

XYREM REMS

PRESCRIBER BROCHURE

Includes important prescribing information
for adult and pediatric patients



XYREM[®]
(sodium oxybate) oral solution ^{III}

Dear Prescriber,

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

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

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

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

Please review the Prescribing Information for XYREM.

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



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

If you require any additional assistance or information, please call the XYREM 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/caregivers against hazardous activities requiring complete mental alertness or motor coordination (e.g., driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYREM does not affect the patient adversely.

Abuse and Misuse

- XYREM is a Schedule III controlled substance.
- The active ingredient of XYREM, sodium oxybate, is the sodium salt of gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse events, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. Illicit GHB has also been associated with drug-facilitated sexual assault.
- The rapid onset of sedation, coupled with the 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. For a patient to be enrolled, patients or caregivers must sign the XYREM REMS Program Patient Enrollment Form and acknowledge that they have been counseled on the serious risks and safe use of XYREM.

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



Depression, Suicidality, and Other Behavioral/Neuropsychiatric Adverse Events

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

Use in Patients Sensitive to High Sodium Intake

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

Most Common Adverse Events

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

Please see Prescribing Information for XYREM.



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Prescribing Information is also included



Prescribing XYREM—A Brief Guide

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

PRESCRIBERS OF XYREM

PRESCRIBER ENROLLMENT

Prescribing XYREM requires a one-time enrollment.

- If you are prescribing XYREM for the first time, complete the **XYREM REMS Program Prescriber Enrollment Form**, found either accompanying this XYREM REMS Program Prescriber Brochure or online at www.XYREMREMS.com. Please:
 - Submit the form online at www.XYREMREMS.com *or*
 - Scan and send via e-mail to XYREMPrescribers@express-scripts.com *or*
 - Mail to **XYREM REMS Program, PO Box 66589, St. Louis, MO 63166-6589** *or*
 - Fax to **1-866-470-1744** (toll free).
- On the **XYREM REMS Program Prescriber Enrollment Form**, please confirm that:
 - You understand that Xyrem is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy
 - You have read and understand the Prescribing Information and this XYREM REMS Program Prescriber Brochure SCREEN
 - You agree to screen each patient for:
 - History of alcohol or substance abuse
 - History of sleep-related breathing disorders
 - History of compromised respiratory function
 - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
 - History of depression or suicidality

COUNSEL

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



ENROLL

- You will enroll each patient in the XYREM REMS Program by completing the one-time XYREM REMS Program Patient Enrollment Form and submitting the form to the XYREM REMS Program. A pediatric patient must have a caregiver
- You will evaluate each patient within the first 3 months of starting XYREM, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while on XYREM therapy:
 - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
 - Serious adverse events
 - Signs of abuse and misuse such as an increase in dose or frequency of dosing; reports of lost, stolen, or spilled medication; and/or drug-seeking behavior

REPORT

- You will report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death, and any cases of suspected abuse, misuse, or diversion to Jazz Pharmaceuticals

PATIENT ENROLLMENT

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

XYREM REMS PROGRAM PATIENT ENROLLMENT FORM
 XYREM® (sodium oxybate) oral solution 0.5 g/mL

Complete and submit form online at www.XYREMREMS.com. QR scan and e-mail to XYREMPrescribers@express-scripts.com. QR fax to XYREM REMS Program at 1-866-470-1744 (toll free). QR 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: _____	*DEA No.: _____
*Street Address: _____		*Phone: _____	
*City: _____	*State: _____	*Zip Code: _____	*Fax: _____
*Office Contact: _____		*Office Contact Phone: _____	*NPI 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: _____
*Caregiver Name: _____	*Relationship to Patient: _____ (if different than above)		

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 (MM/DD/YYYY): _____	
*Insurance Company Name: _____		*Relationship to Patient: _____	
*Insurance Phone: _____	*RxID No.: _____	*RxGrp No.: _____	
*RxBIN No.: _____	*RxPCN No.: _____		

Patient/Caregiver: Form must be signed before enrollment can be processed.
 By signing below, I acknowledge that:

- My doctor/prescriber has counseled me on the serious risks and safe use of XYREM
- I have asked my doctor/prescriber any questions I have about XYREM

■ *Patient/Caregiver Signature: _____ *Date: _____

■ *Printed Caregiver Name (if applicable): _____

Prescriber: Form must be signed before enrollment can be processed.
 By signing below, I acknowledge that:

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

■ *Prescriber Signature: _____ *Date: _____



PRESCRIBING REQUIREMENTS

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



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



PATIENT EVALUATION

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



Follow up frequently during titration to review symptom response and adverse reactions. A follow up of every three months is recommended.

