation and Mitigation Strategy (REMS). A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure that the benefits of the drug outweigh its risks.

This brochure provides valuable information about the XYREM REMS Program that includes important prescribing information, educational and counseling requirements, and materials necessary for program enrollment and prescribing XYREM® (sodium oxybate) oral solution, 0.5 g/mL, including:

- **XYREM REMS Program Prescriber Enrollment Form**—a one-time enrollment is required for all prescribers of XYREM.
- **XYREM REMS Program Patient Enrollment Form**—a one-time patient enrollment in the XYREM REMS Program is required for each new patient for whom XYREM will be prescribed.
- **XYREM REMS Program Prescription Form**—required for prescribing XYREM. This form must be used for initial prescriptions and may also be used for refills and renewals of XYREM prescriptions.
- **XYREM REMS Program Patient Quick Start Guide**—answers important questions for adult patients about how to get XYREM, how to use XYREM properly, and how to store it safely. It also gives important information about the risks associated with XYREM.
- **XYREM REMS Program Brochure for Pediatric Patients and their Caregivers**—this guide answers important questions for caregivers of pediatric patients and pediatric patients about how to use XYREM properly, how to store it safely, and how to get XYREM. It also gives important information about the risks associated with XYREM.

The XYREM REMS Program Prescriber Enrollment Form, XYREM REMS Program Patient Enrollment Form, and XYREM REMS Program Prescription Form must be completed in full and sent to the XYREM REMS Program. For your convenience, all three forms are available online at www.XYREMREMS.com, and can be requested by calling the XYREM REMS Program toll-free at 1-866-997-3688. The central Certified Pharmacy with the XYREM REMS Program is responsible for processing all prescriptions for XYREM. Continue reading this brochure to learn more about the XYREM REMS Program and your responsibilities as a prescriber of XYREM.

Please review the Prescribing Information for XYREM.

XYREM may be dispensed only to patients enrolled in the XYREM REMS Program.

Xyrem is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with Narcolepsy

If you require any additional assistance or information, please call the XYREM REFS Program at 1-866-XYREM88® (1-866-997-3688) or visit www.XYREMREMS.com.

Sincerely,

Jazz Pharmaceuticals
IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
- XYREM is contraindicated in patients being treated with sedative hypnotics.
- Patients should not drink alcohol when using XYREM.
- XYREM is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency.

WARNINGS AND PRECAUTIONS

CNS Depression
- XYREM is a CNS depressant. Concurrent use of XYREM with other CNS depressants, including but not limited to opioid analgesics; benzodiazepines; sedating antidepressants, antipsychotics, or anti-epileptics; general anesthetics; muscle relaxants; and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.
  - If use of these CNS depressants in combination with XYREM is required, dose reduction or discontinuation of one or more CNS depressants (including XYREM) should be considered.
  - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with XYREM should be considered.
- Patients who have sleep apnea or compromised respiratory function may be at a higher risk of developing respiratory depression, loss of consciousness, coma, and death with XYREM use.

Healthcare providers should caution patients/caregivers against hazardous activities requiring complete mental alertness or motor coordination (e.g., driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYREM does not affect the patient adversely.

Abuse and Misuse
- XYREM is a Schedule III controlled substance.
- The active ingredient of XYREM, sodium oxybate, is the sodium salt of gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse events, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. Illicit GHB has also been associated with drug-facilitated sexual assault.
- The rapid onset of sedation, coupled with the amnestic features of XYREM, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).
- You should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of XYREM (e.g., increase in size or frequency of dosing; reports of lost, stolen, or spilled medication; drug-seeking behavior; feigned cataplexy).

XYREM REMS Program
- XYREM is to be prescribed only to patients enrolled in the XYREM REMS Program. XYREM is available only through a restricted distribution program called the XYREM REMS Program. Required components of the XYREM REMS Program are:
  - Healthcare providers who prescribe XYREM must be specially certified. To be certified, prescribers must complete the XYREM REMS Program Enrollment Forms and comply with the REMS requirements.
  - XYREM will be dispensed only by the central pharmacy that is specially certified.
  - XYREM will be shipped only to enrolled patients with documentation of safe use conditions. For a patient to be enrolled, patients or caregivers must sign the XYREM REMS Program Patient Enrollment Form and acknowledge that they have been counseled on the serious risks and safe use of XYREM.

Further information is available at www.XYREMREMS.com or 1-866-XYREM88® (1-866-997-3688).

Reference ID: 4341394
Depression, Suicidality, and Other Behavioral/Neuropsychiatric Adverse Events

- The emergence of depression in patients treated with XYREM was seen in clinical trials and requires careful and immediate attention. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored especially carefully for the emergence of depressive symptoms while taking XYREM. XYREM can cause the emergence of neuropsychiatric adverse events (psychosis, paranoia, hallucination, aggression, and agitation), confusion, and sleepwalking. Patients should be instructed to call their healthcare provider if they experience any of these events.
- Anxiety can also occur in patients treated with XYREM.

Use in Patients Sensitive to High Sodium Intake

- XYREM has a high sodium content.
- Daily sodium intake should be considered in patients on salt-restricted diets or with heart failure, hypertension, or compromised renal function.

Most Common Adverse Events

- In three controlled clinical trials with adult patients, the most common adverse reactions (incidence ≥5% and twice the rate seen with placebo) in XYREM-treated patients were nausea (20%), dizziness (15%), vomiting (11%), somnolence (8%), enuresis (7%), and tremor (5%).
- Of the 398 XYREM-treated adult patients with narcolepsy, 10.3% of patients discontinued because of adverse reactions compared with 2.8% of patients receiving placebo. The most common adverse reaction leading to discontinuation was nausea (2.8%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.
- The overall adverse reaction profile of Xyrem in pediatric patients (7 years of age and older) is similar to that in adult patients. In a study of 104 pediatric narcolepsy patients treated with XYREM, the majority of events were mild or moderate in severity. The most common adverse reactions (>5%) were enuresis (18%), nausea (17%), headache (16%), vomiting (16%), weight decreased (12%), decreased appetite (8%), and dizziness (6%).

Please see Prescribing Information for XYREM.
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Prescribing Information is also included
Prescribing XYREM—A Brief Guide

The procedure for writing and dispensing prescriptions for XYREM is outlined below.

**PRESCRIBERS OF XYREM**

**PRESCRIBER ENROLLMENT**

Prescribing XYREM requires a one-time enrollment.

- **If you are prescribing XYREM for the first time**, complete the XYREM REMS Program Prescriber Enrollment Form, found either accompanying this XYREM REMS Program Prescriber Brochure or online at www.XYREMREMS.com. Please:
  - Submit the form online at www.XYREMREMS.com or
  - Scan and send via e-mail to XYReMPrescribers@express-scripts.com or
  - Mail to XYREM REMS Program, PO Box 66589, St. Louis, MO 63166-6589 or
  - Fax to 1-866-470-1744 (toll free).

- **On the XYREM REMS Program Prescriber Enrollment Form**, please confirm that:
  - You understand that Xyrem is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy
  - You have read and understand the Prescribing Information and this XYREM REMS Program Prescriber Brochure

**SCREEN**

- You agree to screen each patient for:
  - History of alcohol or substance abuse
  - History of sleep-related breathing disorders
  - History of compromised respiratory function
  - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
  - History of depression or suicidality

**COUNSEL**

- You agree to counsel your patients and/or caregivers (for pediatric patients) on:
  - The serious risks associated with XYREM
  - Contraindications (alcohol and sedative hypnotics)
  - Risks of concomitant use of XYREM with alcohol and/or other CNS depressants, including sedating antidepressants, antipsychotics, or anti-epileptics; opioids; benzodiazepines; muscle relaxants; and general anesthetics
  - Risk of engaging in hazardous activities requiring complete mental alertness or motor coordination (e.g., driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYREM does not affect the patient adversely
  - Preparation and dosing instructions for XYREM
  - The risk of abuse and misuse associated with use of XYREM
  - Safe use, handling, and storage of XYREM

**ENROLL**

- You will enroll each patient in the XYREM REMS Program by completing the one-time XYREM REMS Program Patient Enrollment Form and submitting the form to the XYREM REMS Program. A pediatric patient must have a caregiver

- You will evaluate each patient within the first 3 months of starting XYREM, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while on XYREM therapy:
  - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
  - Serious adverse events
  - Signs of abuse and misuse such as an increase in dose or frequency of dosing; reports of lost, stolen, or spilled medication; and/or drug-seeking behavior

**REPORT**
– You will 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.

PATIENT ENROLLMENT

– All patients must be enrolled one time in the XYREM REMS Program, using the XYREM REMS Program Patient Enrollment Form. A pediatric patient must have a caregiver.

– On the XYREM REMS Program Patient Enrollment Form:
  – For adult patients, verify that you have provided counseling to the patient about the serious risks associated with the use of XYREM and its safe use as described in the XYREM REMS Program Patient Quick Start Guide
  – For pediatric patients, verify that you have provided counseling to the caregiver about the serious risks associated with the use of XYREM and its safe use as described in the XYREM REMS Program Brochure for Pediatric Patients and their Caregivers
  – Obtain mandatory patient or caregiver signature acknowledging that he/she has been counseled on the serious risks and safe use conditions of XYREM and has had the opportunity to ask you any questions he/she may have about XYREM
  – Fax the completed XYREM REMS Program Patient Enrollment Form to the XYREM REMS Program at 1-866-470-1744 (toll free) or mail to XYREM REMS Program, PO Box 66589, St. Louis, MO 63166-6589. The form can also be completed online at www.XYREMREMS.com.
PRESCRIBING REQUIREMENTS

- Write prescriptions using the XYREM REMS Program Prescription Form (general prescription forms will not be accepted) for initial prescriptions and for patients who are reinitiating XYREM after a lapse in therapy of 6 months or longer. The prescription form may also be used for refills and renewals.
  - Fill out the form completely and clearly to ensure timely fulfillment of your patient’s prescription
  - Verify that you have screened your patient for:
    - History of alcohol or substance abuse
    - History of sleep-related breathing disorders
    - History of compromised respiratory function
    - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
    - History of depression or suicidality
  - Verify that you have counseled the adult patient or caregiver (for pediatric patients) regarding the information below. Refer to pages 14 and 15 of this brochure for patient counseling information.
    - The serious risks associated with XYREM
    - Contraindications (alcohol and sedative hypnotics)
    - The risks of concomitant use of alcohol or other CNS depressants, including sedating antidepressants, antipsychotics, or anti-epileptics; opioids; benzodiazepines; muscle relaxants; and general anesthetics
    - The risks of engaging in hazardous activities requiring complete mental alertness or motor coordination (e.g. driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYREM does not affect the patient adversely
    - Preparation and dosing instructions for XYREM
    - The risk of abuse and misuse associated with use of XYREM
    - Safe use, handling, and storage of XYREM (refer to pages 14 & 15 of this brochure for Patient Counseling Information)
  - Provide a list of all current prescription and non-prescription medications and dosages that the patient is currently taking, to the best of your knowledge. Additionally, indicate the presence of relevant comorbid medical conditions. This can be done by completing the appropriate fields on the XYREM REMS Program Prescription Form or by faxing a separate page.
  - NOTE: Prior to dispensing each XYREM prescription (including refills), the Certified Pharmacy will complete an online Drug Utilization Review (DUR) and, during the patient counseling process, will ask the patient about the use of other medicines. If the pharmacist learns that the patient is taking a previously undisclosed contraindicated medication (sedative hypnotics), an opioid, or more than one CNS depressant, and the prescriber has not indicated awareness of the concomitant medication, the Certified Pharmacy will contact and inform the prescriber of the concomitant medication use prior to dispensing the XYREM. The pharmacist may also contact the prescriber about other concomitant medications of concern. Verify that you have informed the patient and/or caregiver that the XYREM REMS Program will send him/her a copy of the XYREM Medication Guide with each prescription fill and the appropriate educational material (the XYREM REMS Program Patient Quick Start Guide for adult patients and the XYREM REMS Program Brochure for Pediatric Patients and their Caregivers for caregivers of pediatric patients) prior to his/her first prescription fill, if you haven’t provided one previously. These materials are available through a Jazz Pharmaceuticals Specialty Sales Consultant or may be downloaded at www.XYREMREMS.com
  - A XYREM REMS Program Prescription Form, available online at www.XYREMREMS.com, must be printed, signed, and either faxed to the XYREM REMS Program at 1-866-470-1744 (toll free), or mailed to XYREM REMS Program, PO Box 66589, St. Louis, MO 63166-6589.

Please see Pediatric Patient Supplement for information on dosing for pediatric patients.
PATIENT EVALUATION

- 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 they are taking XYREM for:
  - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
  - Serious adverse events
  - Signs of abuse and misuse, such as an increase in dose or frequency of dosing; reports of lost, stolen, or spilled medication; and/or drug-seeking behavior

REFILL PRESCRIPTIONS

- Prescription refills and renewals may be conveyed by phone, fax, mail, or electronically. The Certified Pharmacy with the XYREM REMS Program will send you a XYREM REMS Program Prescription Form upon your request. The prescription form is also available online at XYREMREMS.com. Prescription refills and renewals must be documented in the XYREM REMS Program Central Database. To phone in refills or renewals, call 1-866-997-3688
- To fax or mail refills or renewals:
  - Fill out the form completely and clearly to ensure timely fulfillment of your patient’s prescription
  - If filling out the prescription online through XYREMREMS.com, you must print and sign the form prior to submitting it to the XYREM REMS Program.
  - Fax the completed XYREM REMS Program Prescription Form and all subsequent prescriptions to the XYREM REMS Program at 1-866-470-1744 (toll free) or mail to XYREM REMS Program, PO Box 66589, St. Louis, MO 63166-6589
- Electronic prescribing for refills and renewals is acceptable by the Certified Pharmacy using approved software. Additional state rules may apply.
Responsibilities of the XYREM REMS Program
Certified Pharmacy

FOLLOWING RECEIPT OF A PATIENT’S PRESCRIPTION, THE CERTIFIED PHARMACY WILL:

- **Provide you with confirmation** of each new XYREM REMS Program Prescription Form received from your office
- **Contact the patient’s insurance provider** to verify XYREM prescription benefits
- **Prior to the first shipment, contact the patient or caregiver and complete the counseling checklist to:**
  - Confirm whether he/she has received a copy of the appropriate educational material (XYREM REMS Program Patient Quick Start Guide for adult patients and XYREM REMS Program Brochure for Pediatric Patients and their Caregivers for caregivers of pediatric patients). The Certified Pharmacy will send a copy of the appropriate educational material
  - Counsel the adult patient and/or caregiver on expectations from XYREM therapy and how to prepare and take XYREM doses safely and effectively
  - Review important XYREM safety information and precautions for XYREM use
  - Review XYREM safe handling and storage procedures
  - Review the adverse events associated with XYREM use
  - Review the patient’s use of concomitant medications
    - Prior to dispensing each XYREM prescription (including refills), the Certified Pharmacy will complete an online Drug Utilization Review (DUR) and, during the patient counseling process, will ask the patient about the use of other medicines.
    - If the pharmacist learns that the patient is taking a previously undisclosed contraindicated medication (sedative hypnotics), an opioid, or more than one CNS depressant, and the prescriber has not indicated awareness of the concomitant medication, the Certified Pharmacy will contact and inform the prescriber of the concomitant medication use prior to dispensing XYREM.
    - The pharmacist may also contact the prescriber about other concomitant medications of concern.
  - Review the patient’s comorbid medical conditions
  - You will be notified of any potential for drug interactions or relevant comorbid medical conditions based on patient counseling
  - Ask if the patient or caregiver has any questions about XYREM and answer the questions and/or refer the patient or caregiver back to the prescriber, as appropriate
- **Provide 24/7 toll-free telephone access to pharmacist support** for prescribers, office staff, patients, and caregivers by answering questions about safety, dosing, and patient care
- **Dispense and ship** XYREM by overnight service to the patient or his/her authorized adult designee
- **Remind** patients about monthly refills
- **Contact** the prescriber if a prescription refill or renewal is required

For your convenience, materials and information regarding the XYREM REMS Program are available online at www.XYREMREMS.com.
Please be sure to review the Prescribing Information prior to prescribing XYREM for your patients.
Guidelines for Dosing and Titrating XYREM

**DOSING XYREM**

The information presented on this page is for adult patients. Please see pages 16‒18 for additional important information on dosing for pediatric patients (7 years of age and older).

XYREM is a liquid medication taken orally at bedtime. Due to its short half-life, XYREM is taken in divided doses at night, with the first dose taken at bedtime and the second dose taken 2.5 to 4 hours later.

- The recommended starting dosage is 4.5 grams (g) per night administered orally divided into two doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later
- The effective dosage range is 6 g to 9 g/night orally
- Doses higher than 9 g/night have not been studied and should not ordinarily be administered
- The dose of XYREM should be titrated to effect
  - Increase the dosage by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dosage range
- An initial XYREM dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking XYREM. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting XYREM dose when introducing XYREM. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of XYREM and divalproex sodium is warranted.
- Improvement may occur during the first weeks of therapy; however, titration to an optimal dose may take longer
- Once a stable dose is established, patients should be evaluated periodically

The patient’s first shipment of XYREM will be limited to a 1-month (30-day) supply, and future shipments cannot exceed a 3-month (90-day) supply.

