XYWAV and XYREM REMS

PRESCRIBER BROCHURE

Includes important prescribing information
for adult and pediatric patients

xywav®
(calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL
C III

XYREM®
(sodium oxybate) oral solution
C III

XYWAV and XYREM REMS

Dear Prescriber,

Welcome to the XYWAV and XYREM REMS, 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 information about the XYWAV and XYREM REMS that includes important prescribing information, educational and counseling requirements, and materials necessary for REMS enrollment and prescribing XYWAV® (calcium, magnesium, potassium, and sodium oxybate) oral solution, and XYREM® (sodium oxybate) oral solution, including:

- **Prescriber Enrollment Form—**a one-time enrollment is required for all prescribers of XYWAV and XYREM.
- **Patient Enrollment Form—**a one-time patient enrollment in the XYWAV and XYREM REMS is required for each new patient for whom XYWAV or XYREM will be prescribed.
- **XYWAV and XYREM Prescription Forms—**required to be completed for treatment initiation and for patients with a lapse in treatment of either XYWAV or XYREM for 6 months or longer. The Prescription Forms are not required to be completed for refills and renewals of XYWAV and XYREM prescriptions.
- **XYWAV and XYREM Patient Quick Start Guides—**these guides answer important questions for adult patients about how to get XYWAV and XYREM, how to use XYWAV and XYREM properly, and how to store them safely. It also gives important information about the risks associated with XYWAV and XYREM.
- **XYWAV and XYREM Brochures for Pediatric Patients and their Caregivers—**these guides answer important questions for caregivers of pediatric patients and pediatric patients about how to use XYWAV and XYREM properly, how to store them safely, and how to get XYWAV and XYREM. It also gives important information about the risks associated with XYWAV and XYREM.

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

Please review the Prescribing Information for XYWAV and XYREM.

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

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

XYWAV is indicated for the treatment of idiopathic hypersomnia (IH) in adults

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 XYWAV and XYREM REMS at **1-866-997-3688** or visit **www.XYWAVXYREMREMS.com**.

Sincerely,
Jazz Pharmaceuticals

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- The use of XYWAV or XYREM in combination with sedative hypnotics is contraindicated.
- The use of XYWAV or XYREM in combination with alcohol is contraindicated.
- XYWAV and XYREM are contraindicated in patients with succinic semialdehyde dehydrogenase deficiency.

WARNINGS AND PRECAUTIONS

CNS Depression

- XYWAV and XYREM are CNS depressants. Concurrent use of XYWAV or 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 XYWAV or XYREM is required, dose reduction or discontinuation of one or more CNS depressants (including XYWAV or XYREM) should be considered.
  - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with XYWAV or 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 XYWAV or 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 XYWAV or XYREM do not affect the patient adversely.

Abuse and Misuse

- XYWAV and XYREM are Schedule III controlled substances.
- The active moiety of XYWAV and XYREM is oxybate, also known as gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse events, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. Illicit GHB has also been associated with drug-facilitated sexual assault.
- The rapid onset of sedation, coupled with the amnestic features of XYWAV and 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 XYWAV or XYREM (e.g., increase in size or frequency of dosing; reports of lost, stolen, or spilled medication; drug-seeking behavior; feigned cataplexy).

XYWAV and XYREM REMS

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

Further information is available at **www.XYWAVXYREMREMS.com** or 1-866-997-3688.

xywav®
(calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL
III

XYREM®
(sodium oxybate) oral solution
III

Depression, Suicidality, and Other Behavioral/Neuropsychiatric Adverse Events

- Depression and suicidal ideation and behavior can occur in patients treated with XYWAV or XYREM
- The emergence of depression in patients treated with XYWAV and 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 XYWAV or XYREM. XYWAV and 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 XYWAV and XYREM.

Use in Patients Sensitive to High Sodium Intake

- XYREM has a high sodium content. Administration of the maximum recommended dose of XYREM (9g/night) delivers 1,640mg of sodium, corresponding to 71% of the recommended maximum daily intake of sodium (2,300 mg/day).
- Daily sodium intake should be considered in patients, particularly those on salt-restricted diets or with heart failure, hypertension, or compromised renal function.

