

XYREM REMS DOCUMENT

NDA 21-196 XYREM[®] (SODIUM OXYBATE) ORAL SOLUTION

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL:

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

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

II. REMS ELEMENTS:

A. Medication Guide

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

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

B. Elements to Assure Safe Use

1. Healthcare Providers who prescribe XYREM are specially certified.

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

3. Drug-seeking behavior.

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

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

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

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

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

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

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

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

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

C. Implementation System

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

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

D. Timetable for Submission of Assessments

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

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

XYREM REMS PROGRAM PRESCRIBER ENROLLMENT FORM

XYREM[®] (sodium oxybate) oral solution 500 mg/mL



**Fax completed form to XYREM REMS Program at 1-866-470-1744 (toll free),
OR scan and e-mail to XYREMPrescribers @express-scripts.com
OR mail to: XYREM REMS Program, PO Box 66589, St. Louis, MO 63166-6589
For further information, please call the XYREM REMS Program at 1-866-997-3688**

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 approved for the treatment of:
- Cataplexy in narcolepsy
 - Excessive daytime sleepiness (EDS) in 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 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)

Prescriber Information			
*FIRST NAME:	M.I.:	*LAST NAME:	*PROF. DESIGNATION (MD, DO, PA, NP):
*DEA No.:	*STATE LICENSE No.:	*NPI No.:	
FACILITY/PRACTICE NAME:			
*STREET ADDRESS:			
*CITY:	*STATE:	*ZIP CODE:	
*PHONE:	*FAX:	E-MAIL:	
OFFICE CONTACT:		OFFICE CONTACT PHONE:	

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**

XYREM[®]
(sodium oxybate) oral solution **III**
REMS
PROGRAM
for prescribers



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, 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 new prescriptions and may also be used for refills and renewals of XYREM prescriptions.
- **XYREM REMS Program Patient Quick Start Guide**—answers important questions for 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.

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, the XYREM REMS Program Prescriber Enrollment Form and the XYREM REMS Program Patient Enrollment Form are available online at www.XYREMREMS.com and all three forms 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
Approved for:**

- Treatment of cataplexy in narcolepsy
- Treatment of excessive daytime sleepiness (EDS) in narcolepsy

If you require any additional assistance or information, please call the XYREM REMS 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 about operating hazardous machinery for the first 6 hours after taking a dose of XYREM.

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 amnesic 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. To be enrolled, patients 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)



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, and agitation), loss of consciousness, 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, the most common adverse reactions (incidence $\geq 5\%$ 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 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.
- Please see Prescribing Information for XYREM.

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Prescribing Information and a Medication Guide are also included.



PRESCRIBING XYREM – A BRIEF GUIDE

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

PRESCRIBERS OF XYREM

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 in this XYREM REMS Program for Prescribers Brochure or online at www.XYREMREMS.com. Please fax it to 1-866-470-1744 (toll free), 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.
- **On the XYREM REMS Program Prescriber Enrollment Form**, please confirm that:
 - You understand that XYREM is approved for:
 - Treatment of cataplexy in patients with narcolepsy
 - Treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy
 - You have read and understand the Prescribing Information and this XYREM REMS Program Prescriber Brochure
 - 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
 - You agree to counsel your 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
 - 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
 - Risk of abuse and misuse associated with use of XYREM
 - Safe use, handling, and storage of XYREM
 - 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
 - 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:
 - Patient's concomitant medications
 - 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
 - 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

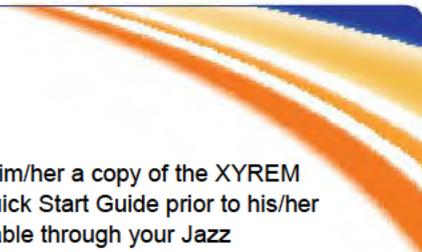
PRESCRIBING XYREM – A BRIEF GUIDE (CONT'D)

PATIENT ENROLLMENT

- All patients must be enrolled one time in the XYREM REMS Program, using the **XYREM REMS Program Patient Enrollment Form**
- On the **XYREM REMS Program Patient Enrollment Form**:
 - Verify that you have provided counseling to each patient 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
 - Obtain mandatory patient 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
 - Complete the accompanying Supplemental Patient Authorization Form by obtaining mandatory patient signature granting you the authority to release personal information to Jazz Pharmaceuticals and its business partners and agents, including the pharmacy that will fill the prescription (Supplemental Patient Authorization Form is not part of the XYREM REMS Program)
 - Fax the completed XYREM REMS Program Patient Enrollment Form including Supplemental Patient Authorization 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**.