### RECOMMENDED ADULT XYREM DOSE REGIMEN

<table>
<thead>
<tr>
<th></th>
<th>1st Dose</th>
<th>2nd Dose</th>
<th>Total Nightly Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended start</td>
<td>2.25 g</td>
<td>2.25 g</td>
<td>4.5 g</td>
</tr>
<tr>
<td>Dose</td>
<td>3 g</td>
<td>3 g</td>
<td>6 g</td>
</tr>
<tr>
<td>Maximum dose</td>
<td>3.75 g</td>
<td>3.75 g</td>
<td>7.5 g</td>
</tr>
<tr>
<td></td>
<td>4.5 g</td>
<td>4.5 g</td>
<td>9 g</td>
</tr>
</tbody>
</table>

**Effective Dosing Range**

### IMPORTANT ADMINISTRATION INSTRUCTIONS

- Inform patients that all bottles contain concentrated medication ONLY and that water for dilution is not contained in the box. Advise patients to keep XYREM in the provided bottle(s)
- Patients should prepare both nighttime doses at bedtime
  - Instruct patients to make sure that pharmacy vials are empty prior to preparing each dose
  - Each dose of XYREM should be diluted with about ¼ cup of water
  - Patients should be instructed to store XYREM bottles and prepared nightly doses in a secure place out of the reach of children and pets
- Doses should be taken at least 2 hours after eating
- Both doses should be taken while in bed and the patient should lie down immediately after dosing
- The first dose should be taken at bedtime and the second dose 2.5 to 4 hours later

Reference ID: 4341394
Additional Information About XYREM

XYREM has been placed in a bifurcated federal schedule. XYREM is a Schedule III controlled substance when used for legitimate medical purposes, as prescribed. The active ingredient of XYREM, sodium oxybate, or gamma-hydroxybutyrate (GHB), is classified as a Schedule I controlled substance when used for any other reason or by anyone other than for whom it was prescribed. Your patients should be informed that federal law prohibits the transfer of XYREM to any persons other than the patient for whom it was prescribed. If you have any questions regarding this, please call the XYREM REMS Program toll free at 1-866-997-3688.

Illicit use and abuse of GHB have been reported, including drug-facilitated sexual assault. Prescribers should carefully evaluate patients for a history of drug abuse and follow patients closely, observing them for signs of misuse or abuse of GHB (e.g., increase in dose or frequency of dosing, reports of lost, stolen, or spilled medication, drug-seeking behavior).

WHEN PRESCRIBING A CONTROLLED SUBSTANCE:

• Be judicious when deciding to increase a dose. Make sure the appropriate medical indicators for increasing or altering a dose are present
• Be suspicious of a pattern of excuses for additional refills or repeated requests for additional refills on an emergency basis
• Be vigilant. Recognize that there is potential to abuse XYREM

It is important you know that the XYREM REMS Program maintains records about who is prescribing XYREM. These records will be made available to any state or federal agency that requests them.

DEPENDENCE AND TOLERANCE

Dependence

• Cases of severe dependence and cravings for GHB have been reported
• There have been case reports of dependence after illicit use of GHB at frequent repeated doses
  – Doses (18 g/day to 250 g/day) were in excess of therapeutic dose range
• Abstinence syndrome has not been reported in clinical trials

Tolerance

• Open-label, long-term (≥6 months) clinical trials did not demonstrate development of tolerance
• There have been some case reports of symptoms of tolerance developing after illicit use at doses far in excess of the recommended XYREM dosage regimen

Discontinuation effects and tolerance of XYREM have not been systematically evaluated in controlled clinical trials.

For your convenience, materials and information regarding the XYREM REMS Program are available online at www.XYREMREMS.com.
Use in Specific Populations

PREGNANCY

There are no adequate data on the developmental risk associated with the use of sodium oxybate in pregnant women. Oral administration of sodium oxybate to pregnant rats (150, 350, or 1,000 mg/kg/day) or rabbits (300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity; however, oral administration to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and growth, at a clinically relevant dose.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

LABOR AND DELIVERY

XYREM has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate, newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid and gamma-hydroxybutyrate (GHB) has been detected in newborns at delivery after intravenous administration of GHB to mothers. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

NURSING MOTHERS

GHB is excreted in human milk after oral administration of sodium oxybate. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Xyrem and any potential adverse effects on the breastfed infant from Xyrem or from the underlying maternal condition.

PEDIATRIC USE

The safety and effectiveness of Xyrem in the treatment of cataplexy or excessive daytime sleepiness in pediatric patients (7 years of age and older) with narcolepsy have been established and pharmacokinetics characterized in a double-blind, placebo-controlled, randomized-withdrawal study. Safety and effectiveness of Xyrem in pediatric patients below the age of 7 years have not been established.

GERIATRIC USE

There is limited experience with sodium oxybate in subjects 65 years and older. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease and other drug therapy.

RACE AND GENDER EFFECTS

There were too few non-Caucasian patients in the narcolepsy clinical trials to permit evaluation of racial effects on safety or efficacy. More than 90% of the subjects in the clinical trials were Caucasian. In the narcolepsy clinical trials, with a database that was 58% female, no important differences in safety or efficacy of sodium oxybate were noted between men and women.

Please read accompanying Prescribing Information.
The XYREM REMS Program is here to support you, your staff, and your patients. For assistance, call 1-866-997-3688 (toll free).

Reference ID: 4341394
Patient Counseling Information

Prior to initiating therapy, counsel each adult patient, caregiver (for pediatric patients 7 years of age and older), and, as appropriate, pediatric patient regarding the serious risks and safe use, handling, and storage of XYREM using the appropriate educational material [XYREM REMS Program Patient Quick Start Guide (for adults) and XYREM REMS Program Brochure for Pediatric Patients and Their Caregivers (for pediatric patients)] and encourage him/her to read the XYREM Medication Guide. Please see pages 16-18 for additional counseling information important for caregivers of pediatric patients and, as appropriate, pediatric patients.

- Inform patients and/or caregivers that XYREM is available only through the central pharmacy certified under a restricted distribution program called the XYREM REMS Program and provide them with the telephone number and website for more information about XYREM and the XYREM REMS Program.

- Confirm that patients understand the serious risks and safe use conditions of XYREM and that you have answered any questions the patient and/or caregiver has about XYREM by having the patient and/or caregiver sign and date the XYREM REMS Program Patient Enrollment Form. Inform the patient and/or caregiver that regular follow-up is recommended.

The contents of the XYREM Medication Guide are reviewed with every patient by the XYREM REMS Program Certified Pharmacy before initiating treatment with XYREM.

To ensure safe and effective use of XYREM, you should provide the adult patient, caregiver (for pediatric patients), and, as appropriate, pediatric patient with the following guidance:

ALCOHOL OR SEDATIVE HYPNOTICS
Advise patients and/or caregivers that alcohol and other sedative hypnotics should not be taken with XYREM.

SEDATION
Inform patients and/or caregivers that the patient is likely to fall asleep quickly after taking XYREM (often within 5 minutes and usually within 15 minutes), but the time it takes to fall asleep can vary from night to night. The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls resulting in injuries, in some cases requiring hospitalization. Instruct patients and/or caregivers that patients should remain in bed following ingestion of their first and second doses, and patients should not take their second dose until 2.5 to 4 hours after the first dose.

FOOD EFFECTS ON XYREM
Inform patients and/or caregivers that the first dose should be taken at least 2 hours after eating.

RESPIRATORY DEPRESSION
Inform patients and/or caregivers that XYREM can be associated with respiratory depression even at recommended doses and with concurrent use of XYREM with other CNS depressants.
PARTICIPATING IN HAZARDOUS ACTIVITIES
Inform patients and/or caregivers that patients should not participate in hazardous activities requiring complete mental alertness or motor coordination (e.g., driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYREM does not affect the patient adversely.

SUICIDALITY
Instruct patients and/or caregivers to contact a healthcare provider immediately if the patient develops depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or suicidal ideation.

SLEEPWALKING
Instruct patients and/or caregivers their families that XYREM has been associated with sleepwalking and to contact their healthcare provider if this occurs.

SODIUM INTAKE
Instruct patients and/or caregivers that Xyrem contains a significant amount of sodium and patients who are sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment) should limit their sodium intake.

SAFE HANDLING, STORAGE, AND DISPOSAL
- Discuss safe and proper use of XYREM and dosing information with patients and/or caregivers prior to the initiation of treatment
- Instruct patients and/or caregivers to store XYREM bottles and XYREM doses in a secure place, out of reach of children and pets
- Patients and/or caregivers should be instructed to divide the total nightly dose into 2 separate doses. They should not further divide each of the 2 separate doses
- Patients and/or caregivers should be informed that patients should be seen by their healthcare provider frequently to review dose titration, symptom response, and adverse reactions
- Instruct patients and/or caregivers to store XYREM at room temperature, between 59°F and 86°F
- Inform patients and/or caregivers that they may safely dispose of XYREM down the sink or toilet drain
- Inform patients and/or caregivers that they must report all instances of lost or stolen XYREM to the local police and to the XYREM REMS Program
This pediatric patient supplement provides information specifically for pediatric patients and their caregivers about the XYREM REMS Program, including important prescribing information, educational and counseling requirements, and materials necessary for program enrollment and prescribing XYREM. If you are prescribing XYREM for a pediatric patient, please read the Prescriber Brochure in its entirety, including this Pediatric Patient Supplement.

**PRESCRIBING XYREM FOR PEDIATRIC PATIENTS**

In addition to the procedure for writing and dispensing prescriptions for XYREM described above, prescribing XYREM to pediatric patients requires the following:
- Verify that you have counseled the caregiver on the serious risks and safe use conditions as described in the XYREM REMS Program Brochure for Pediatric Patients and Their Caregivers and encourage him/her to read the XYREM Medication Guide.

**RESPONSIBILITIES OF THE XYREM REMS PROGRAM CERTIFIED PHARMACY FOR PEDIATRIC PATIENTS**

In addition to the responsibilities described above, for pediatric patients the Certified Pharmacy will:
- Ensure that each enrolled pediatric patient has a caregiver
- Counsel the caregiver of each pediatric patient on the serious risks and safe use of XYREM

Each pediatric patient receiving XYREM must have a caregiver
GUIDELINES FOR DOSING AND TITRATING XYREM FOR PEDIATRIC PATIENTS

- The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight, as specified in table below. The dose might be gradually titrated based on efficacy and tolerability.
- The nightly XYREM dose is divided into two doses; one dose at bedtime and a second dose 2.5 to 4 hours after the first dose. For patients who sleep more than 8 hours per night, the first dose of XYREM may be given at bedtime or after an initial period of sleep.
- Titrate the dose of XYREM to effect and tolerability by increasing the total nightly dose by no more than the titration regimens specified in the table below.
- Total nightly doses higher than 9 g/night have not been studied.
- Follow up frequently during titration to review symptom response and adverse reactions. A follow up of every three months is recommended.
- Improvement may occur during the first weeks of therapy; however, titration to an optimal dose may take longer.
- Once a stable dose is established, it is recommended that patients be re-evaluated every 3 months.

**Recommended Pediatric Xyrem Dosage for Patients 7 Years of Age and Older***

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>Initial Dosage</th>
<th>Maximum Weekly Dosage Increase</th>
<th>Maximum Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take at Bedtime:</td>
<td>Take 2.5 to 4 Hours Later:</td>
<td>Take at Bedtime:</td>
<td>Take 2.5 to 4 Hours Later:</td>
</tr>
<tr>
<td>&lt;20 kg**</td>
<td>There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 kg to &lt;30 kg</td>
<td>≤1 g</td>
<td>≤1 g</td>
<td>0.5 g</td>
</tr>
<tr>
<td>30 kg to &lt;45 kg</td>
<td>≤1.5 g</td>
<td>≤1.5 g</td>
<td>0.5 g</td>
</tr>
<tr>
<td>≥45 kg</td>
<td>≤2.25 g</td>
<td>≤2.25 g</td>
<td>0.75 g</td>
</tr>
</tbody>
</table>

*For patients who sleep more than 8 hours per night, the first dose of XYREM may be given at bedtime or after an initial period of sleep.

**If Xyrem is used in patients 7 years of age and older who weigh less than 20 kg, a lower starting dosage, lower maximum weekly dosage increases and lower total maximum nightly dosage should be considered.

Note: Unequal dosages may be required for some patients to achieve optimal treatment.

IMPORTANT ADMINISTRATION INSTRUCTIONS FOR PEDIATRIC PATIENTS

- Inform caregivers that they should ensure that all XYREM doses are kept in a safe place until given.
- Inform caregivers and patients that all bottles contain concentrated medication ONLY and that water for dilution is not contained in the box. Advise caregivers to keep XYREM in the provided bottle(s).
- Inform caregivers and patients that it is important to follow a consistent nightly routine for taking XYREM. – Caregivers should prepare both nighttime doses at bedtime.
- Instruct caregivers to make sure that pharmacy containers are empty prior to preparing each dose
- Each dose of XYREM should be diluted with about ¼ cup of water
- Caregivers should be instructed to store XYREM bottles and prepared nightly doses in a secure place out of the reach of children and pets
  - Doses should be taken at least 2 hours after eating
  - Both doses should be taken while in bed and the patient should lie down immediately after dosing
  - Encourage the child to urinate prior to taking the first nightly dose of XYREM
  - Caution against hazardous activities requiring complete mental alertness or motor coordination (e.g., driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYREM does not affect the patient adversely

Caregivers should be advised that the pediatric patient in their care is to take XYREM exactly as prescribed

CONSIDERATIONS FOR INCLUDING PEDIATRIC PATIENTS IN THEIR OWN CARE
- Work with the caregiver to determine the child’s readiness to participate in his or her own care
- Ensure that the pediatric patient is counseled on the serious risks and safe use of XYREM either by the prescriber or the Certified Pharmacy
  - Ensure that the patient also reads the XYREM REMS Program Brochure for Pediatric Patients and Their Caregivers and asks any questions he or she may have
XYREM® (sodium oxybate) oral solution 0.5 g/mL

Complete and submit form online at www.XYREMREMS.com, OR scan and e-mail to XYREMPrescribers@express-scripts.com, OR fax to XYREM REMS Program at 1-866-470-1744 (toll free), OR mail to: XYREM REMS Program, PO Box 66589, St. Louis, MO 63166-6589.

For more information, call the XYREM REMS Program at 1-866-997-3688 (toll free).

Please Print (*denotes required field)

<table>
<thead>
<tr>
<th>Prescriber Information</th>
</tr>
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<tbody>
<tr>
<td>*First Name: ___________________________</td>
</tr>
<tr>
<td>*Street Address: ___________________________________________</td>
</tr>
<tr>
<td>*City: ___________________________________________</td>
</tr>
<tr>
<td>Office Contact: ___________________________________________</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>*First Name: ___________________________</td>
</tr>
<tr>
<td>*Date of Birth (MM/DD/YYYY): ___________________________</td>
</tr>
<tr>
<td>*Address: ___________________________________________</td>
</tr>
<tr>
<td>*City: ___________________________________________</td>
</tr>
<tr>
<td>Caregiver Name: ___________________________________________</td>
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<thead>
<tr>
<th>Insurance Information</th>
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</thead>
<tbody>
<tr>
<td>Does Patient Have Prescription Coverage? ☐ Yes (provide photocopy of both sides of insurance identification card with this form) ☐ No</td>
</tr>
<tr>
<td>Policy Holder’s Name: ___________________________________________</td>
</tr>
<tr>
<td>Insurance Company Name: ___________________________________________</td>
</tr>
<tr>
<td>Insurance Phone: ___________________________</td>
</tr>
<tr>
<td>RxBIN No.: ___________________________</td>
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</tbody>
</table>

Patient/Caregiver: Form must be signed before enrollment can be processed.

By signing below, I acknowledge that:
- My doctor/prescriber has counseled me on the serious risks and safe use of XYREM
- I have asked my doctor/prescriber any questions I have about XYREM

*Patient/Caregiver Signature: ___________________________ *Date: ___________________________

*Printed Caregiver Name (if applicable): ___________________________

Prescriber: Form must be signed before enrollment can be processed.

By signing below, I acknowledge that:
- I have counseled the patient and/or caregiver about the serious risks associated with the use of XYREM and the safe use conditions as described in the XYREM REMS Program Patient Quick Start Guide (for adult patients) or the XYREM REMS Program Brochure for Pediatric Patients and their Caregivers (for pediatric patients)
- I have provided the patient and/or caregiver with the appropriate educational material [XYREM REMS Program Patient Quick Start Guide (for adult patients) and XYREM REMS Program Brochure for Pediatric Patients and their Caregivers (for pediatric patients)] (optional)

*Prescriber Signature: ___________________________ *Date: ___________________________
XYREM REMS PROGRAM PRESCRIPTION FORM

XYREM® (sodium oxybate) oral solution

Form available online at www.XYREMS.com, must be printed, signed, and either:
Fax to XYREM REMS Program: 1-866-470-1744 (toll free)
OR mail to XYREM REMS Program, PO Box 66589, St. Louis, MO 63166-6589.
For more information, call the XYREM REMS Program at 1-866-997-3688 (toll free).

