



XYWAV and XYREM REMS

Certified Pharmacy Training

MODULES A AND B

All XYWAV and XYREM REMS Certified Pharmacy staff must complete Module A Knowledge Assessment. Pharmacists must also complete Module B Knowledge Assessment.



Dear XYWAV and XYREM REMS Certified Pharmacy Staff,

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

THE XYWAV and XYREM REMS

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

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

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

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

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

Sincerely,

Jazz Pharmaceuticals



Table of Contents

MODULE A: XYWAV and XYREM REMS	4
IMPORTANT SAFETY INFORMATION	5
INDICATIONS AND USAGE	5
HOW SUPPLIED	5
CONTROLLED SUBSTANCE SCHEDULING	5
BOXED WARNING	6
CONTRAINDICATIONS	6
WARNINGS AND PRECAUTIONS	7
XYWAV and XYREM REMS REQUIREMENTS	7
OVERVIEW OF CERTIFIED PHARMACY RESPONSIBILITIES	8
DATABASE	8
ENROLLMENT PROCESSING AND MAINTENANCE	8
PRESCRIPTION PROCESSING	9
SHIPPING	10
MONITORING FOR INAPPROPRIATE PRESCRIBING, ABUSE, MISUSE, AND DIVERSION	10
ADVERSE EVENT REPORTING	10
ONGOING PATIENT AND CAREGIVER EDUCATION	10
XYWAV AND XYREM TAKEBACK PROGRAM	11
MODULE B: XYWAV and XYREM REMS TRAINING FOR PHARMACISTS	
XYWAV and XYREM REMS REQUIREMENTS	12
CERTIFIED PHARMACY RESPONSIBILITIES	13
PATIENT COUNSELING AND SCREENING	14
CLINICAL USAGE CLARIFICATIONS	15
PRESCRIPTION REFILLS	15
PATIENTS CHANGING BETWEEN XYWAV AND XYREM	16
MONITORING AND ASSESSING FOR SIGNS OF ABUSE, MISUSE, AND DIVERSION	16
SHIPPING PROCEDURES	17
INVENTORY CONTROL	18



XYWAV and XYREM REMS

Certified Pharmacy Training Module A

TRAINING FOR PHARMACY STAFF INVOLVED IN THE XYWAV AND XYREM REMS

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



Module A: XYWAV and XYREM REMS

IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

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

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

HOW SUPPLIED

XYWAV and XYREM are shipped from the XYWAV and XYREM REMS Certified Pharmacy directly to patients. Each shipment to a patient will contain:

- The prescribed amount of medication, contained in one or more bottles of XYWAV or XYREM
- A press-in-bottle adaptor (PIBA) pre-inserted into the bottle
- A XYWAV and XYREM grams-based oral measuring device (plastic syringe) to measure out each nightly dose
- Two empty pharmacy containers with child-resistant caps for preparation of both nightly doses (XYWAV or XYREM dose mixed with water)
- A XYWAV or XYREM Medication Guide

CONTROLLED SUBSTANCE SCHEDULING

XYWAV and XYREM both contain oxybate, or gamma-hydroxybutyrate (GHB, a known drug of abuse). GHB has been used to facilitate sexual assaults. Because of its rapid sedative effects (particularly when mixed with alcohol) and its colorless and odorless appearance, GHB has been used to “spike” the drinks of unsuspecting victims. Because of its abuse potential, GHB is designated a controlled substance by the Drug Enforcement Administration (DEA) and has been placed in a bifurcated federal schedule:

- GHB products approved by the FDA, such as XYWAV and XYREM, and used as prescribed for therapeutic purposes are Schedule III drugs
- The active ingredients of XYWAV and XYREM are classified as Schedule I controlled substances when used for any other reason or by anyone other than for whom it was prescribed. Federal law prohibits the transfer of XYWAV and XYREM to any persons other than the patient for whom it was prescribed.



BOXED WARNINGS

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

- Central Nervous System Depression

XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) is a CNS depressant. Clinically significant respiratory depression and obtundation may occur in patients treated with XYWAV at recommended doses [see Warnings and Precautions (5.1, 5.4)]. Many patients who received XYWAV during clinical trials in narcolepsy were receiving central nervous system stimulants [see Clinical Trials (14.1)].