Most Common Adverse Events

- In three controlled clinical trials with adult patients, the most common adverse reactions (incidence ≥5% and twice the rate seen with placebo) in XYREM-treated patients were nausea (20%), dizziness (15%), vomiting (11%), somnolence (8%), enuresis (7%), and tremor (5%).
- Of the 398 XYREM-treated adult patients with narcolepsy, 10.3% of patients discontinued because of adverse reactions compared with 2.8% of patients receiving placebo. The most common adverse reaction leading to discontinuation was nausea (2.8%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.
- The overall adverse reaction profile of XYREM (same active moiety as XYWAV) in pediatric patients with narcolepsy (7 years of age and older) is similar to that in adult patients. The most common adverse reactions (>5%) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%), and sleepwalking (6%).
- In a 16 week double-blind placebo-controlled randomized withdrawal study in 201 adult patients with narcolepsy with cataplexy the most common adverse reactions (incidence ≥ 5% of XYWAV-treated patients) were headache (20%), nausea (13%), dizziness (10%), decreased appetite (8%), parasomnia (6%), diarrhea (6%), hyperhidrosis (6%), anxiety (5%), and vomiting (5%). 9 out of 201 patients (4%) reported adverse reactions that led to withdrawal from the study (anxiety, decreased appetite, depressed mood, depression, fatigue, headache, irritability, nausea, pain in extremity, parasomnia, somnolence, and vomiting). The most common adverse reaction leading to discontinuation was nausea (1.5%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.
- In Study 2, in 154 adult patients with idiopathic hypersomnia the most common adverse reactions (incidence ≥ 5% of XYWAV-treated patients) were nausea (21%), headache (16%), anxiety (12%), dizziness (12%), insomnia (9%), hyperhidrosis (8%), decreased appetite (8%), vomiting (7%), dry mouth (6%), diarrhea (5%), fatigue (5%), somnolence (5%), tremor (5%), parasomnia (5%). 17 out of 154 patients (11%) reported adverse reactions that led to withdrawal from the study (anxiety, nausea, insomnia, vomiting, fatigue, feeling abnormal, fall, decreased appetite, dizziness, paraesthesia, tremor, parasomnia, confusional state, hallucination visual, and irritability). The most common adverse reaction leading to discontinuation was anxiety (3.2%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.

Please see Prescribing Information for XYWAV and XYREM.

TABLE OF CONTENTS

Prescribing Information is also included

Prescribing XYWAV and XYREM—A Brief Guide

The XYWAV and XYREM REMS applies to XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL, and XYREM® (sodium oxybate) oral solution, 0.5 g/mL. XYWAV and XYREM are both aqueous solutions with the active moiety of oxybate. These products are subject to a REMS because they both contain oxybate, or gamma-hydroxybutyrate (GHB), a CNS depressant and a known drug of abuse. In order to prescribe either of these products, you will need to comply with the prescribing requirements outlined in the XYWAV and XYREM REMS, which are the same for both drugs. **The procedures for writing and dispensing prescriptions for XYWAV and XYREM are outlined below.**

PRESCRIBERS OF XYWAV AND XYREM

PRESCRIBER ENROLLMENT

Prescribing XYWAV and XYREM requires a one-time enrollment.

- **If you are prescribing XYWAV or XYREM for the first time**, complete the **REMS Prescriber Enrollment Form**, found either accompanying this Prescriber Brochure or online at **www.XYWAVXYREMREMS.com**. Please:
  - Submit the form online at **www.XYWAVXYREMREMS.com** or
  - Scan and send via e-mail to **ESSDSPrescribers@express-scripts.com** or
  - Mail to **XYWAV and XYREM REMS, PO Box 66589, St. Louis, MO 63166-6589** or
  - Fax to **1-866-470-1744** (toll free).
- On the **REMS Prescriber Enrollment Form**, please confirm that:
  - You understand that **XYWAV** is indicated for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy. XYWAV is indicated for the treatment of idiopathic hypersomnia in adults.
  - 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 Prescriber Brochure
  - You understand that XYWAV and XYREM are Schedule III CNS depressants and can cause obtundation and clinically significant respiratory depression at recommended doses
  - You understand that the use of XYWAV or XYREM in combination with alcohol or sedative hypnotics is contraindicated
  - You understand that concurrent use of XYWAV or 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
  - You understand that 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 XYWAV or XYREM use
  - Before Treatment Initiation (first dose), you must:
    - Assess the patient's health status to determine if XYWAV or XYREM is medically appropriate by screening for history of alcohol and substance abuse, sleep-related breathing disorders, compromised respiratory function, depression, suicidality, concomitant use of sedative hypnotics and other CNS depressants or potentially interacting agents. Document and submit my findings to the XYWAV and XYREM REMS using the product-specific **Prescription Form**
    - Counsel the patient on the serious risks associated with XYWAV or XYREM safe use, handling, and storage using the product-specific **Patient Quick Start Guide** and **Brochure for Pediatric Patients and their Caregivers**

- Enroll the patient by completing and submitting the **Patient Enrollment Form** to the XYWAV and XYREM REMS
- Order the prescription using the product-specific **Prescription Form** and submit it to the XYWAV and XYREM REMS

– Before Treatment Re-Initiation, you must:

- **For patients disenrolled for suspicion of abuse, misuse, or diversion:** Communicate with the pharmacy regarding all relevant patient history and re-enroll the patient if the pharmacist and I agree
- **For patients with a lapse in treatment of 6 months or longer:** Order the prescription using the product-specific Prescription Form and submit it to the XYWAV and XYREM REMS

– During Treatment, Within the first 3 months of starting treatment, and recommended every 3 months thereafter, you must:

- Assess the patient for concomitant use of sedative hypnotics and other CNS depressants, or potentially interacting agents; serious adverse events, and signs of abuse and misuse, including an increase in dose or frequency of dosing, reports of lost, stolen, or spilled medication, and drug-seeking behavior

– At all times, you must:

- Report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, death, and any cases of suspected abuse, misuse, or diversion to Jazz Pharmaceuticals
- Assess the patient's potential for abuse, misuse, and diversion. Report all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug to the REMS.
- Report all requests to disenroll a patient for suspected abuse, misuse, or diversion to the XYWAV and XYREM REMS

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 XYWAV and XYREM
- Contraindications (alcohol and sedative hypnotics)
- Risks of concomitant use of XYWAV or 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 XYWAV or XYREM does not affect the patient adversely
- Preparation and dosing instructions for XYWAV and XYREM
- The risk of abuse and misuse associated with use of XYWAV and XYREM
- Safe use, handling, and storage of XYWAV and XYREM

XYWAV and XYREM REMS

ENROLL

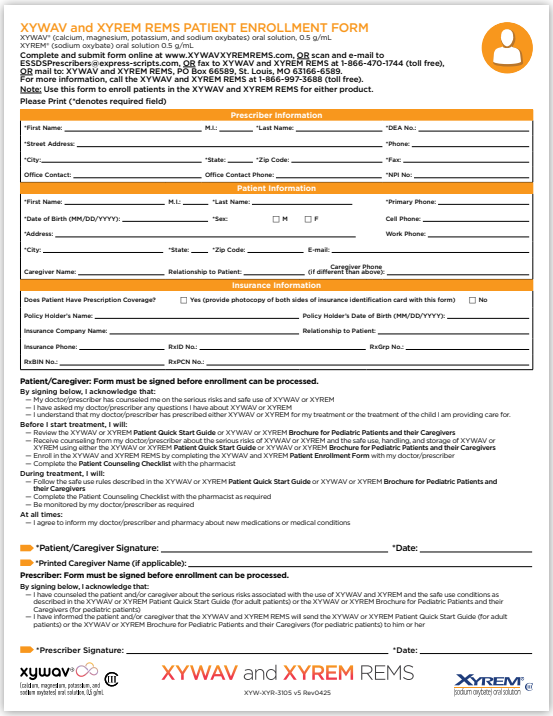
- You will enroll each patient in the XYWAV and XYREM REMS by completing the one-time **REMS Patient Enrollment Form** and submitting the form to the XYWAV and XYREM REMS. A pediatric patient must have a caregiver
- You will evaluate each patient within the first 3 months of starting XYWAV or XYREM, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while on XYWAV or 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
- You will assess the patient's potential for abuse, misuse, and diversion. Report all instances of behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug to the REMS
- You will report requests to disenroll a patient for suspected abuse, misuse, or diversion to the XYWAV and XYREM REMS

PATIENT ENROLLMENT

- All patients must be enrolled one time in the XYWAV and XYREM REMS, using the **REMS Patient Enrollment Form**. A pediatric patient must have a caregiver.
- On the **REMS Patient Enrollment Form**:
  - For adult patients, verify that you have provided counseling to the patient about the serious risks associated with the use of the medication and its safe use as described in the XYWAV or XYREM Patient Quick Start Guides
  - For pediatric patients, verify that you have provided counseling to the caregiver about the serious risks associated with the use of the medication and its safe use as described in the XYWAV or XYREM Brochures 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 XYWAV or XYREM, has had the opportunity to ask you any questions he/she may have about XYWAV or XYREM, and understands that he/she has been prescribed either XYWAV or XYREM for their treatment or the treatment of the child they are providing for.
  - Fax the completed REMS Patient Enrollment Form to the XYWAV and XYREM REMS at 1-866-470-1744 (toll free) or mail to XYWAV and XYREM REMS, PO Box 66589, St. Louis, MO 63166-6589. The form can also be completed online at **www.XYWAVXYREMREMS.com**.



