

# Risk Evaluation and Mitigation Strategy (REMS) Document

## XYWAV (calcium, magnesium, potassium, and sodium oxybates) and XYREM<sup>1</sup> (sodium oxybate) REMS Program

### I. Administrative Information

Application Numbers: NDA 21196 (and Authorized Generic); NDA 212690  
Application Holder: Jazz Pharmaceuticals, Inc (NDA 21196); Jazz Pharmaceuticals Ireland, Ltd. (NDA 212690)  
Initial REMS Approval: 02/2015  
Most Recent REMS Update: [01/2021]

### II. REMS Goal

The goal of the XYWAV and XYREM REMS is to mitigate 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:
  - a. The risk of significant CNS and respiratory depression associated with XYWAV and XYREM
  - b. The contraindication of use of XYWAV and XYREM with sedative hypnotics and alcohol
  - c. The potential for abuse, misuse, and overdose associated with XYWAV and XYREM
  - d. 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:
  - a. Screen for concomitant use of sedative hypnotics and other potentially interacting agents
  - b. Monitor for inappropriate prescribing, misuse, abuse, and diversion of XYWAV and XYREM
  - c. Notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion

### III. REMS Requirements

**Jazz Pharmaceuticals must ensure that healthcare providers, patients, and the pharmacy comply with the following requirements:**

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#### 1. Healthcare providers who prescribe XYWAV and XYREM must:

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To become certified to prescribe

1. Review the XYWAV and XYREM Prescribing Information.
  2. Review the following: [Prescriber Brochure](#).
  3. Enroll in the REMS by completing the [Prescriber Enrollment Form](#) and submitting it to the REMS Program.
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<sup>1</sup> Includes XYREM (sodium oxybate) oral solution and authorized generic sodium oxybate oral solution

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**1. Healthcare providers who prescribe XYWAV and XYREM must:**

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Before treatment initiation (first dose)	<ol style="list-style-type: none"><li>4. Assess the patient’s health status to determine if XYWAV or XYREM is medically appropriate by screening for history of alcohol or substance abuse, sleep-related breathing disorders, compromised respiratory function, and depression or suicidality.</li><li>5. Assess the patient’s health status to determine if XYWAV or XYREM is medically appropriate by screening for concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents. Document and submit to the REMS Program using the product-specific <a href="#">Prescription Form</a>.</li><li>6. Counsel the patient on the serious risks associated with XYWAV and XYREM safe use, handling, and storage using the <a href="#">XYWAV Patient Quick Start Guide</a>, <a href="#">XYREM Patient Quick Start Guide</a>, <a href="#">XYWAV Brochure for Pediatric Patients and their Caregivers</a>, or <a href="#">XYREM Brochure for Pediatric Patients and their Caregivers</a>.</li><li>7. Enroll the patient by completing and submitting the <a href="#">Patient Enrollment Form</a> to the REMS Program.</li><li>8. Order the prescription using either the <a href="#">XYWAV Prescription Form</a> or <a href="#">XYREM Prescription Form</a> and submit it to the REMS Program.</li></ol>
Before treatment re-initiation	<ol style="list-style-type: none"><li>9. For patients dis-enrolled for suspicion of abuse, misuse or diversion: communicate with the pharmacy and agree it is appropriate to re-enroll the patient.</li><li>10. For patients with a lapse in treatment of 6 months or longer: order the prescription using either the <a href="#">XYWAV Prescription Form</a> or <a href="#">XYREM Prescription Form</a> and submit it to the REMS program.</li></ol>
During treatment; within the first 3 months of starting treatment and recommended every 3 months thereafter	<ol style="list-style-type: none"><li>11. Assess the patient for: concomitant use of sedative hypnotics, 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.</li></ol>
At all times	<ol style="list-style-type: none"><li>12. 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.</li></ol>

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## 2. Patients who are prescribed XYWAV and XYREM:

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Before treatment initiation	<ol style="list-style-type: none"><li>1. Review the <a href="#">XYWAV Patient Quick Start Guide</a>, <a href="#">XYREM Patient Quick Start Guide</a>, <a href="#">XYWAV Brochure for Pediatric Patients and their Caregivers</a>, or <a href="#">XYREM Brochure for Pediatric Patients and their Caregivers</a>.</li><li>2. Receive counseling from the prescriber on the serious risks associated with XYWAV and XYREM and safe use, handling, and storage of XYWAV and XYREM using the <a href="#">XYWAV Patient Quick Start Guide</a>, <a href="#">XYREM Patient Quick Start Guide</a>, <a href="#">XYWAV Brochure for Pediatric Patients and their Caregivers</a>, or <a href="#">XYREM Brochure for Pediatric Patients and their Caregivers</a>.</li><li>3. Enroll in the REMS Program by completing the <a href="#">Patient Enrollment Form</a> with the prescriber. Enrollment information will be provided to the REMS Program.</li><li>4. Complete the <a href="#">Patient Counseling Checklist</a> with the pharmacist.</li></ol>
During treatment	<ol style="list-style-type: none"><li>5. Adhere to the safe use conditions described in the <a href="#">XYWAV Patient Quick Start Guide</a>, <a href="#">XYREM Patient Quick Start Guide</a>, <a href="#">XYWAV Brochure for Pediatric Patients and their Caregivers</a>, or <a href="#">XYREM Brochure for Pediatric Patients and their Caregivers</a>.</li><li>6. Complete the <a href="#">Patient Counseling Checklist</a> with the pharmacist based on changes in your medication and/or medical history.</li></ol>
During treatment; within the first 3 months of starting treatment and recommended every 3 months thereafter	<ol style="list-style-type: none"><li>7. Be monitored for concomitant use of sedative hypnotics, other CNS depressants, or potentially interacting agents; serious adverse events; 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.</li></ol>
Before treatment re-initiation, after lapse in treatment for 6 months or longer	<ol style="list-style-type: none"><li>8. Complete the <a href="#">Patient Counseling Checklist</a> with the pharmacist.</li></ol>
At all times	<ol style="list-style-type: none"><li>9. Inform your prescriber and the pharmacy about any new medications you may be taking or medical conditions you may have.</li></ol>

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### 3. The pharmacy that dispenses XYWAV and XYREM must:

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- To become certified to dispense
1. For all relevant staff involved in dispensing: review the [Pharmacy Training Program – Module A](#).
  2. For all relevant staff involved in dispensing: successfully complete the [Module A Knowledge Assessment](#) and submit it to the REMS Program.
  3. For all pharmacists involved in dispensing: review the [Pharmacy Training Program – Module A and B](#).
  4. For all pharmacists involved in dispensing: successfully complete the [Module A Knowledge Assessment](#) and [Module B Knowledge Assessment](#) and submit it to the REMS Program.
  5. Train all pharmacists involved in dispensing per the requirements of the [Pharmacy Training Program – Module B](#).
  6. Establish processes and procedures to verify the following: the patient and prescriber are enrolled, the patient has no other active XYWAV or XYREM prescriptions.
  7. Establish processes and procedures to verify all the prescription information including patient name and two additional identifiers, prescriber name and information, dose, titration information (if applicable), number of refills, dosing directions, total quantity (days' supply), and concomitant medications.
  8. Establish processes and procedures to assess the patient's concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents that either are unknown to the prescriber or pose a high risk of serious interaction.
  9. Establish processes and procedures to provide 24-7 toll-free access to a XYWAV and XYREM REMS Program pharmacist; to dispense no more than a one-month supply for the initial shipment and no more than a three-month supply for subsequent shipments; and to ship, track, and verify receipt of XYWAV and XYREM to the patient or patient-authorized adult designee using an overnight service.
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| Before dispensing | <ol style="list-style-type: none"><li>10. For new patients and existing patients who restart treatment after not receiving XYWAV or XYREM for 6 months or longer: Counsel the patient using the <a href="#">Patient Counseling Checklist</a>. Document and submit to the REMS Program using the Central Database.</li><li>11. For patients who report a change in their medication use or medical history: document and submit to the REMS Program using the Central Database.</li><li>12. Assess the patient’s concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents that either are unknown to the prescriber or pose a high risk of serious interaction using the processes and procedures established as a requirement of the REMS Program.</li><li>13. Verify in the Central Database that the patient and prescriber are enrolled and that the patient has no other active XYWAV or XYREM prescriptions through the processes and procedures established as a requirement of the REMS Program.</li><li>14. For patients previously dis-enrolled for suspicion of abuse, misuse or diversion: communicate all relevant patient history to the prescriber and re-enroll the patient if the prescriber and pharmacist agree.</li><li>15. Verify the patient’s prescription information, including patient name and two additional identifiers, prescriber name and information, dose, titration information (if applicable), number of refills, dosing directions, total quantity (days’ supply), and concomitant medications through the processes and procedures established as a requirement of the REMS Program.</li><li>16. Assess the patient’s potential for abuse, misuse, and diversion by reviewing the alerts and Risk Management Report history in the Central Database.</li><li>17. For patients who request an early refill or if abuse, misuse or diversion is suspected: Discuss the request or concern with the prescriber.</li><li>18. Dispense no more than a one months’ supply for the initial shipment.</li><li>19. Dispense no more than a three months’ supply for subsequent shipments.</li></ol> |
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| Before Shipping | <ol style="list-style-type: none"><li>20. Verify the patient’s shipping address and that the patient or patient-authorized adult designee will be available to receive the shipment through the processes and procedures established as a requirement of the REMS.</li><li>21. Ship XYWAV and XYREM directly to each patient or a patient-authorized adult designee through the processes and procedures established as a requirement of the REMS.</li><li>22. Provide the patient with the <a href="#">XYWAV Patient Quick Start Guide</a>, <a href="#">XYREM Patient Quick Start Guide</a>, <a href="#">XYWAV Brochure for Pediatric Patients and their Caregivers</a>, or <a href="#">XYREM Brochure for Pediatric Patients and their Caregivers</a> with the first shipment.</li></ol> |
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After Shipping	<p>23. Track and verify receipt of each shipment of XYWAV and XYREM through the processes and procedures established as a requirement of the REMS.</p> <p>24. Document and submit the shipment and receipt dates to the Central Database.</p>
To Maintain Certification to Dispense, Every Year	<p>25. For all relevant staff involved in dispensing: review the Pharmacy Training Program – Module A.</p> <p>26. For all relevant staff involved in dispensing: successfully complete the Module A Knowledge Assessment and submit it to the REMS Program.</p> <p>27. For all pharmacists involved in dispensing: review the Pharmacy Training Program – Modules A and B.</p> <p>28. For all pharmacists involved in dispensing: successfully complete the Module A Knowledge Assessment and Module B Knowledge Assessment and submit it to the REMS Program.</p> <p>29. Train all pharmacists involved in dispensing on the requirements of the REMS Program using Pharmacy Training Program – Module B.</p>
At all times	<p>30. Provide 24-7 toll-free access to a XYWAV and XYREM REMS Program pharmacist.</p> <p>31. Ship XYWAV or XYREM directly to the patient or a patient-authorized adult designee using an overnight service.</p> <p>32. Document and report all potential adverse events reported by all sources, including any CNS depression, respiratory depression, loss of consciousness, coma, and death to Jazz Pharmaceuticals.</p> <p>33. Report lost, stolen, destroyed, or spilled drug to the Central Database using the <a href="#">Risk Management Report</a>.</p> <p>34. Monitor for all instances of patient and prescriber behavior that give rise to a reasonable suspicion of abuse, misuse, and diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug. Report to Jazz Pharmaceuticals by documenting into the Central Database using the <a href="#">Risk Management Report</a>.</p> <p>35. Not distribute, transfer, loan, or sell XYWAV or XYREM.</p> <p>36. Not stock XYWAV or XYREM in retail pharmacies.</p> <p>37. Maintain records documenting staff’s completion of the <a href="#">Pharmacy Training Program</a>.</p> <p>38. Comply with audits carried out by Jazz Pharmaceuticals or a third party acting on behalf of Jazz Pharmaceuticals to ensure that all processes and procedures are in place and are being followed.</p>

**Jazz Pharmaceuticals must provide training to healthcare providers who prescribe XYWAV and XYREM.**

The training includes the following educational material: [Prescriber Brochure](#). The training must be available on a website or delivered by Jazz Pharmaceuticals.

**Jazz Pharmaceuticals must provide training to the pharmacy that dispenses XYWAV and XYREM.**

The training includes the following educational materials: [Certified Pharmacy Training Program-Module A and B](#), [Module A Knowledge Assessment](#), and [Module B Knowledge Assessment](#). The training must be available on a website or delivered by Jazz Pharmaceuticals.