Please Print (*denotes required field; †denotes required field for pediatric patients on initial fill and restarts)

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<tr>
<th>Prescriber Information</th>
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<tbody>
<tr>
<td>*First Name: ___________________</td>
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<td>*Street Address: ___________________</td>
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<tr>
<td>*City: ___________________</td>
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<tr>
<td>*DEA No.: ___________________</td>
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<tr>
<td>Office Contact: ___________________</td>
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<table>
<thead>
<tr>
<th>Patient Information</th>
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<tbody>
<tr>
<td>*First Name: ___________________</td>
</tr>
<tr>
<td>*Date of Birth (MM/DD/YYYY): __________</td>
</tr>
<tr>
<td>*Address: ___________________</td>
</tr>
<tr>
<td>*City: ___________________</td>
</tr>
</tbody>
</table>

| MEDICATIONS: (list all known current prescription and non-prescription medications and dosages or submit as a separate page) |
| COMORBIDITIES: (list known comorbidities or submit as a separate page) |

<table>
<thead>
<tr>
<th>Total Quantity</th>
<th>Refills:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2 3 month(s) supply (circle one)</td>
<td>0 1 2 3 4 5 (circle one)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dispensing Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directions: Take first dose p.o., diluted in ¼ cup of water, at bedtime. Take second dose p.o., diluted in ¼ cup of water 2.5 to 4 hours later.</td>
</tr>
<tr>
<td>Note: Prepare both doses at the same time prior to bedtime. The XYREM shipment does not include water for dilution.</td>
</tr>
</tbody>
</table>

Initial prescription fill cannot exceed 1 month of therapy. *Refills cannot exceed 3 months supply. |

Please complete EITHER the titrated dosing OR fixed dosing section.

Please see the Prescriber Brochure and the full Prescribing Information for additional dosing instructions.

Titrated XYREM Dosing: Titrate to Effect

<table>
<thead>
<tr>
<th>Starting Dose:</th>
<th>First dose: ______g + Second dose: ______g = ______g Total Nightly Dose for ______ days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Titration:</td>
<td>First dose: ______g + Second dose: ______g = ______g Total Nightly Dose for ______ days</td>
</tr>
<tr>
<td>2nd Titration:</td>
<td>First dose: ______g + Second dose: ______g = ______g Total Nightly Dose for ______ days</td>
</tr>
<tr>
<td>3rd Titration:</td>
<td>First dose: ______g + Second dose: ______g = ______g Total Nightly Dose for ______ days</td>
</tr>
</tbody>
</table>

First dose is ordinarily taken at bedtime; second dose is taken 2.5 to 4 hours later.
For patients who sleep more than 8 hours per night, the first dose of Xyrem may be given at bedtime or after an initial period of sleep.
**For patients who weigh less than 20 kg, lower starting dosage, maximum weekly dosage increases and total maximum nightly dosage should be considered.
Note: Unequal dosages may be required for some patients to achieve optimal treatment.

Fixed XYREM Dosing

<table>
<thead>
<tr>
<th>Dose:</th>
<th>First dose: ______g + Second dose (2.5 to 4 hours later): ______g = ______g Total Nightly Dose</th>
</tr>
</thead>
</table>

Special Dosing Instructions

Prescriber Verification—My signature below signifies that: I understand the statements and agree to the REMS requirements, which are found on the back of this form; XYREM is medically appropriate for this patient; and I have informed the patient and/or caregiver that the XYREM REMS Program will send him or her a copy of the XYREM Medication Guide with each prescription fill and the appropriate educational material (XYREM REMS Program Patient Quick Start Guide for adult patients and XYREM REMS Program Brochure for Pediatric Patients and their Caregivers for pediatric patients) with the first prescription fill.

*Prescriber Signature: ___________________ | *Date: ___________________

Supervising Physician Signature: ___________________ | Date: ___________________

(If required by state law)
I understand that XYREM is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

I understand that:
- XYREM is a CNS depressant and can cause obtundation and clinically significant respiratory depression at recommended doses
- Alcohol and sedative hypnotics are contraindicated in patients who are using XYREM
- Concurrent use of XYREM with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptics, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death
  - If use of these CNS depressants in combination with XYREM is required, dose reduction or discontinuation of one or more CNS depressants (including XYREM) should be considered
  - If short-term use of an opioid (e.g., perioperative) is required, interruption of treatment with XYREM should be considered
- Patients who have sleep apnea or compromised respiratory function (e.g., asthma, COPD, etc.) may be at higher risk of developing respiratory depression, loss of consciousness, coma, and death with XYREM use
- XYREM is a Schedule III controlled substance with potential for abuse and misuse
- Safe use and handling by patients is important in order to prevent abuse/misuse and accidental exposure to family/friends, including children
- XYREM is to be prescribed only to patients enrolled in the XYREM REMS Program

I have read and understand the Prescribing Information and XYREM REMS Program Prescriber Brochure.

I have screened this patient for:
- History of alcohol or substance abuse
- History of sleep-related breathing disorders
- History of compromised respiratory function
- Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
- History of depression or suicidality

I have counseled this patient and/or caregiver on:
- The serious risks associated with XYREM
- Contraindications (alcohol and sedative hypnotics)
- Risk of concomitant use of XYREM with alcohol, other CNS depressants, or other potentially interacting agents
- Preparation and dosing instructions for XYREM
- Risk of abuse and misuse associated with use of XYREM
- Risk of operating hazardous machinery, including automobiles or airplanes, for the first 6 hours after taking a dose of XYREM
- Preparation and dosing instructions for XYREM
- Safe use, handling, and storage of XYREM
PATIENT QUICK START GUIDE

Important information about the safe use and handling of XYREM
Dear Patient,

Welcome to the XYREM REMS Program. You are receiving these materials because your healthcare provider has prescribed XYREM® (sodium oxybate) oral solution, 0.5 g/mL, for you. XYREM is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. If you are the caregiver of a pediatric patient receiving XYREM, please refer to the Brochure for Pediatric Patients and Their Caregivers instead of this guide for important information about helping your child get started with XYREM.

Because of the serious risks associated with XYREM, the Food and Drug Administration (FDA) has required a special program called a Risk Evaluation and Mitigation Strategy (REMS) for XYREM. The purpose of the XYREM REMS Program is to make sure the benefits of XYREM outweigh the risks. All patients must be enrolled in the XYREM REMS Program to receive XYREM. This Quick Start Guide contains information you need to know about XYREM and will help you to use XYREM correctly. Read this Quick Start Guide before you start taking XYREM.

After your healthcare provider sends in your enrollment form and first prescription for XYREM, you will receive a call from the Certified Pharmacy of the XYREM REMS Program to tell you how the XYREM REMS Program helps you get started with taking XYREM and to answer any questions you may have about XYREM.

Any questions? Please call the XYREM® REMS Program at 1-866-997-3688. Please see the Medication Guide for more detailed information about XYREM.

Reference ID: 4341394
You will also speak with appropriate staff at the Certified Pharmacy, who will go over your insurance information with you. Before you can receive your first shipment of XYREM, a pharmacist at the Certified Pharmacy will ask if your healthcare provider reviewed the XYREM REMS Program Patient Quick Start Guide with you and explain that you will receive this guide with your first shipment, and that all drug shipments will include the XYREM Medication Guide. The pharmacist will also ask you about your medical history and other medications you may be taking, and give you advice on how to prepare and take your XYREM and how to store it safely. **You must take this call before you can get your XYREM.**

Please call your healthcare provider if you have questions about XYREM, or you can contact the XYREM REMS Program toll free at 1-866-XYREM88® (1-866-997-3688). You can reach a pharmacist at this number 24 hours a day, 7 days a week with any questions.

We hope you find this information and the XYREM REMS Program services helpful.

Sincerely,

Jazz Pharmaceuticals

Reference ID: 4341394
XYREM is a prescription medicine used to treat patients with narcolepsy to reduce too much daytime sleepiness and to reduce cataplexy (suddenly weak or paralyzed muscles).

**IMPORTANT INFORMATION ABOUT XYREM INCLUDES THE FOLLOWING:**

- When taking XYREM, do not drink alcohol or take other medicines that slow your breathing or mental activity or make you sleepy. You could have serious side effects.
- XYREM can cause serious side effects, including trouble breathing while asleep, confusion, unusual or disturbing thoughts, depression, and passing out, even at recommended doses. Tell your healthcare provider if you have any of these problems while taking XYREM.
- Abuse of XYREM can lead to dependence (a physical need to take the drug), craving for the medicine, and severe withdrawal symptoms (symptoms that start when the drug is stopped, especially when it is stopped suddenly).
- Patients usually fall asleep in about 5 to 15 minutes, although some patients have reported falling asleep more quickly (without first feeling drowsy) and others take more time. The time that it takes to fall asleep might be different from night to night. You should take each dose of XYREM while in bed. Take the first dose at bedtime and the second 2½ to 4 hours later. You may need to set an alarm to awaken for the second dose.

Any questions? Please call the XYREM® REMS Program at 1-866-997-3688. Please see the Medication Guide for more detailed information about XYREM.
Do not drive a car, use heavy machinery, fly an airplane, or do anything that is dangerous or that requires you to be alert for the first 6 hours after taking XYREM. When you first start taking XYREM, be careful until you know how XYREM affects you.

Keep XYREM out of the reach of children and pets. Get emergency medical help right away if a child drinks your XYREM.

Report all side effects to your healthcare provider.

WHAT WILL YOU FIND IN THIS BOOKLET?
This booklet answers important questions about how to get your XYREM, how to use XYREM properly, and how to store it safely. It also gives you important information about XYREM.

WHAT IS THE XYREM REMS PROGRAM?
Because of the serious risks associated with XYREM, the FDA has required a special program called REMS for XYREM. Enrollment in the XYREM REMS Program by prescribers and patients is required by the FDA to ensure the benefits of XYREM outweigh the risks associated with XYREM. You are enrolled in the program when your healthcare provider sends in the enrollment form you signed. At that time, your healthcare provider also sent your prescription for XYREM to the Certified Pharmacy.

The Certified Pharmacy staff will review important information about XYREM with you. They will also answer any questions you may have about XYREM.
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Enrolling in the XYREM REMS Program

WHAT AM I REQUIRED TO DO IN THIS PROGRAM?

As a patient, your responsibility is to discuss the safe use of XYREM with your healthcare provider and to read this XYREM REMS Program Patient Quick Start Guide before you begin taking XYREM. Be sure to let your healthcare provider know if you are taking other medications or if you have any conditions that might affect your breathing.

DO I HAVE TO ENROLL IN THIS PROGRAM?

Yes. In order for you to receive XYREM, your healthcare provider will have you sign an enrollment form and will send the form to the XYREM REMS Program. You must verify that you have been counseled by your healthcare provider on the serious risks and safe use of XYREM and that you were able to ask your healthcare provider any questions you have about XYREM.
Filling Your XYREM Prescription

HOW IS MY PRESCRIPTION FILLED?
All XYREM prescriptions are filled only by the XYREM REMS Program Certified Pharmacy.

WHAT DOES THE CERTIFIED PHARMACY DO?
Your healthcare provider sends your XYREM prescription directly to the Certified Pharmacy.

After your healthcare provider sends in your first prescription of XYREM, you will receive a call from the Certified Pharmacy to tell you how the XYREM REMS Program helps you get started with taking XYREM and to answer any questions you may have about XYREM. A staff member from the Certified Pharmacy will call you to complete a Patient Counseling Checklist. The Patient Counseling Checklist will include information about other medications that you are taking and other medical conditions which might increase your risk of serious side effects. The Certified Pharmacy will go over the information about how to use XYREM safely and provide a copy of the Medication Guide with each XYREM shipment.

The Certified Pharmacy will always ask you where and when you would like your XYREM delivered and who will sign for the shipment. XYREM will be shipped by an overnight service. When the courier arrives, you or an adult you name must sign for your XYREM.

Any questions? Please call the XYREM® REMS Program at 1-866-997-3688.
Please see the Medication Guide for more detailed information about XYREM.
WHAT WILL I GET WITH MY XYREM PRESCRIPTION?
With each prescription, you will get 1 or more bottles of XYREM (each bottle, whether full or partial, has the concentrated medicine), a XYREM-specific dosing syringe for drawing up your XYREM dose, 2 empty pharmacy containers with child-resistant caps, and a printed Medication Guide.

HOW DO I GET MY XYREM REFILLS?
The Certified Pharmacy will contact you when it is close to your refill time. You may opt-in to receive text, e-mail, or automated voice reminders. You may also call the Certified Pharmacy at 1-866-997-3688 to schedule your refills.

CAN MY LOCAL PHARMACY PROVIDE XYREM?
No. You can get your XYREM only from the XYREM REMS Program central Certified Pharmacy. You may be able to have your XYREM shipped to your place of work or to a local overnight carrier hub for pickup. Saturday deliveries may also be an option for you. The Certified Pharmacy will work with you on the best options available.
How Do I Take My XYREM?

Take XYREM only as your healthcare provider tells you to take it.

**HOW DO I PREPARE MY DOSES?**

Place the bottle on a hard, flat surface and grip the bottle with one hand and firmly press the syringe into the center opening of the bottle with the other. Pull back on the plunger until the medication flows into the syringe and the liquid level is aligned with the corresponding tick mark for your dose. After you draw up the first XYREM dose, remove the syringe from the opening of the XYREM bottle. Empty all of the medicine from the syringe into one of the provided empty pharmacy containers by pushing down on the plunger until it stops.
Using a measuring cup, pour about ¼ cup of water into the pharmacy container. Be careful to add only water to the pharmacy container and not more XYREM. Place the child-resistant cap provided on the filled pharmacy container and turn the cap clockwise (to the right) until it clicks and locks in its child-resistant position.

Repeat the steps described above by drawing up the amount of medicine prescribed for your second dose; emptying the syringe into the second pharmacy container, adding about ¼ cup of water, and closing the pharmacy container.

Put the cap back on the XYREM bottle and store the XYREM bottle and both prepared doses in a safe and secure place. Store in a locked place if needed. Keep the XYREM bottle and both prepared XYREM doses out of the reach of children and pets.

Rinse out the syringe and pharmacy containers with water after each use. Please refer to the Instructions for Use within the Medication Guide for additional details.
HOW DO I TAKE MY DOSES?

You should allow at least 2 hours after a meal before taking your first dose of XYREM.

XYREM is a medicine that can make you sleepy quickly; therefore, take your doses while you are in bed. Take the first dose at bedtime and the second dose 2½ to 4 hours later. As with any medicine that causes sleepiness, if you continue evening activities after taking your dose, such as watching television or walking around, you may experience light-headedness, dizziness, nausea, confusion, or other unpleasant feelings.

WHAT SHOULD I DO IF I MISS A XYREM DOSE?

- It is very important to take both doses of XYREM each night, as prescribed. If you miss the second dose, skip that dose
  - Do not take XYREM again until the next night
  - Never take both XYREM doses at once
- Any unused XYREM doses that you prepared but didn’t take must be thrown away within 24 hours from the time you first prepared your doses
HOW SOON WILL I SEE A CHANGE IN MY SYMPTOMS?

After starting XYREM, it may take a few weeks or longer to see your symptoms improve. It may also take time to find the right dose that works for you. It is important that you talk with your healthcare provider often when you first start taking XYREM. Tell your healthcare provider if you don’t feel any improvements while taking XYREM. XYREM may not be right for you.

WHAT ARE THE SIDE EFFECTS OF XYREM?

XYREM can cause serious side effects, including breathing problems (slower breathing, trouble breathing, and short periods of no breathing while asleep), mental health problems (confusion, seeing or hearing things that are not real, unusual or disturbing thoughts, feeling anxious or upset, depression, thoughts of suicide), and sleepwalking. If you have any of these side effects, call your healthcare provider right away.

The most common side effects with XYREM are nausea, dizziness, throwing up, bedwetting, and diarrhea. Side effects may increase with higher doses.

These are not the only possible side effects with XYREM. If you are worried about any possible side effects with XYREM, talk with your healthcare provider or the pharmacist at the XYREM REMS Program.

You should report all side effects by contacting your healthcare provider, Jazz Pharmaceuticals at 1-800-520-5568, or the FDA at 1-800-FDA-1088.
ARE THERE ANY PRECAUTIONS I SHOULD TAKE WHILE ON XYREM?

- While taking XYREM, do not drink alcohol or take medicines that cause sleepiness.
- Do not drive a car, use heavy machinery, or do anything that is dangerous or requires you to be alert, for the first 6 hours after taking XYREM. When you first start taking XYREM, be careful until you know how it will affect you.
- Before starting XYREM, tell your healthcare provider if you are pregnant, or plan to become pregnant, or if you are breastfeeding. XYREM passes into breast milk. You and your doctor should decide if you will take Xyrem or breastfeed.
- Keep your XYREM in a safe place, out of the reach of children.
- Take XYREM while in bed.

Tell your healthcare provider and pharmacist about any other medicines you are taking, including prescription and non-prescription medicines, vitamins, and supplements.

It is also important to tell other healthcare providers, including pharmacists, that you are taking XYREM before you start or change any medications.
HOW OFTEN SHOULD MY HEALTHCARE PROVIDER CHECK MY PROGRESS WITH XYREM?

When you first start taking XYREM, you may need to talk to your healthcare provider often until he or she has determined the best dose for you. You can expect that your dose may need to be adjusted. After your dose has been established, your healthcare provider should check on you every 3 months while you are taking XYREM.
Storage and Safety Tips at Home

HOW DO I STORE XYREM?