PRESCRIBING REQUIREMENTS

- Write prescriptions for both new and existing patients using the **XYREM REMS Program Prescription Form**. If the patient has a lapse in therapy for 6 months or more, a new prescription will be required.
 - 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 patient regarding:
 - 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 operating hazardous machinery, including automobiles or airplanes, for the first 6 hours after taking a dose of XYREM
 - Preparation and dosing instructions for XYREM
 - The risk of abuse and misuse associated with XYREM
 - Safe use, handling, and storage of XYREM (refer to pages 13 & 14 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. This can be done by completing the Medications field on the XYREM REMS Program Prescription Form or by faxing a separate page from the patient's medical history
- 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 XYREM. The pharmacist may also contact the prescriber about other concomitant medications of concern.



—Verify that you have informed the patient that the XYREM REMS Program will send him/her a copy of the XYREM Medication Guide with each prescription fill and a XYREM REMS Program Patient Quick Start Guide prior to his/her first prescription fill, if you haven't provided one previously. These materials are available through your Jazz Pharmaceuticals Specialty Sales Consultant or may be downloaded at www.XYREMREMS.com

—Fax the completed XYREM REMS Prescription Form and all renewal/refill 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**.

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.
 - 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

- The Certified Pharmacy with the XYREM REMS Program will send you a XYREM REMS Program Prescription Form in advance of a patient's prescription expiring or running out of refills. Prescription refills and renewals may also be conveyed by phone or fax and must be documented in the XYREM REMS Program Central Database.
 - Fill out the form completely and clearly to ensure timely fulfillment of your patient's prescription
 - 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**

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 to:
 - Confirm whether he or she has received a copy of the XYREM REMS Program Patient Quick Start Guide. The Certified Pharmacy will send a copy of the XYREM REMS Program Patient Quick Start Guide to any patient not previously receiving one from his or her prescriber.
 - Counsel the patient 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
 - You will be notified of any potential for drug interactions based on patient counseling
 - Ask if the patient has any questions about XYREM and answer the questions and/or refer the patient back to the prescriber, as appropriate
- Provide 24/7 toll-free telephone access to pharmacist support for prescribers, office staff, and patients by answering questions about safety, dosing, and patient care
- Dispense and ship XYREM by overnight service to the patient or his or 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

XYREM is a liquid medication taken orally at bedtime. Due to its short half-life, XYREM is taken in 2 equal doses at night, with the first dose taken at bedtime and the second dose taken 2.5 to 4 hours later.

- The recommended starting dose is 4.5 g/night divided into 2 equal doses of 2.25 g each
- The effective dose range is 6 g to 9 g/night
- 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
 - XYREM should be titrated in increments of 1.5 g/night at weekly intervals
- 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

Note: 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.

DOSING & TITRATION

	1ST DOSE	2ND DOSE	TOTAL NIGHTLY DOSE	
Recommended starting dose	2.25 g	2.25 g	4.5 g	
	3 g	3 g	6 g	Effective Dosing Range
	3.75 g	3.75 g	7.5 g	
Maximum dose	4.5 g	4.5 g	9 g	

PATIENT DOSING INFORMATION:

- 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 nighttime doses in a secure place out of the reach of children and pets
- Food significantly reduces the bioavailability of XYREM; therefore, doses should be taken at least 2 hours after eating
- Both doses should be taken while in bed
- The first dose should be taken at bedtime and the second dose 2.5 to 4 hours later

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.XYREMRMS.com

USE IN SPECIFIC POPULATIONS

PREGNANCY

Teratogenic Effects: Pregnancy Category C.

Nonteratogenic Effects: Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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, but umbilical vein levels of sodium oxybate were no more than 25% of the maternal concentration. No sodium oxybate was detected in the infant's blood 30 minutes after delivery. Elimination curves of sodium oxybate between a 2-day-old infant and a 15-year-old patient were similar. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

NURSING MOTHERS

It is not known whether sodium oxybate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XYREM is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients 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)**

PATIENT COUNSELING INFORMATION

Prior to initiating therapy, counsel each patient regarding the serious risks and safe use, handling, and storage of XYREM using the XYREM REMS Program Patient Quick Start Guide and encourage all patients to read the XYREM Medication Guide.

- Inform patients 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 has about XYREM by having the patient sign and date the XYREM REMS Program Patient Enrollment Form. Inform the patient that regular follow-up is recommended

As a component of the XYREM REMS Program, 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 your patient with the following guidance:

ALCOHOL OR SEDATIVE HYPNOTICS

Advise patients not to drink alcohol or take other sedative hypnotics if they are taking XYREM.

SEDATION

Inform patients that after taking XYREM they are likely to fall asleep quickly (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 to remain in bed following ingestion of their first dose, and not to take their second dose until 2.5 to 4 hours later.

FOOD EFFECTS ON XYREM

Food significantly decreases the bioavailability of sodium oxybate. Inform patients to take the first dose at least 2 hours after eating.

RESPIRATORY DEPRESSION

Inform patients that XYREM can be associated with respiratory depression even at recommended doses and with concurrent use of XYREM with other CNS depressants.

