CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

212690Orig1s006

Trade Name:	**XYWAV**
Generic or Proper Name:	(calcium, magnesium, potassium, and sodium oxybates)
Sponsor:	**Jazz Pharmaceuticals**
Approval Date:	August 12, 2021
Indication:	XYWAV is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy and Idiopathic Hypersomnia (IH) in adults .

CENTER FOR DRUG EVALUATION AND RESEARCH

212690Orig1s006

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APPLICATION NUMBER:

212690Orig1s006

APPROVAL LETTER

NDA 212690/S-006
NDA 021196/S-036

SUPPLEMENT APPROVAL

Jazz Pharmaceuticals Ireland Limited
Attention: Arthur Merlin d'Estreux, M.Sc.
Director, Global Regulatory Lead – Neurosciences
One Commerce Square
2005 Market Street
Philadelphia, PA 19103

Dear Mr. d'Estreux:

Please refer to your supplemental new drug applications (sNDAs) dated February 12, 2021, received February 12, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) oral solution and NDA 21196 Xyrem (sodium oxybate) oral solution.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated February 26, 2021.

The Prior Approval supplemental new drug application 212690/S-006 provides for the new indication of Idiopathic Hypersomnia (IH) for XYWAV. NDA 212690/S-006 and NDA 021196/S-036 provide for modifications to the approved XYWAV and XYREM risk evaluation and mitigation strategy (REMS) to align with the revisions to the XYWAV prescribing information.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA (NDA 212690), including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for XYREM was originally approved on February 27, 2015, and the REMS for XYWAV was approved on July 21, 2020. The two drugs are subject to the same REMS, known as the XYWAV and XYREM REMS. The most recent REMS modification was approved on February 11, 2021. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of:

- Changes to the REMS materials to align with the new indication of Idiopathic Hypersomnia for XYWAV
- Changes to the REMS assessment timetable

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

- Change of the reporting interval for the Knowledge, Attitude, and Behavior Surveys from annually to every other year.

In accordance with section 505-1 of the FDCA, we have determined that the following REMS modifications are necessary to ensure the benefits of the drug outweigh the risks:

- Changes to the ***Patient Counseling Checklist*** to capture additional information regarding concomitant medication and alcohol use.

Your proposed modified REMS, submitted on February 12, 2021, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS has been revised. Jazz Pharmaceuticals must submit a REMS Assessment on April 26, 2022, and annually thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

Program Implementation and Operations

1. REMS Enrollment Statistics (per reporting period and cumulatively)
    a. Patients:
        i. Number and percentage of newly enrolled patients stratified by age, geographic region (defined by US Census), indication, and gender
        ii. Number and percentage of active patients enrolled (patients who received at least one shipment of XYWAV or XYREM during the reporting period) stratified by age, geographic region (defined by US Census), and gender
        iii. Number and percentage of patients who have discontinued XYWAV or XYREM after receiving at least one shipment of XYWAV or XYREM. Include demographics of discontinued patients and reasons for discontinuation.
        iv. Number and percentage of patients who transitioned from XYREM to XYWAV
        v. Number and percentage of patients who transitioned from XYWAV to XYREM.
    b. Healthcare Providers:
        i. Number and percentage of newly certified healthcare providers stratified by professional designation (i.e. MD, DO, PA, NP), medical specialty, and geographic region (defined by US Census)

ii. Number and percentage of active certified healthcare providers (healthcare providers who have written at least one prescription for XYWAV or XYREM during the reporting period) stratified by professional designation (i.e. MD, DO, PA, NP), medical specialty, and geographic region (defined by US Census)
iii. Number of patients by current enrolled prescriber.

c. Certified Pharmacy
i. If the Certified Pharmacy was decertified during the reporting period and reasons for decertification.

2. Utilization Data (per reporting period and cumulatively)
a. Number and percentage of XYREM prescriptions (new and refills) dispensed
b. Number and percentage of XYWAV prescriptions (new and refills) dispensed
c. Number and percentage of XYREM bottles and shipments sent
d. Number and percentage of XYWAV bottles and shipments sent.

3. REMS Program Operation and Performance Data (per reporting period and cumulatively)
a. REMS Program Central Database Report
i. Number and percentage of contacts by stakeholder type (e.g. patients, healthcare providers, pharmacy, other)
ii. Summary of reasons for contacts (e.g., enrollment questions) by reporter (authorized representative, patient, healthcare provider, other)
iii. Call center report with number of calls received and a summary of reasons for calls by stakeholder type
iv. Summary of frequently asked questions by stakeholder type and topic
v. Summary of any REMS-related problems identified and a description of any corrective actions taken
vi. If the summary reason for the calls indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues
vii. Summary of program or system problems and a description of any corrective actions taken.

4. REMS Program Compliance (per reporting period and cumulatively)
a. Audits: Summary of audit activities including but not limited to:
i. A copy of the audit plan for each audited stakeholder.
ii. The number of audits expected, and the number of audits performed
iii. The number and type of deficiencies noted

iv. For those with deficiencies noted, report the status of corrective and preventative action (CAPA) proposed to address the deficiencies. The status to include completion status.
v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
vi. Provide details on deviations for the CAPA proposed, including timelines, and mitigating steps to address the deviations
vii. Confirm documentation of completion of training for relevant staff
viii. Review of accumulative findings to identify any trends of potential repeat issues, and steps to be taken to address these findingsA summary report of the processes and procedures that are implemented to be in compliance with the REMS requirements.

b. A summary report of noncompliance, associated corrective and preventive actions (CAPA) plans, and the status of CAPA plans including but not limited to:
    i. A copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder, actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
    ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:
        1) The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
        2) The source of the noncompliance data
        3) The results of root cause analysis
        4) What action(s) were taken in response.
c. Healthcare Providers
    i. Number and percentage of certified prescribers who were disenrolled during the reporting period and reasons for disenrollment. Include if any prescribers were re-certified.
    ii. Number of disenrolled prescribers who were associated with a XYWAV and XYREM prescription and number of disenrolled prescribers associated with a XYWAV and XYREM shipment

iii. Number and percentage of XYWAV prescriptions filled from a prescriber who was not enrolled.
iv. Number and percentage of XYREM prescriptions filled from a prescriber who was not enrolled.

d. Certified Pharmacy
   i. Number and percentage of XYWAV prescriptions dispensed for more than a 30 days' supply (first fill) or more than a 90 days' supply (refills) and reasons
   ii. Number and percentage of XYREM prescriptions dispensed for more than a 30 days' supply (first fill) or more than a 90 days' supply (refills) and reasons
   iii. Number and percentage of XYWAV shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and Risk Management Reports (RMRs) completed
   iv. Number and percentage of XYREM shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and Risk Management Reports (RMRs) completed
   v. Number and percentage of initial XYWAV shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist.
   vi. Number and percentage of initial XYREM shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist.

e. Patients
   i. Number and percentage of patients who were disenrolled from the program and reasons for disenrollment
   ii. Number and percentage of patients associated with more than one prescriber during their therapy
   iii. Number and percentage of patients prescribed a daily dose of XYWAV of >9 g
   iv. Number and percentage of patients prescribed a daily dose of XYREM of >9 g
   v. Number and percentage of patients with overlapping prescriptions (more than one active prescription shipped)
   vi. Number and percentage of patients with concurrent XYWAV and XYREM prescriptions
   vii. Number of duplicate patients detected by the Certified Pharmacy

viii. Number and percentage of duplicate patients who were shipped XYWAV or XYREM under more than one name or identifier

ix. Number and percentage of patients who were shipped XYWAV or XYREM after being disenrolled

x. Number and percentage of patients who requested an early refill of XYWAV and reason for the request
   1) Number and percentage of requests approved
   2) Number and percentage of requests denied by the prescriber
   3) Number and percentage of requests denied by the Certified Pharmacy
   4) Number and percentage of patients with multiple requests for early refills.

xi. Number and percentage of patients who requested an early refill of XYREM and reason for request
   1) Number and percentage of requests approved
   2) Number and percentage of requests denied by the prescriber
   3) Number and percentage of requests denied by the Certified Pharmacy
   4) Number and percentage of patients with multiple requests for early refills.

Safe Use Behaviors

5. Pharmacy Notifications (per reporting period and cumulatively, for both XYWAV and XYREM)
   a. A summary of the notifications by pharmacies to prescribers for both XYWAV and XYREM. For each of the following situations, include the number and percentage of notifications, number of unique patients, the outcome of the pharmacy notification (e.g. counseled patient, discussed with prescriber and prescriber's designee) and outcome of XYWAV and XYREM prescription disposition (e.g. prescriber approved shipment, prescriber requested shipment hold, prescriber denied shipment, pharmacy approved shipment):
      i. Use with sedative-hypnotics indicated for sleep (e.g., eszopiclone, zaleplon, zolpidem, temazepam, suvorexant, quazepam, estazolam, flurazepam, triazolam, tasimelteon, ramelteon). Indicate specific actions taken by the prescriber and the prescriber rationale for continuing treatment in response to the notification including the following:
         - Treatment with XYWAV /XYREM will discontinue
         - Sedative hypnotic will be discontinued

- Dosage of sedative hypnotic has been/will be reduced
- Information unavailable
- No action (continue sedative hypnotic with XYWAV or XYREM)
- Prescriber's rationale for continued use of sedative hypnotic with XYWAV or XYREM
    - Sedative hypnotic will not be taken at the same time asXYWAV /XYREM
    - Sedative hypnotic will be taken at the same time as XYWAV /XYREM
    - Sedative hypnotic will be taken as a sleep aid
    - Sedative hypnotic will be taken for different indication per medical need
    - XYWAV /XYREM dose regimen changed
    - No rationale provided

ii. Benzodiazepines (e.g., diazepam, alprazolam or any not listed in metric 5.a.i.). Indicate specific actions taken by the prescriber and the prescriber rationale for continuing treatment in response to the notification including the following:

- Treatment with XYWAV /XYREM will discontinue
- Benzodiazepine will be discontinued
- Dosage of benzodiazepine has been/will be reduced
- Information unavailable
- No action (continue benzodiazepine with XYWAV or XYREM)
- Prescriber's rationale for continued use of benzodiazepine with XYWAV or XYREM
    - Benzodiazepine will not be taken at the same time as XYWAV /XYREM
    - Benzodiazepine will be taken at the same time as XYWAV /XYREM
    - Benzodiazepine will be taken as a sleep aid
    - Benzodiazepine will be taken for different indication per medical need
    - XYWAV /XYREM dose regimen changed
    - No rationale provided

iii. Use with other concomitant CNS-depressant medications (sedating antidepressants or antipsychotics, sedating anti-epileptics, sedating antihistamines, general anesthetics, muscle relaxants, opioid analgesics, or illicit CNS depressants)
iv. Patient report of alcohol use
v. Patient report of diagnosis of sleep apnea
vi. Patient report of diagnosis of asthma, COPD, or other conditions affecting breathing
vii. Suspected abuse, misuse, or diversion
viii. Alerts regarding potential abuse, misuse, or diversion on the patient profiles
ix. Prescription error
x. Early refill requests

6. Risk Management Reports (RMRs) (per reporting period and cumulatively, for both XYWAV and XYREM)
    a. Number and percentage of RMRs submitted
    b. Number and percentage of unique patients with a RMR
    c. Number and percentage of unique patients with multiple RMRs
    d. Number and percentage of alerts generated from RMRs
    e. Number and percentage of RMRs generated from early refill requests
    f. Number and percentage of RMRs generated for other reasons (list reasons)
    g. Number and percentage of prescriber-related RMRs
    h. Number and percentage of RMRs that included an adverse event.
7. REMS Program Patient Counseling Checklist (per reporting period and cumulatively, for both XYWAV and XYREM)
    a. Summary table for both XYWAV and XYREM from REMS Program Patient Counseling Checklists of the number and percentage of patients taking the following concomitant medications and who subsequently received at least one shipment of drug:
        i. Sedative hypnotics indicated for sleep (e.g., eszopiclone, zaleplon, zolpidem, temazepam, suvorexant, quazepam, estazolam, flurazepam, triazolam, tasimelteon, ramelteon)
        ii. Alcohol
        iii. Other potentially interacting agents:
            - Benzodiazepines (e.g., diazepam, alprazolam or any not listed in metric 7.a.i.)
            - Sedating antidepressants or antipsychotics, sedating anti epileptics, and sedating antihistamines
            - General anesthetics
            - Muscle relaxants

- Opioid analgesics
- Divalproex sodium or other valproate drug (e.g.,valproic acid)
- Illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB]).

b. Summary tables for both XYWAV and XYREM from REMS Program Patient Counseling Checklists of the number and percentage of patients who have been diagnosed with the following conditions and who subsequently received at least one shipment of drug:
c. Sleep apnea
d. Asthma, COPD, or other conditions affecting the respiratory system.

Health Outcomes and/or Surrogates of Health Outcomes

8. Pharmacovigilance/surveillance (per reporting period)
   a. Separate summary tables for XYWAV and XYREM of the number of reports of serious adverse events. The summary tables will include the following data fields (CIOMS II line listings): date, report ID, report type, notifier, age, gender, indication, start and stop date, dose, frequency, onset date, system organ class, outcome, and causality. All tables should include an overall narrative summary of the adverse events and data fields reported.
      i. All cases of death
         1) Number, percentage, and type of RMRs, notifications, and alerts associated with any reported deaths.
      ii. All outcomes of death, emergency department visits (when admitted to hospital), or hospitalizations resulting from or associated with the following:
         1) Use with concurrent sedative hypnotics and alcohol. Provide a breakdown of concomitant sedative hypnotics usage (ex. zolpidem=6%, eszopiclone=3%)
         2) Intentional misuse
         3) Abuse
         4) Overdose
         5) Medication error
      iii. Cases of sexual abuse
      iv. Proportion of discontinued patients who were associated with a report of a serious adverse event, including death.

Knowledge

9. Knowledge, Attitude, and Behavior (KAB) Surveys of Patients, Caregivers, and Healthcare Providers (to be submitted every other year beginning with the April 2023 assessment)
    a. Assessment of patients'/caregivers' and healthcare providers' understanding of the following:
        i. The risk of significant CNS and respiratory depression associated with XYWAV and XYREM even at recommended doses
        ii. The contraindicated uses of XYWAV and XYREM
        iii. The potential for abuse, misuse, and overdose associated with XYWAV and XYREM
        iv. The safe use, handling, and storage of XYWAV and XYREM
        v. The XYWAV and XYREM REMS Program requirements.
10. Knowledge, Attitude, and Behavior (KAB) Surveys of Pharmacists (to be submitted every other year beginning with the April 2023 assessment)
    a. Assessment of pharmacists' understanding of the following:
        i. The risk of significant CNS and respiratory depression associated with XYWAV and XYREM even at recommended doses
        ii. The contraindicated uses of XYWAV and XYREM
        iii. The potential for abuse, misuse, and overdose associated with XYWAV and XYREM
        iv. The safe use, handling, and storage of XYWAV and XYREM
        v. The XYWAV and XYREM REMS Program requirements.
11. Certified Pharmacy knowledge assessments (per reporting period and cumulatively)
    a. Number of pharmacy staff who completed post-training knowledge assessments including method of completion and the number of attempts needed to complete.
        i. Provide a breakdown of scores within Module A and B
    b. Summary of the most frequently missed post-training knowledge assessment questions
    c. Summary of potential comprehension or perception issues identified with the post-training knowledge assessment by module
    d. Number of pharmacy staff who did not pass the knowledge assessments.

12. The requirements for assessments of an approved REMS under section 505-1 (g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each

element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA ###### REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA ###### REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA ######/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA ######/S-000
PRIOR APPROVAL SUPPLEMENT

PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA ######/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA ######/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA ######

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-*

Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Teresa Wheelous, Regulatory Project Manager, at teresa.wheelous@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Acting Director
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- REMS

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERESA J BURACCHIO on behalf of ERIC P BASTINGS
08/12/2021 01:15:04 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s006

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XYWAV safely and effectively. See full prescribing information for XYWAV.

XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII
Initial U.S. Approval: 2002

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and ABUSE AND MISUSE.
See full prescribing information for complete boxed warning.

Central Nervous System Depression
- **XYWAV is a CNS depressant, and respiratory depression can occur with XYWAV use (5.1, 5.4)**

Abuse and Misuse
- **The active moiety of XYWAV is oxybate or gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death (5.2, 9.2)**

XYWAV is available only through a restricted program called the XYWAV and XYREM REMS (5.3)

----------RECENT MAJOR CHANGES----------

• Boxed Warning	08/2021
• Indications and Usage (1.2)	08/2021
• Dosage and Administration (2.3, 2.4)	08/2021
• Warnings and Precautions (5.5, 5.6, 5.7)	08/2021

----------INDICATIONS AND USAGE----------

XYWAV is a central nervous system depressant indicated for the treatment of:
- Cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy (1.1).
- Idiopathic Hypersomnia (IH) in adults (1.2).