XYWAV and XYREM REMS PATIENT ENROLLMENT FORM

XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL
XYREM® (sodium oxybate) oral solution 0.5 g/mL

Complete and submit form online at www.XYWAVXYREMREMS.com, OR scan and e-mail to ESODSPrescribers@express-scripts.com, OR fax to XYWAV and XYREM REMS at 1-866-470-1744 (toll free), OR mail to: XYWAV and XYREM REMS, PO Box 66589, St. Louis, MO 63166-6589.
For more information, call the XYWAV and XYREM REMS at 1-866-997-3688 (toll free).
Note: Use this form to enroll patients in the XYWAV and XYREM REMS for either product.
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): _____ *Sex: ☐ M ☐ F Cell Phone: _____
*Address: _____ Work Phone: _____
*City: _____ *State: _____ *Zip Code: _____ E-mail: _____
Caregiver Name: _____ Relationship to Patient: _____ Caregiver Phone (if different than above): _____

Insurance Information

Does Patient Have Prescription Coverage? ☐ Yes (provide photocopy of both sides of insurance identification card with this form) ☐ 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 XYWAV or XYREM
— I have asked my doctor/prescriber any questions I have about XYWAV or XYREM
— I understand that my doctor/prescriber has prescribed either XYWAV or XYREM for my treatment or the treatment of the child I am providing care for.
Before I start treatment, I will:
— Review the XYWAV or XYREM **Patient Quick Start Guide** or XYWAV or XYREM **Brochure for Pediatric Patients and their Caregivers**
— Receive counseling from my doctor/prescriber about the serious risks of XYWAV or XYREM and the safe use, handling, and storage of XYWAV or XYREM using either the XYWAV or XYREM **Patient Quick Start Guide** or XYWAV or XYREM **Brochure for Pediatric Patients and their Caregivers**
— Enroll in the XYWAV and XYREM REMS by completing the XYWAV and XYREM **Patient Enrollment Form** with my doctor/prescriber
— Complete the **Patient Counseling Checklist** with the pharmacist
During treatment, I will:
— Follow the safe use rules described in the XYWAV or XYREM **Patient Quick Start Guide** or XYWAV or XYREM **Brochure for Pediatric Patients and their Caregivers**
— Complete the Patient Counseling Checklist with the pharmacist as required
— Be monitored by my doctor/prescriber as required
At all times:
— I agree to inform my doctor/prescriber and pharmacy about new medications or medical conditions

➡ *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 XYWAV and XYREM and the safe use conditions as described in the XYWAV or XYREM Patient Quick Start Guide (for adult patients) or the XYWAV or XYREM Brochure for Pediatric Patients and their Caregivers (for pediatric patients)
— I have informed the patient and/or caregiver that the XYWAV and XYREM REMS will send the XYWAV or XYREM Patient Quick Start Guide (for adult patients) or the XYWAV or XYREM Brochure for Pediatric Patients and their Caregivers (for pediatric patients) to him or her

➡ *Prescriber Signature: _____ *Date: _____

xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL
XYWAV and XYREM REMS
XYREM® (sodium oxybate) oral solution
XYW-XYR-3105 v5 Rev042S

PRESCRIBING REQUIREMENTS

- Write prescriptions using either the **XYREM Prescription Form** or the **XYWAV Prescription Form** (general prescription forms will not be accepted) for the initial prescription of either product, and for patients who are reinitiating XYWAV or XYREM after a lapse in therapy of either XYWAV or XYREM for 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
  - Complete the Indication for Use section by checking the appropriate box on the XYWAV or XYREM Prescription Form
  - 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 17–19 of this brochure for patient counseling information.
    - The serious risks associated with XYWAV or 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 XYWAV or XYREM does not affect the patient adversely
    - Preparation and dosing instructions for XYWAV or XYREM
    - The risk of abuse and misuse associated with use of XYWAV or XYREM
    - Safe use, handling, and storage of XYWAV or XYREM (refer to pages 17–19 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 **XYWAV** or **XYREM Prescription Form** or by faxing a separate page.
  - **NOTE:** Prior to dispensing each XYWAV or 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 XYWAV or XYREM.
    - The pharmacist may also contact the prescriber about other concomitant medications of concern.

- **NOTE:** Verify that you have informed the patient and/or caregiver that the REMS will send him/her a copy of the appropriate educational material (the XYWAV or XYREM Patient Quick Start Guide for adult patients and the XYWAV or XYREM 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 Jazz Pharmaceuticals or may be downloaded at **www.XYWAVXYREMREMS.com**

Both the **XYWAV Prescription Form** and the **XYREM Prescription Form** are available online at **www.XYWAVXYREMREMS.com**. Options include:

- Submit online using the DEA electronic prescribing compliant option through **www.XYWAVXYREMREMS.com**.

OR

- Download, print and sign. Either fax to the XYWAV and XYREM REMS at **1-866-470-1744** (toll free), or mail to the **XYWAV and XYREM REMS, PO Box 66589, St. Louis, MO 63166-6589**.