OPERATING HAZARDOUS MACHINERY

Inform patients that until they are reasonably certain that XYREM does not affect them adversely (e.g., impair judgment, thinking, or motor skills) they should not operate hazardous machinery, including automobiles or airplanes.

SUICIDALITY

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

SODIUM INTAKE

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

SAFE HANDLING, STORAGE, AND DISPOSAL

- Discuss safe and proper use of XYREM and dosing information with patients prior to the initiation of treatment
- Instruct patients to store XYREM bottles and XYREM doses in a secure place, out of reach of children and pets
- Patients should be instructed to divide their **total nightly dose** into 2 separate doses. They should not further divide each of the 2 separate doses
- Patients should be informed that they should be seen by their healthcare provider frequently to review dose titration, symptom response, and adverse reactions
- Instruct patients to store XYREM at room temperature, between 59°F and 86°F
- Inform patients that they may safely dispose of XYREM down the sink or toilet drain
- Inform patients that they must report all instances of lost or stolen XYREM to the local police and to the XYREM REMS Program

XYREM REMS PROGRAM PATIENT ENROLLMENT FORM

XYREM[®] (sodium oxybate) oral solution 500 mg/mL



Fax completed form 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)

Patient Information

*FIRST NAME:	M.I.:	*LAST NAME:	*PRIMARY PHONE:
*DATE OF BIRTH (MM/DD/YYYY):	*Gender: <input type="checkbox"/> M <input type="checkbox"/> F		CELL PHONE:
*ADDRESS:			WORK PHONE:
*CITY:	*STATE:	*ZIP CODE:	E-MAIL:

Insurance Information

Does Patient Have Prescription Coverage? <input type="checkbox"/> Yes (Provide photocopy of both sides of Insurance Identification Card with this form) <input type="checkbox"/> No	
POLICY HOLDER'S NAME:	POLICY HOLDER'S DATE OF BIRTH:
INSURANCE COMPANY NAME:	RELATIONSHIP TO PATIENT:
INSURANCE PHONE:	RxID No.: RxGrp No.:
RxBIN No.:	RxPCN No.:

Prescriber Information

*FIRST NAME:	M.I.:	*LAST NAME:	*DEA No.:
*STREET ADDRESS:			*PHONE:
*CITY:	*STATE:	*ZIP CODE:	*FAX:
OFFICE CONTACT:	OFFICE CONTACT PHONE:	*NPI No.:	

PATIENT: 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/Guardian Signature: _____ *Date: _____

*Printed Guardian Name (if applicable): _____

PRESCRIBER: FORM MUST BE SIGNED BEFORE ENROLLMENT CAN BE PROCESSED.

By signing below, I acknowledge that:

- I have counseled the patient 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
- I have provided the patient with the XYREM REMS Program Patient Quick Start Guide (optional)

*Prescriber Signature: _____ *Date: _____

XYREM REMS PROGRAM PRESCRIPTION FORM

XYREM[®] (sodium oxybate) oral solution 500 mg/mL



Fax completed form 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)

Prescriber Information

*FIRST NAME:	M.I.:	*LAST NAME:	*NPI No.:	*DEA No.:
*STREET ADDRESS:				*PHONE:
*CITY:	*STATE:	*ZIP CODE:	*FAX:	
OFFICE CONTACT:		OFFICE CONTACT PHONE:	*STATE LICENSE No.:	

Patient Information

*FIRST NAME:	M.I.:	*LAST NAME:	*PRIMARY PHONE:
*DATE OF BIRTH (MM/DD/YYYY):		*Gender: <input type="checkbox"/> M <input type="checkbox"/> F	CELL PHONE:
*ADDRESS:			WORK PHONE:
*CITY:	*STATE:	*ZIP CODE:	E-MAIL:

*MEDICATIONS: (list all known current prescription and non-prescription medications and dosages or submit as a separate page)
 Check box if separate page attached

Please complete either the fixed dosing or titrated dosing section.

Fixed XYREM Dosing

Dose: First dose (bedtime): _____ g + Second dose (2.5 to 4 hours later): _____ g = _____ g Total Nightly Dose

Titrated XYREM Dosing (First dose is at bedtime; second dose is taken 2.5 to 4 hours later)

Starting Dose:	First dose: _____ g	+	Second dose: _____ g	=	_____ g	Total Nightly Dose for _____ days
1 st Titration:	First dose: _____ g	+	Second dose: _____ g	=	_____ g	Total Nightly Dose for _____ days
2 nd Titration:	First dose: _____ g	+	Second dose: _____ g	=	_____ g	Total Nightly Dose for _____ days
3 rd Titration:	First dose: _____ g	+	Second dose: _____ g	=	_____ g	Total Nightly Dose for _____ days

Dispensing Instructions

Total Quantity: 1 2 3 month(s) supply (circle one) (initial prescription fill cannot exceed 1 month of therapy; refills cannot exceed 3 months)	Refills: 0 1 2 3 4 5 (circle one)
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.	
Note: Prepare both doses at the same time prior to bedtime. The XYREM shipment does not include water for dilution.	
Special 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 that the XYREM REMS Program will send him or her a copy of the XYREM Medication Guide with each prescription fill and a XYREM REMS Program Patient Quick Start Guide prior to his or her first prescription fill, if I have not previously provided one.