----------DOSAGE AND ADMINISTRATION----------

See Full Prescribing Information for complete dosing instructions (2.1-2.7).

Dosage for Adult Patients with Narcolepsy
- Initiate dosage at 4.5 g per night orally, divided into two doses (2.1).
- Titrate to effect in increments of up to 1.5 g per night per week (2.1).
- Recommended dosage range: 6 g to 9 g per night orally, divided into two doses (2.1).
- 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 (2.1).

Dosage for Pediatric Patients with Narcolepsy (7 Years of Age and Older)
- The recommended starting dosage, titration regimen, and maximum total nightly dosage are based on body weight (2.2).

Dosage for Adult Patients with Idiopathic Hypersomnia
- XYWAV can be administered as a twice or once nightly regimen in adults (2.3).
- Twice nightly: Initiate dosage at 4.5 g or less per night orally, divided into two doses. Titrate to effect in increments of up to 1.5 g per night per week, up to 9 g total nightly dose (2.3).
- Once nightly: Initiate dosage at 3 g or less per night orally, as one dose. Titrate to effect in increments of up to 1.5 g per night per week, up to 6 g total nightly dose (2.3).

Important Administration Information
- Administer XYWAV at least 2 hours after eating (2.4).
- Prepare XYWAV prior to bedtime; dilute with approximately ¼ cup of water in pharmacy-provided containers (2.4).
- Take XYWAV while in bed and lie down after dosing (2.4).

For Patients Transitioning from Xyrem to XYWAV: Initiate at the same dose and regimen as Xyrem (gram for gram). Titrate as needed based on efficacy and tolerability (2.5).

Patients with Hepatic Impairment
Recommended starting dosage is one-half of the original dosage per night administered orally, divided into two doses (2.6).

----------DOSAGE FORMS AND STRENGTHS----------

Oral solution: 0.5 g/mL total salts (equivalent to 0.413 g/mL of oxybate) (3)

----------CONTRAINDICATIONS----------

- In combination with sedative hypnotics or alcohol (4)
- Succinic semialdehyde dehydrogenase deficiency (4)

----------WARNINGS AND PRECAUTIONS----------

- CNS depression: Use caution when considering the concurrent use of XYWAV with other CNS depressants (5.1).
- Caution patients against hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that XYWAV does not affect them adversely (5.1).
- Depression and suicidality: Monitor patients for emergent or increased depression and suicidality (5.5).
- Confusion/Anxiety: Monitor for impaired motor/cognitive function (5.6).
- Parasomnias: Evaluate episodes of sleepwalking (5.7).

----------ADVERSE REACTIONS----------

Most common adverse reactions in adults with narcolepsy or IH (≥5%) were nausea, headache, dizziness, anxiety, insomnia, decreased appetite, hyperhidrosis, vomiting, diarrhea, dry mouth, parasomnia, somnolence, fatigue, and tremor (6.1).

In a pediatric study with sodium oxybate (same active moiety as XYWAV), the most common adverse reactions (≥5%) were nausea, enuresis, vomiting, headache, weight decreased, decreased appetite, dizziness, and sleepwalking (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals, Inc. at 1-800-520-5568, or FDA at 1-800-FDA-1088 or www.fda.gov/Medwatch.

----------DRUG INTERACTIONS----------

- Concomitant use with divalproex sodium: An initial reduction in XYWAV dose of at least 20% is recommended (2.7, 7.2).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Geriatric patients: Monitor for impaired motor and/or cognitive function when taking XYWAV (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 08/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

- **Central Nervous System Depression**
  XYWAV 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 and idiopathic hypersomnia were receiving central nervous system stimulants *[see Clinical Studies (14.1, 14.2, 14.3)]*.

- **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)]*.

1 INDICATIONS AND USAGE

1.1 Narcolepsy

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

1.2 Idiopathic Hypersomnia

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information in Adult Patients with Narcolepsy

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 (see Table 1). Increase the dosage by up to 1.5 g per night per week (e.g., 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. The dosage may be gradually titrated based on efficacy and tolerability. Some patients may achieve better responses with unequal doses at bedtime and 2.5 to 4 hours later. Doses higher than 9 g per night have not been studied and ordinarily should not be administered.

Table 1: Recommended Adult XYWAV Dosage Regimen (g = grams)

If a Patient's Total Nightly Dosage Is:	Take at Bedtime:	Take 2.5 to 4 Hours Later:
4.5 g per night	2.25 g	2.25 g
6 g per night	3 g	3 g
7.5 g per night	3.75 g	3.75 g
9 g per night	4.5 g	4.5 g

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

2.2 Dosing Information in Pediatric Patients with Narcolepsy

For pediatric patients 7 years of age and older, XYWAV is administered orally twice per night. The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight, as specified in Table 2. The dosage may be gradually titrated based on efficacy and tolerability. Doses higher than 9 g per night have not been studied and ordinarily should not be administered.

Table 2: Recommended XYWAV 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 nightly dose of XYWAV may be given at bedtime or after an initial period of sleep.

** If XYWAV 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 nightly doses at bedtime and 2.5 to 4 hours later.

2.3 Dosing Information in Adult Patients with Idiopathic Hypersomnia (IH)

The dosage and regimen of XYWAV should be individualized based on clinical presentation *[see Clinical Studies (14.3)]*.

XYWAV can be administered as a twice nightly or once nightly regimen. The recommended starting dose, titration guidance, and maximum nightly doses appear in Table 3:

Table 3: 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., 2.25 g 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.

The increase in the total nightly dose should not exceed 1.5 g /week. During titration, the dosing regimen may be changed between twice nightly and once nightly, as needed based on efficacy and tolerability *[see Clinical Studies (14.3)]*. Doses higher than 9 g per night or single dose administrations higher than 6 g have not been studied and should not be administered.

2.4 Important Administration Instructions for All Patients

Administer XYWAV at least 2 hours after eating *[see Clinical Pharmacology (12.3)]*. Prepare all doses of XYWAV prior to bedtime. Prior to ingestion, each dose of XYWAV should be diluted with approximately ¼ cup (approximately 60 mL) of water in the empty pharmacy-provided containers. Solutions prepared following dilution should be consumed within 24 hours.

Patients should take each dose of XYWAV while in bed and lie down immediately after dosing, and remain in bed following ingestion of each dose. XYWAV may cause patients to fall asleep abruptly without first feeling drowsy *[see Adverse Reactions (6.2)]*.

Patients will often fall asleep within 5 minutes of taking XYWAV, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night.

If dosing twice nightly, patients may need to set an alarm to awaken for the second dose. If the second dose is missed, that dose should be skipped and XYWAV should not be taken again until the next night. Two XYWAV doses should never be taken at one time.

2.5 Patients Transitioning from Xyrem to XYWAV

On the first night of dosing with XYWAV, initiate treatment at the same dose (gram for gram) and regimen as Xyrem. Titrate as needed based on efficacy and tolerability *[see Dosage and Administration (2.1)]*.

2.6 Dosage Modification in Patients with Hepatic Impairment

The recommended starting dosage in patients with hepatic impairment is one-half of the original dosage per night administered orally, divided into two doses *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.7 Dosage Adjustment with Co-administration of Divalproex Sodium

When initiating divalproex sodium in patients taking a stable dosage of XYWAV, a reduction of the XYWAV dosage by at least 20% is recommended with initial concomitant use *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. When initiating XYWAV in patients already taking divalproex sodium, a lower starting dosage of XYWAV is recommended.

Subsequently, the dosage of XYWAV can be adjusted based on individual clinical response and tolerability.

3 DOSAGE FORMS AND STRENGTHS

XYWAV is a clear to slightly opalescent oral solution at a total salt concentration of 0.5 g per mL. Each mL contains 0.5 g of total salts present as 0.234 g calcium oxybate, 0.096 g magnesium oxybate, 0.13 g potassium oxybate, and 0.04 g sodium oxybate (equivalent to 0.413 g total oxybate).

4 CONTRAINDICATIONS

XYWAV is contraindicated for use in:

- combination with sedative hypnotics *[see Warnings and Precautions (5.1)]*.
- combination with alcohol *[see Warnings and Precautions (5.1, 5.2)]*.
- patients with succinic semialdehyde dehydrogenase deficiency *[see Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Depression

XYWAV is a central nervous system (CNS) depressant. Clinically significant respiratory depression and obtundation has occurred in adult patients taking sodium oxybate (same active moiety as XYWAV) at recommended doses in clinical trials and may occur in patients treated with XYWAV at recommended doses. XYWAV is contraindicated in combination with alcohol and sedative hypnotics. The concurrent use of XYWAV 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 is required, dose reduction or discontinuation of one or more CNS depressants (including XYWAV) should be considered. In addition, if short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with XYWAV should be considered.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that XYWAV does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking XYWAV. Patients should be queried about CNS depression-related events upon initiation of XYWAV therapy and periodically thereafter.

XYWAV is available only through a restricted program under a REMS *[see Warnings and Precautions (5.3)]*.

5.2 Abuse and Misuse

XYWAV is a Schedule III controlled substance. The active moiety of XYWAV 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 reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim). Because illicit use and abuse of GHB have been

reported, healthcare providers should carefully evaluate patients for a history of drug abuse and follow them closely, particularly for signs of misuse or abuse of GHB (including but not limited to increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy) *[see Drug Abuse and Dependence (9.2)]*. If abuse is suspected, treatment with XYWAV should be discontinued.

XYWAV is available only through a restricted program under a REMS *[see Warnings and Precautions (5.3)]*.

5.3 XYWAV and XYREM REMS

XYWAV is available only through a restricted distribution program called the XYWAV and XYREM REMS because of the risks of central nervous system depression, and abuse and misuse *[see Warnings and Precautions (5.1, 5.2)]*.

Notable requirements of the XYWAV and XYREM REMS include the following:

- Healthcare Providers who prescribe XYWAV are specially certified
- XYWAV will be dispensed only by the central pharmacy that is specially certified
- XYWAV will be dispensed and shipped only to patients who are enrolled in the XYWAV and XYREM REMS with documentation of safe use.

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

5.4 Respiratory Depression and Sleep-Disordered Breathing

XYWAV may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses of oxybate and with illicit use of GHB, life-threatening respiratory depression has been reported *[see Overdosage (10)]*.

Increased apnea and reduced oxygenation may occur with XYWAV administration in adult and pediatric patients. A significant increase in the number of central apneas and clinically significant oxygen desaturation may occur in patients with obstructive sleep apnea treated with XYWAV.

In a study assessing the respiratory-depressant effects of Xyrem (same active moiety as XYWAV) at doses up to 9 g per night in 21 adult patients with narcolepsy, no dose-related changes in oxygen saturation were demonstrated in the group as a whole. One of the four patients with preexisting moderate-to-severe sleep apnea had significant worsening of the apnea/hypopnea index during treatment.

In a study assessing the effects of Xyrem 9 g per night in 50 adult patients with obstructive sleep apnea, Xyrem did not increase the severity of sleep-disordered breathing and did not adversely affect the average duration and severity of oxygen desaturation overall. However, there was a significant increase in the number of central apneas in patients taking Xyrem, and clinically significant oxygen desaturation (≤55%) was measured in three patients (6%) after Xyrem administration, with one patient withdrawing from the study and two continuing after single brief instances of desaturation.

During polysomnographic evaluation (PSG), central sleep apnea and oxygen desaturation were observed in pediatric patients with narcolepsy treated with Xyrem.

Prescribers should be aware that increased central apneas and clinically relevant oxygen desaturation events have been observed with sodium oxybate administration in adult and pediatric patients.

In clinical trials of Xyrem in 128 adult patients with narcolepsy, two patients had profound CNS depression, which resolved after supportive respiratory intervention. Two other patients discontinued sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea. In two controlled trials assessing PSG measures in adult patients with narcolepsy, 40 of 477 patients were included with a baseline apnea/hypopnea index of 16 to

67 events per hour, indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a clinically significant worsening of respiratory function, as measured by apnea/hypopnea index and pulse oximetry at doses of 4.5 g to 9 g per night.

Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not on hormone replacement therapy, and among patients with narcolepsy.

5.5 Depression and Suicidality

Depression, and suicidal ideation and behavior can occur in patients treated with XYWAV.

In Study 1 *[see Clinical Studies (14.1)]*, depression and depressed mood were reported in 3% and 4%, respectively, of patients treated with XYWAV. Two patients (1%) discontinued XYWAV because of depression, but in most cases, no change in XYWAV treatment was required.

In Study 2 *[see Clinical Studies (14.3)]*, depression and depressed mood were reported in 1 patient (1%) and in 5 patients (3%), respectively, of patients treated with XYWAV, all of whom continued XYWAV treatment.

In clinical trials of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy (n=781), there were two suicides and two attempted suicides in patients treated with Xyrem, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used Xyrem in conjunction with other drugs. Xyrem was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 patients treated with Xyrem, with four patients (<1%) discontinuing because of depression. In most cases, no change in Xyrem treatment was required. In a clinical trial with Xyrem in pediatric patients with narcolepsy (n=104), one patient experienced suicidal ideation and two patients reported depression while taking Xyrem.

The emergence of depression in patients treated with XYWAV requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking XYWAV.

5.6 Other Behavioral or Psychiatric Adverse Reactions

Other behavioral and psychiatric adverse reactions can occur in patients taking XYWAV.

In Study 1, confusion occurred in 1% of patients treated with XYWAV and anxiety occurred in 5% of patients treated with XYWAV. One patient experienced visual hallucinations and confusion after ingesting approximately 9 grams of XYWAV.

In Study 2, confusion occurred in 3% of patients treated with XYWAV, and anxiety occurred in 16% patients treated with XYWAV. One patient experienced visual hallucinations which led to discontinuation of XYWAV.

Other neuropsychiatric reactions reported in clinical trials of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy and in the postmarketing setting included hallucinations, paranoia, psychosis, aggression, and agitation.

In a pediatric clinical trial with Xyrem in patients with narcolepsy, neuropsychiatric reactions, including acute psychosis, confusion, and anxiety, were reported while taking Xyrem.

The emergence or increase in the occurrence of behavioral or psychiatric events in patients taking XYWAV should be carefully monitored.

5.7 Parasomnias

Parasomnias can occur in patients taking XYWAV.

In Study 1, parasomnias, including sleepwalking, were reported in 6% of patients treated with XYWAV.

In Study 2, parasomnias, including sleepwalking, were reported in 5% of patients treated with XYWAV.

In a clinical trial of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy, five instances of sleepwalking with potential injury or significant injury were reported. Parasomnias, including sleepwalking, also have been reported in a pediatric clinical trial with sodium oxybate and in postmarketing experience with sodium oxybate.

Episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions appear in other sections of the labeling:

- CNS depression *[see Warnings and Precautions (5.1)]*
- Abuse and Misuse *[see Warnings and Precautions (5.2)]*
- Respiratory Depression and Sleep-Disordered Breathing *[see Warnings and Precautions (5.4)]*
- Depression and Suicidality *[see Warnings and Precautions (5.5)]*
- Other Behavioral or Psychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Parasomnias *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adult Patients with Narcolepsy

The safety of XYWAV was evaluated in a 16-week double-blind placebo-controlled randomized-withdrawal study in patients with narcolepsy with cataplexy (Study 1), which was followed by an open-label extension phase lasting 24 weeks *[see Clinical Studies (14.1)]*. Study 1 included an open-label titration period (OL OTTP), a stable-dose period (SDP), and a double-blind, placebo-controlled, randomized-withdrawal period (DB RWP). A total of 201 patients, ages 18 to 70 years, received XYWAV at individually titrated doses for 14 weeks, followed by randomization to XYWAV or matching placebo for 2 weeks of treatment. The mean exposure to XYWAV during this study, including titration, the randomized withdrawal period, and the open-label extension, was 151 days. In patients who remained on treatment, adverse reactions tended to occur early and diminish over time.

Adverse Reactions Leading to Treatment Discontinuation in Study 1

In Study 1, 9 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.

Commonly Observed Adverse Reactions

The most common adverse reactions in Study 1 (incidence ≥5% of XYWAV-treated patients) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting.

Adverse Reactions Occurring at an Incidence of 2% or Greater:

Table 4 lists adverse reactions observed in the open-label titration and stable dose periods of Study 1 that occurred at a frequency of 2% or greater in adult patients treated with XYWAV.