PATIENT EVALUATION

- Evaluate each patient within the first 3 months of starting XYWAV or XYREM therapy, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while they are taking XYWAV or 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 electronically or by phone, fax, or mail; the forms can be found at **www.XYWAVXYREMREMS.com**. In addition, the Certified Pharmacy with the XYWAV and XYREM REMS will send you the **XYWAV Prescription Form** or the **XYREM Prescription Form** upon your request. Prescription refills and renewals must be documented in the XYWAV and XYREM REMS Central Database.
- Submit online using the DEA electronic prescribing compliant option through **www.XYWAVXYREMREMS.com**
- To phone in refills or renewals for XYWAV or XYREM, call 1-866-997-3688
- To fax or mail refills or renewals for XYWAV or XYREM:
  - Fill out the **XYWAV Prescription Form** or the **XYREM Prescription Form** completely and clearly to ensure timely fulfillment of your patient's prescription
    - If downloading the XYWAV Prescription Form or XYREM Prescription Form online through **www.XYWAVXYREMREMS.com**, you must print and sign the form prior to submitting it to the XYWAV and XYREM REMS.

- Fax the completed **XYWAV** or **XYREM Prescription Form** to the XYWAV and XYREM REMS at **1-866-470-1744** (toll free) or mail to XYWAV and XYREM REMS, PO Box 66589, St. Louis, MO 63166-6589.

Please see Idiopathic Hypersomnia (IH) specific patient information in the dosing section.

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

Responsibilities of the XYWAV and XYREM REMS Certified Pharmacy

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

- **Provide you with confirmation** of each new **XYWAV** or **XYREM Prescription Form** received from your office
- **Contact the patient's insurance provider** to verify XYWAV or 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 (XYWAV or XYREM Patient Quick Start Guide for adult patients and XYWAV or XYREM 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 XYWAV or XYREM therapy and how to prepare and take XYWAV or XYREM doses safely and effectively
  - Review important XYWAV and XYREM safety information and precautions for XYWAV or XYREM use
  - Review XYWAV and XYREM safe handling and storage procedures
  - Review the adverse events associated with XYWAV and XYREM use
  - Review the patient's use of concomitant medications
    - Prior to dispensing each XYWAV or 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 XYWAV or 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 XYWAV or 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** XYWAV or 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 XYWAV and XYREM REMS are available online at www.XYWAVXYREMREMS.com.
Please be sure to review the Prescribing Information prior to prescribing XYWAV or XYREM for your patients.

Guidelines for Dosing and Titrating XYWAV and XYREM

DOSING XYWAV AND XYREM

The information presented in this section is for adult patients with narcolepsy. Please see pages 19–21 for additional important information on dosing for pediatric patients (7 years of age and older) with narcolepsy.

XYWAV and XYREM are liquid medications taken orally at bedtime. Due to their short half-life, XYWAV and XYREM are 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 dose of XYWAV and XYREM should be titrated to effect
  - Increase the dosage by up to 1.5 g per night per week (eg, additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the recommended dosage range of 6 g to 9 g per night, based on efficacy and tolerability.
- Doses may be divided equally or unequally and the first dose taken at bedtime and the second dose taken 2.5 to 4 hours later.
- Doses higher than 9 g/night have not been studied and ordinarily should not be administered
- An initial XYWAV or XYREM dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking XYWAV or XYREM. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting XYWAV or XYREM dose when introducing XYWAV or XYREM. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of XYWAV or XYREM with divalproex sodium is warranted.
- In some patients, improvement may occur during the first weeks of therapy; however, titration to an optimal dose may take longer
- Once a stable dose is established, patients should be evaluated periodically

The patient's first shipment of oxybate-containing product within the XYWAV and XYREM REMS will be limited to a 1-month (30-day) supply, and future shipments cannot exceed a 3-month (90-day) supply.

RECOMMENDED ADULT XYWAV and XYREM DOSAGE 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	Recommended Dose Range
	3.75 g	3.75 g	7.5 g	
Maximum dose	4.5 g	4.5 g	9 g	

Note: Some patients may achieve better responses with unequal nightly doses at bedtime and 2.5 to 4 hours later

THE INFORMATION PRESENTED ON THIS PAGE IS FOR ADULT PATIENTS WITH IDIOPATHIC HYPERSOMNIA.

The dosage and regimen of XYWAV should be individualized based on clinical presentation. XYWAV can be administered as a twice nightly or once nightly regimen. The recommended starting dose, titration guidance, and maximum nightly doses appear in the table below.