*Prescriber Signature: _____ *Date: _____

Supervising Physician Signature: _____ Date: _____
(If required by state law for prescriptions written by NPs or PAs)

XYREM REMS PROGRAM PRESCRIPTION FORM

XYREM[®] (sodium oxybate) oral solution 500 mg/mL



Prescriber: Signature verification is required on the **front** page of this XYREM REMS Program Prescription Form as acknowledgment that you have an understanding of and/or agree to the following:

I understand that XYREM is approved for:

- Treatment of cataplexy in narcolepsy
- Treatment of excessive daytime sleepiness (EDS) in 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., post- or 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 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

Read this **Quick Start Guide** and the
XYREM Medication Guide carefully
before you start taking XYREM.

YOUR DOCTOR HAS PRESCRIBED
XYREM[®] (sodium oxybate)
oral solution



- Frequently asked questions 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 for you. XYREM is a medicine used to treat excessive daytime sleepiness and/or cataplexy in patients with narcolepsy.

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 and the XYREM Medication Guide contain information you need to know about XYREM and will help you to use XYREM correctly. Read this Quick Start Guide and the XYREM Medication 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.

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 must confirm whether you have read and understood this Quick Start Guide, 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



**WARNING: XYREM can cause
serious side effects.**
**Do not drink alcohol or take other medicines that make you
sleepy**

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)
(continued on next page)

- 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
- 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

**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 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 in his or her office. 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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**Any questions? Please call the XYREM
REMS Program at 1-866-997-3688.**

Please see the Medication Guide for more
detailed information 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.



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 receiving your first XYREM prescription. 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.

You must also read the XYREM Medication Guide that you will receive with each prescription from the Certified Pharmacy.

Do I have to enroll in this program?

You will be required to sign an enrollment form at your healthcare provider's office in order to receive XYREM. 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.



FILLING YOUR XYREM PRESCRIPTION (cont'd)

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.

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.

HOW DO I TAKE MY XYREM?

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



How do I prepare my doses?

Before going to bed, draw up each of your XYREM doses with the syringe that comes in your shipment. Add each XYREM dose into 1 of the 2 empty pharmacy containers by pushing down on the plunger. Be sure each pharmacy container is empty before adding XYREM into it.

Any questions? Please call the XYREM REMS Program at 1-866-997-3688.

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



HOW DO I TAKE MY XYREM? (cont'd)

How do I prepare my doses? (cont'd)

Add about ¼ cup of water to each dose of XYREM. Then place the child-resistant caps onto the pharmacy containers and turn each cap clockwise (to the right) until it clicks and locks in its child-resistant position.

Then put the 2 prepared doses in a safe place by your bed, out of the reach of children and pets.

Place the cap back on the XYREM bottle and store it in a safe and secure place (locked up if needed), out of the reach of children and pets.

XYREM should always be stored in the bottle provided. Rinse out the syringe and pharmacy containers with water after each use.

How do I take my doses?

Food will lower the amount of XYREM that passes into your body. 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.

**Any questions? Please call the XYREM
REMS Program at 1-866-997-3688.**

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



HOW DO I TAKE MY XYREM? (cont'd)

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.

**Any questions? Please call the XYREM
REMS Program at 1-866-997-3688.**

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



HOW DO I TAKE MY XYREM? (cont'd)

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. It is not known whether XYREM can pass through your breast milk
- 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.

**Any questions? Please call the XYREM
REMS Program at 1-866-997-3688.**

Please see the Medication Guide for more detailed information about 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?

When you have finished a bottle, pour any unused XYREM down the sink or toilet drain. Mark out over the prescription label with a marker to protect your confidentiality 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

**Any questions? Please call the XYREM
REMS Program at 1-866-997-3688.**

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



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



Keep this booklet as a helpful reminder

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

**Any questions? Please call the XYREM
REMS Program at 1-866-997-3688.**

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



PSB-01 Rev 2015

Risk Evaluation and Mitigation Strategy (REMS)

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

1. Informing prescribers, pharmacists, and patients of:

- i. The risk of significant CNS and respiratory depression associated with XYREM
- ii. The contraindication of use of XYREM with sedative hypnotics and alcohol
- iii. The potential for abuse, misuse, and overdose associated with XYREM
- iv. The safe use, handling, and storage of XYREM

2. Ensuring that pharmacy controls exist prior to filling prescriptions for XYREM that:

- i. Screen for concomitant use of sedative hypnotics, and other potentially interacting agents
- ii. Monitor for inappropriate prescribing, misuse, abuse, and diversion of XYREM
- iii. Notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion

MATERIALS FOR HEALTHCARE PROFESSIONALS

- XYREM Prescribing Information
- XYREM REMS Program Prescriber Enrollment Form
- XYREM REMS Program Patient Enrollment Form
- XYREM REMS Program Prescription Form
- XYREM REMS Program Patient Counseling Checklist
- XYREM REMS Program Prescriber Brochure
- XYREM REMS Program Pharmacy Training Program

MATERIALS FOR PATIENTS

- Medication Guide
- XYREM REMS Program Patient Quick Start Guide

XYREM REMS Program Overview

- 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 Program 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 specially certified central pharmacy

XYREM is approved for:

- Treatment of cataplexy in patients with narcolepsy
- Treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy

If you require any additional assistance or information, please call the XYREM REMS Program at 1-866-XYREM88® (1-866-997-3688)



BACK TO TOP

Risk Evaluation and Mitigation Strategy (REMS)

Prescriber Roles & Responsibilities

To become certified, each prescriber must complete a one-time enrollment by completing the XYREM REMS Program Prescriber Enrollment Form and submitting it to the XYREM REMS Program via facsimile, E-mail, or mail.

Prescribers enrolled in the XYREM REMS Program agree to:

1. Review the Prescribing Information (PI) and the XYREM REMS Program Prescriber Brochure.
2. 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
3. Counsel each patient prior to initiating therapy with XYREM on the serious risks and safe use and handling 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 Patient 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. It is recommended that patients be re-evaluated every 3 months thereafter while taking XYREM.
 - 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:
 - i. an increase in dose or frequency of dosing
 - ii. reports of lost, stolen, or spilled medication
 - iii. drug-seeking behavior
6. 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.

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. By completing and signing this form, the prescriber acknowledges:

1. Having an understanding of:
 - a. The approved indications for XYREM:
 - i. Treatment of cataplexy in narcolepsy
 - ii. Treatment of excessive daytime sleepiness in narcolepsy
 - b. The serious risks associated with XYREM
 - c. The Prescribing Information and XYREM REMS Program Prescriber Brochure
2. 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
3. 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
4. That XYREM is medically appropriate for the patient
5. Having listed all known prescription and nonprescription medications and doses on the XYREM REMS Program Prescription Form



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 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 approved for:

- Treatment of cataplexy in narcolepsy
- Treatment of excessive daytime sleepiness (EDS) in 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.



MODULE A: XYREM REMS PROGRAM

Important Safety Information

Indications and Usage

XYREM® (sodium oxybate) oral solution is a central nervous system (CNS) depressant that is indicated for the following:

- Treatment of cataplexy in narcolepsy
- Treatment of excessive daytime sleepiness (EDS) in 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) inserted into the bottle by the Certified Pharmacy
- 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

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 MISUSE AND ABUSE.

XYREM (sodium oxybate) is a CNS depressant. In clinical trials at recommended doses obtundation and clinically significant respiratory depression occurred in XYREM-treated patients. Almost all of the patients who received XYREM during clinical trials in narcolepsy were receiving central nervous system stimulants.

XYREM[®] (sodium oxybate) is the sodium salt of gamma hydroxybutyrate (GHB). Abuse of 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, abuse, and misuse, XYREM is available only through a restricted distribution program called the XYREM [REMS] Program, using a centralized pharmacy. Prescribers and patients must enroll in the program. For further information go to www.XYREMRMS.com or call 1-866-XYREM88[®] (1-866-997-3688).

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 about operating hazardous machinery for the first 6 hours after taking a dose of XYREM.

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 amnesic 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.
- To receive XYREM, patients must be enrolled in the XYREM REMS Program and be counseled on the serious risks and safe use of XYREM treatment. 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.



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 and prescribers.

Enrollment Processing and Maintenance

- Prescriber and patient enrollment forms are sent to the XYREM REMS Program by the prescriber.
- Information from the enrollment forms is maintained in the Central Database.
- 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 must confirm that they have been counseled on the serious risks and safe use of XYREM; the Certified Pharmacy will provide counseling if it was not provided by the prescriber.
- 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 is being resolved, the patient 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 will be notified by a XYREM REMS Program pharmacist.
 - The prescriber will be notified that he/she cannot be enrolled due to 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 and state license 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 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 and state license 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.
- 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 if the patient has not already received it from his or her prescriber.
 - A pharmacist must counsel the patient 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 may request an alternate shipping address, which is subject to approval by a pharmacist
- 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 a Risk Management Report (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 suspects 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 Education

Patients in the XYREM REMS Program have access to ongoing education while taking XYREM:

- 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 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 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 or fax 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
 - 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 no more than a 3-month supply for subsequent prescription fills
- 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 patient and prescriber enrollment information
 - 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
 - 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, 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