- Always store XYREM in its original bottle
- Store XYREM at room temperature. Do not refrigerate XYREM
- Keep XYREM in a safe place, out of the reach of children and pets. Get emergency medical help (call 911) right away if a child drinks your XYREM

HOW DO I PROPERLY DISPOSE OF XYREM?

To properly dispose of XYREM, pour any unused XYREM down the sink or toilet drain. Mark out all personal information on the prescription label, including the XYREM name, to make it unreadable before putting the empty bottle in the trash.

If you misplace, lose, or damage your XYREM dosing syringe, contact the Certified Pharmacy to have it replaced. Do not use a different syringe or try to guess the correct dose.
WHAT IF I HAVE CONCERNS ABOUT HAVING XYREM IN MY HOME?

- If your XYREM is lost or stolen, report the incident right away to the local police and to the Certified Pharmacy.
- Use XYREM only as your healthcare provider tells you. Remember that use of your XYREM by others is illegal.
- If you have any questions or concerns, or if you need advice about XYREM, call your healthcare provider or the Certified Pharmacy.
Insurance Coverage

WILL INSURANCE PAY FOR MY XYREM?
In most cases, YES. A staff member from the Certified Pharmacy will call and work with your insurance company to help you get coverage for XYREM. In the unlikely event your insurance does not cover XYREM or you can’t afford the out-of-pocket costs, ask the Certified Pharmacy about available financial assistance programs.

WHAT IS THE PHARMACY’S ROLE WITH MY INSURANCE?
An experienced staff member will:
• Call you to go over your prescription benefits and coverage
• Tell you what your co-pay is, if applicable
• Tell you about any XYREM prescription savings plans for which you may qualify
• Work with your healthcare provider on prior authorizations, if required by your insurance company
• Provide information about any financial help that may be available to you

The Certified Pharmacy’s attempt to get coverage from a third-party payer does not guarantee that you will get coverage.

Any questions? Please call the XYREM® REMS Program at 1-866-997-3688.
Please see the Medication Guide for more detailed information.
Reference ID: 4341394
Getting More Information

WHERE CAN I GET MORE INFORMATION ABOUT XYREM?

For more information about XYREM, contact the XYREM REMS Program:

- **Phone**: 1-866-XYREM88® (1-866-997-3688)
- **Fax**: 1-866-470-1744 (toll free)
- **Outside the US**: +314-475-6000, ext 361 587
- **Website**: www.XYREMREMS.com
Any questions? Please call the XYREM® REMS Program at 1-866-997-3688.

Please see the Medication Guide for more detailed information about XYREM.

Reference ID: 4341394
KEEP THIS BOOKLET AS A HELPFUL REMINDER

If you have questions or need information, contact the XYREM® REMS Program.

Please see the Medication Guide for more detailed information about XYREM.
BROCHURE FOR PEDIATRIC PATIENTS AND THEIR CAREGIVERS

Important information about the safe use and handling of XYREM
Dear Caregiver,

Welcome to the XYREM REMS Program. You are receiving these materials because your child’s healthcare provider has prescribed XYREM® (sodium oxybate) oral solution, 0.5 g/mL, for your child. XYREM is a medicine used to treat cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. XYREM may only be given to patients enrolled in the XYREM REMS Program.

Because of the serious risks associated with XYREM, the Food and Drug Administration (FDA) has required a special program called a Risk Evaluation and Mitigation Strategy (REMS). The purpose of the XYREM REMS Program is to make sure the benefits of XYREM outweigh the risks. All patients must be enrolled in the XYREM REMS Program to receive XYREM. Each pediatric patient must have a caregiver who is counseled on the serious risks and safe use of XYREM. This brochure contains information you need to know about XYREM and will help you give XYREM to your child correctly. Read this brochure before you start giving your child XYREM.

Any questions? Please call the XYREM REMS Program at 1-866-997-3688. Please see the Medication Guide for more-detailed information about XYREM.

Reference ID: 4341394
After your child’s healthcare provider sends in your child’s enrollment form and first prescription for XYREM, you will receive a call from the Certified Pharmacy of the XYREM REMS Program to counsel you on the serious risks and safe use of Xyrem, to tell you how the XYREM REMS Program helps you get your child started with taking XYREM, and to answer any questions you or your child may have about XYREM.

A few things must happen before you receive your child’s first shipment of XYREM:

- The Certified Pharmacy will call to:
  - Ask if your child’s healthcare provider reviewed the XYREM REMS Program Brochure for Pediatric Patients and Their Caregivers with you
  - Explain that you will receive this brochure with your child’s first shipment, and that all drug shipments will include the XYREM Medication Guide
  - Ask you about your child’s medical history and other medications he or she may be taking
  - Give you advice on how to prepare and give XYREM to your child and how to store it safely
  - Go over your child’s insurance information

- You must take this call before you can get your child’s XYREM
If you have any additional questions about XYREM, please call your child’s healthcare provider, or you can contact the XYREM REMS Program toll free at 1-866-XYREM88® (1-866-997-3688). You can reach a pharmacist at this number 24 hours a day, 7 days a week with any questions. We hope you find this information and the XYREM REMS Program helpful.

Sincerely,

Jazz Pharmaceuticals
XYREM is a prescription medicine used to treat patients with narcolepsy to reduce too much daytime sleepiness and to reduce cataplexy (suddenly weak or paralyzed muscles).

**IMPORTANT INFORMATION ABOUT XYREM INCLUDES THE FOLLOWING:**

- When taking XYREM, your child should not drink alcohol or take other medicines that may slow his or her breathing or mental activity or make him or her sleepy. Your child could have serious side effects.
- XYREM can cause serious side effects, including slow breathing or changes in alertness. Call your child’s doctor right away if your child has any of these serious side effects.
- Abuse of XYREM can lead to dependence (a physical need to take the drug), craving for the medicine, and severe withdrawal symptoms (symptoms that start when the drug is stopped, especially when it is stopped suddenly).

**WARNING: XYREM can cause serious side effects. Your child should not drink alcohol or take other medicines that cause sleepiness.**
• Patients usually fall asleep in about 5 to 15 minutes, although some patients have reported falling asleep more quickly (without first feeling drowsy) and others take more time. The time that it takes to fall asleep might be different from night to night. You should give each dose of XYREM while your child is sitting up in bed and have your child lie down immediately after. Give the first dose at the time prescribed by your child’s healthcare provider, and the second dose 2 ½ to 4 hours later. You may need to set an alarm to awaken to give the second dose.

• Your child should not do anything that requires him or her to be fully alert for the first 6 hours after taking XYREM. When your child first starts taking XYREM, you and your child will need to be careful until you know how XYREM affects him or her.

• Keep XYREM out of the reach of children and pets. Get emergency medical help right away if a child who has not been prescribed XYREM drinks XYREM.

• Report all side effects to your child’s healthcare provider.

WHAT WILL YOU FIND IN THIS BROCHURE?

This brochure provides information on the serious risks and safe use of XYREM, answers important questions about how to use XYREM properly, how to store it safely, and how to get your child’s XYREM.

Any questions? Please call the XYREM REMS Program at 1-866-997-3688. Please see the Medication Guide for more-detailed information about XYREM.
WHAT IS THE XYREM REMS PROGRAM?

Because of the serious risks associated with XYREM, the FDA has required a special program called REMS for XYREM. Enrollment in the XYREM REMS Program by prescribers and patients is required by the FDA to ensure the benefits of XYREM outweigh the risks associated with XYREM. Your child is enrolled in the program when your child’s healthcare provider sends in your signed enrollment form. At that time, your child’s healthcare provider also will send your child’s prescription for XYREM to the Certified Pharmacy.

The Certified Pharmacy staff will review important information about XYREM with you. They will also answer any questions you and your child may have about XYREM.
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Any questions? Please call the XYREM REMS Program at 1-866-997-3688.
Please see the Medication Guide for more-detailed information about XYREM.
# IMPORTANT INFORMATION YOUR CHILD MUST KNOW ABOUT TAKING XYREM

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<td>What should my child know about taking XYREM?</td>
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# INCLUDING YOUR CHILD IN HIS OR HER CARE

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<td>How can I prepare my child to be able to carry out one or more safe use activities?</td>
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# ENROLLING YOUR CHILD IN THE XYREM REMS PROGRAM

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</tr>
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<td>What am I required to do in this program?</td>
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<tr>
<td>How is my child’s prescription filled?</td>
</tr>
<tr>
<td>What else does the Certified Pharmacy do?</td>
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<tr>
<td>How do I get XYREM refills for my child?</td>
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<tr>
<td>Can my local pharmacy provide XYREM for my child?</td>
</tr>
</tbody>
</table>
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- Will insurance pay for my child’s XYREM?
- What is the pharmacy’s role with my child’s insurance?

CONTACT INFORMATION
- Whom should I contact with concerns or for more information about XYREM?

Any questions? Please call the XYREM REMS Program at 1-866-997-3688. Please see the Medication Guide for more-detailed information about XYREM.

Reference ID: 4341394
Preparation and Administration of XYREM

XYREM should be prepared and taken only as prescribed by your child’s healthcare provider.

WHAT WILL I GET WITH MY CHILD’S XYREM PRESCRIPTION?

With each prescription, you will get 1 or more bottles of XYREM (each bottle, whether full or partial, contains the concentrated medicine), a XYREM-specific dosing syringe for drawing up your child’s XYREM dose, 2 empty pharmacy containers with child-resistant caps, and a printed Medication Guide (Figure 1).
HOW DO I PREPARE MY CHILD’S DOSES?

Place the bottle on a hard, flat surface and grip the bottle with one hand and firmly press the syringe into the center opening of the bottle with the other. Pull back on the plunger until the medication flows into the syringe and the liquid level is aligned with the corresponding tick mark for your child’s dose. After you draw up the first XYREM dose, remove the syringe from the opening of the XYREM bottle. Empty all of the medicine from the syringe into one of the provided empty pharmacy containers by pushing down on the plunger until it stops (Figure 2).

Figure 2

Any questions? Please call the XYREM REMS Program at 1-866-997-3688.
Please see the Medication Guide for more-detailed information about XYREM.

Reference ID: 4341394
Using a measuring cup, pour about ¼ cup of water into the pharmacy container. Be careful to add only water to the pharmacy container and not more XYREM. Place the child-resistant cap provided on the filled pharmacy container and turn the cap clockwise (to the right) until it clicks and locks in its child-resistant position.

Repeat the steps described above by drawing up the amount of medicine prescribed for your child’s second dose; emptying the syringe into the second pharmacy container, adding about ¼ cup of water, and closing the pharmacy container.

Put the cap back on the XYREM bottle and store the XYREM bottle and both prepared doses in a safe and secure place. Store in a locked place if needed. Keep the XYREM bottle and both prepared XYREM doses out of the reach of children and pets.

Rinse out the syringe and pharmacy containers with water after each use. Please refer to the Instructions for Use within the Medication Guide for additional details.
HOW DO I GIVE MY CHILD’S DOSES?

You should allow at least 2 hours after your child eats a meal before giving the first dose of XYREM.

XYREM is a medicine that can make your child sleepy quickly; therefore, give your child’s doses while he or she is sitting up in bed and have your child lie down immediately after dosing and remain in bed. Ensure your child is fully prepared for bed prior to taking the first nightly dose of XYREM (for example, has brushed teeth, gone to the bathroom). Give the first dose at the time prescribed by your child’s healthcare provider, and the second dose 2 ½ to 4 hours later. Ensure that all XYREM doses are kept in a safe place until given. If your child continues evening activities after taking his or her dose, such as watching television or walking around, your child may experience light-headedness, dizziness, nausea, confusion, or other unpleasant feelings. Have the child lie down immediately after dosing and remain in bed (Figure 4).
*For children who sleep more than 8 hours per night, the first dose of XYREM may be given at bedtime or after an initial period of sleep.

**WHAT DO I DO IF MY CHILD MISSES A DOSE?**

- It is very important to give both doses of XYREM each night as prescribed. If the second dose is missed, skip that dose
  - Do not give your child XYREM again until the next night
  - Never give your child both XYREM doses at once
- Any unused XYREM doses that you prepared but didn’t give to your child must be thrown away within 24 hours from the time you first prepared your child’s doses
HOW SOON WILL WE SEE A CHANGE IN SYMPTOMS?

After starting XYREM, it may take a few weeks or longer to see your child’s symptoms improve. It may also take time to find the right dose that works for your child. It is important that you talk with your child’s healthcare provider often when your child first starts taking XYREM.

Tell your child’s healthcare provider if you or your child do not see any improvements.

WHAT ARE THE SIDE EFFECTS OF XYREM?

XYREM can cause serious side effects, including breathing problems (slower breathing, trouble breathing, and short periods of no breathing while asleep), mental health problems (confusion, seeing or hearing things that are not real, unusual or disturbing thoughts, feeling anxious or upset, depression, thoughts of suicide), and sleepwalking. If your child has any of these side effects, call your child’s healthcare provider right away.

The most common side effects with XYREM in pediatric patients are bedwetting, nausea, headache, throwing up, and weight loss. Side effects may increase with higher doses.

These are not the only possible side effects with XYREM. If you or your child are worried about any possible side effects with XYREM, talk with your child’s healthcare provider or the pharmacist at the XYREM REMS Program.

You should report all side effects by contacting your child’s healthcare provider, Jazz Pharmaceuticals at 1-800-520-5568, or the FDA at 1-800-FDA-1088.
ARE THERE ANY PRECAUTIONS THAT SHOULD BE TAKEN WHILE MY CHILD IS ON XYREM?

- While taking XYREM, your child should not drink alcohol or take medicines that cause sleepiness
- Your child should not do anything that requires him or her to be fully alert for the first 6 hours after taking XYREM. When your child first starts taking XYREM, you and your child will need to be careful until you know how XYREM affects him or her.
- Before starting XYREM, tell your child’s healthcare provider if your child is pregnant, or plans to become pregnant, or is breastfeeding. XYREM passes into breast milk. You and your child’s healthcare provider should decide if your child will take XYREM or breastfeed.
- Keep XYREM in a safe place, out of the reach of children
- Give XYREM to your child while he or she is sitting up in bed and have your child lie down immediately and remain in bed after dosing

Tell your child’s healthcare provider and pharmacist about any other medicines he or she is taking, including if your child begins a new medicine while taking XYREM. This would include prescription and non-prescription medicines, vitamins, and supplements.

It is also important to tell other healthcare providers, including pharmacists, that your child is taking XYREM before your child starts or changes any medications.
How Often Should My Child’s Healthcare Provider Check on My Child’s Progress On XYREM?

When your child first starts taking XYREM, you may need to talk to his or her healthcare provider often until he or she has determined the best dose for your child. You can expect that your child’s dose may need to be adjusted. After your child’s dose has been established, his or her healthcare provider should check on your child every 3 months while taking XYREM.

Any questions? Please call the XYREM REMS Program at 1-866-997-3688. Please see the Medication Guide for more-detailed information about XYREM.

Reference ID: 4341394
Storage and Safety Tips at Home

HOW DO I STORE XYREM?

• Always store XYREM in its original bottle
• Store XYREM at room temperature. Do not refrigerate XYREM
• Keep XYREM in a safe place, out of the reach of children and pets. Get emergency medical help (call 911) right away if a child not prescribed XYREM drinks XYREM

HOW DO I PROPERLY DISPOSE OF XYREM?

To properly dispose of XYREM, pour any unused XYREM down the sink or toilet drain. Mark out all personal information on the prescription label, including the XYREM name, to make it unreadable before putting the empty bottle in the trash.

If you misplace, lose, or damage your child’s XYREM dosing syringe, contact the Certified Pharmacy to have it replaced. Do not use a different syringe or try to guess the correct dose.

WHAT IF I HAVE CONCERNS ABOUT HAVING XYREM IN MY HOME?

• If your child’s XYREM is lost or stolen, report the incident right away to the local police and to the Certified Pharmacy
• Give XYREM only as your child’s healthcare provider tells you. Remember that use of your child’s XYREM by others is illegal
• If you have any questions or concerns, or if you need advice about XYREM, call your child’s healthcare provider or the Certified Pharmacy

Reference ID: 4341394
Important Information Your Child Must Know About Taking XYREM

You can use these pages to help teach your young child what he or she needs to know about taking his or her XYREM.

WHAT SHOULD MY CHILD KNOW ABOUT TAKING XYREM?

Get Ready

• Get ready for bed before you drink your XYREM
• Finish your bedtime routine before you get in bed and drink your XYREM

Any questions? Please call the XYREM REMS Program at 1-866-997-3688. Please see the Medication Guide for more-detailed information about XYREM.

Reference ID: 4341394
Stay in Bed

- Drink your XYREM while sitting up in bed. Lie down right away after you drink it and stay in bed.
- Call for a grown-up if you want to get out of bed after taking XYREM.
- It may take a while, or you may fall asleep quickly after taking XYREM.
Be Careful
- Be careful in the morning
- Call for a grown-up to help you if you still feel sleepy in the morning
Always Remember!