**To support REMS Program operations, Jazz Pharmaceuticals must:**

1. Certify a pharmacy through a contract and distribute XYWAV and XYREM only to the certified pharmacy for dispensing.
2. Not stock XYWAV or XYREM in retail pharmacies.
3. Establish and maintain a REMS Program website, [www.XYWAVXYREMREMS.com](http://www.XYWAVXYREMREMS.com). The REMS Program website must include the capability to complete prescriber certification and patient enrollment, and the option to print the Prescribing Information and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS Program website must not link back to the promotional product website(s).
4. Make the REMS Program website fully operational and all REMS materials available through the website or call center within 180 calendar days of REMS modification (07/21/2020).
5. Establish and maintain a REMS Program call center for REMS participants at 1-866-997-3688.
6. Establish and maintain a validated, secure database, called the Central Database, of all REMS participants who have been or are enrolled and/or certified in the XYWAV and XYREM REMS Program. The database must include the following information: prescriber and patient enrollment status, all completed forms, prescription and shipment data as well as dosing, concomitant medications, behavior that raises suspicion of abuse, misuse, or diversion including all alerts and risk management reports.
7. Ensure prescribers are able to submit the [Prescriber Enrollment Form](#) by facsimile, mail, email, and online.
8. Ensure prescribers are able to submit the [Patient Enrollment Form](#) by facsimile, mail, and online.
9. Ensure prescribers are able to submit the [Prescription Form](#) by facsimile and mail.
10. Ensure prescribers are able to add refills and renew prescriptions by phone, facsimile, mail, and electronically
11. Ensure pediatric patients are able to change caregivers provided that the new caregiver has been counseled by the pharmacy on the serious risks and safe use of XYWAV and XYREM and acknowledges that he/she had any questions about XYWAV and XYREM answered before drug product is dispensed and shipped.
12. Ensure patients are able to change prescribers.
13. Ensure that the pharmacy is able to report lost, stolen, destroyed or spilled drug by completing a Risk Management Report in the Central Database.

14. Ensure that the pharmacy is able to report repeated incidents of lost, stolen, destroyed, or spilled drug by creating an alert on the patient's profile in the Central Database.
15. Ensure that the pharmacy is able to disenroll patients, in consultation with the prescriber and/or Jazz Pharmaceuticals, after review of incidents suggestive of abuse, misuse, or diversion by changing the patient's enrollment status in the Central Database.
16. Notify Prescribers within 2 business days after they become certified in the REMS Program.
17. Provide the certified pharmacy access to the database of certified prescribers and enrolled patients.

**To ensure REMS participants' compliance with the REMS Program, Jazz Pharmaceuticals must:**

18. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: XYREM distribution and dispensing; XYWAV distribution and dispensing, certification of prescribers, and the certified pharmacy; enrolled patients; and audits of REMS participants. These records must be readily available for FDA inspections.
19. Ensure that a prescriber is enrolled in the REMS Program only after verification that the [Prescriber Enrollment Form](#) is complete and all enrollment requirements are met.
20. Establish a plan for addressing noncompliance with REMS Program requirements.
21. Monitor prescribers and the certified pharmacy on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
22. Monitor the certified pharmacy for timely reporting to Jazz Pharmaceuticals of all potential adverse events and any behavior by patients or prescribers enrolled in the REMS Program that raises suspicion of abuse, misuse or diversion.
23. Monitor the Central Database on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified.
24. Audit the certified pharmacy at least annually.
25. Take reasonable steps to improve implementation of and compliance with the requirements in the XYWAV and XYREM REMS Program based on monitoring and evaluation of the XYWAV and XYREM REMS Program.

## **IV. REMS Assessment Timetable**

Jazz Pharmaceuticals must submit REMS Assessments every 6 months from the date of the REMS approval (02/2015) for the first year, and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Jazz Pharmaceuticals must submit each assessment so that it will be received by the FDA on or before the due date.

## **V. REMS Materials**

The following materials are part of the XYWAV and XYREM REMS:

**Enrollment Forms**

Prescriber:

1. [Prescriber Enrollment Form](#)

Patient:

2. [Patient Enrollment Form](#)

**Training and Educational Materials**

Prescriber:

3. [Prescriber Brochure](#)

Patient:

4. [XYREM Patient Quick Start Guide](#)
5. [XYREM Brochure for Pediatric Patients and their Caregivers](#)
6. [XYWAV Patient Quick Start Guide](#)
7. [XYWAV Brochure for Pediatric Patients and their Caregivers](#)

Pharmacy

8. [Certified Pharmacy Training Program](#)
9. [Module A Knowledge Assessment](#)
10. [Module B Knowledge Assessment](#)

**Patient Care Forms**

11. [XYREM Prescription Form](#)
12. [XYWAV Prescription Form](#)
13. [Patient Counseling Checklist](#)

**Other Materials**

14. [Risk Management Report](#)
15. [REMS Program website](#)