REFILL PRESCRIPTIONS

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


(sodium oxybate) oral solution ^{III}

Responsibilities of the XYREM REMS Program Certified Pharmacy

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

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



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



Guidelines for Dosing and Titrating XYREM

DOSING XYREM

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

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

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



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

RECOMMENDED ADULT XYREM DOSE REGIMEN			
	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
	3.75 g	3.75 g	7.5 g
Maximum dose	4.5 g	4.5 g	9 g

Effective Dosing Range

IMPORTANT ADMINISTRATION INSTRUCTIONS

- Inform patients that all bottles contain concentrated medication ONLY and that water for dilution is not contained in the box. Advise patients to keep XYREM in the provided bottle(s)
- Patients should prepare both nighttime doses at bedtime
 - Instruct patients to make sure that pharmacy vials are empty prior to preparing each dose
 - Each dose of XYREM should be diluted with about 1/4 cup of water
 - Patients should be instructed to store XYREM bottles and prepared nightly doses in a secure place out of the reach of children and pets
- Doses should be taken at least 2 hours after eating
- Both doses should be taken while in bed and the patient should lie down immediately after dosing
- The first dose should be taken at bedtime and the second dose 2.5 to 4 hours later



Additional Information About XYREM

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

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

WHEN PRESCRIBING A CONTROLLED SUBSTANCE:

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

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

DEPENDENCE AND TOLERANCE

Dependence

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

Tolerance

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

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



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



Use in Specific Populations

PREGNANCY

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

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

LABOR AND DELIVERY

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

NURSING MOTHERS

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

PEDIATRIC USE

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

GERIATRIC USE

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

RACE AND GENDER EFFECTS

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



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


(sodium oxybate) oral solution

Patient Counseling Information

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

- Inform patients and/or caregivers that XYREM is available only through the central pharmacy certified under a restricted distribution program called the XYREM REMS Program and provide them with the telephone number and website for more information about XYREM and the XYREM REMS Program
- Confirm that patients understand the serious risks and safe use conditions of XYREM and that you have answered any questions the patient and/or caregiver has about XYREM by having the patient and/or caregiver sign and date the XYREM REMS Program Patient Enrollment Form. Inform the patient and/or caregiver that regular follow-up is recommended

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

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

ALCOHOL OR SEDATIVE HYPNOTICS

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

SEDATION

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

FOOD EFFECTS ON XYREM

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

RESPIRATORY DEPRESSION

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



PARTICIPATING IN HAZARDOUS ACTIVITIES

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

SUICIDALITY

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

SLEEPWALKING

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

SODIUM INTAKE

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

SAFE HANDLING, STORAGE, AND DISPOSAL

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


(sodium oxybate) oral solution

Pediatric Patient Supplement

This pediatric patient supplement provides information specifically for pediatric patients and their caregivers about the XYREM REMS Program, including important prescribing information, educational and counseling requirements, and materials necessary for program enrollment and prescribing XYREM. **If you are prescribing XYREM for a pediatric patient, please read the Prescriber Brochure in its entirety, including this Pediatric Patient Supplement.**

PRESCRIBING XYREM FOR PEDIATRIC PATIENTS

In addition to the procedure for writing and dispensing prescriptions for XYREM described above, prescribing XYREM to pediatric patients requires the following:

- Verify that you have counseled the caregiver on the serious risks and safe use conditions as described in the XYREM REMS Program Brochure for Pediatric Patients and Their Caregivers and encourage him/her to read the XYREM Medication Guide.

RESPONSIBILITIES OF THE XYREM REMS PROGRAM CERTIFIED PHARMACY FOR PEDIATRIC PATIENTS

In addition to the responsibilities described above, for pediatric patients the Certified Pharmacy will:

- Ensure that each enrolled pediatric patient has a caregiver
- Counsel the caregiver of each pediatric patient on the serious risks and safe use of XYREM



Each pediatric patient receiving XYREM must have a caregiver



GUIDELINES FOR DOSING AND TITRATING XYREM FOR PEDIATRIC PATIENTS

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

Recommended Pediatric Xyrem Dosage for Patients 7 Years of Age and Older*						
Patient Weight	Initial Dosage		Maximum Weekly Dosage Increase		Maximum Recommended Dosage	
	Take at Bedtime:	Take 2.5 to 4 Hours Later:	Take at Bedtime:	Take 2.5 to 4 Hours Later:	Take at Bedtime:	Take 2.5 to 4 Hours Later:
<20 kg**	There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.					
20 kg to <30 kg	≤1 g	≤1 g	0.5 g	0.5 g	3 g	3 g
30 kg to <45 kg	≤1.5 g	≤1.5 g	0.5 g	0.5 g	3.75 g	3.75 g
≥45 kg	≤2.25 g	≤2.25 g	0.75 g	0.75 g	4.5 g	4.5 g