- Don’t share your XYREM with anyone else
  – This medicine is only for you!
- Don’t drink too much XYREM
  – Never drink more than one of your XYREM cups at a time
  – Only drink XYREM from your XYREM cup
- Tell a grown-up how you are feeling and about any changes in how you are feeling
Including Your Child in His or Her Care

HOW CAN I PREPARE MY CHILD TO BE ABLE TO CARRY OUT ONE OR MORE SAFE USE ACTIVITIES?

It is important for your child to take an active part in the safe use of his or her XYREM. This is especially true for teenagers and those going to college. This brochure can help you talk with your child about taking XYREM.

Before your child moves away from your home (for example, going away to college), talk with your healthcare provider and the Certified Pharmacy about additional ways to ensure safe use, handling, and storage. To help prepare your child for this transition, make sure that he or she is counseled about the serious risks and safe use of XYREM by a member of your child’s XYREM healthcare team (for example, your child’s healthcare provider or the Certified Pharmacy). Your child should also read this brochure and ask his or her healthcare provider any questions he or she may have.

Any questions? Please call the XYREM REMS Program at 1-866-997-3688. Please see the Medication Guide for more-detailed information about XYREM.

Reference ID: 4341394
Enrolling Your Child in the XYREM REMS Program

DOES MY CHILD HAVE TO ENROLL IN THIS PROGRAM?
Yes. In order for your child to receive XYREM, your healthcare provider will have you sign an enrollment form and will send the form to the XYREM REMS Program. You must verify that you have been counseled by your child’s healthcare provider on the serious risks and safe use of XYREM and that you were able to ask your child’s healthcare provider any questions you have about XYREM. You may choose to have your child also receive counseling from your healthcare provider on the serious risks and safe use of XYREM.

WHAT AM I REQUIRED TO DO IN THIS PROGRAM?
As a caregiver of a pediatric patient who is in the XYREM REMS Program, you are required to:
• Read this brochure and ask your child’s healthcare provider any questions you have about XYREM.
• Ensure that XYREM is prepared and given only as prescribed
• Ensure that XYREM is kept in a safe place, away from children and pets, and protected from theft
• Notify your child’s healthcare provider right away if you notice any serious side effects while your child is taking XYREM

Also be sure to let your child’s healthcare provider know if your child is taking other medicines or if your child has any medical conditions that might affect his or her breathing.

If you need to give your responsibilities as your child’s caregiver to someone else, please notify your child’s healthcare provider. You also can contact the XYREM REMS Program toll free at 1-866-XYREM88® (1-866-997-3688) to make sure that the new caregiver is counseled on the risks and safe use of XYREM.
Filling Your Child’s XYREM Prescription

HOW IS MY CHILD’S PRESCRIPTION FILLED?
All XYREM prescriptions are filled and shipped directly to your home only by the XYREM REMS Program Certified Pharmacy.

WHAT ELSE DOES THE CERTIFIED PHARMACY DO?
Your child’s healthcare provider sends your child’s XYREM prescription directly to the Certified Pharmacy.

You will then receive a call from the Certified Pharmacy to counsel you on the serious risks and safe use of XYREM, to tell you how to get your child started on XYREM and to answer any questions about XYREM. A staff member from the Certified Pharmacy will call you to complete a counseling checklist. The counseling checklist will include information about other medicines that your child is taking and other medical conditions that might increase your child’s risk of serious side effects. The Certified Pharmacy will go over the information about how to use XYREM safely and provide a copy of the Medication Guide with each XYREM shipment.

The Certified Pharmacy will always ask you where and when you would like your child’s XYREM delivered and who will sign for the shipment. XYREM will be shipped by an overnight service. You may be able to have your child’s XYREM shipped to your place of work or to a local overnight carrier hub for pickup. Saturday deliveries may also be an option for you. The Certified Pharmacy will work with you to find the best options available. When the courier arrives, you or another adult you previously named must sign for your child’s XYREM.

Reference ID: 4341394
Finally, the Certified Pharmacy will call you soon after you receive your child’s first XYREM shipment to confirm receipt and answer any questions you may have about your child’s first few days taking XYREM.

**HOW DO I GET XYREM REFILLS FOR MY CHILD?**

The Certified Pharmacy will contact you when it is close to your child’s refill time. You may opt-in to receive text, e-mail, or automated voice reminders for refills. You may also call the Certified Pharmacy at 1-866-997-3688 to schedule your child’s refills.

**CAN MY LOCAL PHARMACY PROVIDE XYREM FOR MY CHILD?**

No. You can get your child’s XYREM only from the XYREM REMS Program central Certified Pharmacy.

Any questions? Please call the XYREM REMS Program at 1-866-997-3688. Please see the Medication Guide for more-detailed information about XYREM.
Insurance Coverage

**WILL INSURANCE PAY FOR MY CHILD’S XYREM?**

In most cases, YES. A staff member from the Certified Pharmacy will call and work with your child’s insurance company to help you get coverage for your child’s XYREM. In the unlikely event your child’s insurance does not cover XYREM or you can’t afford the out-of-pocket costs, ask the Certified Pharmacy about available financial assistance programs.

**WHAT IS THE PHARMACY’S ROLE WITH MY CHILD’S INSURANCE?**

An experienced staff member will:

- Call you to go over your child’s prescription benefits and coverage
- Tell you what your co-pay is, if applicable
- Tell you about any XYREM prescription savings plans for which you may qualify
- Work with your child’s healthcare provider on prior authorizations, if required by the insurance company
- Provide information about any financial help that may be available to you

The Certified Pharmacy’s attempt to get coverage from a third-party payer does not guarantee that you will get coverage.
Contact Information

WHOM SHOULD I CONTACT WITH CONCERNS OR FOR MORE INFORMATION ABOUT XYREM?

FOR QUESTIONS ABOUT SIDE EFFECTS OR FOR MORE INFORMATION ABOUT XYREM, CONTACT YOUR CHILD’S HEALTHCARE PROVIDER:

Name: ________________________________
Phone: ________________________________
Email: ________________________________

FOR MORE INFORMATION ABOUT XYREM, CONTACT THE CERTIFIED PHARMACY:

- **Phone:** 1-866-XYREM88® (1-866-997-3688)
- **Fax:** 1-866-470-1744 (toll free)
- **Outside the US:** +314-475-6000, ext. 361 587
- **Website:** [www.XYREMREMS.com](http://www.XYREMREMS.com)

TO REPORT ALL SIDE EFFECTS, YOU CAN CONTACT:

- Jazz Pharmaceuticals at 1-800-520-5568
- The FDA at 1-800-FDA-1088

FOR EMERGENCIES:

- Call 911

Any questions? Please call the XYREM REMS Program at 1-866-997-3688. Please see the Medication Guide for more-detailed information about XYREM.

Reference ID: 4341394
KEEP THIS BOOKLET AS A HELPFUL REMINDER

If you have questions or need information, contact the XYREM REMS Program.

Please see the Medication Guide for more detailed information about XYREM.

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Reference ID: 4341394
XYREM REMS Program

Certified Pharmacy Training
Modules A and B

All XYREM REMS Program Certified Pharmacy staff must complete Module A and the Module A Knowledge Assessment. Pharmacists must also complete Module B and the Module B Knowledge Assessment.
Dear XYREM REMS Program Certified Pharmacy Staff,

Welcome to the XYREM REMS Program, which has been approved by the Food and Drug Administration (FDA) as a Risk Evaluation and Mitigation Strategy (REMS).

THE XYREM REMS PROGRAM
The FDA has determined that a REMS is necessary to ensure that the benefits of XYREM® (sodium oxybate) oral solution 0.5 g/mL outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of XYREM by:

1. Informing prescribers, pharmacists, and patients of:
   - The risk of significant central nervous system (CNS) 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
   - The safe use, handling, and storage of XYREM

2. Ensuring that pharmacy controls exist prior to filling prescriptions for XYREM that:
   - Screen for concomitant use of sedative hypnotics and other potentially interacting agents
   - Monitor for inappropriate prescribing, misuse, abuse, and diversion of XYREM
   - Notify prescribers when patients are receiving concomitant contraindicated medications or when there are signs of potential abuse, misuse, or diversion.

This training provides information about the XYREM REMS Program that includes important information about XYREM and the responsibilities of the Certified Pharmacy staff involved in the dispensing of XYREM.

Xyrem is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy

XYREM may be prescribed only by prescribers enrolled in the XYREM REMS Program and dispensed only to patients enrolled in the XYREM REMS Program.

Sincerely,

Jazz Pharmaceuticals
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XYREM REMS Program

Certified Pharmacy Training Module A
Training for Pharmacy Staff Involved in the XYREM REMS Program

All XYREM REMS Program Certified Pharmacy staff must complete training on Module A and successfully complete the associated Knowledge Assessment. Training must be completed annually.
IMPORTANT SAFETY INFORMATION

Indications and Usage
Xyrem is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.
XYREM may be prescribed only by prescribers enrolled in the XYREM REMS Program and dispensed only to patients enrolled in the XYREM REMS Program.

How Supplied
XYREM is shipped from the XYREM REMS Program Certified Pharmacy directly to patients. Each shipment to a patient will contain:
- The prescribed amount of medication, contained in one or more bottles of XYREM
- A press-in-bottle adaptor (PIBA) pre-inserted into the bottle
- A XYREM-specific grams-based oral measuring device (plastic syringe) to measure out each nightly dose
- Two empty pharmacy containers with child-resistant caps for preparation of both nightly doses (XYREM dose mixed with water)
- A XYREM Medication Guide

Controlled Substance Scheduling
The active ingredient in XYREM is sodium oxybate or gamma-hydroxybutyrate (GHB, a known drug of abuse). GHB has been used to facilitate sexual assaults. Because of its rapid sedative effects (particularly when mixed with alcohol) and its colorless and odorless appearance, GHB has been used to “spike” the drinks of unsuspecting victims. Because of its abuse potential, GHB is designated a controlled substance by the Drug Enforcement Administration (DEA) and has been placed in a bifurcated federal schedule:
- GHB products approved by the FDA, such as XYREM, and used as prescribed for therapeutic purposes are Schedule III drugs
- The active ingredient of XYREM is classified as a Schedule I controlled substance when used for any other reason or by anyone other than for whom it was prescribed. Federal law prohibits the transfer of XYREM to any persons other than the patient for whom it was prescribed.
Boxed Warning

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

- **Central Nervous System Depression**
  Xyrem (sodium oxybate) is a CNS depressant. In clinical trials at recommended doses, obtundation and clinically significant respiratory depression occurred in adult patients treated with Xyrem. Many patients who received Xyrem during clinical trials in narcolepsy were receiving central nervous system stimulants.

- **Abuse and Misuse**
  Xyrem® (sodium oxybate) is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death.

Because of the risks of CNS depression and abuse and misuse, Xyrem is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Xyrem REMS Program.

Contraindications
- XYREM is contraindicated in:
  - Patients who take sedative hypnotic agents
  - Patients who drink alcohol while using XYREM
  - Patients with succinic semialdehyde dehydrogenase deficiency, a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.

Warnings and Precautions

**CNS Depression**
- XYREM is a CNS depressant.
- Concurrent use of XYREM with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.
  - If use of these CNS depressants in combination with XYREM is required, dose reduction or discontinuation of one or more CNS depressants (including XYREM) should be considered.
  - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with XYREM should be considered.
- Patients who have sleep apnea or compromised respiratory function may be at a higher risk of developing respiratory depression, loss of consciousness, coma, and death with XYREM use.
- Healthcare providers should caution patients/caregivers against hazardous activities requiring complete mental alertness or motor coordination (e.g., driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYREM does not affect the patient adversely.

Reference ID: 4341394
**Abuse, Misuse, and Diversion**

- The active ingredient of XYREM, sodium oxybate or GHB, is a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse events, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death.
- The rapid onset of sedation, coupled with the amnestic features of XYREM, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).
- Patients should be carefully evaluated for a history of substance abuse. Patients with a history of drug abuse should be closely monitored for signs of misuse or abuse of GHB (e.g., increase in dose or frequency of dosing, drug-seeking behavior, feigned cataplexy).

For complete safety information, please see the full Prescribing Information for XYREM.

**XYREM REMS Program Requirements**

XYREM may be prescribed only by prescribers enrolled in the XYREM REMS Program and dispensed only to patients enrolled in the XYREM REMS Program. Because of the risks of central nervous system depression, abuse, misuse, and diversion, XYREM is available only through a restricted distribution program called the XYREM REMS Program.

Required Components of this program include:
- Use of the central Certified Pharmacy.
- Healthcare Providers who prescribe XYREM must have completed the XYREM REMS Program Prescriber Enrollment Form and must comply with the requirements of the XYREM REMS Program.
- To receive XYREM, patients must be enrolled in the XYREM REMS Program and adult patients or caregivers (for pediatric patients) must be counseled on the serious risks and safe use of XYREM. Patients are enrolled by prescribers who must fill out and submit the XYREM REMS Program Patient Enrollment Form. Prescribers must also complete and submit the XYREM REMS Program Prescription Form for all new XYREM prescriptions and for XYREM prescriptions for patients restarting XYREM treatment after not receiving XYREM for 6 months or more.
- Further information is available at [www.XYREMREMS.com](http://www.XYREMREMS.com).

**Overview of Certified Pharmacy Responsibilities**

**DATABASE**

The Certified Pharmacy will utilize the secure and validated XYREM REMS Program Central Database containing the following types of information:
- Patient and prescriber enrollment
- Patient medical history
- Prescription
- Risk management
- Shipment
- Interactions with patients, caregivers (for pediatric patients), and prescribers.
ENROLLMENT PROCESSING AND MAINTENANCE

- Prescriber and patient enrollment forms are submitted to the XYREM REMS Program by the prescriber.
- Information from the enrollment forms is maintained in the Central Database.
  - The Central Database will assign a unique identifier to each prescriber, patient or caregiver once their information is entered within the database by Certified Pharmacy staff.
- No duplicate patients may be enrolled:
  - When a new Patient Enrollment Form is received, the Central Database must be searched to determine if the patient is already enrolled in the XYREM REMS Program.
  - If a match (duplicate patient) is found, the Certified Pharmacy will contact the patient and/or prescriber(s) to determine why a duplicate enrollment form was sent to the program.
  - If abuse, misuse, or diversion is suspected, the new enrollment will not be processed, the prescriber(s) will be notified, and a XYREM REMS Program Risk Management Report (RMR) will be completed and submitted to Jazz Pharmaceuticals.
- Patients or caregivers (for pediatric patients) attest that they have been counseled on the serious risks and safe use of XYREM; the Certified Pharmacy will also provide counseling for new patients and those restarting treatment, as required (after more than a 6 month lapse in treatment), as well as for new caregivers (for pediatric patients).
- The Certified Pharmacy will notify the prescriber of successful enrollment in the XYREM REMS Program, and that he or she is eligible to prescribe XYREM.
  - If there is a delay in shipping while a question about the prescriber’s credentials could not be resolved, the patient/caregiver will be notified by the Certified Pharmacy.
  - If the prescription cannot be filled because a question about the prescriber’s credentials could not be resolved, the patient/caregiver will be notified by a XYREM REMS Program pharmacist.
  - The prescriber will be notified that he or she cannot be enrolled in the event of credential verification failure.
- The Certified Pharmacy will notify the prescriber of successful patient enrollment in the XYREM REMS Program.
- Enrollment status is maintained in the XYREM REMS Program Central Database.
  - The Certified Pharmacy will confirm that the prescriber’s DEA, state license, and NPI numbers are active and that the prescriber has provided all REMS-required attestations.
  - A prescriber may be disenrolled from the program for expired DEA or NPI numbers, for expired state licensures, or for noncompliance with the XYREM REMS Program.
  - Following enrollment the patient remains in the XYREM REMS Program unless the Certified Pharmacy and/or the prescriber determines that the patient should be disenrolled.
  - A patient may be disenrolled from the program for noncompliance with the XYREM REMS Program, including for multiple suspicious early refill requests, or other information that indicates abuse, misuse, or diversion.
  - The Certified Pharmacy will contact a prescriber if an enrollment form is received for a patient previously disenrolled from the program at prescriber request, or for suspicions of abuse, misuse, or diversion, and will provide the prescriber with all relevant patient history.

PRESCRIPTION PROCESSING

- Upon receipt of a XYREM REMS Program Prescription Form, the prescription information will be entered into the Central Database.
- The Certified Pharmacy will validate all prescriptions prior to dispensing XYREM. This includes verifying that:
  - The prescription form is complete and signed by the prescriber.
The prescriber is enrolled in the XYREM REMS Program and has active DEA, state license, and NPI numbers.

The patient is enrolled in the XYREM REMS Program and has no other active XYREM prescriptions.

▪ If the Certified Pharmacy receives overlapping prescriptions for XYREM for a patient, the Certified Pharmacy will notify and consult each prescriber.
  ♦ Prescriptions are considered overlapping when more than one prescription for XYREM is received for a patient from multiple prescribers within an overlapping timeframe.
  ▪ If the Certified Pharmacy suspects abuse, misuse, or diversion, the prescription will not be filled, the prescriber will be notified, and an RMR will be completed.
  ♦ There are valid reasons why a patient may have overlapping prescriptions, including if the patient moves or changes prescribers, or if the prescriber sends in a new prescription prior to the completion of all refills.
  ♦ The Certified Pharmacy will ensure that under these situations a patient does not receive multiple overlapping shipments of XYREM.