- The increase in total nightly dose should not exceed 1.5 g per week.
- During titration, the dosing regimen may be changed between twice nightly and once nightly, as needed based on efficacy and tolerability.
- Doses higher than 9 g per night or single dose administrations higher than 6 g have not been studied and should not be administered.
- An initial XYWAV or XYREM dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking XYWAV or XYREM. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting XYWAV or XYREM dose when introducing XYWAV or XYREM. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of XYWAV or XYREM with divalproex sodium is warranted.
- In some patients, 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

RECOMMENDED NIGHTLY DOSAGE in ADULT PATIENTS with IH			
Dosing Regimen	**Starting Nightly Dose**	**Titration increments**	**Maximum Total nightly Dose**
Twice nightly*,†	≤4.5 g per night divided into two doses (e.g., 2.25g each)	≤1.5 g per night per week (divided into two doses)	9 g (divided into two doses)
Once nightly	≤ 3 g per night	≤ 1.5 g per night per week	6 g

* Some patients may achieve better responses with unequal nightly doses at bedtime and 2.5 to 4 hours later.
† The first dose should be taken at bedtime and the second dose taken 2.5 to 4 hours later.

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 XYWAV and 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 XYWAV and XYREM should be diluted with about ¼ cup of water
  - Patients should be instructed to store XYWAV and XYREM bottles and prepared nightly doses in a secure place out of the reach of children and pets

xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL

XYREM® (sodium oxybate) oral solution

- XYWAV and XYREM 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

CHANGING BETWEEN XYWAV AND XYREM

A gram of XYWAV and a gram of XYREM both contain the same amount of the active drug, oxybate. Patients changing between XYWAV and XYREM should be started on the same dose as the previously administered product. For example, if a patient on a stable dose of 4.5 g of XYREM twice nightly changes to XYWAV, they should be prescribed 4.5 g of XYWAV twice nightly. Patients should then be evaluated and dosing adjustments made if necessary.

When changing a patient's therapy:

- Inform patients that the safe use and administration instructions are the same for both products
- XYWAV and XYREM may taste differently, but work the same.
- Advise patients to never take XYWAV and XYREM at the same time.
- For patients changing to XYREM therapy: Instruct patients and/or caregivers that XYREM contains a significant amount of sodium and XYREM-treated patients, particularly those who are sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment) should limit their sodium intake.

Additional Information about XYWAV and XYREM

XYWAV and XYREM have been placed in a bifurcated federal schedule. XYWAV and XYREM are Schedule III controlled substances when used for legitimate medical purposes, as prescribed. XYWAV and XYREM are both aqueous solutions with the active moiety of oxybate, or gamma-hydroxybutyrate (GHB), which 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 XYWAV and XYREM to any persons other than the patient for whom it was prescribed. If you have any questions regarding this, please call the XYWAV and XYREM REMS 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 XYWAV and XYREM

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

DISENROLLMENT FROM THE XYWAV AND XYREM REMS:

There may be situations when a patient should not continue on XYWAV or XYREM therapy due to suspected abuse, misuse, or diversion. Suspected abuse, misuse, or diversion is managed at the XYWAV and XYREM REMS through a risk management reporting process. The Certified Pharmacy will contact you if such issues arise to discuss next steps for your patient. Also, you can contact the Certified Pharmacy with the XYWAV and XYREM REMS to review a patient's risk management history at any time.

In the event that you believe your patient should not continue on XYWAV or XYREM and be disenrolled from the REMS due to suspected abuse, misuse, or diversion, you are required to report these situations to the XYWAV and XYREM REMS.

Once a patient is disenrolled from the XYWAV and XYREM REMS, the patient will no longer receive XYWAV or XYREM. If you decide to re-enroll a patient that has been previously disenrolled for suspicions of abuse, misuse, or diversion, the Certified Pharmacy will communicate all relevant patient history and the patient will be re-enrolled if you and the Certified Pharmacy agree that it is appropriate.

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

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 XYWAV and XYREM dosage regimen

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

XYWAV AND XYREM TAKEBACK PROGRAM

XYWAV and XYREM patients have an option to return any unused, leftover or expired XYWAV and/or XYREM product through a reverse distribution drug takeback program, upon request. Patients interested in this option can call the XYWAV and XYREM REMS for more information. The REMS Certified Pharmacy will be provided shippers that can be sent to the patient. Patients will be instructed to black out or remove their personal information from the bottle(s) and to place the bottles in the shipper.

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

Use in Specific Populations

PREGNANCY

There are no adequate data on the developmental risk associated with the use of XYWAV or 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

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

NURSING MOTHERS

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

PEDIATRIC USE

Safety and effectiveness of XYWAV for the treatment of idiopathic hypersomnia in pediatric patients have not been established.