Table 4: Adverse Reactions Occurring in ≥2% of Adult Patients Treated with XYWAV in the Open-Label Titration and Stable Dose Periods in Study 1[*]

Adverse Reaction	Open-Label Titration Period + Stable Dose Period (14 weeks) (N=201) %
Headache	20
Nausea	13
Dizziness	10
Decreased appetite	8
Parasomnia[†]	6
Diarrhea	6
Hyperhidrosis[‡]	6
Anxiety[§]	5
Vomiting	5
Fatigue[¶]	4
Dry mouth	4
Depressed mood	4
Enuresis	4
Irritability	3
Paresthesia	3
Depression	3
Tremor	3
Somnolence	2
Muscle spasms	2

[*]Adverse reactions related to XYWAV were reported less frequently, as an overall incidence, in patients on Xyrem at study entry than in Xyrem-naïve patients.
[†]Includes abnormal dreams, abnormal sleep-related event, rapid eye movements sleep abnormal, sleep paralysis, sleep talking, sleep terror, sleep-related eating disorder, somnambulism
[‡]Includes hyperhidrosis and night sweats
[§]Includes anxiety, agitation, panic attack, tension
[¶]Includes fatigue and asthenia

Pediatric Patients (7 Years of Age and Older) with Narcolepsy

In the pediatric clinical trial with Xyrem (same active moiety as XYWAV), 104 patients aged 7 to 17 years (37 patients aged 7 to 11 years; 67 patients aged 12 to 17 years) with narcolepsy received Xyrem for up to one year *[see Clinical Studies (14.2)]*. This study included

an open-label safety continuation period in which eligible patients received Xyrem for up to an additional 2 years. The median and maximum exposure across the entire study were 371 and 987 days, respectively.

Adverse Reactions Leading to Treatment Discontinuation

In the pediatric clinical trial with Xyrem, 7 of 104 patients reported adverse reactions that led to withdrawal from the study (hallucination, tactile; suicidal ideation; weight decreased; sleep apnea syndrome; affect lability; anger, anxiety, depression; and headache).

Adverse Reactions in the Xyrem Pediatric Clinical Trial

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%).

Additional information regarding safety in pediatric patients appears in the following sections:

- Respiratory Depression and Sleep-Disordered Breathing *[see Warnings and Precautions (5.4)]*
- Depression and Suicidality *[see Warnings and Precautions (5.5)]*
- Other Behavioral or Psychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Parasomnias *[see Warnings and Precautions (5.7)]*

The overall adverse reaction profile of Xyrem in the pediatric clinical trial was similar to that seen in the adult clinical trial program. The safety profile in pediatric patients with XYWAV is expected to be similar to that of adult patients treated with XYWAV and to that of pediatric patients treated with Xyrem.

Adult Patients with Idiopathic Hypersomnia

The safety of XYWAV was evaluated in a double-blind placebo-controlled randomized-withdrawal study in patients with IH (Study 2). This study consisted of an open-label titration period (OL OTTP) up to 14 weeks, a stable-dose period (SDP) for 2 weeks, a double-blind, placebo-controlled, randomized-withdrawal period (DB RWP) for 2 weeks, and an open-label extension period for 24 weeks (all study periods up to 42 weeks) *[see Clinical Studies (14.3)]*. The study was conducted in 154 adult male and female patients ages 19 to 75 years of age with IH. The mean exposure to XYWAV during this study, including titration, the randomized withdrawal period, and the open-label extension, was 204 days. In patients who remained on treatment, adverse reactions tended to occur early and diminish over time.

Adverse Reactions Leading to Treatment Discontinuation in Study 2

In Study 2, across all study periods (excluding placebo during the DB RWP) (up to 42 weeks), 17 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, paresthesia, 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.

Commonly Observed Adverse Reactions

The most common adverse reactions in Study 2 (incidence ≥5% of XYWAV-treated patients) in addition to those observed in Study 1 as most common were insomnia, dry mouth, fatigue, somnolence, and tremor.

The safety profile observed in Study 2 was similar to that of Study 1. Adverse reactions occurring in ≥2% of patients treated with XYWAV in the open-label titration and stable dose periods in Study 2 are shown in Table 5:

Table 5: Adverse Reactions Occurring in ≥2% of Patients Treated with XYWAV in the Open-Label Titration and Stable Dose Periods in Study 2

Adverse Reaction	**Open-Label Titration Period + Stable Dose Period (up to 16 weeks) (N=154) %**
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
Balance disorder[♠]	3
Muscle spasms	3
Fall	3
Paresthesia	3
Snoring	3
Weight decreased	3
Bruxism	3
Confusional state	3
Depressed mood	3
Feeling drunk	3
Irritability	3

Table 5: Adverse Reactions Occurring in ≥2% of Patients Treated with XYWAV in the Open-Label Titration and Stable Dose Periods in Study 2

Adverse Reaction	Open-Label Titration Period + Stable Dose Period (up to 16 weeks) (N=154) %

[*]includes anxiety, nervousness, and panic attack
[†]includes middle insomnia, initial insomnia, insomnia, and terminal insomnia
[‡] includes hyperhidrosis and night sweats
[§] includes fatigue and asthenia
[¶]includes somnolence and sedation
[#] includes confusional arousal, sleep paralysis, nightmare, sleep talking, somnambulism, and hypnopompic hallucination
[♠]includes balance disorder and ataxia

Additional Adverse Reactions

Adverse reactions observed in clinical studies with Xyrem (≥2%), but not observed in Study 1 or Study 2 at a frequency of higher than 2%, and which may be relevant for XYWAV:

Pain, pain in extremity, cataplexy, disturbance in attention, sleep paralysis, and disorientation.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sodium oxybate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Arthralgia, fall*, fluid retention, hangover, hypersensitivity, hypertension, memory impairment, nocturia, and vision blurred.

*The sudden onset of sleep in patients taking sodium oxybate, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization.

7 DRUG INTERACTIONS

7.1 Alcohol, Sedative Hypnotics, and CNS Depressants

XYWAV is contraindicated for use in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of XYWAV *[see Warnings and Precautions (5.1)]*.

7.2 Divalproex Sodium

Concomitant use of sodium oxybate with divalproex sodium results in an increase in systemic exposure to GHB, which was shown to cause a greater impairment on some tests of attention and working memory in a clinical study *[see Clinical Pharmacology (12.3)]*. A similar increase in exposure is expected with concomitant use of XYWAV and divalproex sodium; therefore, an initial dose reduction of XYWAV is recommended when used concomitantly with divalproex sodium *[see Dosage and Administration (2.7)]*. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of XYWAV and divalproex sodium is warranted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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 (0, 150, 350, or 1,000 mg/kg/day) or rabbits (0, 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 *[see Data]*.

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.

Clinical Considerations

Labor or Delivery

XYWAV has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate, newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid, and 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.

Data

Animal Data

Oral administration of sodium oxybate to pregnant rats (0, 150, 350, or 1,000 mg/kg/day) or rabbits (0, 300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity. The highest doses of sodium oxybate tested in rats and rabbits were approximately 1 and 3 times, respectively, the maximum recommended human dose (MRHD) of 9 g per night on a body surface area (mg/m^2) basis.

Additionally, oral administration of sodium oxybate (0, 150, 350, or 1,000 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and body weight gain at the highest dose tested. The no-effect dose for pre- and post-natal developmental toxicity in rats is less than the MRHD on a mg/m^2 basis.

8.2 Lactation

Risk Summary

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 and any potential adverse effects on the breastfed infant from XYWAV or from the underlying maternal condition.

8.4 Pediatric Use

Narcolepsy

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 *[see Adverse Reactions (6.1) and Clinical Studies (14.1, 14.2)]*.

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; depression; suicidal ideation; neuropsychiatric reactions including acute psychosis, confusion, and anxiety; and parasomnias, including sleepwalking, have been reported *[see Warnings and Precautions (5.4, 5.5, 5.6, 5.7) and Adverse Reactions (6.1)]*.

Safety and effectiveness of XYWAV for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients below the age of 7 years have not been established.

Idiopathic Hypersomnia

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

Juvenile Animal Toxicity Data

In a study in which sodium oxybate (0, 100, 300, or 900 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 21 through 90), mortality was observed at the two highest doses tested. Deaths occurred during the first week of dosing and were associated with clinical signs (including decreased activity and respiratory rate) consistent with the pharmacological effects of the drug. Reduced body weight gain in males and females and delayed sexual maturation in males were observed at the highest dose tested. The no-effect dose for adverse effects in juvenile rats is associated with plasma exposures (AUC) less than that at the maximum recommended human dose (9 g/night).

8.5 Geriatric Use

Clinical studies of XYWAV or Xyrem in patients with narcolepsy or IH did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

In clinical studies of sodium oxybate in another population, 39 (5%) of 874 patients were 65 years or older. Discontinuations of treatment due to adverse reactions were increased in the elderly compared to younger adults (21% vs. 19%). Frequency of headaches was markedly increased in the elderly (39% vs. 19%). The most common adverse reactions were similar in both age categories. 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 or other drug therapy.

8.6 Hepatic Impairment

Because of an increase in exposure to XYWAV, the starting dose should be reduced by half in patients with hepatic impairment *[see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

XYWAV is a Schedule III controlled substance under the Federal Controlled Substances Act. Non-medical use of XYWAV could lead to penalties assessed under the higher Schedule I controls.

9.2 Abuse

The active moiety of XYWAV, oxybate, produces dose-dependent central nervous system effects, including hypnotic and positive subjective reinforcing effects. The onset of effect is rapid, enhancing its potential for abuse or misuse.

Drug abuse is the intentional non-therapeutic use of a drug product or substance, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug misuse and abuse may occur with or without progression to addiction. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).

Illicit GHB is abused in social settings primarily by young adults. Some of the doses estimated to be abused are in a similar dosage range to that used for treatment of patients with cataplexy. GHB has some commonalities with ethanol over a limited dose range, and some cross tolerance with ethanol has been reported as well. Cases of severe dependence and craving for GHB have been reported when the drug is taken around the clock. Patterns of abuse indicative of dependence include: 1) the use of increasingly large doses, 2) increased frequency of use, and 3) continued use despite adverse consequences.

Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy). Dispose of XYWAV according to state and federal regulations. It is safe to dispose of XYWAV down the sanitary sewer.

9.3 Dependence

Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the recommended dosage range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required. In the clinical trial experience with Xyrem in narcolepsy/cataplexy patients at recommended doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time. In the XYWAV clinical trial in adult narcolepsy/cataplexy patients at recommended doses, one patient reported insomnia following abrupt discontinuation of XYWAV. In the XYWAV clinical trial in adult idiopathic hypersomnia patients at recommended doses, six patients reported insomnia, two patients reported early insomnia, and

one patient reported visual and auditory hallucinations following abrupt discontinuation of XYWAV.

Tolerance

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to XYWAV has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended XYWAV dosage regimen. Clinical studies of sodium oxybate in the treatment of alcohol withdrawal suggest a potential cross-tolerance with alcohol. The safety and effectiveness of XYWAV in the treatment of alcohol withdrawal have not been established.

10 OVERDOSAGE

10.1 Human Experience

Information regarding overdose with XYWAV is derived largely from reports in the medical literature that describe symptoms and signs in individuals who have ingested GHB illicitly. In these circumstances the co-ingestion of other drugs and alcohol was common, and may have influenced the presentation and severity of clinical manifestations of overdose.

In adult clinical trials with Xyrem (same active moiety as XYWAV), two cases of overdose were reported. In the first case, an estimated dose of 150 g, more than 15 times the maximum recommended dose, caused a patient to be unresponsive with brief periods of apnea and to be incontinent of urine and feces. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of Xyrem and numerous other drugs. No cases of overdose (greater than 9 g) with XYWAV were reported in the XYWAV clinical trials.

10.2 Signs and Symptoms

Information about signs and symptoms associated with overdosage with XYWAV derives from reports of illicit use of GHB. Patient presentation following overdose is influenced by the dose ingested, the time since ingestion, the co-ingestion of other drugs and alcohol, and the fed or fasted state. Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even when obtunded), diaphoresis, headache, and impaired psychomotor skills have been observed. No typical pupillary changes have been described to assist in diagnosis; pupillary reactivity to light is maintained. Blurred vision has been reported. An increasing depth of coma has been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported. Respiration may be unaffected or compromised in rate and depth. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact.

10.3 Recommended Treatment of Overdose

General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with GHB overdose has been responsive to atropine intravenous administration. No reversal of the central depressant

effects of XYWAV can be expected from naloxone or flumazenil administration. The use of hemodialysis and other forms of extracorporeal drug removal have not been studied in GHB overdose. However, due to the rapid metabolism of oxybate, these measures are not warranted.

10.4 Poison Control Center

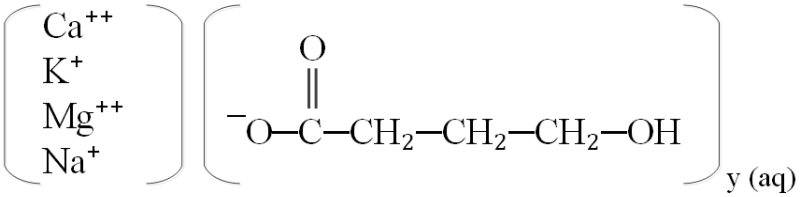
As with the management of all cases of drug overdosage, the possibility of multiple drug ingestion should be considered. The healthcare provider is encouraged to collect urine and blood samples for routine toxicologic screening, and to consult with a regional poison control center (1-800-222-1222) for current treatment recommendations.

11 DESCRIPTION

XYWAV oral solution contains oxybate, a CNS depressant. The chemical name of oxybate is gamma-hydroxybutyrate (GHB). XYWAV contains a mixture of calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate equivalent to 0.5 g/mL, which corresponds to 0.413 g/mL oxybate.

Each mL of XYWAV contains: 0.234 g calcium oxybate, $Ca(C_4H_7O_3)_2$; 0.096 g magnesium oxybate, $Mg(C_4H_7O_3)_2$; 0.13 g potassium oxybate, $K(C_4H_7O_3)$; and 0.04 g sodium oxybate, $Na(C_4H_7O_3)$ in dissociated form in the solution. The molecular weights of each are as follows: calcium oxybate is 246.3, magnesium oxybate is 230.5, potassium oxybate is 142.2, and sodium oxybate is 126.1.

The chemical structure is:



y=1 for Na^+ and K^+; *y*=2 for Mg^{2+} and Ca^{2+}

The inactive ingredients are purified water and sucralose.

XYWAV contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

XYWAV is a CNS depressant. The exact mechanism of action of XYWAV in the treatment of narcolepsy and idiopathic hypersomnia is unknown. XYWAV is a mixture of calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate (gamma-hydroxybutyrate). Gamma-hydroxybutyrate (GHB) is an endogenous compound and metabolite of the neurotransmitter GABA. It is hypothesized that the therapeutic effects of XYWAV are mediated through $GABA_B$ actions during sleep at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.

12.3 Pharmacokinetics

Pharmacokinetics of GHB are nonlinear and are similar following single or repeat dosing. The pharmacokinetics of oxybate following administration of XYWAV are similar between healthy subjects and patients with narcolepsy or patients with idiopathic hypersomnia.

Absorption

Following oral administration of XYWAV, the average time to peak plasma concentration (T_{max}) was about 1.3 hours in healthy adults in the fasted state.

Following oral administration of XYWAV, the plasma levels of GHB increased more than dose-proportionally, with C_{max} increasing approximately 2-fold and AUC increasing 2.9-fold as the dose was doubled from 2.25 g to 4.5 g.

Effect of Food

Administration of XYWAV immediately after a high-fat meal resulted in a mean reduction in C_{max} of GHB by 33%, and mean reduction in systemic exposure (AUC) by 16% *[see Dosage and Administration (2.4)]*.

Distribution

GHB has an apparent volume of distribution averaging 190 mL/kg to 384 mL/kg. At GHB concentrations ranging from 3 mcg/mL to 300 mcg/mL. Less than 1% is bound to plasma proteins.

Elimination

Metabolism

Animal studies indicate that metabolism is the major elimination pathway for GHB, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. The primary pathway involves a cytosolic $NADP^+$-linked enzyme, GHB dehydrogenase, that catalyzes the conversion of GHB to succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle where it is metabolized to carbon dioxide and water. A second mitochondrial oxidoreductase enzyme, a transhydrogenase, also catalyzes the conversion to succinic semialdehyde in the presence of α-ketoglutarate. An alternate pathway of biotransformation involves β-oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

Excretion

The clearance of GHB is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible. GHB has a mean terminal elimination half-life of 0.66 hours.

Specific Populations

Geriatric Patients

There is limited experience with sodium oxybate and no experience with XYWAV in the elderly. Results from a pharmacokinetic study (n=20) in another studied population indicate that the pharmacokinetic characteristics of GHB are consistent among younger (ages 48 to 64 years) and older (ages 65 to 75 years) adults.

Pediatric Patients

The pharmacokinetics of XYWAV has not been directly evaluated in pediatric patients.