- The Certified Pharmacy must complete the XYREM REMS Program Patient Counseling Checklist (documented in the Central Database) prior to shipment of XYREM.
 - For initial prescriptions, and for patients who are restarting after not receiving Xyrem for 6 or more months, the XYREM REMS Program Patient Counseling Checklist must be completed in its entirety.
 - For prescription renewals and refills, if the patient has indicated a change in his or her health or medications, the patient will be transferred to the pharmacist and Steps 1, 3, 4, and 5 of the Counseling Checklist must be completed.
- 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 the patient for concomitant use of contraindicated medications (sedative hypnotics), alcohol, other CNS depressants, and other potentially interacting agents.
 - The pharmacist asks the patient if he or she 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.
 - Screen the patient for other medical conditions.
 - The pharmacist asks the patient what other medical conditions he or she has.
 - If the patient indicates that he or she has a certain medical condition listed on the XYREM REMS Program Patient Counseling Checklist, the pharmacist counsels the patient, and notifies the prescriber about the medical condition prior to shipping XYREM.
 - 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.
- Patients 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

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 may be conveyed by phone or fax from the prescriber and must be documented in the Central Database.
- Changes in dose require a new prescription
- Refill orders are opened at the Certified Pharmacy when the patient has approximately 10 days of therapy remaining from the previous shipment.
 - A Certified Pharmacy technician will contact the patient and schedule a shipment. The technician will ask the patient if there has been any change in his or her medications or medical history.
 - If the patient indicates a change, the technician will transfer him or her to a pharmacist who must complete Steps 1, 3, 4, and 5 of the counseling checklist. The patient should be counseled on the use or diagnosis of:
 - Sedative hypnotics (for example, diazepam, phenobarbital, or 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 his or her 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 (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 to evaluate his/her 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 Risk Management Report 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 only after obtaining a copy of the police report filed by the patient
 - Document the discussion and outcome in the Central Database by completing a XYREM REMS Program Risk Management Report.



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 Risk Management Report.
 - 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 and prescriber identifying information (patient names to be concealed)
 - Reason for report
 - Certified Pharmacy actions
 - Prescriber contact
 - Supporting documentation (if applicable, such as 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.

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 may request an alternate shipping address, which is then subject to approval by a pharmacist.
- If the patient 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 inserted into the bottle by the Certified Pharmacy
 - 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 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.



XYREM REMS PROGRAM PATIENT COUNSELING CHECKLIST

(To be completed by the pharmacist and entered in the XYREM REMS Program Central Database prior to dispensing each XYREM shipment. 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 any change in medication and/or medical history)

- New/restart
- Scheduled refill
- Early refill approved through RMR process

Patient Name: _____ Patient ID Number: _____

Prescriber Name: _____ Prescriber 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)

- Verify that the patient will receive the XYREM REMS Program Patient Quick Start Guide (if not already received) and that the drug shipment to the patient will include the XYREM Medication Guide

_____ (Pharmacist Name) ___/___/___ (Date Time)

- Verify that patient 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 you. Your doctor will determine the dose that is appropriate for you.
 - Be sure to talk to your doctor about any troubling side effects or if you don't feel any benefits while taking XYREM.
 - For any changes to your prescription, have your doctor call or fax the new prescription change to the pharmacy and NEVER attempt to change the dose yourself.

_____ (Pharmacist Name) ___/___/___ (Date Time)



- Verify that patient has been counseled on **Preparation and Administration** information below
 - XYREM should be taken as directed by your doctor (review prescriber’s instructions with patient).
 - Prepare each of your doses by placing ___ grams of XYREM in one of the provided pharmacy containers and place ___ grams in the second container. Add 1/4 cup of water to each pharmacy container. The water does not come with XYREM. You can use either tap or bottled water. The solution should remain clear and it will taste salty. Place the child-resistant cap onto the containers and put them in a safe place, out of the reach of children or pets, by your bed.
 - Feel free to call the XYREM REMS Program if you have any questions regarding preparation or how to take your XYREM doses. We are 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.
 - Refer to the Medication Guide for additional information on preparation of your XYREM doses.
 - Set alarm to go off 2.5 to 4 hours after you take your first dose.
 - When you are ready to go to sleep, sit at your bedside and drink one dose of XYREM and then lie down.
 - Your first dose of XYREM should be taken at least 2 hours after eating as food will decrease the amount of XYREM that your body absorbs.
 - 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 may take longer to fall asleep. The time that it takes to fall asleep might be different from night to night.
 - Upon waking up, take the second dose of medication as prescribed by your physician.
 - A minimum of 2.5 hours must separate each dose.
 - If you happen to miss a dose, 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 drain or toilet.
 - When you can no longer draw medication out of the bottle with the dispensing device, dispose of your bottle. Use a marker or pen to deface the bottle to protect your confidentiality.
 - Be sure to store XYREM in the original bottle in a safe and secure place out of the reach of children and pets. Get emergency help (call 911) right away if a child drinks your XYREM.
 - XYREM should be stored at room temperature.