- Abuse and Misuse

The active moiety of XYWAV is oxybate or gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death [see Warnings and Precautions (5.2)].

Because of the risks of CNS depression and abuse and misuse, XYWAV is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XYWAV and XYREM REMS [see Warnings and Precautions (5.3)].

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

- Central Nervous System Depression

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

- Abuse and Misuse

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

CNS Depression

- 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 or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle



relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.

- If use of these CNS depressants in combination with 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 and 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 with XYWAV or XYREM until certain that the drug does not affect the patient adversely.

Abuse, Misuse, and Diversion

- The active ingredients of XYWAV and XYREM contain oxybate, or 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.
- The rapid onset of sedation, coupled with the amnesic 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).
- Patients should be carefully evaluated for a history of substance abuse. Patients with a history of drug abuse should be closely monitored for signs of misuse or abuse of GHB (e.g., increase in dose or frequency of dosing, drug-seeking behavior, feigned cataplexy).

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

XYWAV and XYREM REMS Requirements

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

Required Components of this program include:

- Use of the central Certified Pharmacy.
- Healthcare Providers who prescribe XYWAV and XYREM must have completed the XYWAV and XYREM REMS Prescriber Enrollment Form and must comply with the requirements of the XYWAV and XYREM REMS.



- To receive XYWAV or XYREM, patients must be enrolled in the XYWAV and XYREM REMS and adult patients or caregivers (for pediatric patients) must be counseled on the serious risks and safe use of XYWAV and XYREM. Patients are enrolled by prescribers who must fill out and submit the XYWAV and XYREM REMS Patient Enrollment Form. Prescribers must also complete and submit either a XYWAV Prescription Form or a XYREM Prescription Form for all new XYWAV and XYREM prescriptions and for XYWAV and XYREM prescriptions for patients restarting treatment after not receiving either of the drug products for 6 months or more.
- Further information is available at www.XYWAVXYREMREMS.com.

Overview of Certified Pharmacy Responsibilities

DATABASE

The Certified Pharmacy will utilize the secure and validated XYWAV and XYREM REMS Central Database containing the following types of information:

- Patient and prescriber enrollment
- Patient medical history
- Prescription
- Risk management
- Shipment
- Interactions with patients, caregivers (for pediatric patients), and prescribers.

ENROLLMENT PROCESSING AND MAINTENANCE

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



- Following enrollment, the patient remains in the XYWAV and XYREM REMS unless the Certified Pharmacy and/or the prescriber determines that the patient should be disenrolled.
- A patient may be disenrolled from the program for noncompliance with the XYWAV and XYREM REMS, including for multiple suspicious early refill requests, or other information that indicates abuse, misuse, or diversion.
- The Certified Pharmacy will contact a prescriber if an enrollment form is received for a patient previously disenrolled from the program at prescriber request, or for suspicions of abuse, misuse, or diversion, and will provide the prescriber with all relevant patient history.