The pharmacokinetics of sodium oxybate was evaluated in pediatric patients aged 7 to 17 years and demonstrated similar PK properties as adults. A population pharmacokinetic model was developed with sodium oxybate data from pediatric and adult patients and healthy volunteers and with XYWAV data from healthy adult volunteers. The population PK model analyses demonstrate that body weight is the major intrinsic factor affecting GHB pharmacokinetics following sodium oxybate or XYWAV dosing. Additionally, XYWAV has

similar PK characteristics (more than dose proportionality) as sodium oxybate in pediatric patients, supporting the same dose regimen as sodium oxybate and 1-to-1 dose switch from sodium oxybate to XYWAV in pediatric patients.

Male and Female Patients

In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of GHB following a single Xyrem oral dose of 4.5 g.

Racial or Ethnic Groups

There are insufficient data to evaluate any pharmacokinetic differences among races.

Patients with Renal Impairment

No pharmacokinetic study in patients with renal impairment has been conducted.

Patients with Hepatic Impairment

The pharmacokinetics of GHB in 16 cirrhotic patients, half without ascites (Child's Class A) and half with ascites (Child's Class C), were compared to the kinetics in 8 subjects with normal hepatic function after a single sodium oxybate oral dose of 25 mg/kg. AUC values were double in the cirrhotic patients, with apparent oral clearance reduced from 9.1 mL/min/kg in healthy adults to 4.5 and 4.1 mL/min/kg in Class A and Class C patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control patients (mean $t_{1/2}$ of 59 and 32 minutes, respectively, versus 22 minutes). The starting dose of XYWAV should be reduced in patients with hepatic impairment *[see Dosage and Administration (2.6) and Use in Specific Populations (8.6)]*.

Drug Interactions Studies

Studies *in vitro* with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A up to the concentration of 3 mM (378 mcg/mL), a level considerably higher than levels achieved with recommended doses.

Drug interaction studies in healthy adults (age 18 to 50 years) were conducted with sodium oxybate and divalproex sodium, diclofenac, and ibuprofen.

- Divalproex sodium: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with divalproex sodium (valproic acid, 1250 mg per day) increased mean systemic exposure to GHB as shown by AUC by approximately 25% (AUC ratio range of 0.8 to 1.7), while C_{max} was comparable. Co-administration did not appear to affect the pharmacokinetics of valproic acid. A greater impairment on some tests of attention and working memory was observed with co-administration of both drugs than with either drug alone *[see Drug Interactions (7.2) and Dosage and Administration (2.7)]*.
- Diclofenac: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with diclofenac (50 mg/dose twice per day) showed no significant differences in systemic exposure to GHB. Co-administration did not appear to affect the pharmacokinetics of diclofenac.
- Ibuprofen: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with ibuprofen (800 mg/dose four times per day also dosed four hours apart) resulted in comparable systemic exposure to GHB as shown by plasma C_{max} and AUC values. Co-administration did not affect the pharmacokinetics of ibuprofen.

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. Also, there were no pharmacokinetic interactions with the alcohol dehydrogenase inhibitor fomepizole. However, pharmacodynamic interactions with these drugs cannot be ruled out. Alteration of gastric pH with omeprazole produced no significant change in the pharmacokinetics of GHB. In addition, drug interaction studies in healthy adults demonstrated no pharmacokinetic or clinically significant pharmacodynamic interactions between sodium oxybate and duloxetine HCl.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Administration of sodium oxybate to rats at oral doses of up to 1,000 mg/kg/day for 83 (males) or 104 (females) weeks resulted in no increase in tumors. Plasma exposure (AUC) at the highest dose tested was 2 times that in humans at the maximum recommended human dose (MRHD) of 9 g per night.

The results of 2-year carcinogenicity studies in mouse and rat with gamma-butyrolactone, a compound that is metabolized to oxybate *in vivo,* showed no clear evidence of carcinogenic activity. The plasma AUCs of oxybate achieved at the highest doses tested in these studies were less than that in humans at the MRHD.

Mutagenesis

Sodium oxybate was negative in the *in vitro* bacterial gene mutation assay, an *in vitro* chromosomal aberration assay in mammalian cells, and in an *in vivo* rat micronucleus assay.

Impairment of Fertility

Oral administration of sodium oxybate (0, 150, 350, or 1,000 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females through early gestation resulted in no adverse effects on fertility. The highest dose tested is approximately equal to the MRHD on a mg/m^2 basis.

14 CLINICAL STUDIES

14.1 Cataplexy and Excessive Daytime Sleepiness (EDS) in Adult Narcolepsy

Efficacy of XYWAV for the treatment of cataplexy and excessive daytime sleepiness in adult patients with narcolepsy was established in a double-blind, placebo-controlled, randomized-withdrawal study (Study 1; NCT03030599). This study had two parts, consisting of the main study, followed by an optional 24-week open-label extension (OLE). The main study consisted of a 12-week open-label optimized treatment and titration period (OL OTTP), followed by a 2-week stable-dose period (SDP), and finally a 2-week double-blind randomized-withdrawal period (DB RWP).

Study 1 enrolled 201 patients with narcolepsy with cataplexy, 18 to 70 years of age, with a baseline history of at least 14 cataplexy attacks in a typical 2-week period prior to any treatment for narcolepsy symptoms. Of the 201 patients, 134 were randomized 1:1 to continue treatment with XYWAV or to placebo in the 2-week DB RWP. In the safety population, overall, the median age was 36.0 years (range: 18 to 70). The majority of subjects were female (61%), and most were white (88%) and not Hispanic or Latino (84%).

Patients entering the study were taking a stable dosage of 1) Xyrem only, 2) Xyrem + another anticataplectic, 3) a non-Xyrem anticataplectic, or 4) were cataplexy-treatment naïve. Patients taking Xyrem at study entry were switched (at a gram for gram dose) from Xyrem to XYWAV for a minimum of 2 weeks and titrated, if needed, to a stable, tolerable, and effective dosage over 8 weeks. Most patients who switched from Xyrem to XYWAV (41/59; 69%) had no

change in dosage from study entry to the stable dose period; 27% (16/59) had an increase in dosage, and 3% (2/59) had a decrease in dosage. Among patients whose dosage was changed, most changes were within one titration step (≤1.5 g). Patients not taking Xyrem at study entry were initiated at 4.5 g/night of XYWAV and titrated at a rate of 1 or 1.5 g/night/week to a tolerable dose of XYWAV. Patients taking an anticataplectic other than Xyrem were tapered off the non-Xyrem anticataplectic over 2 to 8 weeks. All patients continued to receive XYWAV only, for the treatment of cataplexy during the last 2 weeks of the OL OTTP.

CNS stimulants were allowed at entry, and approximately 59% of patients continued taking a stable dose of stimulant throughout the SDP and DB RWP.

The total nightly dose of XYWAV was administered in two equally divided doses in 90% (62/69) of patients. Unequal doses were administered in 10% (7/69) of patients treated with XYWAV.

The primary efficacy endpoint was the change in frequency of cataplexy attacks from the 2 weeks of the SDP to the 2 weeks of the DB RWP. The key secondary endpoint was the change in the Epworth Sleepiness Scale (ESS) score, as a measure of reduction in EDS from the end of the SDP to the end of the DB RWP.

Patients taking stable doses of XYWAV who discontinued XYWAV treatment and were randomized to placebo during the DB RWP experienced a significant worsening in the average weekly number of cataplexy attacks and in ESS score, compared with patients randomized to continue treatment with XYWAV (see Table 6).

Table 6: Mean and Median Number of Weekly Cataplexy Attacks and Epworth Sleepiness Scale (ESS)

	Average Weekly Number of Cataplexy Attacks		**ESS SCORE**	
	Placebo (N=65)	**XYWAV (N=69)**	**Placebo (N=65)**	**XYWAV (N=69)**
Baseline (2 Weeks of the Stable Dose Period)				
Mean (SD)	7.2 (14.4)	8.9 (16.8)	12.6 (5.5)	13.6 (5.3)
Median	1.0	1.1	13.0	14.0
Change from Baseline (2 Weeks of the Stable Dose Period) to the 2 Weeks of the DB RWP			**Change from End of Stable Dose Period to End of DB RWP**	
Mean (SD)	11.5 (24.8)	0.1 (5.8)	3.0 (4.7)	0.0 (2.9)
Median	2.4	0.0	2.0	0.0
p-value	<0.0001		<0.0001	

DB RWP=Double-blind Randomized-withdrawal Period; SD=standard deviation

14.2 Cataplexy and Excessive Daytime Sleepiness in Pediatric Narcolepsy

The effectiveness of XYWAV in pediatric patients is based upon a clinical study in patients treated with Xyrem, as described below, and additional pharmacokinetic information *[see Use in Specific Populations (8.4)]*.

The effectiveness of Xyrem in the treatment of cataplexy and excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy was established in a double-blind, placebo-controlled, randomized-withdrawal study (NCT02221869). The study was conducted in 106 pediatric patients (median age: 12 years; range: 7 to 17 years) with a baseline history of at least 14 cataplexy attacks in a typical 2-week period prior to any treatment for narcolepsy symptoms. Of the 106 patients, 2 did not receive study drug and 63 patients were randomized 1:1

either to continued treatment with Xyrem or to placebo. Randomization to placebo was stopped early as the efficacy criterion was met at the pre-planned interim analysis.

Patients entered the study either taking a stable dosage of Xyrem or were Xyrem-naïve. CNS stimulants were allowed at entry, and approximately 50% of patients continued taking a stable dose of stimulant throughout the stable-dose and double-blind periods. Xyrem-naïve patients were initiated and titrated based on body weight over a period of up to 10 weeks. The total nightly dose was administered in two divided doses, with the first dose given at nighttime and the second given 2.5 to 4 hours later *[see Dosage and Administration (2.2)]*. Once a stable dosage of Xyrem had been achieved, these patients entered the 2-week stable-dose period; patients on a stable dosage of Xyrem at study entry remained on this dosage for 3 weeks prior to randomization. Efficacy was established at dosages ranging from 3 g to 9 g of Xyrem per night.

The primary efficacy measure was the change in frequency of cataplexy attacks. In addition, change in cataplexy severity was evaluated with the Clinical Global Impression of Change for cataplexy severity. The efficacy of Xyrem in the treatment of excessive daytime sleepiness in pediatric patients with narcolepsy was evaluated with the change in the Epworth Sleepiness Scale (Child and Adolescent) score. The Epworth Sleepiness Scale (Child and Adolescent) is a modified version of the scale used in the adult clinical trial described above. The overall change in narcolepsy condition was assessed by the Clinical Global Impression of Change for narcolepsy overall. Efficacy was assessed during or at the end of the 2-week double-blind treatment period, relative to the last 2 weeks or end of the stable-dose period (see Tables 7 and 8).

Pediatric patients taking stable dosages of Xyrem who discontinued Xyrem treatment and were randomized to placebo during the double-blind treatment period experienced a statistically significant increase in weekly cataplexy attacks compared with patients who were randomized to continue treatment with Xyrem. Patients randomized to receive placebo during the double-blind treatment period experienced a statistically significant worsening of EDS compared with patients randomized to continue receiving Xyrem (see Table 7).

Table 7: Number of Weekly Cataplexy Attacks and Epworth Sleepiness Scale (Child and Adolescent) Score

Treatment Group	Baseline[*,†]	Double-blind Treatment Period[‡,§]	Median Change from Baseline	Comparison to Placebo (p-value[¶])
Median Number of Cataplexy Attacks (attacks/week)				
Placebo (n=32)	4.7	21.3	12.7	-
Xyrem (n=31)	3.5	3.8	0.3	<0.0001
Median Epworth Sleepiness Scale (Child and Adolescent) Score				
Placebo (n=31**)	11	12	3	-
Xyrem (n=30**)	8	9	0	0.0004

[*] For weekly number of cataplexy attacks, baseline value is calculated from the last 14 days of the stable-dose period.
[†] For Epworth Sleepiness Scale score, baseline value is collected at the end of stable-dose period.
[‡] Weekly number of cataplexy attacks is calculated from all days within the double-blind treatment period.
[§] For Epworth Sleepiness Scale, value is collected at the end of the double-blind treatment period.
[¶] P-value from rank-based analysis of covariance (ANCOVA) with treatment as a factor and rank baseline value as a covariate.
** One patient in each of the treatment groups did not have baseline ESS score available and were not included in this analysis.

Patients randomized to receive placebo during the double-blind treatment period experienced a statistically significant worsening of cataplexy severity and narcolepsy overall according to the clinician's assessment compared with patients randomized to continue receiving Xyrem (see Table 8).

Table 8: Clinical Global Impression of Change (CGIc) for Cataplexy Severity and Narcolepsy Overall

	CGIc Cataplexy Severity*		CGIc Narcolepsy Overall*	
Worsened, %†	Placebo (n=32)	Xyrem (n=29) ‡	Placebo (n=32)	Xyrem (n=29) ‡
Much worse or very much worse	66%	17%	59%	10%
p-value§	0.0001		<0.0001	

* Responses indicate change of severity or symptoms relative to receiving Xyrem treatment at baseline.
† Percentages based on total number of observed values.
‡ Two patients randomized to Xyrem did not have the CGIc assessments completed and were excluded from the analysis.
§ P-value from Pearson's chi-square test.

14.3 Idiopathic Hypersomnia (IH) in Adults

Efficacy of XYWAV for the treatment of IH in adult patients as a once or twice nightly regimen was established in a double-blind, placebo-controlled, randomized-withdrawal, study (Study 2, NCT03533114). Study 2 consisted of a minimum of 10-week open-label treatment titration and optimization period (OL OTTP), (with up to 4 additional weeks) to allow for an optimally effective and tolerable dose and regimen followed by a 2-week stable dose period (SDP), a 2-week double-blind, randomized withdrawal period (DB RWP), and a 24-week open label safety extension period (OLE).

Study 2 enrolled 154 patients with idiopathic hypersomnia, 19 to 75 years of age. Of the 154 patients, 115 were evaluable for efficacy data and were randomized 1:1 to continue treatment with XYWAV or to placebo in the 2-week DB RWP. In the safety population, overall, the median age was 39 years (range: 19 to 75). At baseline, 2% of patients were taking Xyrem only, 4% of patients were taking Xyrem and an additional stimulant or alerting agent, 54% of patients were not currently taking Xyrem but were taking a stimulant or alerting agent, and 41% were treatment naïve. CNS stimulants were allowed at entry, and approximately 57% of patients continued taking a stable dose of stimulant throughout the SDP and DB RWP.

The majority of subjects were female (71%), and most were white (81%) and not Hispanic or Latino (79%).

The XYWAV dosing regimen was initiated at the discretion of the investigator according to clinical presentation. Patients were considered for XYWAV once nightly if they reported difficulty awakening as a result of sleep inertia or long sleep time. Patients were considered for twice nightly dosing if they reported disrupted nighttime sleep or difficulty with sleep maintenance. For twice nightly regimens, doses were divided equally or unequally, with the first dose administered at bedtime and the second dose administered 2.5 to 4 hours later.

Based on clinical response during the OTTP, investigators were permitted to switch patients between twice nightly and once nightly dosing regimens. When patients were switched from a twice nightly to a once nightly dosing regimen, the total nightly dose was initially the same as the first dose of the twice nightly dosing regimen. When patients were switched from a once nightly to a twice nightly dosing regimen, the total nightly dose was no more than 1.5 g higher than the current dose, divided into two doses.

At the start of the DB RWP, 23% (27/115) of patients were taking XYWAV once nightly (median nightly dose 4.5 g), and 77% (88/115) of patients were taking XYWAV twice nightly (median nightly dose 7.5 g). There were no meaningful differences in demographics, baseline characteristics or disease severity between patients receiving XYWAV once nightly vs twice nightly.

The primary efficacy endpoint was the change in Epworth Sleepiness Scale (ESS) score, as a measure of reduction in EDS from the end of the SDP to the end of the DB RWP. The ESS is an 8-item self-reported questionnaire by which patients rate their perceived likelihood of falling asleep during usual daily life activities. Each of the 8 items on the ESS is rated from 0 (would never doze) to 3 (high chance of dozing), with a maximum score of 24. Key secondary efficacy endpoints included patient global impression of change (PGIc) and the Idiopathic Hypersomnia Severity Scale (IHSS), both assessed as a change from the end of the SDP to the end of the DB RWP. The IHSS is a 14-item self-reported questionnaire assessing the severity of IH symptoms of excessive sleepiness, prolonged sleep duration, cognitive impairment, and sleep inertia. Total scores can range from 0-50, with higher scores indicating a greater severity or frequency of symptoms.

Change in ESS

Patients in Study 2 taking stable doses of XYWAV who were withdrawn from XYWAV treatment and randomized to placebo during DB RWP experienced significant worsening in ESS score compared with patients randomized to continue treatment with XYWAV ($p<0.0001$) across all dosing regimens (see Table 9). These two treatment groups had comparable median ESS scores (Placebo=17; XYWAV=16) at entry into the OTTP.