▪ The prescription form was received from the prescriber’s office.
▪ The prescription is dated within the last 6 months.
▪ The prescription is for only a one-month supply on a patient’s first XYREM fill and no more than a 3-month supply on subsequent fills.
▪ There are no discrepancies or concerns with the dosing and titration.
  ▪ If there are discrepancies, or if the prescription form is incomplete, the Certified Pharmacy must contact the prescriber.

Prior to dispensing XYREM to pediatric patients, the Certified Pharmacy will ensure each pediatric patient has a caregiver that has been counseled on the serious risks and safe use, handling and storage of XYREM.

Once the prescription is validated, the Certified Pharmacy will contact the patient to schedule shipment and complete the required counseling
– For a new patient, the Certified Pharmacy provides the XYREM REMS Program Patient Quick Start Guide (for adult patients) or XYREM REMS Program Brochure for Pediatric Patients and Their Caregivers (for pediatric patients).
– A pharmacist must counsel the patient or caregiver (for pediatric patients) by completing the XYREM REMS Program Patient Counseling Checklist prior to the initial dispensing of XYREM.

SHIPPING
All XYREM is shipped to patients (or their adult designee) by an overnight service with receipt signature required.

▪ The patient or caregiver (for pediatric patients) may request an alternate shipping address, which is subject to approval by the Certified Pharmacy.
▪ See How Supplied for details of the contents of each XYREM shipment
▪ Daily tracking reports are generated to confirm the receipt of each order shipped
▪ Lost shipments are investigated.

MONITORING FOR INAPPROPRIATE PRESCRIBING, ABUSE, MISUSE, AND DIVERSION
The Certified Pharmacy must conduct detailed monitoring on an ongoing basis of patients and prescribers for signs of inappropriate prescribing, abuse, misuse, and diversion. The Certified Pharmacy will:

▪ Document early refill requests and instances of patient and prescriber behavior that suggest potential abuse, misuse, or diversion by completing an RMR. This information is maintained in the Central Database.
▪ Review the patient’s RMR history and alerts in the Central Database prior to granting an early refill request or if abuse, misuse, or diversion is suspected.
• Discuss early refill requests or other patient incidents with the prescriber so that the prescriber can make a decision to allow or deny the early refill, or to take some other action based on the patient’s behavior and history.
• Report all RMRs to Jazz Pharmaceuticals.
• Determine whether an alert should be placed in the patient’s profile within the Central Database for repeated reports of lost, stolen, destroyed, or spilled drug for review prior to shipping XYREM.
• Inform a XYREM REMS Program pharmacist immediately if Certified Pharmacy staff suspect patients, or prescribers of abuse, misuse, or diversion.

ADVERSE EVENT REPORTING
• Everyone on the Certified Pharmacy staff has an essential role to play in the process of collecting information on potential adverse events for reporting to Jazz Pharmaceuticals. Potential adverse events must be reported to Jazz Pharmaceuticals within one business day. Jazz Pharmaceuticals reports adverse event information to the FDA.

ONGOING PATIENT AND CAREGIVER EDUCATION
Patients and caregivers in the XYREM REMS Program have access to ongoing education during XYREM treatment:
• 24-hour toll-free telephone help line staffed by a XYREM REMS Program pharmacist
• Continued contact with the Certified Pharmacy for every refill
• XYREM REMS Program website (www.XYREMREMS.com).
XYREM REMS Program

Certified Pharmacy Training Module B
XYREM REMS Program Training for Pharmacists Involved in the Dispensing of XYREM

All XYREM REMS Program Certified Pharmacy pharmacists must complete training on Module B (in addition to Module A) and successfully complete the associated Knowledge Assessment. For all pharmacists who dispense XYREM, training must be completed annually.
Module B: XYREM REMS Program Training for Pharmacists

All pharmacists involved in dispensing XYREM must complete the following additional training at least annually. The XYREM REMS Program and functional training for pharmacists typically ranges from three to four weeks, depending upon job function and individual learning curve. Training may be extended as information retention of the trainee dictates. Training will be conducted by a pharmacist currently specializing in the XYREM REMS Program. Upon completion of formal training, a new pharmacist employee will perform assigned duties with a senior pharmacist employee as a resource and a mentor. The mentor will observe and monitor the performance of duties by the new employee to ensure competency. These duties will include:

- Execution of the XYREM REMS Program Patient Counseling Checklist
- Detailed monitoring including completion of an RMR
- Follow-up interactions with patients, caregivers (for pediatric patients), and prescribers
- System documentation

The mentoring senior pharmacist will release the trainee from observation upon confirmation that the new pharmacist employee has mastered the required skills.

XYREM REMS Program Requirements

XYREM may be prescribed and dispensed only to patients enrolled in the XYREM REMS Program. Because of the risks of central nervous system (CNS) depression, abuse, misuse, and diversion, XYREM is available only through a restricted distribution program called the XYREM REMS Program.

Required components of this program include:

- Use of a central Certified Pharmacy
- Healthcare providers who prescribe XYREM must complete and submit the following to the XYREM REMS Program:
  - The XYREM REMS Program Prescriber Enrollment Form
  - The XYREM REMS Program Patient Enrollment Form
  - Prescriptions for XYREM on the XYREM REMS Program Prescription Form
    - Prescription refills and renewals may be conveyed by phone, by fax, or electronically and must be documented in the XYREM REMS Program Central Database.
- To receive XYREM, patients must be:
  - Enrolled in the XYREM REMS Program
  - Prescribed XYREM by a prescriber enrolled in the XYREM REMS Program
  - Counseled on the serious risks and safe use of XYREM
    - For pediatric patients, the caregiver must be counseled on the serious risks and safe use of XYREM
  - Have only one active XYREM prescription.
CERTIFIED PHARMACY RESPONSIBILITIES

The central Certified Pharmacy will:

- Limit the first prescription fill to a one-month supply of XYREM and limit subsequent prescription fills to no more than a 3-month supply
- Report potential adverse events to the XYREM REMS Program
- Notify prescribers when there are signs of potential abuse or misuse or when patients are taking sedative hypnotics, other CNS depressants, or other potentially interacting agents of which the prescriber is not already aware
- Utilize the Central Database containing the following:
  - Complete prescriber enrollment information
  - Complete patient information, including:
    - Name and two additional identifiers (date of birth, phone number, address, gender)
    - Current and previous prescribers
    - Comorbid conditions and concomitant medications reported by the patient
    - Prescription history
    - Caregiver(s) (for pediatric patients)
  - Prescription information, including:
    - Date
    - Dose
    - Titration instructions
    - Number of refills
    - Directions
    - Total quantity (volume and number of days’ supply)
    - Concomitant medications
  - Risk Management Reports (RMRs)
  - Shipment information, including:
    - Dates of shipments
    - Dates of shipment receipts
    - Patient addresses
    - Designee information
    - Number of shipments sent daily
    - Quantity of XYREM dispensed daily
  - Documentation of interactions with prescribers, patients, caregivers (for pediatric patients), and other parties.

These data must be available to the Certified Pharmacy for review on an ongoing basis to ensure that XYREM is dispensed to enrolled patients only after completion and documentation of safe use conditions. In certain cases, a pharmacist must access a patient's or prescriber's historical data in the Central Database and review it prior to dispensing XYREM.
PATIENT COUNSELING AND SCREENING

- Prior to dispensing Xyrem, the XYREM REMS Program Certified Pharmacy ensures the completion of the XYREM REMS Program Patient Counseling Checklist and its requirements and the documentation of the information received in the XYREM REMS Program Central Database.
  - For new patients (first shipment of XYREM), and for patients who are restarting XYREM treatment after not receiving XYREM for 6 months or longer, the XYREM REMS Program Patient Counseling Checklist must be completed in its entirety.
  - For a new caregiver of an already enrolled pediatric patient, confirmation should be obtained, that he or she has been counseled on the serious risks and safe use of XYREM and that he or she has asked any questions he or she has about XYREM; the XYREM REMS Program Patient Counseling Checklist must be completed in its entirety.
  - For prescription renewals and refills, if the patient or caregiver has indicated a change in the patient’s health or medications, the patient or caregiver will be transferred to the pharmacist to determine if further counseling and prescriber outreach is required. Steps 1, 3, 4 and 5 of the Counseling Checklist must be completed if the patient or caregiver indicates that the patient is taking a new medication or has a new comorbid medical condition that is listed in Step 4 of the Counseling Checklist.

- Each time a pharmacist completes the XYREM REMS Program Patient Counseling Checklist, the pharmacist must:
  - Verify that early refill requests have been thoroughly questioned and approved through the RMR procedure (see below).
  - Screen for concomitant use of contraindicated medications (sedative hypnotics), alcohol, other CNS depressants, and other potentially interacting agents by the patient.
    - The pharmacist asks the patient or caregiver if the patient is taking any other medications and can consult external pharmacy databases to identify drug interactions or prescriptions for other drug products that might have been filled at different pharmacies before filling the prescription.
    - If patient use of a contraindicated medication or other potentially interacting agent is confirmed, and if the prescriber has not indicated prior knowledge, then the pharmacist will notify and consult the prescriber about the risks of concomitant medication use prior to shipping XYREM.
    - Instruct the patient/caregiver to alert the pharmacy to any new medication the patient begins as soon as possible.
  - Screen for other medical conditions.
    - The pharmacist asks the patient or caregiver what other medical conditions the patient has.
    - If the patient or caregiver indicates that the patient has a certain medical condition listed on the XYREM REMS Program Patient Counseling Checklist, the pharmacist counsels the patient or caregiver, and notifies the prescriber about the medical condition, if the prescriber has not indicated prior knowledge, prior to shipping XYREM.
    - Steps 4 and 5 of the counseling checklist may be completed after the patient/caregiver phone call.
  - Document the results of the patient screening, all reported concomitant medications and comorbid medical conditions, the action(s) taken, and the date the checklist is completed in the Central Database.
  - Document the completion of the XYREM REMS Program Patient Counseling Checklist in the Central Database.
  - Include additional requirements (if any) per federal or state requirements that need to be collected as part of the patient counseling process.

- Patients or caregivers will also have access to a XYREM REMS Program pharmacist via the 24/7 toll-free telephone help line.
CLINICAL USAGE CLARIFICATIONS

The pharmacist must:

- Review the information on each XYREM REMS Program Prescription Form
- Notify and consult the prescriber if there are any clinical usage clarifications required, such as:
  - Dose over maximum recommended dose (9 g/night)
  - Non-standard doses or instructions
  - Possible errors in dosing or titration amounts or directions
  - Weight has not been given for pediatric patients on initial and restart fills
- If the issue is not resolved with the prescriber, the pharmacist may consult with the Pharmacist in Charge at the Certified Pharmacy and with Jazz Pharmaceuticals.

PRESCRIPTION REFILLS

- Up to 5 refills are allowed on a XYREM prescription (per DEA regulations for CIII controlled substances).
- Refills and renewals may be conveyed by phone, by fax, or electronically from the prescriber and must be documented in the Central Database. Refill orders are opened at the Certified Pharmacy when the patient has approximately 10 days of XYREM therapy remaining from the previous shipment.
  - The Certified Pharmacy will contact the patient or caregiver and schedule a shipment if the patient or caregiver has not already contacted the Certified Pharmacy to request a refill.
  - The Certified Pharmacy will ask the patient or caregiver if there has been any change in the patient’s medications or medical history. If the patient or caregiver indicates a change, the patient or caregiver will be transferred to a pharmacist, who determines if additional counseling and prescriber notification is required. Steps 1, 3, 4, and 5 of the XYREM REMS Program Patient Counseling Checklist must be completed if the patient or caregiver indicates that the patient is taking a new medication or has a new comorbid medical condition listed in Step 4 of the Counseling Checklist. Steps 4 and 5 should be completed post-call and should summarize the information learned on the call. The patient or caregiver should be counseled on:
    - Sedative hypnotics (e.g., diazepam, phenobarbital, zolpidem)
    - CNS depressants: including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, and muscle relaxants
    - Alcohol
    - Sleep apnea
    - Asthma, COPD, or other conditions affecting the patient’s breathing
    - Other current medical conditions
  - The pharmacist must document refill counseling information and confirmation of prescriber consultation or notification in the Central Database.
- All patient requests for early refills are to be questioned and documented by the pharmacist.
  - An early refill request is a request for XYREM shipment prior to the date of the next shipment.
  - Requests to accommodate shipment logistics (e.g., scheduled delivery date falls on a Sunday, holidays, and vacations) are not considered early refills.
  - If the early refill is required due to a dosage increase, a pharmacist must:
    - Confirm the new dosage with the prescriber prior to processing the prescription.
  - If an early refill is requested for any other reason, a pharmacist must:
    - Discuss the request with the patient or caregiver to evaluate the patient’s compliance with therapy, assessing for misuse, abuse, and diversion
▪ Evaluate the patient’s record in the Central Database and review the patient’s prior XYREM REMS Program RMR history to identify previous reports of early refills or other incidents suggestive of abuse, misuse, and diversion
▪ Contact the prescriber to discuss the request and any prior early refill requests or incidents suggestive of abuse, misuse, and diversion
▪ Send new shipments of XYREM to the patient only if approved by the prescriber
▪ Send new shipments to replace XYREM reported stolen by a patient or caregiver only after obtaining a copy of the police report filed by the patient or caregiver
▪ Document the discussion and outcome in the Central Database by completing a XYREM REMS Program RMR.

MONITORING AND ASSESSING FOR SIGNS OF ABUSE, MISUSE, AND DIVERSION

• Risk management events must be documented in the Central Database by completing a XYREM REMS Program RMR.
  – Risk management events are reported or discovered events outside the norm that give rise to a reasonable suspicion of abuse, misuse, or diversion
  – Examples of events that should generate an RMR include but are not limited to:
    ▪ Requests for early refills
    ▪ Patient’s misuse or abuse of product
    ▪ Lost, stolen, destroyed, or spilled drug
    ▪ Delivery to incorrect address and not returned
    ▪ Patient claims that product was not delivered while carrier shows receipt of delivery
    ▪ Product tampering
    ▪ Counterfeit product
    ▪ Contaminated product
    ▪ Inquiries and/or arrests by law or regulatory enforcement agencies associated with the misuse, abuse, or diversion of the product
    ▪ Crimes related to the product
  – RMRs must document:
    ▪ Patient, caregiver (for pediatric patients), and prescriber identifying information (patient name to be concealed)
    ▪ Reason for report
    ▪ Certified Pharmacy actions
    ▪ Prescriber contact
    ▪ Supporting documentation if applicable (e.g., a police report, fire report, DEA Form 106, or shipper investigation report)
  – If abuse, misuse, or diversion is suspected, the pharmacist must review the patient’s RMR history and discuss the incident with the prescriber prior to shipping XYREM.
  – Repeated reports of lost, stolen, destroyed, or spilled drug will be documented as an alert to the patient record stored in the Central Database and will be accessible to the dispensing pharmacist for review prior to shipping drug.
  – The Certified Pharmacy and/or prescriber may disenroll a patient from the XYREM REMS Program after review and discussion of incidents suggestive of abuse and misuse.
  – All RMRs must be reported to Jazz Pharmaceuticals.

Reference ID: 4341394
SHIPPING PROCEDURES

- XYREM must be shipped via an overnight service with receipt signature required.
  - XYREM is shipped directly to the patient or adult designee (≥18 years, or ≥21 years if required by carrier) if the patient is not available to receive the order.
- The patient or caregiver (for pediatric patients) may request an alternate shipping address, which is then subject to approval by the Certified Pharmacy.
- If the patient or caregiver requests Saturday delivery, the Certified Pharmacy will verify with the overnight shipping service that it is available for the shipping address.
- Each XYREM shipment includes:
  - The prescribed amount of medication, contained in one or more bottles of XYREM
  - A press-in-bottle adaptor (PIBA) that is pre-inserted into the bottle
  - A XYREM-specific grams-based oral measuring device (plastic syringe) to measure out each nightly dose
  - Two empty pharmacy vials with child-resistant caps for preparation of both nightly doses (XYREM dose mixed with water)
  - A XYREM Medication Guide.
- Daily tracking reports are generated to confirm the receipt of each order shipped during the previous 48 hours. Saturday deliveries are confirmed the following Monday.
  - A patient or caregiver (for pediatric patients) will be contacted if there is no proof of patient or designee signature, if the patient or designee on file did not sign for the shipment, or if there is a potential incomplete delivery.
  - If a shipment is reported lost, an investigation will be launched to find it.