_____ (Pharmacist Name)

___/___/___ (Date Time)



- Verify that patient 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. Sodium oxybate is converted to gamma-hydroxybutyrate (GHB) in the body. 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 CNS depressants (for example nortriptyline, oxycodone, or heroin) including alcohol can lead to seizure, trouble breathing, decreases in the level of consciousness, coma, and death.
 - Tell your doctor if you:
 - Are pregnant or plan to become pregnant. It is not known if XYREM can affect your unborn baby.
 - Are breastfeeding. It is not known whether XYREM can pass through the breast milk. Talk to your doctor about the best way to feed your baby if you take XYREM.
 - Have or had depression or tried to harm yourself. You should be watched for new signs of depression.
 - Have liver problems. Your dose may need to be adjusted.
 - Have sleep apnea (short periods of not breathing while you sleep), snoring, or breathing or lung problems. You may have a higher chance of serious breathing problems with XYREM.
 - Have mental health problems.
 - Walk in your sleep.
 - Are on a salt-restricted diet, have high blood pressure, heart failure, or kidney problems. XYREM contains sodium (salt) and may not be right for you.

_____ (Pharmacist Name)

___/___/___ (Date Time)



Verify that patient has been counseled on Side Effects

- In clinical trials, the most commonly observed side effects associated with the use of XYREM included: headache, nausea, dizziness, sleepiness, vomiting, urinary incontinence, and inflammation of the area around the nostrils and the back of the mouth. 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. Tell your doctor if you have any of these problems while taking XYREM.
- Remember that you must not drive a car, operate heavy machinery, or perform any activity that is dangerous or that requires mental alertness or motor coordination for the first 6 hours after taking a dose of XYREM.
- When taking XYREM, do not drink alcohol or take medicines that make you sleepy, including antidepressants, antipsychotics, anti-epileptics, opioids, general anesthetics, muscle relaxants and/or illicit CNS depressants (for example, heroin or GHB).
- These are not all of the side effects that you might experience. Contact your doctor if you are concerned about any possible side effects. *Refer to the Medication Guide for additional information on possible side effects.*

_____ (Pharmacist Name)

___/___/___ (Date Time)



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 any change in medication and/or medical history)

1. Is the patient taking sedative hypnotics (for example, diazepam, phenobarbital, or zolpidem)?

- Yes Counseled Patient
- No

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 (for example, heroin or gamma-hydroxybutyrate [GHB])?

- Yes Counseled Patient
- No

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 Counseled Patient
- No

5. Has the patient been diagnosed with sleep apnea (short periods of not breathing while asleep)?

- Yes Counseled Patient
- No



6. Does the patient have a diagnosis of or suffer from asthma, COPD, or other conditions affecting his/her breathing (slower breathing, trouble breathing)?

- Yes Counseled Patient
- No

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
- No

Please list the condition(s) if known:

8. Does the patient have any clinical questions about XYREM?

- Yes Counseled Patient
- Referred patient to prescriber
- No

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 any change in medication and/or medical history)

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 their breathing
- History of depression or suicidality
- History of drug or alcohol abuse
- Seizure disorders
- Hepatic impairment
- High blood pressure, heart problems, kidney problems, or are on a salt-restricted diet

If any of the medication types or medical conditions listed above are checked, or any of the questions in Section 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 not receiving XYREM for 6 months, and patients who report any change in medication and/or medical history)

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)

MEDICATION GUIDE

Xyrem[®] (ZīE-rem)

(sodium oxybate)

oral solution C III

Read this Medication Guide carefully before you start taking Xyrem and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about Xyrem?

Xyrem can cause serious side effects including slow breathing or changes in your alertness. Do not drink alcohol or take medicines intended to make you fall asleep while you are taking Xyrem because they can make these side effects worse. Call your doctor right away if you have any of these serious side effects.

- The active ingredient of Xyrem is a form of gamma-hydroxybutyrate (GHB). GHB is a chemical that has been abused and misused. Abuse and misuse of Xyrem can cause serious medical problems, including:
 - seizures
 - trouble breathing
 - changes in alertness
 - coma
 - death
- Do not drive a car, use heavy machinery, fly an airplane, or do anything that is dangerous or that requires you to be fully awake for at least 6 hours after you take Xyrem. You should not do those activities until you know how Xyrem affects you.
- Xyrem is available only by prescription and filled through the central pharmacy in the Xyrem REMS Program. Before you receive Xyrem, your doctor or pharmacist will make sure that you understand how to use Xyrem safely and effectively. If you have any questions about Xyrem, ask your doctor or call the Xyrem REMS Program at 1-866-997-3688.

What is Xyrem?