PRESCRIPTION PROCESSING

- Upon receipt of a XYWAV or XYREM Prescription Form, the prescription information will be entered into the Central Database.
 - The Certified Pharmacy will validate all prescriptions prior to dispensing XYWAV or XYREM. This includes verifying that:
 - The prescription form is complete and signed by the prescriber.
 - The prescriber is enrolled in the XYWAV and XYREM REMS and has active DEA, state license, and NPI numbers.
 - The patient is enrolled in the XYWAV and XYREM REMS and has no other active XYWAV or XYREM prescriptions.
 - If the Certified Pharmacy receives overlapping prescriptions for XYWAV or XYREM for a patient, the Certified Pharmacy will notify and consult each prescriber.
 - Prescriptions are considered overlapping when more than one prescription for XYWAV or XYREM is received for a patient from multiple prescribers within an overlapping timeframe.
 - If the Certified Pharmacy suspects abuse, misuse, or diversion, the prescription will not be filled, the prescriber will be notified, and an RMR will be completed.
 - There are valid reasons why a patient may have overlapping prescriptions, including if the patient moves or changes prescribers, or if the prescriber sends in a new prescription prior to the completion of all refills.
 - The Certified Pharmacy will ensure that under these situations a patient does not receive multiple overlapping shipments of XYWAV or XYREM.
 - The prescription form was received from the prescriber's office.
 - The prescription is dated within the last 6 months.
 - The prescription is for only a one-month supply on a patient's first shipment of any oxybate-containing product within the XYWAV and XYREM REMS, and no more than a 3-month supply on subsequent fills.
 - There are no discrepancies or concerns with the dosing and titration.
 - If there are discrepancies, or if the prescription form is incomplete, the Certified Pharmacy must contact the prescriber.
- Note: If a patient changes from XYREM to XYWAV, a XYWAV Prescription Form must be completed.
- Prior to dispensing XYWAV or XYREM to pediatric patients, the Certified Pharmacy will ensure each pediatric patient has a caregiver that has been counseled on the serious risks and safe use, handling and storage of XYWAV and XYREM.
 - Once the prescription is validated, the Certified Pharmacy will contact the patient to schedule shipment and complete the required counseling
 - For a new patient, the Certified Pharmacy provides the XYWAV or XYREM Patient Quick Start Guide (for adult patients) or XYWAV or XYREM Brochure for Pediatric Patients and Their Caregivers (for pediatric patients).
 - A pharmacist must counsel the patient or caregiver (for pediatric patients) by completing the XYWAV and XYREM REMS Patient Counseling Checklist prior to the initial dispensing of XYWAV or XYREM.

SHIPPING

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

- The patient or caregiver (for pediatric patients) may request an alternate shipping address, which is subject to approval by the Certified Pharmacy.



- See How Supplied for details of the contents of each XYWAV and XYREM shipment
- Daily tracking reports are generated to confirm the receipt of each order shipped
- Lost shipments are investigated.

MONITORING FOR INAPPROPRIATE PRESCRIBING, ABUSE, MISUSE, AND DIVERSION

The Certified Pharmacy must conduct detailed monitoring on an ongoing basis of patients and prescribers for signs of inappropriate prescribing, abuse, misuse, and diversion. The Certified Pharmacy will:

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

ADVERSE EVENT REPORTING

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

ONGOING PATIENT AND CAREGIVER EDUCATION

Patients and caregivers in the XYWAV and XYREM REMS have access to ongoing education during XYWAV and XYREM treatment:

- 24-hour toll-free telephone help line staffed by a XYWAV and XYREM REMS pharmacist
- Continued contact with the Certified Pharmacy for every refill
- XYWAV and XYREM REMS website (www.XYWAVXYREMREMS.com).

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.



XYWAV and XYREM REMS

Certified Pharmacy Training Module B

XYWAV AND XYREM REMS TRAINING FOR PHARMACISTS INVOLVED IN THE DISPENSING OF XYWAV AND XYREM

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



Module B: XYWAV and XYREM REMS Training for Pharmacists

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

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

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

XYWAV and XYREM REMS Requirements

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

Required components of this program include:

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

CERTIFIED PHARMACY RESPONSIBILITIES

The central Certified Pharmacy will:

- Limit the first prescription fill to a one-month supply of XYWAV or XYREM and limit subsequent prescription fills to no more than a 3-month supply
- Report potential adverse events to Jazz Pharmaceuticals within one business day.



- Notify prescribers when there are signs of potential abuse or misuse or when patients are taking sedative hypnotics, other CNS depressants, or other potentially interacting agents of which the prescriber is not already aware
- Utilize the Central Database containing the following:
 - Complete prescriber enrollment information
 - Complete patient information, including:
 - Name and two additional identifiers (date of birth, phone number, address, gender)
 - Current and previous prescribers
 - Comorbid conditions and concomitant medications reported by the patient
 - Prescription history
 - Caregiver(s) (for pediatric patients)
 - Prescription information, including:
 - XYWAV or XYREM
 - Date
 - Dose
 - Titration instructions
 - Number of refills
 - Directions
 - Total quantity (volume and number of days' supply)
 - Concomitant medications
 - Risk Management Reports (RMRs)
 - Shipment information, including:
 - Dates of shipments
 - Dates of shipment receipts
 - Patient addresses
 - Designee information
 - Number of shipments sent daily
 - Quantities of XYWAV and XYREM dispensed daily
 - Documentation of interactions with prescribers, patients, caregivers (for pediatric patients), and other parties.