INVENTORY CONTROL

The XYREM inventory must be reconciled at the start and end of each business day and recorded in the Central Database. A physical count must match the count in the Central Database. If not, no other patient orders can be processed until an investigation is completed and approved by the Pharmacist in Charge.
Knowledge Assessment: Module A

XYREM REMS Program Overview

1. XYREM® (sodium oxybate) oral solution, 0.5 g/mL, is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.
   A. True
   B. False
   (Answer: A)

2. GHB, the active ingredient in XYREM, is a controlled substance because:
   A. It must be administered twice nightly
   B. It has abuse potential
   C. It requires dilution before dosing
   D. It is a central nervous system (CNS) depressant
   (Answer: B)

3. XYREM is contraindicated in patients:
   A. Who take sedative hypnotics
   B. Who drink alcohol while using XYREM
   C. Who have succinic semialdehyde dehydrogenase deficiency, a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia
   D. A, B, and C
   (Answer: D)

4. XYREM is a CNS depressant. Which of the following is NOT a warning related to CNS depression?
   A. Concurrent use with other CNS depressants may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death
   B. Patients who have sleep apnea or compromised respiratory function may be at a higher risk of developing respiratory depression, loss of consciousness, coma, and death with XYREM use
   C. All surgeries and procedures must be reported as adverse events
   D. Healthcare providers should caution patients/caregivers against hazardous activities requiring complete mental alertness or motor coordination (e.g., driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYREM does not affect the patient adversely
   (Answer: C)
5. The XYREM REMS Program has which of the following requirements?
   A. Use of the central Certified Pharmacy
   B. Healthcare providers who prescribe XYREM must have completed the XYREM REMS Program Prescriber Enrollment Form and must comply with the requirements of the XYREM REMS Program
   C. For adult patients to receive XYREM, they must be enrolled in the XYREM REMS Program and be counseled on the serious risks and safe use of XYREM treatment
   D. For pediatric patients to receive XYREM, they must be enrolled in the XYREM REMS Program and their caregiver must be counseled on the serious risks and safe use of XYREM
   E. All of the above
   (Answer: E)

6. In processing enrollment information, the XYREM REMS Program requires all of the following EXCEPT:
   A. The Certified Pharmacy will confirm that the prescriber’s DEA, state license, and NPI numbers are active and that the prescriber has provided all REMS-related attestations
   B. Prescribers are notified when they are enrolled in the XYREM REMS Program and can prescribe XYREM
   C. When a patient enrollment form is received, the Central Database is searched to determine if a patient is already enrolled (duplicate patient)
   D. The Certified Pharmacy will ensure that refill orders are shipped when a patient has approximately 10 days of therapy remaining from the previous shipment
   E. A patient or prescriber may be disenrolled for noncompliance with the XYREM REMS Program
   (Answer: D)

7. Which of the following is NOT true of caregivers of pediatric patients within the XYREM REMS Program?
   A. A caregiver for a pediatric patient can be changed
   B. They must complete a separate enrollment form
   C. They must sign the patient enrollment form attesting that they have been counseled
   D. They must be counseled on the serious risks and safe use of XYREM
   (Answer: B)

8. Which of the following is NOT entered in the Central Database in the XYREM REMS Program?
   A. Patient and prescriber enrollment information
   B. Patient medical history
   C. Interactions with patients, caregivers and prescribers
   D. Prescription information
   E. Shipment information
   F. All of the above are entered
   (Answer: F)
9. In validating a prescription for XYREM, the Certified Pharmacy will verify that:

- The XYREM REMS Program Prescription Form was received from the prescriber’s office, is complete and signed by the prescriber, and is dated within the last 6 months;
- The prescriber is enrolled in the XYREM REMS Program and has active DEA, state license, and NPI numbers;
- The patient is enrolled in the XYREM REMS Program and has no other active XYREM prescriptions; and
- The prescription is for only a one-month supply (first fill) or no more than a 3-month supply (refills).

A. True  
B. False  
(Answer: A)

10. In monitoring patients and prescribers for signs of inappropriate prescribing, abuse, misuse, and diversion, the pharmacy will:

A. Document early refill requests and instances of patient and prescriber behavior that suggest potential abuse, misuse, or diversion by completing a Risk Management Report  
B. Place an alert in the patient’s profile within the Central Database for repeated reports of lost, stolen, destroyed, or spilled drug for review prior to shipping XYREM  
C. Inform a XYREM REMS Program pharmacist immediately if pharmacy staff suspects a patient or prescriber of abuse, misuse, or diversion  
D. A and B only  
E. A, B, and C  
(Answer: E)

11. All potential adverse events must be reported to Jazz Pharmaceuticals within one business day.

A. True  
B. False  
(Answer: A)
Knowledge Assessment: Module B
In-Depth Pharmacy Training for the XYREM REMS Program

1. Upon completion of formal training, a new pharmacist will perform which of the following assigned duties under the observation of a senior pharmacy mentor?
   A. Execution of the XYREM REMS Program Patient Counseling Checklist with new patients (or their caregiver for pediatric patients) and patients (or their caregiver for pediatric patients) who have not received XYREM for 6 months or longer
   B. Detailed monitoring, including completion of a Risk Management Report (RMR)
   C. Follow-up interactions with patients, caregivers (for pediatric patients), and prescribers
   D. A, B, and C
   **(Answer: D)**

2. The Central Pharmacy certified through the XYREM REMS Program will:
   A. Limit the first prescription to a one-month supply and subsequent prescriptions to a three-month supply
   B. Report potential adverse events to Jazz Pharmaceuticals
   C. Notify prescribers when patients are taking sedative hypnotics, other CNS depressants, or other potentially interacting agents of which the prescriber is not already aware or there are signs of potential abuse or misuse
   D. A, B, and C
   **(Answer: D)**

3. The Central Database will contain the following information that must be available for ongoing review to ensure XYREM (sodium oxybate) oral solution, 0.5 g/mL, is dispensed to enrolled patients only after completion and documentation of safe use conditions:
   A. Complete patient and prescriber enrollment information
   B. Patient information, including two additional identifiers, current and previous prescribers, comorbid conditions and concomitant medications reported by the patient or caregiver (for pediatric patients), and prescription history
   C. Caregiver information (for pediatric patients)
   D. Prescription information, including date, dose, titration instructions, number of refills, and total quantity
   E. RMRs, shipment information, and documentation of interactions with patients, caregivers, and prescribers
   F. All of the above
   **(Answer: F)**
4. Prior to shipment of XYREM, the XYREM REMS Program Patient Counseling Checklist must be completed as follows:
   - For initial prescriptions and for patients restarting XYREM after not receiving XYREM for 6 months or more, complete the entire checklist
   - For prescription renewals and refills, if the patient or caregiver indicates a change in the patient's health or medications, transfer the patient or caregiver to the pharmacist to determine if further counseling and prescriber outreach is required. Steps 1, 3, 4, and 5 of the Counseling Checklist must be completed if the patient or caregiver indicates that the patient is taking a new medication or has a new comorbid medical condition that is listed in Step 4 of the Counseling Checklist.
   - For new caregivers of already enrolled pediatric patients, complete the entire checklist

A. True
B. False
(Answer: A)

5. If patient use of a contraindicated medication is confirmed and the prescriber has not indicated prior knowledge, the pharmacist will contact and consult the prescriber prior to shipping XYREM.

A. True
B. False
(Answer: A)

6. If there are any clinical usage clarifications needed for a prescription, the pharmacist will:

A. Refuse to fill the prescription
B. Notify and consult the prescriber
C. Fill out an RMR
D. Disenroll the prescriber

(Answer: B)

7. Which of the following is NOT true for the prescription refill process?

A. Up to 5 refills are allowed on a XYREM prescription
B. Refill prescriptions can be submitted electronically
C. Refill orders are opened when the patient has approximately 10 days of therapy remaining from the previous prescription
D. All refills must be countersigned by the prescriber

(Answer: D)
8. As part of processing a prescription refill, the pharmacist may discuss the following with the patient or caregiver (for pediatric patients) EXCEPT:
   A. Use of sedative hypnotics (e.g., diazepam, phenobarbital, or zolpidem)
   B. Use of alcohol
   C. History of sleep apnea
   D. Choice of prescriber
   E. History of asthma, COPD, or other conditions affecting breathing
   (Answer: D)

9. If the pharmacist identifies that the patient is taking a potentially interacting agent that may present a risk to the patient, the pharmacist should consider which of the following actions before filling the prescription?
   A. Notifying law enforcement
   B. Taking no action
   C. Consulting the prescriber
   D. Consulting the insurance provider
   (Answer: C)

10. In monitoring and assessing for signs of abuse, misuse, or diversion, a pharmacist must document risk management events in the XYREM REMS Program Central Database by completing a XYREM REMS RMR. Events that should generate an RMR include, but are not limited to (choose BEST answer):
    A. Early refill requests (excluding requests to accommodate shipment logistics)
    B. Lost, stolen, destroyed, or spilled drug
    C. Patient or caregiver claims that product was not delivered while carrier shows receipt of delivery
    D. Counterfeit or contaminated product
    E. All of the above
    (Answer: E)

11. When is weight required on the prescription form?
    A. For all patients on every prescription form
    B. For all patients on initial and restart fills only
    C. For adult patients on every prescription form
    D. For adult patients on initial and restart fills only
    E. For pediatric patients on every prescription form
    F. For pediatric patients on initial and restart fills only
    (Answer: F)
(Prior to dispensing XYREM, the XYREM REMS Program Certified Pharmacy ensures the completion of the checklist and its requirements and documents the information received in the XYREM REMS Program Central Database. Include additional requirements (if any) per federal or state requirements that need to be collected as part of the patient counseling process.)

Step 1: Patient Information

(Complete this section for new patients [first shipment of XYREM], existing patients who are restarting XYREM treatment after not receiving XYREM for 6 months or longer, and patients who report a new medication or new comorbid medical condition listed in Step 4 of this checklist)

☐ New/restart
☐ Scheduled refill
☐ Early refill approved through RMR process
☐ Change of care responsibility

Patient Name: ___________________________  Patient ID Number: __________________
Prescriber Name: ________________________  Prescriber ID Number: ________________

For pediatric patients, include caregiver information below.

Caregiver Name: ________________________  Caregiver ID Number: ________________

Include Pharmacist name and date time stamp for each section completed.

Step 2: Counseling

(Complete this section ONLY for new patients and existing patients who are restarting XYREM treatment after not receiving XYREM for 6 months or longer)

☐ Ask if the prescriber reviewed the appropriate XYREM REMS Program material with the patient/caregiver (Patient Quick Start Guide for adult patients, Program Brochure for Pediatric Patients and Their Caregivers for pediatric patients) and explain that this material will be included with the first shipment and that all drug shipments to the patient will include the XYREM Medication Guide

______________________________ (Pharmacist Name)  _____/_____/_______ (Date/Time)

☐ Verify that the patient/caregiver has been counseled on Therapy Expectations below
  • During clinical trials with XYREM, many patients with narcolepsy saw some improvement with excessive daytime sleepiness and/or cataplexy in the first weeks after beginning XYREM therapy. However, the response to XYREM varies from patient to patient. It may also take time to find the right dose that works for the patient. The prescriber will determine the dose that is appropriate.
  • The patient/caregiver should talk to the prescriber about any troubling side effects or if the patient does not feel any benefits while taking XYREM.
  • For any prescription changes, the prescriber should call or fax the new prescription change to the pharmacy; patients or caregivers should NEVER attempt to change the dose themselves.

______________________________ (Pharmacist Name)  _____/_____/_______ (Date/Time)
Verify that the patient/caregiver has been counseled on Preparation and Administration information below

- XYREM should be prepared and taken only as directed by the prescriber (review prescriber’s instructions with patient/caregiver). Prepare the first dose by placing _____ grams of XYREM into one of the provided pharmacy containers. Add 1/4 cup of water to the container and turn the cap clockwise (to the right) until it clicks and locks into its child-resistant position. Then, prepare the second dose by placing _____ grams of XYREM into the second pharmacy container, adding about 1/4 cup of water, and closing the pharmacy container. The water does not come with XYREM. The patient/caregiver can use either tap or bottled water. The solution should remain clear, and it will taste salty. Place the containers in a safe place, out of the reach of children or pets.
  - For adult patients, the recommended location for the second dose is a safe place near the patient’s bed.
  - For pediatric patients, it is recommended that the caregiver ensure that all XYREM doses are kept in a safe place until given.
- The patient/caregiver should call the XYREM REMS Program with any questions regarding how XYREM is to be prepared or taken. The pharmacy is available Monday through Friday, from 7 AM to 8 PM Central Time, at 1-866-997-3688, and a pharmacist is always available, 24 hours a day, 7 days a week, if needed.
- The patient/caregiver should refer to the Medication Guide for additional information on preparation of XYREM doses.
- When the patient is ready to go to sleep, the first dose of XYREM should be taken while sitting in bed and the patient should lie down immediately after dosing.
  - The first dose of XYREM should be taken at least 2 hours after eating.
  - The time that it takes to fall asleep might be different from night to night. The patient may fall asleep quickly, in about 5 to 15 minutes, although some patients have reported falling asleep more quickly (without first feeling drowsy) and others may take longer to fall asleep.
  - The patient/caregiver may want to set an alarm to make sure the patient wakes up to take the second dose. The second dose of XYREM should be taken 2.5 to 4 hours after the first dose of XYREM is taken.
  - If a dose is missed, the patient should NEVER take two doses of XYREM at once.
- The diluted medication MUST be used within 24 hours of preparation. Discard any unused medication down the sink or toilet drain.
- When XYREM can no longer be drawn out of the bottle with the dispensing device, the patient/caregiver should dispose of the bottle. Remind the patient/caregiver to mark out information on the prescription label, including all personal information and the XYREM name, to make it unreadable before throwing out the empty bottle or other empty medicine packaging.
- The patient/caregiver should be sure to store both the XYREM bottle and all prepared doses in a safe and secure place out of the reach of children and pets. Emergency medical help should be sought right away if a child who has not been prescribed XYREM drinks XYREM.
- XYREM should be stored at room temperature.

_______________________________ (Pharmacist Name)  _____/_____/_________ (Date/Time)
Verify that the patient/caregiver has been counseled on **Precautions Needed for XYREM Use**

- XYREM is classified as a controlled substance medication. XYREM must be used only by the person for whom it is prescribed and as directed by the physician. All lost or stolen medication must be reported.
- Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.
- The active ingredient in XYREM is sodium oxybate, which is a form of gamma-hydroxybutyrate (GHB). GHB has been used as a substance of abuse and has been associated with drug-facilitated sexual assault (date rape).
- Abuse of GHB can lead to dependence (a physical need to take the drug), craving for the medicine, and severe withdrawal symptoms (symptoms that start when the drug is stopped, especially when it is stopped suddenly). Abuse of GHB, with or without other central nervous system (CNS) depressants (e.g., nortriptyline, oxycodone, or heroin), including alcohol, can lead to seizure, trouble breathing, decreases in the level of consciousness, coma, and death.

_________________________________________________ (Pharmacist Name)    _____/_____/_________ (Date/Time)

Verify that the patient/caregiver has been counseled on **Side Effects**

- In clinical trials in adult patients, the most commonly observed side effects associated with the use of XYREM included: nausea, dizziness, vomiting, somnolence, enuresis, and tremor. In clinical trials in pediatric patients, the most commonly observed side effects associated with the use of XYREM included: enuresis, nausea, headache, vomiting, weight decreased, decreased appetite, and dizziness. Some side effects may be more likely to be observed with higher doses of XYREM.
- XYREM can cause serious side effects, including trouble breathing while asleep, confusion, unusual or disturbing thoughts, depression, and passing out, even at recommended doses. The patient/caregiver should consult with the prescriber if the patient has any of these problems while taking XYREM.
- Patients should not participate in hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that XYREM does not affect them adversely.
- When taking XYREM, patients should not drink alcohol or take medicines that make them sleepy, including antidepressants, antipsychotics, anti-epileptics, opioids, general anesthetics, muscle relaxants, and/or illicit CNS depressants (e.g., heroin or GHB).
- These are not all of the side effects that patients may experience. The patient/caregiver should contact the prescriber if there are concerns about any possible side effects. Refer to the Medication Guide for additional information on possible side effects.

_________________________________________________ (Pharmacist Name)    _____/_____/_________ (Date/Time)
Instruct patients/caregivers to call the prescriber if:

- Patient is pregnant or plans to become pregnant. It is not known if XYREM can affect an unborn baby.
- Patient is breastfeeding. XYREM passes into breast milk. The patient/caregiver should talk to the prescriber to decide if the patient will take XYREM or breastfeed.
- Patient has or has had depression or tried to harm him- or herself. Patients should be watched for new signs of depression.
- Patient has liver problems. The dose may need to be adjusted.
- Patient has sleep apnea (short periods of not breathing while asleep), snoring, or breathing or lung problems. Patients with these may have a higher chance of serious breathing problems with XYREM.
- Patient has mental health problems.
- Patient walks during sleep.
- Patient is on a salt-restricted diet, has high blood pressure, heart failure, or kidney problems. XYREM contains sodium (salt) and may not be right for patients with these conditions.