Xyrem is a prescription medicine used to treat the following symptoms in people who fall asleep frequently during the day, often at unexpected times (narcolepsy):

- suddenly weak or paralyzed muscles when they feel strong emotions (cataplexy)
- excessive daytime sleepiness (EDS) in people who have narcolepsy

It is not known if Xyrem is safe and effective in children.

Xyrem is a controlled substance (CIII) because it contains sodium oxybate that can be a target for people who abuse prescription medicines or street drugs. Keep your Xyrem in a safe place to protect it from theft. Never give your Xyrem to anyone else because it may cause death or harm them. Selling or giving away this medicine is against the law.

Who should not take Xyrem?

Do not take Xyrem if you:

- take other sleep medicines or sedatives (medicines that cause sleepiness)
- drink alcohol
- have a rare problem called succinic semialdehyde dehydrogenase deficiency

Before you take Xyrem, tell your doctor if you:

- have short periods of not breathing while you sleep (sleep apnea)
- snore, have trouble breathing, or have lung problems. You may have a higher chance of having serious breathing problems when you take Xyrem.
- have or had depression or have tried to harm yourself. You should be watched carefully for new symptoms of depression.
- have liver problems
- are on a salt-restricted diet. Xyrem contains a lot of sodium (salt) and may not be right for you.
- have high blood pressure
- have heart failure
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if Xyrem can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Xyrem passes into your breast milk. You and your doctor should decide if you will take Xyrem or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially, tell your doctor if you take other medicines to help you sleep (sedatives). Do not take medicines that make you sleepy with Xyrem.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take Xyrem?

- Read the **Instructions for Use** at the end of this Medication Guide for detailed instructions on how to take Xyrem.
- Take Xyrem exactly as your doctor tells you to take it.
- Never change your Xyrem dose without talking to your doctor.
- Xyrem can cause sleep very quickly. You should fall asleep soon. Some patients fall asleep within 5 minutes and most fall asleep within 15 minutes. Some patients take less time to fall asleep and some take more time. The time it takes you to fall asleep might be different from night to night.
- Take your first Xyrem dose at bedtime while you are in bed. Take your second Xyrem dose 2 ½ to 4 hours after you take your first Xyrem dose. You may want to set an alarm clock to make sure you wake up to take your second Xyrem dose. You should remain in bed after taking the first and second doses of Xyrem.
- If you miss your second Xyrem dose, skip that dose and do not take Xyrem again until the next night. Never take 2 Xyrem doses at 1 time.
- Wait at least 2 hours after eating before you take Xyrem.
- You should see your doctor every 3 months for a check-up while taking Xyrem. Your doctor should check to see if Xyrem is helping to lessen your symptoms and if you feel any side effects while you take Xyrem.
- If you take too much Xyrem, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of Xyrem?

Xyrem can cause serious side effects, including:

- See **“What is the most important information I should know about Xyrem?”**
- **Breathing problems, including:**
 - slower breathing
 - trouble breathing
 - short periods of not breathing while sleeping (sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they use Xyrem.
- **Mental health problems, including:**
 - confusion
 - seeing or hearing things that are not real (hallucinations)
 - unusual or disturbing thoughts (abnormal thinking)
 - feeling anxious or upset
 - depression
 - thoughts of killing yourself or trying to kill yourself

Call your doctor right away if you have symptoms of mental health problems.

- **Sleepwalking.** Sleepwalking can cause injuries. Call your doctor if you start sleepwalking. Your doctor should check you.

The most common side effects of Xyrem include:

- nausea
- dizziness
- vomiting
- bedwetting
- diarrhea

Your side effects may increase when you take higher doses of Xyrem.

Xyrem can cause physical dependence and craving for the medicine when it is not taken as directed.

These are not all the possible side effects of Xyrem. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Xyrem?

- **Always store Xyrem in the original bottle or in pharmacy containers with child-resistant caps provided by the pharmacy.**
- **Keep Xyrem in a safe place out of the reach of children and pets.**
- **Get emergency medical help right away if a child drinks your Xyrem.**
- Store Xyrem between 68°F to 77°F (20°C to 24°C). When you have finished using a Xyrem bottle:
 - empty any unused Xyrem down the sink drain
 - cross out the label on the Xyrem bottle with a marker
 - place the empty Xyrem bottle in the trash

General information about the safe and effective use of Xyrem

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Xyrem for a condition for which it was not prescribed. Do not give Xyrem to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Xyrem. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Xyrem that is written for health professionals.

For more information, go to www.XYREMREMS.com or call the Xyrem REMS Program at 1-866-997-3688.

What are the ingredients in Xyrem?

Active Ingredients: sodium oxybate

Inactive Ingredients: purified water and malic acid

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed By:

Jazz Pharmaceuticals, Inc.

Palo Alto, CA 94304

Revised: April 2015

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

/s/

WILLIAM H Dunn
07/15/2015