The safety and effectiveness of XYWAV for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy have been established. XYWAV has not been studied in a pediatric clinical trial. Use of XYWAV in pediatric patients 7 years of age and older with narcolepsy is supported by evidence from an adequate and well-controlled study of sodium oxybate in pediatric patients 7 to 17 years of age, a study in adults showing a treatment effect of XYWAV similar to that observed with sodium oxybate, pharmacokinetic data of sodium oxybate from adult and pediatric patients, and pharmacokinetic data of XYWAV from healthy adult volunteers.

In the pediatric clinical trial with sodium oxybate administration in patients with narcolepsy, serious adverse reactions of central sleep apnea and oxygen desaturation documented by polysomnography evaluation; suicidal ideation in one patient; neuropsychiatric reactions including acute psychosis, confusion, and anxiety; and parasomnias, including sleepwalking, have been reported. The safety and effectiveness of XYREM in the treatment of cataplexy or excessive daytime sleepiness in pediatric patients (7 years of age and older) with narcolepsy have been established and pharmacokinetics characterized in a double-blind, placebo-controlled, randomized-withdrawal study. Safety and effectiveness of XYWAV or XYREM in pediatric patients below the age of 7 years have not been established.

GERIATRIC USE

There is limited experience with 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 SEX 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 XYWAV and XYREM REMS 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 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 XYWAV and XYREM using the appropriate educational material [XYWAV or XYREM Patient Quick Start Guide (for adults) and XYWAV or XYREM Brochure for Pediatric Patients and Their Caregivers (for pediatric patients)] and encourage him/her to read the XYWAV or XYREM Medication Guide. **Please see pages 19–21 for additional counseling information important for caregivers of pediatric patients and, as appropriate, pediatric patients.**

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

To ensure safe and effective use of XYWAV and 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 XYWAV or XYREM. Advise patients to never take XYWAV and XYREM at the same time.

SEDATION

Inform patients and/or caregivers that the patient is likely to fall asleep quickly after taking XYWAV or 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 lie down immediately and 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 XYWAV/XYREM

Inform patients and/or caregivers that XYWAV and XYREM doses should be taken at least 2 hours after eating.

RESPIRATORY DEPRESSION

Inform patients and/or caregivers that XYWAV and XYREM can be associated with respiratory depression even at recommended doses and with concurrent use of XYWAV or 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 XYWAV or 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 and their families that XYWAV and XYREM have been associated with sleepwalking and to contact their healthcare provider if this occurs.

SODIUM INTAKE (FOR PATIENTS TAKING XYREM)

Instruct patients and/or caregivers that XYREM contains a significant amount of sodium and XYREM-treated patients, particularly those 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 XYWAV and XYREM and dosing information with patients and/or caregivers prior to the initiation of treatment
- Instruct patients and/or caregivers to store XYWAV and XYREM bottles and XYWAV and XYREM doses in a secure place, out of reach of children and pets
- For patients prescribed twice nightly dosing, 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
- Inform patients that their nightly dose may require multiple draws. Instruct patients on how to perform the draws from the bottle.

- 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 XYWAV and XYREM at room temperature, between 59°F and 86°F
- Inform patients and/or caregivers that they may safely dispose of XYWAV and XYREM down the sink or toilet drain
- Inform patients and/or caregivers that they must report all instances of lost or stolen XYWAV and XYREM to the local police and to the XYWAV and XYREM REMS

Pediatric Patient Supplement

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

PRESCRIBING XYWAV AND XYREM FOR PEDIATRIC PATIENTS

In addition to the procedure for writing and dispensing prescriptions for XYWAV and XYREM described above, prescribing XYWAV or 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 XYWAV or XYREM Brochure for Pediatric Patients and Their Caregivers and encourage him/her to read the XYWAV or XYREM Medication Guide.

RESPONSIBILITIES OF THE XYWAV AND XYREM REMS 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 XYWAV and XYREM

Each pediatric patient receiving XYWAV or XYREM must have a caregiver

GUIDELINES FOR DOSING AND TITRATING XYWAV AND XYREM FOR PEDIATRIC PATIENTS

- The safety and effectiveness of XYWAV in the treatment of cataplexy or excessive daytime sleepiness in pediatric patients (7 years of age and older) with narcolepsy were established in a pediatric clinical trial with XYREM (sodium oxybate). XYWAV has not been studied in a pediatric clinical trial.
- 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 XYWAV or 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 XYWAV or XYREM may be given at bedtime or after an initial period of sleep

xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL III

XYREM® (sodium oxybate) oral solution III

- Titrate the dose of XYWAV or 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 for some patients 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 XYWAV and 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 XYWAV or XYREM may be given at bedtime or after an initial period of sleep.

**If XYWAV or 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: Some patients may achieve better responses with unequal doses at bedtime and 2.5 to 4 hours later.