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



PATIENT COUNSELING AND SCREENING

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

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



- Document the results of the patient screening, all reported concomitant medications and comorbid medical conditions, the action(s) taken, and the date the checklist is completed in the Central Database.
- Document the completion of the XYWAV and XYREM REMS Patient Counseling Checklist in the Central Database.
- Include additional requirements (if any) per federal or state requirements that need to be collected as part of the patient counseling process.
- Patients or caregivers will also have access to a XYWAV and XYREM REMS pharmacist via the 24/7 toll-free telephone help line.

CLINICAL USAGE CLARIFICATIONS

The pharmacist must:

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

PRESCRIPTION REFILLS

- Up to 5 refills are allowed on a XYWAV or XYREM prescription (per DEA regulations for CIII controlled substances).
- Refills and renewals may be conveyed by phone, by fax, or electronically from the prescriber and must be documented in the Central Database. Refill orders are opened at the Certified Pharmacy when the patient has approximately 10 days of XYWAV or XYREM therapy remaining from the previous shipment.
 - The Certified Pharmacy will contact the patient or caregiver and schedule a shipment if the patient or caregiver has not already contacted the Certified Pharmacy to request a refill.
 - The Certified Pharmacy will ask the patient or caregiver if there has been any change in the patient's medications or medical history. If the patient or caregiver indicates a change, the patient or caregiver will be transferred to a pharmacist, who determines if additional counseling and prescriber notification is required. Steps 1, 3, 4, and 5 of the XYWAV and XYREM REMS Patient Counseling Checklist must be completed if the patient or caregiver indicates that the patient is taking a new medication or has a new comorbid medical condition listed in Step 4 of the Counseling Checklist. Steps 4 and 5 should be completed post-call and should summarize the information learned on the call. The patient or caregiver should be counseled on:
 - Sedative hypnotics (e.g., diazepam, phenobarbital, zolpidem)
 - CNS depressants: including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, and muscle relaxants
 - Alcohol
 - Sleep apnea
 - Asthma, COPD, or other conditions affecting the patient's breathing
 - Other current medical conditions
 - The pharmacist must document refill counseling information and confirmation of prescriber consultation or notification in the Central Database.
- All patient requests for early refills are to be questioned and documented by the pharmacist.
 - An early refill request is a request for a XYWAV or XYREM shipment prior to the date of the next shipment.
 - Requests to accommodate shipment logistics (e.g., scheduled delivery date falls on a Sunday, holidays, and vacations) are not considered early refills.
 - If the early refill is required due to a dosage increase, a pharmacist must:



- Confirm the new dosage with the prescriber prior to processing the prescription.
- If an early refill is requested for any other reason, a pharmacist must:
 - Discuss the request with the patient or caregiver to evaluate the patient’s compliance with therapy, assessing for misuse, abuse, and diversion
 - Evaluate the patient’s record in the Central Database and review the patient’s prior XYWAV and XYREM REMS RMR history to identify previous reports of early refills or other incidents suggestive of abuse, misuse, and diversion
 - Contact the prescriber to discuss the request and any prior early refill requests or incidents suggestive of abuse, misuse, and diversion
 - Send new shipments of XYWAV or XYREM to the patient only if approved by the prescriber
 - Send new shipments to replace XYWAV or XYREM reported stolen by a patient or caregiver only after obtaining a copy of the police report filed by the patient or caregiver
 - Document the discussion and outcome in the Central Database by completing a XYWAV and XYREM REMS RMR.