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

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

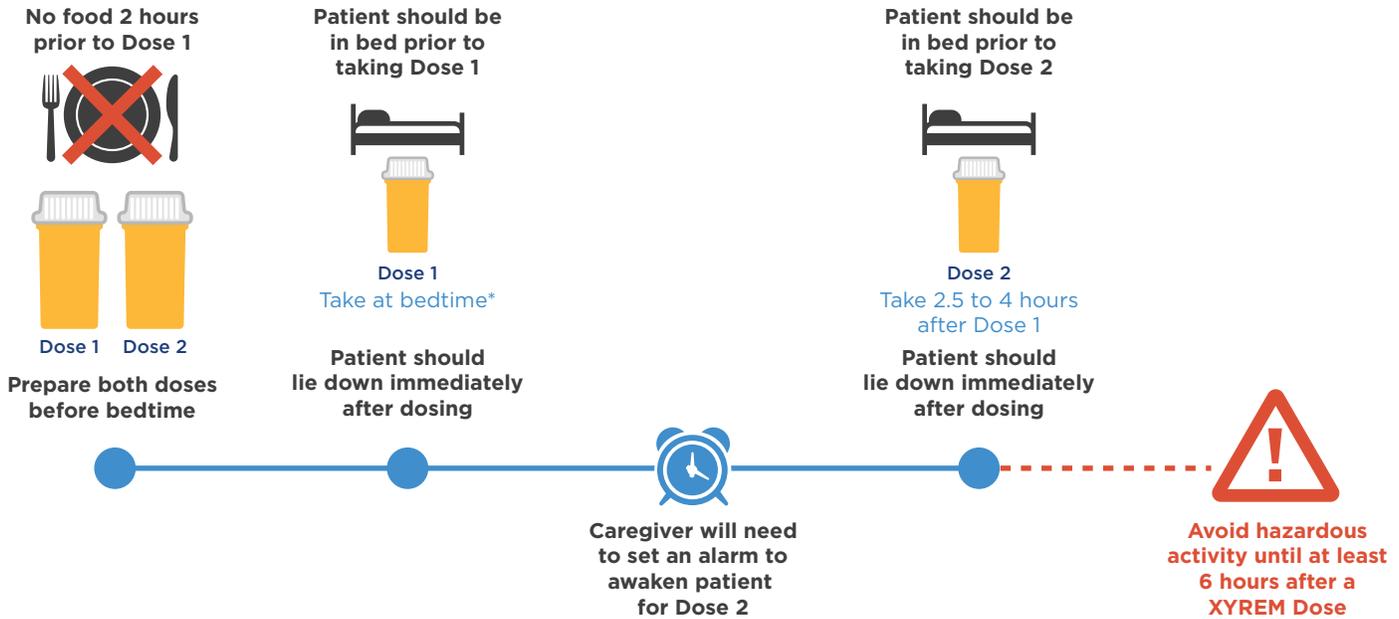
Note: Unequal dosages may be required for some patients to achieve optimal treatment.

IMPORTANT ADMINISTRATION INSTRUCTIONS FOR PEDIATRIC PATIENTS

- Inform caregivers that they should ensure that all XYREM doses are kept in a safe place until given
- Inform caregivers and patients that all bottles contain concentrated medication ONLY and that water for dilution is not contained in the box. Advise caregivers to keep XYREM in the provided bottle(s)
- Inform caregivers and patients that it is important to follow a consistent nightly routine for taking XYREM
 - Caregivers should prepare both nighttime doses at bedtime
 - Instruct caregivers to make sure that pharmacy containers are empty prior to preparing each dose
 - Each dose of XYREM should be diluted with about 1/4 cup of water
 - Caregivers should be instructed to store XYREM bottles and prepared nightly doses in a secure place out of the reach of children and pets
 - Doses should be taken at least 2 hours after eating
 - Both doses should be taken while in bed and the patient should lie down immediately after dosing
 - Encourage the child to urinate prior to taking the first nightly dose of XYREM
 - Caution against hazardous activities requiring complete mental alertness or motor coordination (e.g., driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYREM does not affect the patient adversely



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



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

CONSIDERATIONS FOR INCLUDING PEDIATRIC PATIENTS IN THEIR OWN CARE

- Work with the caregiver to determine the child's readiness to participate in his or her own care
- Ensure that the pediatric patient is counseled on the serious risks and safe use of XYREM either by the prescriber or the Certified Pharmacy
 - Ensure that the patient also reads the XYREM REMS Program Brochure for Pediatric Patients and Their Caregivers and asks any questions he or she may have



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