Table 9: Median Change in Epworth Sleepiness Scale (ESS)

ESS Score		
	Placebo (N=59)	**XYWAV (N=56)**
Baseline End of 2-Week SDP		
Median	5.0	6.5
End of 2-Week DB RWP		
Median	14.0	7.0
Median Change from End of 2-Week SDP to End of 2-Week DB RWP		
Median	8.0	0.0
p-value	<0.0001	

SDP=Stable Dose Period
DB RWP=Double-blind Randomized-withdrawal Period

PGIc

Patient Global Impression of change (PGIc) ratings showed that patients randomized to placebo experienced a worsening of symptoms of idiopathic hypersomnia overall compared with patients randomized to XYWAV (Table 10). The percentage of patients with worsening PGIc scores for IH overall (defined as scores of Minimally, Much Worse, or Very Much Worse) was

greater for patients receiving placebo (88.1%) compared with patients receiving XYWAV (21.4%) (p<0.0001).

Table 10: PGIc* at End of the DB RWP†

	PGIc* IH Overall	
Worsened,% ‡†	**Placebo (N=59) n (%)**	**XYWAV (N=56) n (%)**
Proportion Worsened (minimally, much, or very much worse)	52 (88.1)	12 (21.4)
p-value	<0.0001	n/a

*PGIc is a 7-point patient-reported scale by which patients rated their symptom change from "very much improved" to "very much worse."
†DB RWP=Double-blind Randomized-withdrawal Period
‡At the end of the DB RWP/early termination visit, patients rated the change in their condition since the end of the Open-Label Stable-Dose Period.

IHSS

At end of DB RWP, patients randomized to placebo experienced a worsening in IHSS total score, compared to patients randomized to XYWAV (p<0.0001) (see Table 11). These two treatment groups had comparable median IHSS scores (Placebo=33; XYWAV=33) at entry into the OTTP.

Table 11: Median Changes in IHSS Total Score

Total Score		
	Placebo (N=59)	**XYWAV (N=56)**
Baseline End of 2-Week SDP		
Median	14.0	14.0
End of 2-Week DB RWP		
Median	29.0	16.0
Median Change from End of 2-Week SDP to End of 2-Week DB RWP		
Median	14.0	0.0
p-value	<0.0001	

SDP=Stable Dose Period
DB RWP=Double-blind Randomized-withdrawal Period

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

XYWAV is a clear to slightly opalescent oral solution. Each prescription includes at least one bottle of XYWAV with attached press in bottle adaptor, an oral measuring device (plastic syringe), and a Medication Guide. The pharmacy provides two empty containers with child-resistant caps with each XYWAV shipment.

Each amber bottle contains XYWAV oral solution at a concentration of 0.5 g/mL and has a child-resistant cap.

One 180 mL bottle: NDC 68727-150-01

16.2 Storage

Keep out of reach of children.

XYWAV should be stored between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) (see USP Controlled Room Temperature).

Dispense in tight containers.

Solutions prepared following dilution should be consumed within 24 hours.

16.3 Handling and Disposal

XYWAV is a Schedule III drug under the Controlled Substances Act. XYWAV should be handled according to state and federal regulations. It is safe to dispose of XYWAV down the sanitary sewer.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Central Nervous System Depression

Inform patients and/or caregivers that XYWAV can cause central nervous system depression, including respiratory depression, hypotension, profound sedation, syncope, and death. Instruct patients not to engage in activities requiring mental alertness or motor coordination, including operating hazardous machinery, for at least 6 hours after taking XYWAV. Instruct patients and/or their caregivers to inform their healthcare providers of all the medications they take *[see Warnings and Precautions (5.1)]*.

Abuse and Misuse

Inform patients and/or caregivers that the active ingredient of XYWAV is gamma-hydroxybutyrate (GHB), which is associated with serious adverse reactions with illicit use and abuse *[see Warnings and Precautions (5.2)]*.

XYWAV and XYREM REMS

XYWAV is available only through a restricted program called the XYWAV and XYREM REMS *[see Warnings and Precautions (5.3)]*. Inform the patient and/or caregiver of the following notable requirements:

- XYWAV is dispensed only by the central pharmacy
- XYWAV will be dispensed and shipped only to patients enrolled in the XYWAV and XYREM REMS

XYWAV is available only from the central pharmacy participating in the program. Therefore, provide patients and/or caregivers with the telephone number and website for information on how to obtain the product.

Alcohol or Sedative Hypnotics

Advise patients and/or caregivers that alcohol and other sedative hypnotics should not be taken with XYWAV *[see Contraindications (4)]*.

Sedation

Inform patients and/or caregivers that the patient is likely to fall asleep quickly after taking XYWAV (often within 5 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 complicated by injuries, in some cases requiring hospitalization *[see Adverse Reactions (6.2)]*. Instruct patients and/or caregivers that the patient should remain in bed following ingestion of each dose. Instruct patients and/or caregivers that the patient should

not take a subsequent nightly dose until at least 2.5 to 4 hours after the previous dose *[see Dosage and Administration (2.4)]*.

Administration Instructions

Inform patients to administer XYWAV at least 2 hours after eating. Inform patients and/or caregivers of patients taking XYWAV twice nightly, that the total nightly dosage of XYWAV is divided into two doses *[see Dosage and Administration (2.4)]*.

Inform patients if their nightly dose requires multiple draws. Instruct patients on how to perform the draws from the bottle.

Respiratory Depression and Sleep-Disordered Breathing

Inform patients that XYWAV may impair respiratory drive, especially in patients with compromised respiratory function, and may cause apnea *[see Warnings and Precautions (5.4)]*.

Depression and 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 *[see Warnings and Precautions (5.5)]*.

Other Behavioral or Psychiatric Adverse Reactions

Inform patients and/or caregivers that XYWAV can cause behavioral or psychiatric adverse reactions, including confusion, anxiety, and psychosis. Instruct them to notify their healthcare provider if any of these types of symptoms occur *[see Warnings and Precautions (5.6)]*.

Sleepwalking

Instruct patients and/or caregivers that XYWAV has been associated with sleepwalking and other behaviors during sleep, and to contact their healthcare provider if this occurs *[see Warnings and Precautions (5.7)]*.

Distributed By:

Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

Protected by U.S. Patent Nos. 8,591,922; 8,731,963; 8,772,306; 8,901,173; 9,050,302; 9,132,107; 9,486,426; 9,555,017; 10,195,168; 10,213,400; and 10,675,258.

MEDICATION GUIDE
XYWAV® (ZYE wave)
(calcium, magnesium, potassium, and sodium oxybates)
oral solution, CIII

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

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

- XYWAV is a central nervous system (CNS) depressant. Taking XYWAV with other CNS depressants, such as medicines used to make you or your child fall asleep, including opioid analgesics, benzodiazepines, sedating antidepressants, antipsychotics, sedating anti-epileptic medicines, general anesthetics, muscle relaxants, alcohol, or street drugs, may cause serious medical problems, including:
  - trouble breathing (respiratory depression)
  - low blood pressure (hypotension)
  - changes in alertness (drowsiness)
  - fainting (syncope)
  - death

  Ask your doctor if you are not sure if you are, or your child is, taking a medicine listed above.
- XYWAV is a federal controlled substance (CIII). The active ingredient of XYWAV is a form of gamma-hydroxybutyrate (GHB) that is also a federal controlled substance (CI). Abuse of illegal GHB, either alone or with other CNS depressants, may cause serious medical problems, including:
  - seizure
  - trouble breathing (respiratory depression)
  - changes in alertness (drowsiness)
  - coma
  - death

  Call your doctor right away if you have or your child has any of these serious side effects.
- Anyone who takes XYWAV should not do anything that requires them to be fully awake or is dangerous, including driving a car, using heavy machinery, or flying an airplane, for at least 6 hours after taking XYWAV. Those activities should not be done until you know how XYWAV affects you or your child.
- Keep XYWAV in a safe place to prevent abuse and misuse. Selling or giving away XYWAV may harm others and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
- Because of the risk of CNS depression, abuse, and misuse, XYWAV is available only by prescription, and filled through the central pharmacy in the XYWAV and XYREM REMS. You or your child must be enrolled in the XYWAV and XYREM REMS to receive XYWAV. For information on how to receive XYWAV, visit www.XYWAVXYREMREMS.com. Before you receive or your child receives XYWAV, your doctor or pharmacist will make sure that you understand how to take XYWAV safely and effectively. If you have any questions about XYWAV, ask your doctor or call the XYWAV and XYREM REMS at 1-866-997-3688.

What is XYWAV?

XYWAV is a prescription medicine used to treat:

- the following symptoms in people 7 years of age or older with narcolepsy:
  - sudden onset of weak or paralyzed muscles (cataplexy), or
  - excessive daytime sleepiness (EDS)
- idiopathic hypersomnia (IH) in adults

It is not known if XYWAV is safe and effective in children less than 7 years of age with narcolepsy.
It is not known if XYWAV is safe and effective in children with IH.

Do not take XYWAV if you or your child:

- takes other sleep medicines or sedatives (medicines that cause sleepiness)
- drinks alcohol
- has a rare problem called succinic semialdehyde dehydrogenase deficiency

Before taking XYWAV, tell your doctor about all medical conditions, including if you or your child:

- have a history of drug abuse.
- have short periods of not breathing while sleeping (sleep apnea).
- has trouble breathing or has lung problems. You or your child may have a higher chance of having serious breathing problems when taking XYWAV.
- have or had depression or has tried to harm yourself or themselves. You or your child should be watched carefully for new symptoms of depression.
- has or had behavior or other psychiatric problems such as:

o anxiety	o seeing or hearing things that are not real (hallucinations)
o feeling more suspicious (paranoia)	o being out of touch with reality (psychosis)
o acting aggressive	o agitation

- have liver problems.
- are pregnant or plan to become pregnant. It is not known if XYWAV can harm your unborn baby.
- are breastfeeding or plan to breastfeed. XYWAV passes into breast milk. You and your doctor should decide if you or your child will take XYWAV or breastfeed.

Tell your doctor about all the medicines you take or your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially, tell your doctor if you take or your child takes other medicines to help you or your child sleep (sedatives). Know the medicines you take or your child takes. Keep a list of them to show your doctor and pharmacist when you get or your child gets a new medicine.

How should I take or give XYWAV?

- Read the **Instructions for Use** at the end of this Medication Guide for detailed instructions on how to take XYWAV.
- Take or give XYWAV exactly as your doctor tells you to take or give it. Your doctor may change the dose or dosing routine if needed.
- Wait at least 2 hours after eating before taking or giving XYWAV.
- XYWAV can cause physical dependence and craving for the medicine when it is not taken as directed.
- Never change the dose without talking to your doctor.
- XYWAV can cause sleep very quickly without feeling drowsy. Some people fall asleep within 5 minutes and most fall asleep within 15 minutes. The time it takes to fall asleep might be different from night to night.
- Falling asleep quickly, including while standing or while getting up from the bed, has led to falls with injuries that have required some people to be hospitalized.
- XYWAV can be taken 1 time or 2 times a night as prescribed by your doctor.
- **If you or your child have been prescribed XYWAV 2 times a night**: divide the total nightly dose into 2 doses to be taken at bedtime and 2½ to 4 hours later.
  - **Adults:** Take the first XYWAV dose at bedtime while you are in bed and lie down immediately. Take the second XYWAV dose 2½ to 4 hours after the first XYWAV dose. You may want to set an alarm clock to make sure you wake up to take the second XYWAV dose. You should remain in bed after taking the first and second doses of XYWAV.
  - **Children:** Give the first XYWAV dose at bedtime or after an initial period of sleep, while your child is in bed and have them lie down immediately. Give the second XYWAV dose 2½ to 4 hours after the first XYWAV dose. You may want to set an alarm clock to make sure you wake up to give the second XYWAV dose. Your child should remain in bed after taking the first and second doses of XYWAV.
  - If you miss or your child misses the second XYWAV dose, skip that dose and do not take or give XYWAV again until the next night. Never take or give 2 XYWAV doses at 1 time.
- **If you have been prescribed XYWAV 1 time a night:** Take your XYWAV dose at bedtime while you are in bed and lie down immediately. You should remain in bed after taking XYWAV.
- If you take or your child takes too much XYWAV, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of XYWAV?

XYWAV can cause serious side effects, including:

- See **"What is the most important information I should know about XYWAV?"**
- **breathing problems, including:**
  - slower breathing.
  - trouble breathing.
  - short periods of not breathing while sleeping (sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they take XYWAV.
- **mental health problems, including:**
  - confusion
  - seeing or hearing things that are not real (hallucinations)
  - unusual or disturbing thoughts (abnormal thinking)
  - feeling anxious or upset
  - depression
  - thoughts of killing yourself or trying to kill yourself
  - increased tiredness
  - feelings of guilt or worthlessness
  - difficulty concentrating

  Call your doctor right away if you have or your child has symptoms of mental health problems, or a change in weight or appetite.
- **sleepwalking.** Sleepwalking can cause injuries. Call your doctor if you start or your child starts sleepwalking. Your doctor should check you or your child.

The most common side effects of XYWAV in adults with narcolepsy or IH include:

- nausea
- headache
- dizziness
- anxiety
- insomnia
- decreased appetite
- excessive sweating (hyperhidrosis)
- vomiting
- diarrhea
- dry mouth
- parasomnia (a sleep disorder that can include abnormal dreams, abnormal rapid eye movement (REM) sleep, sleep paralysis, sleep talking, sleep terror, sleep-related eating disorder, sleepwalking and other abnormal sleep-related events)
- somnolence
- fatigue
- tremor

The most common side effects of XYREM (which also contains oxybate like XYWAV) in children include:

- nausea
- bedwetting
- vomiting
- headache
- weight decrease
- decreased appetite
- dizziness
- sleepwalking

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

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

How should I store XYWAV?

- Store XYWAV in the original bottle prior to mixing with water. After mixing with water, store XYWAV in the pharmacy containers with child-resistant caps provided by the pharmacy.
- Store XYWAV at room temperature between 68°F to 77°F (20°C to 25°C).
- XYWAV solution prepared after mixing with water should be taken within 24 hours.
- When you have finished using a XYWAV bottle:
  - empty any unused XYWAV down the sink drain.
  - cross out the label on the XYWAV bottle with a marker.
  - place the empty XYWAV bottle in the trash.

XYWAV comes in a child-resistant package.

Keep XYWAV and all medicines out of the reach of children and pets.

General information about the safe and effective use of XYWAV.

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

You can ask your pharmacist or doctor for information about XYWAV that is written for health professionals.

What are the ingredients in XYWAV?
Active ingredients: calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate (gamma-hydroxybutyrate (GHB)).
Inactive ingredients: purified water and sucralose
Distributed By:
Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304
For more information, go to www.XYWAVXYREMREMS.com or call the XYWAV and XYREM REMS at 1-866-997-3688**.**

This Medication Guide has been approved by he U.S. Food and Drug Administration Revised: 08/2021

INSTRUCTIONS FOR USE
XYWAV® (ZYE wave)
(calcium, magnesium, potassium, and sodium oxybates)
oral solution, CIII

This Instructions for Use contains information on how to take XYWAV. Read this Instructions for Use carefully before you (or your child) start taking XYWAV and each time you (or your child) get a refill. There may be new information. This information does not take the place of talking to your doctor about your (or your child's) medical condition or treatment.