PATIENTS CHANGING BETWEEN XYWAV AND XYREM

Patients may change therapies while enrolled in the XYWAV and XYREM REMS provided that the following requirements have been met:

- The patient does not have overlapping active prescriptions of XYWAV and XYREM
- If a patient is changing between XYWAV and XYREM for the first time, or has not changed between them within the past 6 months, the Certified Pharmacy must contact the patient or caregiver and:
 - Inform the patient or caregiver that:
 - The safe use and administration instructions and REMS requirements for both products are the same
 - It is important that XYWAV or XYREM are taken as instructed by you or your child’s doctor
 - Never take both XYWAV and XYREM at the same time
 - If the patient is changing from XYWAV to XYREM:
 - XYREM contains a high amount of sodium (salt) and may not be right for them, particularly if the patient is on a salt-restricted diet or has heart failure, hypertension, or compromised renal function.
 - Determine if the patient is on a salt-restricted diet, has high blood pressure, heart failure, or kidney problems. If the patient has any of these conditions, the patient and/or caregiver must complete Steps 1, 3, 4, and 5 of the XYWAV and XYREM REMS Patient Counseling Checklist (as described on page 15).

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

- Risk management events must be documented in the Central Database by completing a XYWAV and XYREM REMS RMR.
 - Risk management events are reported or discovered events outside the norm that give rise to a reasonable suspicion of abuse, misuse, or diversion
 - Examples of events that should generate an RMR include but are not limited to:
 - Requests for early refills
 - Patient’s misuse or abuse of product
 - Lost, stolen, destroyed, or spilled drug
 - Delivery to incorrect address and not returned
 - Patient claims that product was not delivered while carrier shows receipt of delivery
 - Product tampering
 - Counterfeit product
 - Contaminated product
 - Inquiries and/or arrests by law or regulatory enforcement agencies associated with the misuse, abuse, or diversion of the product



- Crimes related to the product
- RMRs must document:
 - Patient, caregiver (for pediatric patients), and prescriber identifying information (patient name to be concealed)
 - Reason for report
 - Certified Pharmacy actions
 - Prescriber contact
 - Supporting documentation if applicable (e.g., a police report, fire report, DEA Form 106, or shipper investigation report)
- If abuse, misuse, or diversion is suspected, the pharmacist must review the patient’s RMR history and discuss the incident with the prescriber prior to shipping XYWAV or XYREM.
- Repeated reports of lost, stolen, destroyed, or spilled drug will be documented as an alert to the patient record stored in the Central Database and will be accessible to the dispensing pharmacist for review prior to shipping drug.
- The Certified Pharmacy and/or prescriber may disenroll a patient from the XYWAV and XYREM REMS after review and discussion of incidents suggestive of abuse and misuse.
- All RMRs must be reported to Jazz Pharmaceuticals.

SHIPPING PROCEDURES

- XYWAV and XYREM must be shipped via an overnight service with receipt signature required.
 - XYWAV and XYREM are shipped directly to the patient or adult designee (≥ 18 years, or ≥ 21 years if required by carrier) if the patient is not available to receive the order.
- The patient or caregiver (for pediatric patients) may request an alternate shipping address, which is then subject to approval by the Certified Pharmacy.
- If the patient or caregiver requests Saturday delivery, the Certified Pharmacy will verify with the overnight shipping service that it is available for the shipping address.



- Each XYWAV and XYREM shipment includes:
 - The prescribed amount of medication, contained in one or more bottles of XYWAV or XYREM
 - A press-in-bottle adaptor (PIBA) that is pre-inserted into the bottle
 - A XYWAV and XYREM grams-based oral measuring device (plastic syringe) to measure out each nightly dose
 - Two empty pharmacy vials with child-resistant caps for preparation of both nightly doses (XYWAV or XYREM dose mixed with water)
 - A XYWAV or XYREM Medication Guide.
- Daily tracking reports are generated to confirm the receipt of each order shipped during the previous 48 hours. Saturday deliveries are confirmed the following Monday.
 - A patient or caregiver (for pediatric patients) will be contacted if there is no proof of patient or designee signature, if the patient or designee on file did not sign for the shipment, or if there is a potential incomplete delivery.
 - If a shipment is reported lost, an investigation will be launched to find it.

INVENTORY CONTROL

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