IMPORTANT ADMINISTRATION INSTRUCTIONS FOR PEDIATRIC PATIENTS

- Inform caregivers that they should ensure that all XYWAV and 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 XYWAV and XYREM in the provided bottle(s)
- Inform caregivers and patients that it is important to follow a consistent nightly routine for taking XYWAV or 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 XYWAV or XYREM should be diluted with about ¼ cup of water
    - Caregivers should be instructed to store XYWAV and XYREM bottles and prepared nightly doses in a secure place out of the reach of children and pets
  - XYWAV and XYREM 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 XYWAV or 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 XYWAV or XYREM does not affect the patient adversely

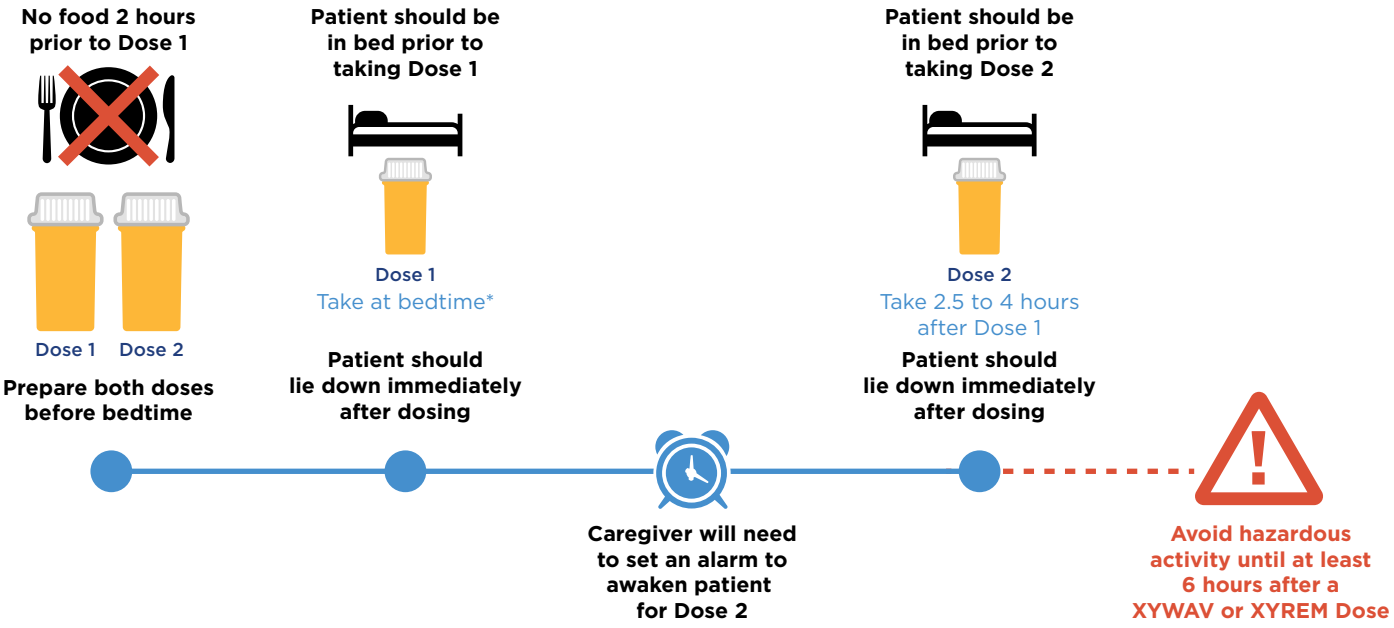
CHANGING BETWEEN XYWAV AND XYREM

A gram of XYWAV and a gram of XYREM both contain the same amount of the active drug, oxybate. Patients changing between XYWAV and XYREM should be started on the same dose as the previously administered product. For example, if a patient on a stable dose of 4.5g of XYREM twice nightly changes to XYWAV, they should be prescribed 4.5g of XYWAV twice nightly. Patients should then be evaluated and dosing adjustments made if necessary.

When changing a patient's therapy:

- Inform patients that the safe use and administration instructions are the same for both products
- XYWAV and XYREM may taste differently, but work the same.
- Advise patients to never take XYWAV and XYREM at the same time.
- For patients changing to XYREM therapy: Instruct patients and/or caregivers that XYREM contains a significant amount of sodium and XYREM-treated patients, particularly those who are sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment) should limit their sodium intake.

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



*For patients who sleep more than 8 hours per night, the first dose of XYWAV or 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 XYWAV and XYREM either by the prescriber or the Certified Pharmacy
  - Ensure that the patient also reads the XYWAV or XYREM Brochure for Pediatric Patients and Their Caregivers and asks any questions he or she may have

Notes

FPO

PI

Jazz Pharmaceuticals®

xywav®
(calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL
C III

XYREM®
(sodium oxybate) oral solution
C III

XYW-XYR-3101 v5 Rev0425