Important Information:

- **Your doctor and pharmacist will provide instructions to take XYWAV 2 times a night or 1 time a night.**
  - **For 2 times a night, you will need to split your (or your child's) prescribed XYWAV dose into 2 separate pharmacy containers for mixing.**
  - **For 1 time a night, you will use the dosing syringe to draw up your prescribed XYWAV dose and empty the dose into 1 pharmacy container for mixing. You will only need 1 pharmacy container to prepare your dose.**
- **You (or your child) should take XYWAV while in bed. Lie down immediately after taking XYWAV and remain in bed afterwards.**
- **You will need to mix XYWAV with water before you take or give your child the dose.**
- **Safely store the prepared XYWAV doses and take within 24 hours after mixing. If the prepared dose was not taken within this time, throw the mixture away. See "Throwing away (disposing of) XYWAV" section below for instructions about how to safely throw away XYWAV.**
- **The pharmacy container(s) may be rinsed out with water and emptied into the sink drain.**

Supplies you will need for mixing and taking (or giving your child) XYWAV. See Figure A:

- Bottle of XYWAV medicine
- Dosing syringe for measuring and dispensing the XYWAV dose
- Measuring cup that is able to measure about ¼ cup of water (not provided with the XYWAV shipment)
- 1 or 2 **empty** pharmacy containers with child-resistant caps for mixing, storing, and taking the XYWAV doses
- Alarm clock if you take XYWAV 2 times a night (not pictured)
- Medication Guide

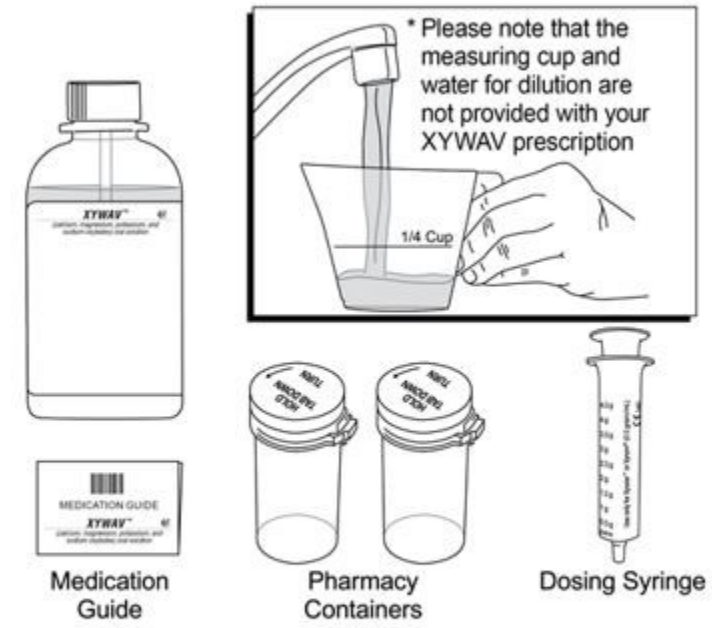


Figure A

Note: If you or your child are prescribed XYWAV 2 times a night, see the instructions for 2 times a night dosing. If you are prescribed XYWAV 1 time a night, see the instructions for 1 time a night dosing.

2 times a night dosing

Step 1. Setup

- Take the XYWAV bottle, syringe, and pharmacy containers out of the shipping box.
- Take the syringe out of the plastic wrapper. Use only the syringe provided with the XYWAV prescription.
- Fill a measuring cup (not provided) with about ¼ cup of water available for mixing your (or your child's) dose.

- **Make sure the pharmacy containers are empty.**
- Open both pharmacy containers by holding the tab under the cap and turning counterclockwise (to the left). See Figure B

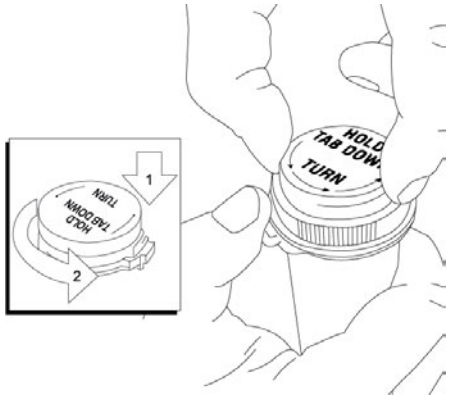


Figure B

- Remove the tamper evident band by pulling at the perforations and then remove the child-resistant bottle cap from the XYWAV bottle by pushing down while turning the cap counterclockwise. See Figure C

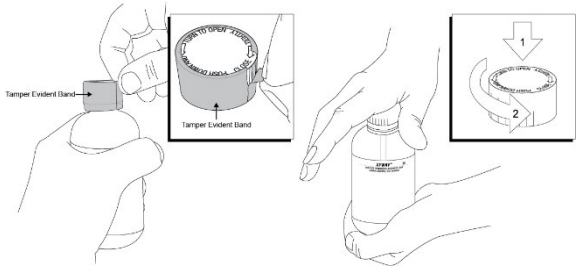


Figure C

Step 2. Prepare the first XYWAV dose (prepare before bedtime).

Place the XYWAV bottle on a hard, flat surface and grip the bottle with one hand. Firmly press the syringe into the center opening of the bottle with the other hand. See Figure D

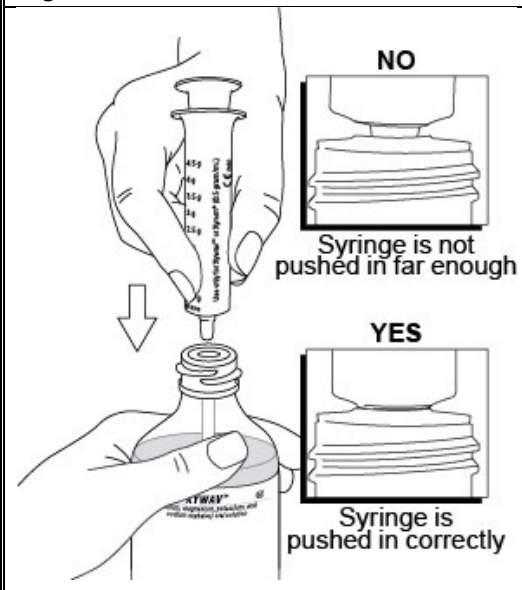
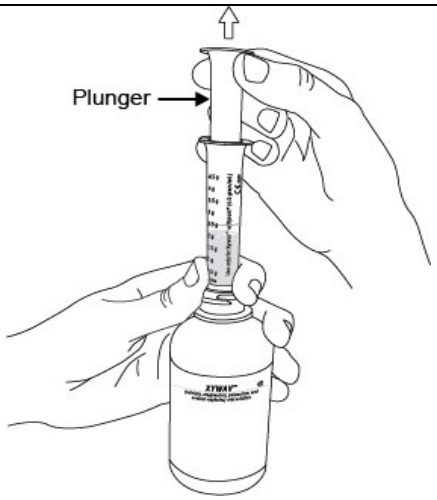
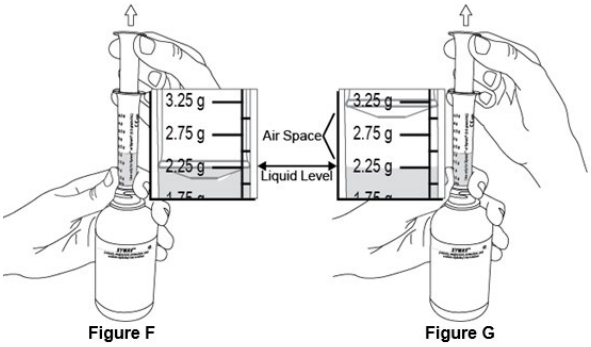
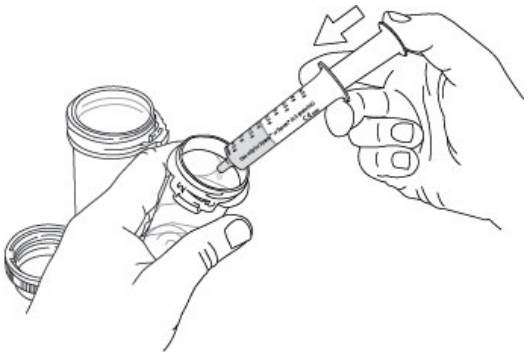


Figure D

Pull back on the plunger until the medicine flows into the syringe and the liquid level is lined up with the marking on the syringe that matches your or your child's dose. See Figure E	 **Figure E** **Note: The XYWAV medicine will not flow into the syringe unless you keep the bottle upright.**
Figure F shows an example of drawing up a 2.25 g dose of XYWAV. Figure G shows an example if an air space forms when drawing up the medicine. **Note:** If an air space forms between the plunger and the liquid when drawing up the medicine, line up the liquid level with the marking on the syringe that matches your (or your child's) dose. See Figure G	 **Figure F** **Figure G**
• After you draw up the first divided dose, remove the syringe from the opening of the XYWAV bottle. • Empty all of the medicine from the syringe into one of the provided **empty** pharmacy containers by pushing down on the plunger until it stops. See Figure H	 **Figure H**

- Using a measuring cup, pour about ¼ cup of water into the pharmacy container. **Be careful to add only water to the pharmacy container and not more XYWAV.**
- **All shipped bottles of XYWAV contain the concentrated medicine. Water for mixing the medicine is not provided in the shipment.**
- Place the child-resistant cap provided with the filled pharmacy container on the pharmacy container and turn the cap clockwise (to the right) until it clicks and locks into its child-resistant position. See Figure I

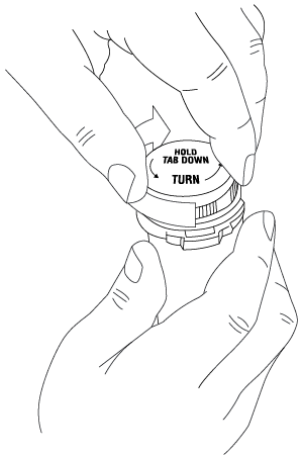


Figure I

Step 3. Prepare the second XYWAV dose (prepare before bedtime)

- Repeat Step 2 drawing up the amount of medicine prescribed for your (or your child's) second dose:
  - emptying the syringe into the second pharmacy container
  - adding about ¼ cup of water and
  - closing the pharmacy container

Step 4. Store the prepared XYWAV doses

- Put the cap back on the XYWAV bottle and store the XYWAV bottle and both prepared doses in a safe and secure place. Store in a locked place if needed.
- Keep the XYWAV bottle and both prepared XYWAV doses out of the reach of children and pets.
- Rinse the syringe out with water and squirt the liquid into the sink drain by pushing down on the plunger until it stops.

Step 5. Take or give the first XYWAV dose

- At bedtime, and before you take (or give) the first XYWAV dose, put the second XYWAV dose in a safe place. Caregivers should make sure all XYWAV doses are kept in a safe place until given. You may want to set an alarm clock for 2½ to 4 hours later to make sure you wake up to take (or give) the second dose.
- When it is time to take (or give) the first XYWAV dose, remove the cap from the pharmacy container by pressing down on the child-resistant locking tab and turning the cap counterclockwise.
- Drink (or have your child drink) all of the first XYWAV dose while sitting in bed. Put the cap back on the first pharmacy container and immediately lie down to sleep (or have your child lie down to sleep).
- You (or your child) should fall asleep soon. Some people fall asleep within 5 minutes and most fall asleep within 15 minutes. Some patients take less time to fall asleep, and some take more time. The time it takes you (or your child) to fall asleep might be different from night to night.

Step 6. Take or give the second XYWAV dose

- When you wake up 2½ to 4 hours later for your (or your child's) second dose of XYWAV, take the cap off the second pharmacy container.
- If you (or your child) wake up before the alarm and it has been at least 2½ hours since the first XYWAV dose, turn off the alarm and take (or give your child) the second XYWAV dose.
- Drink (or have your child drink) all of the second XYWAV dose while sitting in bed. Put the cap back on the second pharmacy container and immediately lie down (or have your child lie down) to continue sleeping.

1 time a night dosing
for use in adults with idiopathic hypersomnia

Step 1: Setup

- Take the XYWAV bottle, syringe, and 1 pharmacy container out of the shipping box.
- Take the syringe out of the plastic wrapper. Use only the syringe provided with the XYWAV prescription.
- Fill a measuring cup (not provided) with about ¼ cup of water available for mixing with your dose.

- **Make sure the pharmacy container is empty.**
- Open the pharmacy container by holding the tab under the cap and turning counterclockwise (to the left). See Figure B

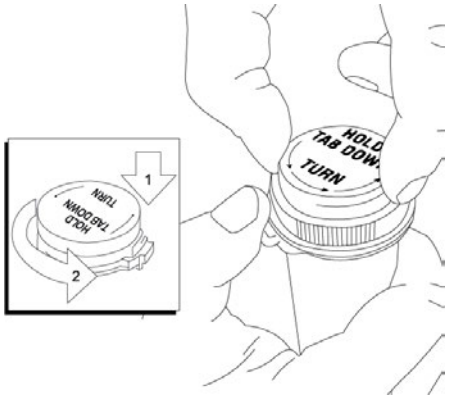


Figure B

- Remove the tamper evident band by pulling at the perforations and then remove the child-resistant bottle cap from the XYWAV bottle by pushing down while turning the cap counterclockwise. See Figure C

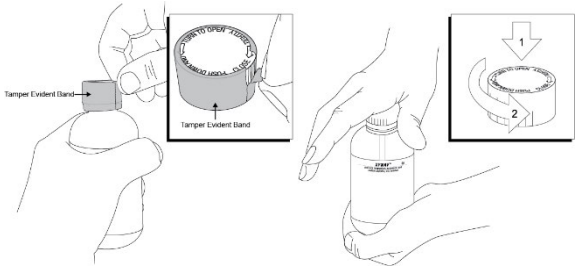


Figure C

Step 2. Prepare the XYWAV dose (prepare before bedtime).

Place the XYWAV bottle on a hard, flat surface and grip the bottle with one hand. Firmly press the syringe into the center opening of the bottle with the other hand. See Figure D

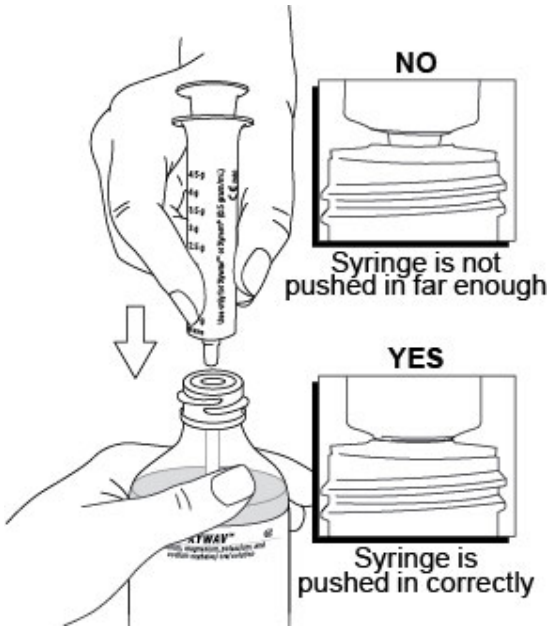
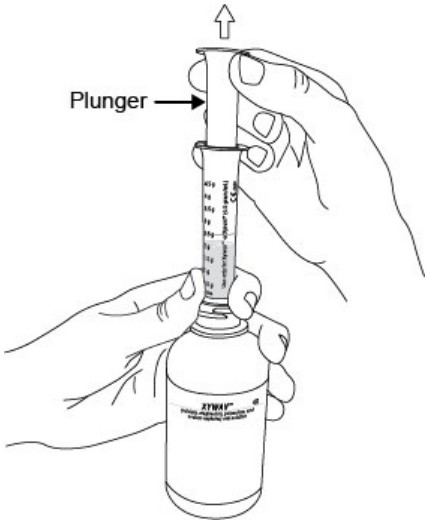
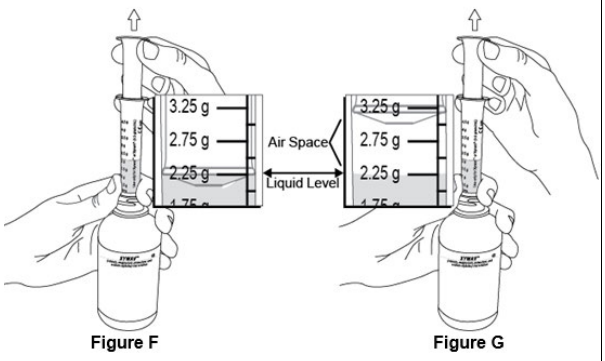
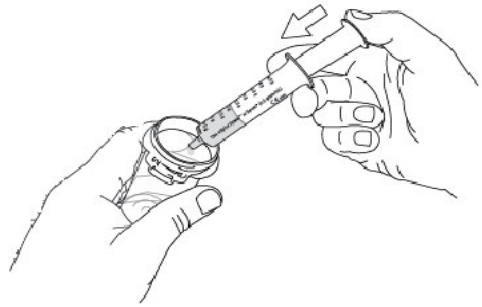


Figure D

Pull back on the plunger until the medicine flows into the syringe and the liquid level is lined up with the marking on the syringe that matches your dose. You may need to draw up the medicine a second time to make up your total prescribed dose. See Figure E	 **Figure E** **Note: The XYWAV medicine will not flow into the syringe unless you keep the bottle upright.**
Figure F shows an example of drawing up 2.25 g of XYWAV. Figure G shows an example if an air space forms when drawing up the medicine. **Note:** If an air space forms between the plunger and the liquid when drawing up the medicine, line up the liquid level with the marking on the syringe that matches your dose. See Figure G	 **Figure F** **Figure G**
• After you draw up the medicine, remove the syringe from the opening of the XYWAV bottle. • Empty all of the medicine from the syringe into a single provided **empty** pharmacy container by pushing down on the plunger until it stops. See Figure H • For doses requiring 2 draws from the XYWAV bottle, empty the second draw into the same pharmacy container.	 **Figure H**

- After you finish adding your XYWAV dose to the pharmacy container, use a measuring cup to pour about ¼ cup of water into the pharmacy container. **Be careful to add only water to the pharmacy container and not more XYWAV.**
- **All shipped bottles of XYWAV contain the concentrated medicine. Water for mixing the medicine is not provided in the shipment.**
- Place the child-resistant cap provided with the filled pharmacy container on the pharmacy container and turn the cap clockwise (to the right) until it clicks and locks into its child-resistant position. See Figure I

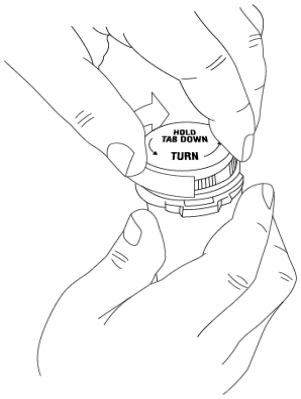


Figure I

Step 3. Store the prepared XYWAV dose

- Put the cap back on the XYWAV bottle and store the XYWAV bottle and the prepared dose in a safe and secure place. Store in a locked place if needed.
- Keep the XYWAV bottle and the prepared XYWAV dose out of the reach of children and pets.
- Rinse the syringe out with water and squirt the liquid into the sink drain by pushing down on the plunger until it stops.