____________________________ (Pharmacist Name)  ____/____/_______ (Date/Time)

For situations involving a change of care responsibility:

- Inform caregiver/patient that this completes this section of the checklist. Confirm that the caregiver/patient has asked any questions he or she has about XYREM.
Step 3: Screening

(Complete this section for new patients, existing patients who are restarting XYREM treatment after not receiving XYREM for 6 months or longer, and patients who report a new medication or new comorbid medical condition listed in Step 4 of this checklist)

1. Is the patient taking sedative hypnotics (e.g., diazepam, phenobarbital, or zolpidem)?
   - [ ] Yes    [ ] No
   - [ ] Yes    [ ] Counseled Patient/Caregiver
   - Please list the drug(s) and dose of each: ______________________________
     ______________________________
     ______________________________

2. Is the patient taking sedating antidepressants, antipsychotics, or anti-epileptics such as divalproex sodium (Depakote); general anesthetics; muscle relaxants; opioid analgesics; or illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB])?
   - [ ] Yes    [ ] No
   - [ ] Yes    [ ] Counseled Patient/Caregiver
   - Please list the drug(s) and dose of each: ______________________________
     ______________________________
     ______________________________

3. What other prescription and non-prescription medications is the patient taking?
   - Please list the drug(s) and dose of each: ______________________________
     ______________________________
     ______________________________

4. Does the patient drink alcohol?
   - [ ] Yes    [ ] No
   - [ ] Yes    [ ] Counseled Patient/Caregiver

5. Has the patient been diagnosed with sleep apnea (short periods of not breathing while asleep)?
   - [ ] Yes    [ ] No
   - [ ] Yes    [ ] Counseled Patient/Caregiver

6. Does the patient have a diagnosis of or suffer from asthma, chronic obstructive pulmonary disease (COPD), or other conditions affecting his/her breathing (slower breathing, trouble breathing)?
   - [ ] Yes    [ ] No
   - [ ] Yes    [ ] Counseled Patient/Caregiver
   - Please list the drug(s) used to treat, and dose of each, if known:
     ______________________________
     ______________________________
     ______________________________
7. Does the patient have any other current medical conditions for which the patient is under a healthcare provider’s care?
   - [ ] Yes  [ ] Counseled Patient/Caregiver
   - [ ] No  

   Please list the conditions(s) if known:  
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________

8. Does the patient/caregiver have any clinical questions about XYREM?
   - [ ] Yes  [ ] Counseled Patient/Caregiver
   - [ ] No  [ ] Referred Patient/Caregiver to Prescriber

   Please list the question(s):  
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________

   ________________________________  (Pharmacist Name)  _____/____/_______ (Date/Time)
Step 4: Concomitant Medication & Comorbidity Summary

(Complete this section for new patients, existing patients who are restarting XYREM treatment after not receiving XYREM for 6 months or longer, and patients who report a new medication or new comorbid medical condition listed in Step 4 of this checklist)

Medication Type

☐ 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])

Medical Conditions

☐ Sleep apnea
☐ Asthma
☐ COPD
☐ Other conditions affecting the patient’s breathing
☐ History of depression or suicidality
☐ History of drug or alcohol abuse
☐ Seizure disorders
☐ Hepatic impairment
☐ High blood pressure, heart problems, kidney problems, or a salt-restricted diet

If any medication types or medical conditions listed above are checked, or any questions in Step 3 were answered yes and there is no confirmation of prior prescriber knowledge, call the prescriber to consult:

Is a prescriber consult required?

☐ Yes
☐ No

If no, please provide reason: __________________________________________________________

If yes, action(s) taken (check all that apply and document details in prescriber consult outcome section below):

☐ Called prescriber: _____/_____/_______
☐ Other: _____/_____/_______

Prescriber consult outcome: ________________________________________________________________

________________________________________ (Pharmacist Name)  _____/_____/_______ (Date/Time)
Step 5: Completion Summary

(Complete this section for new patients, existing patients who are restarting XYREM treatment after no receiving XYREM for 6 months, and patients who report a new medication or new comorbid medical condition listed in Step 4 of this checklist)

Checklist Completed
☐ Yes
☐ No (XYREM is not shipped until checklist is completed.)

If yes, date checklist completed: _____/_____/__________ (Date Time)

If no, reason for non-completion:

_________________________________________________________________________

_________________________________________________________________________

_________________________________________________________________________

____________________________________ (Pharmacist Name)  _____/_____/_______ (Date/Time)
Risk Management Reports (RMRs) are filled out by the central Certified Pharmacy to document and report events that give rise to a reasonable suspicion of abuse, misuse, diversion, or any behavior or information that may indicate the drug is not being used according to the prescriber’s instructions. The RMR history of a patient allows for the review of prior events of suspected abuse, misuse, or diversion and gives the pharmacist a more complete picture of the patient’s history. The availability of individual patient RMRs enables the pharmacist to track and monitor for trends suggesting abuse, misuse, or diversion in individual patients. A trend or pattern of behavior in a patient’s RMR history can be an indicator of abuse, misuse, or diversion and identifies patients who may require additional scrutiny when another event, such as an early refill request, occurs. In these cases, the RMR history informs actions of the pharmacist.

Examples of events that would require completion of an RMR under the XYREM REMS Program include, but are not limited to, the following:

- Patient requests for early refills.
- Patient’s loss/misuse of the product.
- Patient claim that he or she did not receive the product but the delivery service shows receipt of delivery, or that the shipment was lost or stolen or delivered to an incorrect address and was not returned.
- Tampering with or counterfeiting or contaminating the product.
- Inquiries and/or arrests by law and regulatory enforcement agencies associated with the misuse or diversion of the product, or crimes related to the product.
- Prescribers whose DEA and/or state license numbers cannot be validated and the prescriber is submitting a XYREM REMS Program Prescriber Enrollment Form, Prescription Form, or Patient Enrollment Form.

To complete an RMR:

- Assign a unique Control Number to each report in the Central Database.
- Complete investigation of the event, which may include contacting the patient, prescriber, law enforcement agency, or other parties.
- Attach any additional documentation required to support the investigation, including but not limited to the following: DEA 106 Form, police or fire report, or report from the shipping service.
- Complete review, follow up, and sign-off on the RMR.
  - When the event involves suspected abuse, misuse, or diversion, the prescriber will be contacted and an alert may be placed in the prescriber or patient profile of the Central Database to ensure prescriber and pharmacist awareness.
  - The Certified Pharmacy will monitor any associated patient or prescriber activity in the XYREM REMS Program during the course of the investigation and for a period after the investigation, where appropriate.
  - The Certified Pharmacy will work with Jazz Pharmaceuticals to determine the need to notify local, state, or federal agencies.
- Ensure that the information contained in the RMR is maintained in the Central Database.
- Send the RMR to Jazz Pharmaceuticals within one business day.

If the RMR includes a potential adverse event, the potential adverse event is reported through the Jazz Pharmaceuticals adverse event reporting system. If the RMR includes a product complaint, the event is also reported through the Jazz Pharmaceuticals product complaint system.
XYREM REMS Program Risk Management Report

Date: ________________

Control No.: JRM-______________

Addendum: Yes ☐ No ☐

Type of reporter (e.g., patient, pharmacist, physician): ____________________________

If not patient, name of reporter: ________________________________________________

Nature of report (e.g., early refill request, lost or stolen bottle, package not received, other): ____________________________

Identification number(s) (patient and/or prescriber ID associated with RMR): ________________

Date enrolled in program (from patient or prescriber record): ____________________________

Reviewed alerts and RMR history for individual? Yes ☐ No ☐

RMR event (please provide detail): ________________________________________________

Date(s) of RMR event: Start: ___________ End: ___________

Early refill requested? Yes ☐ No ☐

If yes, reason for early refill request (e.g., dose increase, spilled medication, lost/stolen product): ________________

Prescriber contacted? Yes ☐ No ☐

If yes, outcome: ____________________________ If no, reason: ____________________________

Early refill status: Approved ☐ Denied ☐ Early refill status reason: ____________________________

Potential adverse event associated with report? Yes ☐ No ☐ If yes, AE number: ________________

Summary of investigation: ________________________________________________

Attachments (check all that apply): DEA 106 Form ☐ Police/Fire Report ☐ Shipping Service Report ☐

Other ☐ (specify) ________________

Monitor (alert placed): Yes ☐ No ☐ N/A ☐

Report closed: Yes ☐ No ☐

Operations Director (or designee): ____________________________ Signature (date/time) ________________

Pharmacist in Charge (or designee): ____________________________ Signature (date/time) ________________

Reference ID: 4341394
Welcome to the XYREM® REMS Program

A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure that the benefits of the drug outweigh its risks.

This program ensures that XYREM® (sodium oxybate) is dispensed only by the Certified Pharmacy.

What is XYREM®?

XYREM® is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

Important Safety Information

Enroll in the XYREM® REMS Program

Prescriber

XYREM® (sodium oxybate) oral solution, 0.5 g/mL, is available only through a restricted distribution program called the XYREM REMS Program. Use this website to enroll yourself, enroll your patients, and prescribe XYREM.

Enroll as Prescriber ➤

Patient or Caregiver

Learn more about the XYREM REMS Program, a special program required by the Food and Drug Administration (FDA) to make sure the benefits of XYREM outweigh the risks. All patients must be enrolled in the XYREM REMS Program to receive XYREM.

Enroll as Patient or Caregiver ➤

Program Overview

The XYREM REMS Program is designed to ensure that prescribers and patients are educated on and understand the risks and safe use conditions of XYREM and agree to follow the requirements of the XYREM REMS Program.

XYREM may only be dispensed to patients enrolled in the XYREM REMS Program.

- All prescribers must enroll in the XYREM REMS Program and comply with requirements for prescribing XYREM
- All patients must be enrolled in the XYREM REMS Programs to receive XYREM
- All patients are required to be counseled on the serious risks and safe use of XYREM
- XYREM will be dispensed only by the central pharmacy that is specially certified

Program 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:

- Instructing prescribers, pharmacists, patients, and caregivers of:
  - The risk of significant CNS 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
  - The safe use, handling, and storage of XYREM

- Ensuring that pharmacy controls exist prior to filling prescriptions for XYREM that:
  - Minimize for concurrent use of sedative hypnotics and other potentially interacting agents
  - Minimize for inappropriate prescribing, misuse, abuse, and diversion of XYREM
  - Minimize for potential misuse when patients are receiving concurrent benzodiazepine medications or there are signs of potential abuse, misuse, or diversion

Please call the XYREM REMS Program at 1-866-XYREM (1-866-997-3688) for needed assistance.
To become certified, each prescriber must complete a XYREM REMS Program Prescriber Enrollment Form once and submit it to the XYREM REMS Program via fax, email, or mail.

In addition to enrolling, use the links below to access important information concerning what you need to know as a prescriber of XYREM.

Important Update for Prescribers

Enroll as Prescriber

The enrollment process for prescribers is quick, easy, and secure. Choose one of the two methods described below. Complete your enrollment form and submit it to the Certified Pharmacy for processing.

Two Ways To Enroll

Complete enrollment online by filling out the form below.

Submit Form Online

Begin Enrollment

Simply enter your name and e-mail to begin your online enrollment.

* = Required Fields

First Name*

Last Name*

E-mail Address*

Confirm E-mail Address

Continue Online Enrollment

DocuSign® makes enrollment easy. By using DocuSign, the XYREM REMS can ensure that your personal information can stay safe, secure, and protected.

Download Prescriber Enrollment Form

or

Submit Printed Form

or

Mail to:

XYREM REMS Program
PO Box 66589
St. Louis, MO 63166-6589

Fax to:

XYREM REMS Program
1-866-470-1744 (toll free)
Prescriber Read & Enroll

Before enrolling in the XYREM REMS program, ensure you're familiar with reading the XYREM REMS Program. Just by reviewing the Prescribing Information and the Prescribing Brochure.

Then, complete the one-time Prescriber Enrollment Form below.

Roles & Responsibilities

Prescriber Roles & Responsibilities

Prescribers enrolled in the XYREM REMS Program agree to perform the following:

1. Review the Prescribing Information (PI) and the XYREM REMS Program Brochure.
2. Screen each patient for:
   - History of alcohol or substance abuse
   - History of seizures related to brain disorder
   - History of complicated respiratory function
   - Concomitant use of sedative hypnotics, other OTC depressants, or other potentially interacting agents
   - History of depression or suicidality
3. Counsel each patient prior to initiating therapy with XYREM on the serious risks and risks associated with use of XYREM using the XYREM REMS Program Quick Start Guide.
4. Enroll each patient in the XYREM REMS program by completing the XYREM Rems Program Enrollment Form and submitting the form to the XYREM REMS Program.
5. Evaluate each patient within the first 3 months of starting XYREM therapy, including an evaluation of the following:
   - History of seizures related to brain disorder
   - History of complicated respiratory function
   - Concomitant use of sedative hypnotics, other OTC depressants, or other potentially interacting agents
   - Serious suicide risk
   - Signs of abuse and misuse, including:
     - Use in dose or frequency of dosing in excess of the recommended dose
     - Failure to follow label instructions
   - Self-harm behavior
6. Report all potential serious adverse events, including abuse, misuse, or medication error and do not discontinue therapy due to suspected abuse, misuse, or deviation to local pharmacists.

Each time a new prescription is written the prescriber will complete the XYREM REMS Program Prescription Form and submit it to the XYREM REMS Program. For completeness and signing this form, the prescriber acknowledges:

1. Having an understanding of:
   - The approved indications for XYREM
   - Treatment of cataplexy in narcolepsy
   - Treatment of excessive daytime sleepiness in narcolepsy
   - The serious risks associated with XYREM
   - The Prescribing Information and XYREM REMS Program Brochure
2. Having screened the patient for the following:
   - History of alcohol or substance abuse
   - History of seizure-related brain disorders
   - History of complicated respiratory function
   - Concomitant use of sedative hypnotics, other OTC depressants, or other potentially interacting agents
   - History of depression or suicidality
3. Having counseled the patient on:
   - The serious risks associated with XYREM
   - The potential of abuse, misuse, or medication error and implications of concomitant use of XYREM with other potentially interacting agents
   - Preparation and dosing instructions for XYREM
   - Signs of abuse and misuse as appropriate
   - Avoidance of activities or avoid using Xyrem for the first 6 hours after administration or until alertness is achieved
   - Safes use, handling, and storage of XYREM
4. That XYREM is medically appropriate for the patient
5. Having listed all known prescription and nonprescription medications and dosages on the XYREM REMS Program Prescription Form

First Name

Last Name

E-mail Address

Confirm E-mail Address

Continue Online Enrollment

DocuSign makes enrollment easy. By using DocuSign, the XYREM REMS can ensure that your personal information can stay safe, secure, and protected.

Download Prescriber Enrollment Form

Scan and e-mail to:
XYREM@express-scripts.com

Fax to:
XYREM REMS Program
1-866-470-1744 (toll free)

Mail to:
XYREM REMS Program
PO Box 66589
St. Louis, MO 63166-6589

Reference ID: 4341394
Counsel & Enroll Patients

Before enrolling, patients can use the Quick Start Guide and Brochure for Pediatric Patients and Their Caregivers below to find out more concerning the use of XYLEM.

A Guide for Adult Patients
Click below to read the Patient Quick Start guide for counseling adult patients.
Access Patient Quick Start Guide

For Caregivers of Pediatric Patients
Use the brochure for Pediatric Patients and Their Caregivers to gain counsel for designated caregivers of pediatric patients.
Access Brochure for Pediatric Patients and Their Caregivers

Enroll Patients

Choose one of the two methods described below. Complete your application and submit it to the Certified Pharmacy for processing.

Two Ways To Enroll Patients

Submit Form Online
Simply enter your name and e-mail to begin your online enrollment.

Required Fields:
First Name* 
Last Name* 
E-Mail Address*
Confirm E-Mail Address

Submit Online Enrollment

DescSoft makes enrollment easy. By using DescSoft, the XYLEM REMS Program will ensure that your personal information is stay safe, secure, and private.

Download Patient Enrollment Form

If you downloaded the patient enrollment form, have your patient sign the enrollment form in your office. You will then submit it to the Certified Pharmacy by e-mail, fax, or mail.
Prescribe XYREM® (sodium oxybate)

Utilize the resources below to understand the benefits and risks of XYREM® and prescribe XYREM® to patients. For more information, please call the XYREM REMS Program toll free at 1-866-XYREM (1-866-997-3683).

Begin Prescription Form Online »

Prescribing XYREM

To prescribe XYREM, both prescriber and patient must be enrolled in the XYREM REMS Program.

Enroll as Prescriber »  Enroll Patients »

Complete the Prescription Form

All prescription forms must be submitted via fax or mail only. Choose one of the two methods described below to prescribe XYREM.

Ways To Complete the Prescription Form

Online

Start the prescription process by filling in the online form. The form will be checked by the Certified Pharmacy for completeness. You will be notified once your enrollment is complete.

Start Prescription Form

Complete Online

Begin Enrollment

Enter your name and e-mail to start the prescription process.

* Required Fields

First Name*  Last Name*

Email Address*

Confirm Email Address*

Continue to Prescription Form

Print

Please contact your Jazz Pharmaceuticals Specialty Sales Consultant or call the XYREM REMS Program at 1-866-997-3683 to obtain a XYREM REMS Program Prescription Form.

Submit Printed Form

Complete Offline: Sign the completed prescription form

Fax to: XYREM® REMS Program 1-866-470-1744 (toll free)

Mail to: XYREM® REMS Program PO Box 66680 St. Louis, MO 63170-6680
Resources and Materials

Materials for Prescribers

XYREM® (sodium oxybate) Prescribing Information
Download >

XYREM® REMS Program Prescriber Enrollment Form
Download > Enroll Online >

XYREM® REMS Program Prescription Form
Download > Begin Online >

XYREM® REMS Program Prescriber Brochure
Download >

Materials for Adult Patients

XYREM® REMS Program Patient Quick Start Guide
Download >

XYREM® REMS Program Patient Enrollment Form
Download > Enroll Online >

Materials for Caregivers of Pediatric Patients

XYREM® REMS Program Brochure for Pediatric Patients & their Caregivers
Download >

 XYREM® REMS Program Patient Enrollment Form
Download > Enroll Online >
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