Step 4. Take the XYWAV dose

- Make sure the XYWAV dose is kept in a safe place until taken.
- When it is time to take the XYWAV dose, remove the cap from the pharmacy container by pressing down on the child-resistant locking tab and turning the cap counterclockwise.
- Drink all of the XYWAV dose while sitting in bed. Put the cap back on the pharmacy container and immediately lie down to sleep.
- You should fall asleep soon. Some people fall asleep within 5 minutes and most fall asleep within 15 minutes. Some patients take less time to fall asleep, and some take more time. The time it takes you to fall asleep might be different from night to night.

How should I store XYWAV?

- Store XYWAV in the original bottle prior to mixing with water. After mixing, store XYWAV in the pharmacy containers provided by the pharmacy. The caps on the original bottle and pharmacy containers are child-resistant.
- Store XYWAV at room temperature between 68°F to 77°F (20°C to 25°C).
- XYWAV solution prepared after mixing with water should be taken within 24 hours or emptied down the sink drain.

Throwing away (disposing of) XYWAV

- When you have finished using a XYWAV bottle:
  - empty any unused XYWAV down the sink drain
  - cross out the label on the XYWAV bottle with a marker (not provided with the XYWAV shipment)
  - place the empty XYWAV bottle in the trash
- **Keep XYWAV and all medicines out of the reach of children and pets.**

Distributed By:
Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: 08/2021

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s006

REMS

Risk Evaluation and Mitigation Strategy (REMS) Document

XYWAV (calcium, magnesium, potassium, and sodium oxybates) and XYREM (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: 08/2021

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:

1. Healthcare providers who prescribe XYWAV and XYREM must:	
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.
Before treatment initiation (first dose)	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.

1. Healthcare providers who prescribe XYWAV and XYREM must:	
	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 Prescription Form. 6. Counsel the patient on the serious risks associated with XYWAV and XYREM safe use, handling, and storage using the XYWAV Patient Quick Start Guide, XYREM Patient Quick Start Guide, XYWAV Brochure for Pediatric Patients and their Caregivers, or XYREM Brochure for Pediatric Patients and their Caregivers. 7. Enroll the patient by completing and submitting the Patient Enrollment Form to the REMS Program. 8. Order the prescription using either the XYWAV Prescription Form or XYREM Prescription Form and submit it to the REMS Program.
Before treatment re-initiation	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. 10. For patients with a lapse in treatment of 6 months or longer: order the prescription using either the XYWAV Prescription Form or XYREM Prescription Form and submit it to the REMS program.
During treatment; within the first 3 months of starting treatment and recommended every 3 months thereafter	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.
At all times	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.

2. Patients who are prescribed XYWAV and XYREM:

Before treatment initiation	1. Review the XYWAV Patient Quick Start Guide, XYREM Patient Quick Start Guide, XYWAV Brochure for Pediatric Patients and their Caregivers, or XYREM Brochure for Pediatric Patients and their Caregivers. 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 XYWAV Patient Quick Start Guide, XYREM Patient Quick Start Guide, XYWAV Brochure for Pediatric Patients and their Caregivers, or XYREM Brochure for Pediatric Patients and their Caregivers. 3. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program. 4. Complete the Patient Counseling Checklist with the pharmacist.
During treatment	5. Adhere to the safe use conditions described in the XYWAV Patient Quick Start Guide, XYREM Patient Quick Start Guide, XYWAV Brochure for Pediatric Patients and their Caregivers, or XYREM Brochure for Pediatric Patients and their Caregivers. 6. Complete the Patient Counseling Checklist with the pharmacist based on changes in your medication and/or medical history.
During treatment; within the first 3 months of starting treatment and recommended every 3 months thereafter	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.
Before treatment re-initiation, after lapse in treatment for 6 months or longer	8. Complete the Patient Counseling Checklist with the pharmacist.
At all times	9. Inform your prescriber and the pharmacy about any new medications you may be taking or medical conditions you may have.

3.The pharmacy that dispenses XYWAV and XYREM must:

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.

Before dispensing	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 Patient Counseling Checklist. Document and submit to the REMS Program using the Central Database.
	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.
	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.
	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.
	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.
	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.
	16.	Assess the patient's potential for abuse, misuse, and diversion by reviewing the alerts and Risk Management Report history in the Central Database.
	17.	For patients who request an early refill or if abuse, misuse or diversion is suspected: Discuss the request or concern with the prescriber.
	18.	Dispense no more than a one months' supply for the initial shipment.
	19.	Dispense no more than a three months' supply for subsequent shipments.
Before Shipping	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.
	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.
	22.	Provide the patient with the XYWAV Patient Quick Start Guide, XYREM Patient Quick Start Guide, XYWAV Brochure for Pediatric Patients and their Caregivers, or XYREM Brochure for Pediatric Patients and their Caregivers with the first shipment.

After Shipping	23.	Track and verify receipt of each shipment of XYWAV and XYREM through the processes and procedures established as a requirement of the REMS.
	24.	Document and submit the shipment and receipt dates to the Central Database.
To Maintain Certification to Dispense, Every Year	25.	For all relevant staff involved in dispensing: review the Pharmacy Training Program – Module A.
	26.	For all relevant staff involved in dispensing: successfully complete the Module A Knowledge Assessment and submit it to the REMS Program.
	27.	For all pharmacists involved in dispensing: review the Pharmacy Training Program – Modules A and B.
	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.
	29.	Train all pharmacists involved in dispensing on the requirements of the REMS Program using Pharmacy Training Program – Module B.
At all times	30.	Provide 24-7 toll-free access to a XYWAV and XYREM REMS Program pharmacist.
	31.	Ship XYWAV or XYREM directly to the patient or a patient-authorized adult designee using an overnight service.
	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.
	33.	Report lost, stolen, destroyed, or spilled drug to the Central Database using the Risk Management Report.
	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 Risk Management Report.
	35.	Not distribute, transfer, loan, or sell XYWAV or XYREM.
	36.	Not stock XYWAV or XYREM in retail pharmacies.
	37.	Maintain records documenting staff's completion of the Pharmacy Training Program.
	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.

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. 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 (08/12/2021).

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 a REMS Assessment on April 26, 2022 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

XYWAV and XYREM REMS

XYWAV and XYREM REMS PRESCRIBER 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 ESSDSPrescribers@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, please call the XYWAV and XYREM REMS at 1-866-997-3688 (toll free).

Note: Completion of this form and enrollment in the REMS allows you to prescribe both XYWAV and XYREM.

Step 1: ALL BOXES BELOW MUST BE CHECKED (☑) IN ORDER FOR THE ENROLLMENT PROCESS TO BE COMPLETE AND BEFORE YOU CAN ENROLL PATIENTS AND PRESCRIBE XYWAV or XYREM

☐ I 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 (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

☐ I have read the Prescribing Information (PI) and the XYWAV and XYREM REMS Prescriber Brochure and understand that:
- XYWAV and XYREM are Schedule III CNS depressants and can cause obtundation and clinically significant respiratory depression at recommended doses
- The use of XYWAV or XYREM in combination with alcohol or sedative hypnotics is contraindicated
- 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
- 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

☐ I agree to:
- Enroll each patient in the XYWAV and XYREM REMS
- Screen each patient for history of alcohol or substance abuse, sleep-related breathing disorders, compromised respiratory function, depression, suicidality, and concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
- Counsel each patient and/or caregiver prior to initiating therapy on the serious risks and safe use, handling, and storage of XYWAV or XYREM
- Evaluate patients within the first 3 months of starting XYWAV or XYREM. It is recommended that patients be re-evaluated every 3 months thereafter while taking XYWAV or XYREM
- Report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death, and any cases of suspected abuse, misuse, or diversion to Jazz Pharmaceuticals

Step 2: To help expedite the enrollment process, please **PRINT** clearly (*denotes required field)

Prescriber Information

*First Name: _____ M.I.: _____ *Last Name: _____ Prof. Designation (MD, DO, PA, NP): _____

*DEA No.: _____ *State License No.: _____ *NPI no.: _____

Facility/Practice Name: _____

*Street Address: _____

*City: _____ *State: _____ *Zip Code: _____

*Phone: _____ *Fax: _____ E-mail: _____

Office Contact: _____ Office Contact Phone: _____

Additional office locations and contacts can be entered online at XYWAVXYREMREMS.com.

Step 3: Prescriber signature is required below for enrollment in the XYWAV and XYREM REMS

By signing below, I acknowledge the above attestations, and I understand that my personally identifiable information provided above will be shared with Jazz Pharmaceuticals, Inc., its agents, contractors, and affiliates and entered into a prescriber database for the XYWAV and XYREM REMS. I agree that I may be contacted in the future by mail, e-mail, fax, and/or telephone concerning XYWAV, XYREM, and the XYWAV and XYREM REMS.

*Prescriber Signature: _____ *Date: _____

Report SERIOUS ADVERSE EVENTS by contacting Jazz Pharmaceuticals at 1-800-520-5568 or AEReporting@jazzpharma.com.

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

XYREM® (sodium oxybate) oral solution III

XYWAV and XYREM REMS

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 ESSDSPrescribers@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, please 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): _____ *Gender: ☐ 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 and XYREM
- I have asked my doctor/prescriber any questions I have about XYWAV and XYREM

*Patient/Caregiver Signature: _____ *Date: _____

*Printed Caregiver Name (if applicable): _____

Prescriber: Form must be signed before enrollment can be processed.

By signing below, I acknowledge that:

- I have counseled the patient and/or caregiver about the serious risks associated with the use of XYWAV and XYREM and the safe use conditions as descr bed 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 him or her the appropriate educational material

*Prescriber Signature: _____ *Date: _____

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 program enrollment and prescribing XYWAV® (calcium, magnesium, potassium, and sodium oxybates) 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 for prescribing XYWAV and XYREM. These forms must be used for initial prescriptions and may also be used 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

XYREM® (sodium oxybate) oral solution

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 (9 g/night) delivers 1,640 mg 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

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

ENROLL

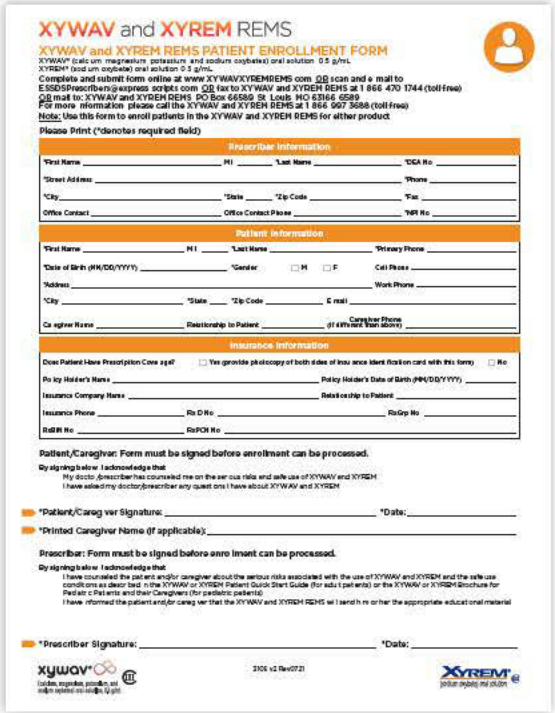
- You will enroll each patient in the XYWAV and XYREM REMS by completing the one-time **REMS Patient Enrollment Form** and submitting the form to the XYWAV and XYREM REMS. A pediatric patient must have a caregiver
- You will evaluate each patient within the first 3 months of starting XYWAV or XYREM, 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

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 and has had the opportunity to ask you any questions he/she may have about XYWAV or XYREM
  - 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

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 ESDSPrescribers@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, please 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 _____ MI _____ *Last Name _____ *DEA No _____
*Street Address _____ *Phone _____
*City _____ *State _____ *Zip Code _____ *Fax _____
Office Contact _____ Office Contact Phone _____ *NPI No _____

Patient Information

*First Name _____ MI _____ *Last Name _____ *Primary Phone _____
*Date of Birth (MM/DD/YYYY) _____ *Gender ☐ 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 _____ Rx ID No _____ RxGrp No _____
BIN 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 and XYREM
I have asked my doctor/prescriber any questions I have about XYWAV and XYREM

*Patient/Caregiver Signature: _____ *Date: _____
*Printed Caregiver Name (if applicable): _____

Prescriber: Form must be signed before enrollment can be processed.

By signing below, I acknowledge that:
I have counseled the patient and/or caregiver about the serious risks associated with the use of 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 him or her the appropriate educational material

*Prescriber Signature: _____ *Date: _____

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

3106 v2 Rev07.21

XYREM® (sodium oxybate) oral solution CIII

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 14 and 15 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 14 and 15 of this brochure for Patient Counseling Information)
  - Provide a list of all current prescription and non-prescription medications and dosages that the patient is currently taking, to the best of your knowledge. Additionally, indicate the presence of relevant comorbid medical conditions. This can be done by completing the appropriate fields on the **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** for download. Downloaded forms must be printed, signed, and either faxed to the XYWAV and XYREM REMS at **1-866-470-1744** (toll free), or mailed 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 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.
- 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** and all subsequent prescriptions 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.

XYWAV and XYREM REMS

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 on this page is for adult patients with narcolepsy. Please see pages 16–18 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 any 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

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

XYREM® (sodium oxybate) oral solution C III

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.

Reference ID: 4840646

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 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
- 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.

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 Program 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 GENDER EFFECTS

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

Please read accompanying Prescribing Information.
The 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 16-18 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 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 program 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
- 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

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

XYREM® (sodium oxybate) oral solution

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
  - 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

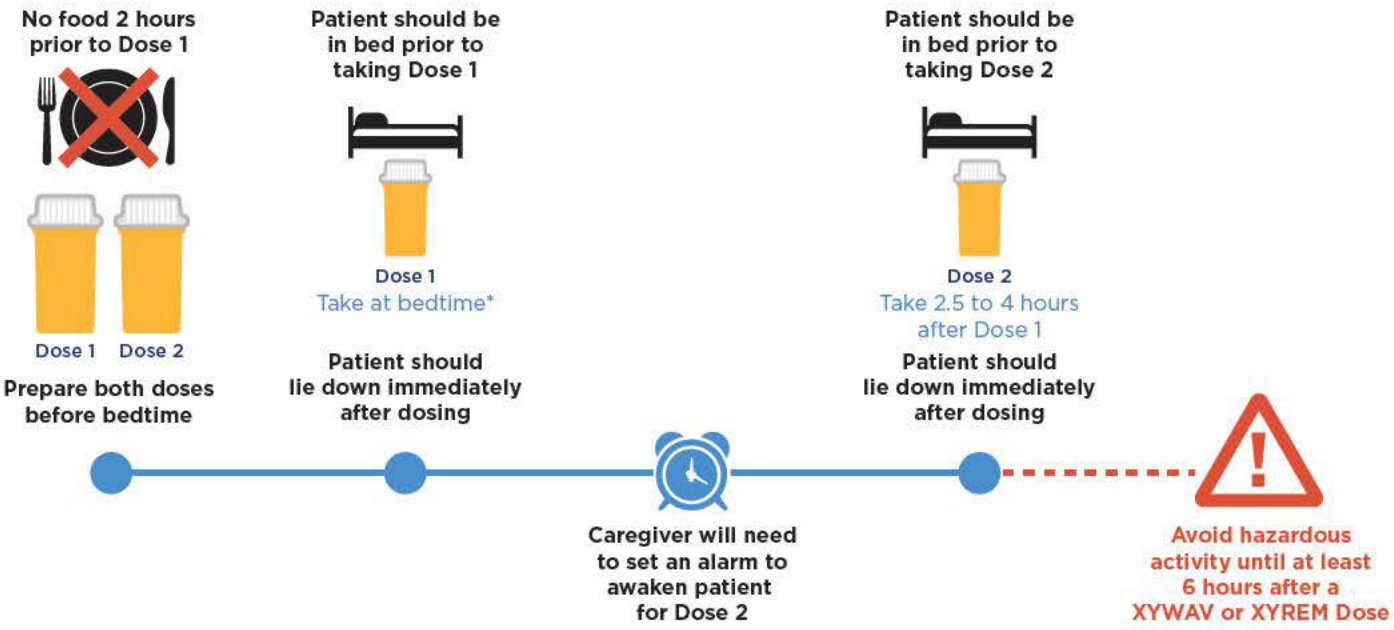
CHANGING BETWEEN XYWAV AND XYREM

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 4.5 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
- 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

XYREM®
(sodium oxybate) oral solution

3101 v2 Rev0721

XYWAV and XYREM REMS

PATIENT QUICK START GUIDE

Important information about the safe use and handling of XYREM

XYREM® (sodium oxybate) oral solution

Reference ID: 4840646

Dear Patient,

Welcome to the XYWAV and XYREM REMS. You are receiving these materials because your healthcare provider has prescribed XYREM® (sodium oxybate) oral solution, 0.5 g/mL, for you. 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 are the caregiver of a pediatric patient receiving XYREM, please refer to the XYREM Brochure for Pediatric Patients and Their Caregivers instead of this guide for important information about helping your child get started with XYREM.*

Because of the serious risks associated with XYREM, the Food and Drug Administration (FDA) has required a special program called a Risk Evaluation and Mitigation Strategy (REMS). The purpose of this REMS is to make sure the benefits of XYREM outweigh the risks. All patients must be enrolled in the REMS to receive XYREM. This Quick Start Guide contains information you need to know about XYREM and will help you to use XYREM correctly. Read this Quick Start Guide before you start taking XYREM.

After your healthcare provider sends in your enrollment form and first prescription for XYREM, you will receive a call from the Certified Pharmacy of the REMS to tell you how the REMS helps you get started with taking XYREM and to answer any questions you may have about XYREM.

You will also speak with appropriate staff at the Certified Pharmacy, who will go over your insurance information with you. Before you can receive your first shipment of XYREM, a pharmacist at the Certified Pharmacy will ask if your healthcare provider reviewed the XYREM Patient Quick Start Guide with you and explain that you will receive this guide with your first shipment, and that all drug shipments will include the XYREM Medication Guide. The pharmacist will also ask you about your medical history and other medications you may be taking, and give you advice on how to prepare and take your XYREM and how to store it safely. **You must take this call before you can get your XYREM.**

Please call your healthcare provider if you have questions about XYREM, or you can contact the REMS toll free at 1-866-997-3688. You can reach a pharmacist at this number 24 hours a day, 7 days a week with any questions.

We hope you find this information and the REMS services helpful.

Sincerely,

Jazz Pharmaceuticals

XYREM® (sodium oxybate) oral solution

XYWAV and XYREM REMS

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

XYREM is a prescription medicine used to treat patients 7 years of age and older with narcolepsy to reduce too much daytime sleepiness and to reduce cataplexy (suddenly weak or paralyzed muscles).

IMPORTANT INFORMATION ABOUT XYREM INCLUDES THE FOLLOWING:

- When taking XYREM, do not drink alcohol or take other medicines that slow your breathing or mental activity or make you sleepy. You could have serious side effects
- XYREM can cause serious side effects, including trouble breathing while asleep, confusion, unusual or disturbing thoughts, depression, and passing out, even at recommended doses. Tell your healthcare provider if you have any of these problems while taking XYREM
- Abuse of XYREM can lead to dependence (a physical need to take the drug), craving for the medicine, and severe withdrawal symptoms (symptoms that start when the drug is stopped, especially when it is stopped suddenly)
- Patients usually fall asleep in about 5 to 15 minutes, although some patients have reported falling asleep more quickly (without first feeling drowsy) and others take more time. The time that it takes to fall asleep might be different from night to night. You should take each dose of XYREM while in bed. Take the first dose at bedtime and the second 2½ to 4 hours later. You may need to set an alarm to awaken for the second dose

Any questions? Please call the XYWAV and XYREM REMS at 1-866-997-3688.
Please see the Medication Guide for more detailed information about XYREM.

- Do not drive a car, use heavy machinery, fly an airplane, or do anything that is dangerous or that requires you to be alert for the first 6 hours after taking XYREM. When you first start taking XYREM, be careful until you know how XYREM affects you
- Keep XYREM out of the reach of children and pets. Get emergency medical help right away if a child drinks your XYREM
- Report all side effects to your healthcare provider

WHAT WILL YOU FIND IN THIS BOOKLET?

This booklet answers important questions about how to get your XYREM, how to use XYREM properly, and how to store it safely. It also gives you important information about XYREM.

WHAT IS THE XYWAV AND XYREM REMS PROGRAM?

Because of the serious risks associated with XYREM, the FDA has required a special program called REMS for XYWAV and XYREM. Enrollment in the REMS by prescribers and patients is required by the FDA to ensure the benefits of XYREM outweigh the risks associated with XYREM. You are enrolled in the program when your healthcare provider sends in the enrollment form you signed. At that time, your healthcare provider also sent your prescription for XYREM to the Certified Pharmacy.

The Certified Pharmacy staff will review important information about XYREM with you. They will also answer any questions you may have about XYREM.

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XYREM® (sodium oxybate) oral solution

ENROLLING IN THE XYWAV AND XYREM REMS

WHAT AM I REQUIRED TO DO IN THE XYWAV AND XYREM PROGRAM?

As a patient, your responsibility is to discuss the safe use of XYREM with your healthcare provider and to read this XYREM Patient Quick Start Guide before you begin taking XYREM. Be sure to let your healthcare provider know if you are taking other medications or if you have any conditions that might affect your breathing.

DO I HAVE TO ENROLL IN THIS PROGRAM?

Yes. In order for you to receive XYREM, your healthcare provider will have you sign an enrollment form and will send the form to the REMS. You must verify that you have been counseled by your healthcare provider on the serious risks and safe use of XYREM and that you were able to ask your healthcare provider any questions you have about XYREM.

FILLING YOUR XYREM PRESCRIPTION

HOW IS MY PRESCRIPTION FILLED?

All XYREM prescriptions are filled only by the REMS Certified Pharmacy.

WHAT DOES THE CERTIFIED PHARMACY DO?

Your healthcare provider sends your XYREM prescription directly to the Certified Pharmacy.

After your healthcare provider sends in your first prescription of XYREM, you will receive a call from the Certified Pharmacy to tell you how the REMS helps you get started with taking XYREM and to answer any questions you may have about XYREM. A staff member from the Certified Pharmacy will call you to complete a Patient Counseling Checklist. The Patient Counseling Checklist will include information about other medications that you are taking and other medical conditions which might increase your risk of serious side effects. The Certified Pharmacy will go over the information about how to use XYREM safely and provide a copy of the Medication Guide with each XYREM shipment.

The Certified Pharmacy will always ask you where and when you would like your XYREM delivered and who will sign for the shipment. XYREM will be shipped by an overnight service. When the courier arrives, you or an adult you name must sign for your XYREM.

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WHAT WILL I GET WITH MY XYREM PRESCRIPTION?

With each prescription, you will get 1 or more bottles of XYREM (each bottle, whether full or partial, has the concentrated medicine), a dosing syringe for drawing up your XYREM dose, 2 **empty** pharmacy containers with child-resistant caps, and a printed Medication Guide.

HOW DO I GET MY XYREM REFILLS?

The Certified Pharmacy will contact you when it is close to your refill time. You may opt-in to receive text, e-mail, or automated voice reminders. You may also call the Certified Pharmacy at 1-866-997-3688 to schedule your refills.

CAN MY LOCAL PHARMACY PROVIDE XYREM?

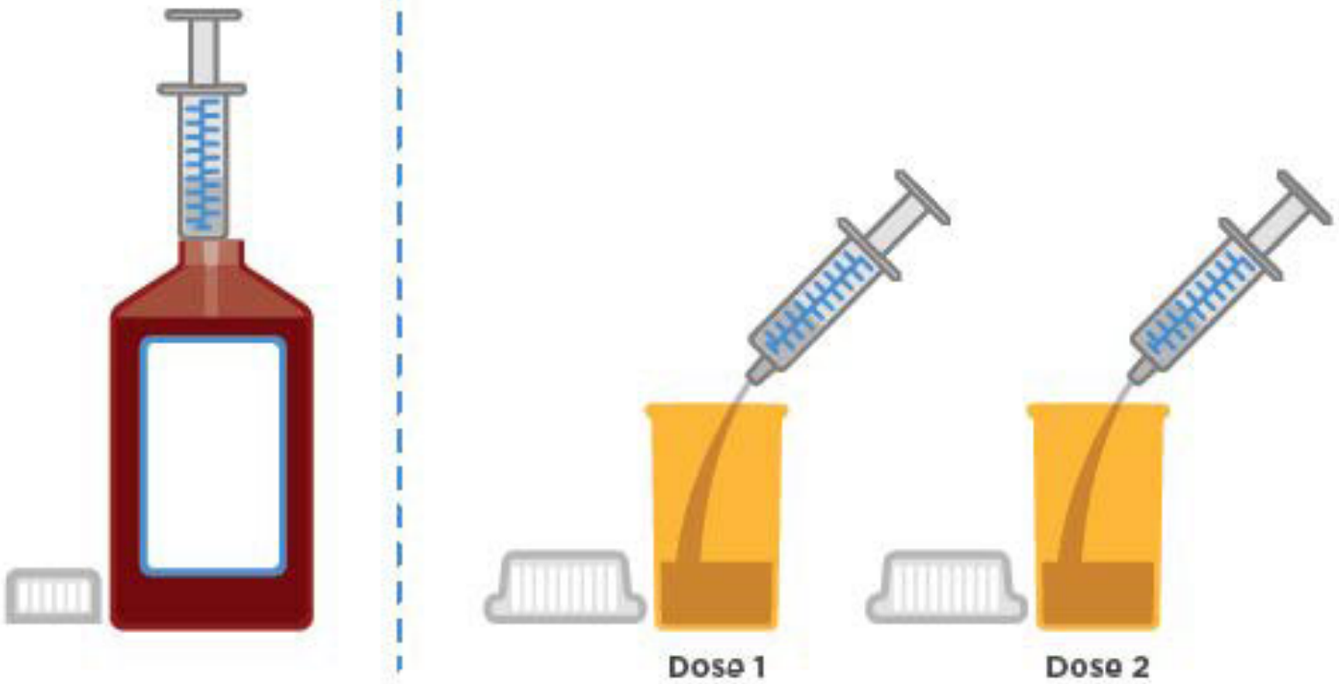
No. You can get your XYREM only from the REMS central Certified Pharmacy. You may be able to have your XYREM shipped to your place of work or to a local overnight carrier hub for pickup. Saturday deliveries may also be an option for you. The Certified Pharmacy will work with you on the best options available.

HOW DO I TAKE MY XYREM?

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

HOW DO I PREPARE MY DOSES?

Place the bottle on a hard, flat surface and grip the bottle with one hand and firmly press the syringe into the center opening of the bottle with the other. Pull back on the plunger until the medicine flows into the syringe and the liquid level is lined up with the marking on the syringe that matches your dose. After you draw up the first XYREM dose, remove the syringe from the opening of the XYREM bottle. Empty all of the medicine from the syringe into 1 of the provided **empty** pharmacy containers by pushing down on the plunger until it stops.



XYREM® (sodium oxybate) oral solution

Using a measuring cup, pour about ¼ cup of water into the pharmacy container. **Be careful to add only water to the pharmacy container and not more XYREM.** Place the child-resistant cap provided on the filled pharmacy container and turn the cap clockwise (to the right) until it clicks and locks in its child-resistant position.

Repeat the steps described above by drawing up the amount of medicine prescribed for your second dose; emptying the syringe into the second pharmacy container, adding about ¼ cup of water, and closing the pharmacy container.

Put the cap back on the XYREM bottle and store the XYREM bottle and both prepared doses in a safe and secure place. Store in a locked place if needed. Keep the XYREM bottle and both prepared XYREM doses out of the reach of children and pets.

Rinse out the syringe and pharmacy containers with water after each use. Please refer to the Instructions for Use within the Medication Guide for additional details.

HOW DO I TAKE MY DOSES?

Wait at least 2 hours after eating before taking XYREM.

XYREM is a medicine that can make you sleepy quickly; therefore, take your doses while you are in bed. Take the first dose at bedtime and the second dose 2½ to 4 hours later. If you continue evening activities after taking your dose, such as watching television or walking around, you may experience light-headedness, dizziness, nausea, confusion, or other unpleasant feelings.

WHAT SHOULD I DO IF I MISS A XYREM DOSE?

- It is very important to take both doses of XYREM each night, as prescribed. If you miss the second dose, skip that dose
  - Do not take XYREM again until the next night
  - Never take both XYREM doses at once
- Any unused XYREM doses that you prepared but didn't take must be thrown away within 24 hours from the time you first prepared your doses

XYREM® (sodium oxybate) oral solution

HOW SOON WILL I SEE A CHANGE IN MY SYMPTOMS?

After starting XYREM, it may take a few weeks or longer to see your symptoms improve. It may also take time to find the right dose that works for you. It is important that you talk with your healthcare provider often when you first start taking XYREM.

Tell your healthcare provider if you don't feel any improvements while taking XYREM. XYREM may not be right for you.

WHAT ARE THE SIDE EFFECTS OF XYREM?

XYREM can cause serious side effects, including breathing problems (slower breathing, trouble breathing, and short periods of no breathing while asleep), mental health problems (confusion, seeing or hearing things that are not real, unusual or disturbing thoughts, feeling anxious or upset, depression, thoughts of suicide), and sleepwalking. If you have any of these side effects, call your healthcare provider right away.

The most common side effects with XYREM are nausea, dizziness, throwing up, bedwetting, and diarrhea. Side effects may increase with higher doses.

These are not the only possible side effects with XYREM. If you are worried about any possible side effects with XYREM, talk with your healthcare provider or the pharmacist at the REMS.

You should report all side effects by contacting your healthcare provider,

Jazz Pharmaceuticals at 1-800-520-5568, or the FDA at 1-800-FDA-1088.

ARE THERE ANY PRECAUTIONS I SHOULD TAKE WHILE ON XYREM?

- While taking XYREM, do not drink alcohol or take medicines that cause sleepiness
- Do not drive a car, use heavy machinery, or do anything that is dangerous or requires you to be alert, for the first 6 hours after taking XYREM. When you first start taking XYREM, be careful until you know how it will affect you
- Before starting XYREM, tell your healthcare provider if you are pregnant, or plan to become pregnant, or if you are breastfeeding. XYREM passes into breast milk. You and your doctor should decide if you will take XYREM or breastfeed.
- Keep your XYREM in a safe place, out of the reach of children
- Take XYREM while in bed

Tell your healthcare provider and pharmacist about any other medicines you are taking, including prescription and non-prescription medicines, vitamins, and supplements.

It is also important to tell other healthcare providers, including pharmacists, that you are taking XYREM before you start or change any medications.

HOW OFTEN SHOULD MY HEALTHCARE PROVIDER CHECK MY PROGRESS WITH XYREM?

When you first start taking XYREM, you may need to talk to your healthcare provider often until he or she has determined the best dose for you. You can expect that your dose may need to be adjusted. After your dose has been established, your healthcare provider should check on you every 3 months while you are taking XYREM.

WHAT DO I NEED TO DO IF I AM TAKING XYWAV® AND MY DOCTOR PRESCRIBES XYREM FOR ME?

- **Never take both XYREM and XYWAV at the same time, it can lead to serious side effects**
- XYREM contains the same medicine as XYWAV, which is called oxybate, but with more sodium
- Take your XYREM exactly as instructed by your doctor
- Prepare your XYREM the same way you prepared XYWAV
- Do not mix XYREM and XYWAV together. If you have unused XYWAV, dispose of it before starting XYREM. Refer to "HOW DO I PROPERLY DISPOSE OF XYREM?" for further instructions
- The Certified Pharmacy will contact you to talk to you about how to make this change
- XYREM contains a high amount of sodium (salt) and may not be right for you, especially if you are on a salt-restricted diet or have had heart failure, high blood pressure (hypertension), or kidney problems. Make sure to tell your doctor if you have any of these conditions before you start XYREM.

STORAGE AND SAFETY TIPS AT HOME

HOW DO I STORE XYREM?

- Always store XYREM in its original bottle
- Store XYREM at room temperature. Do not refrigerate XYREM
- Keep XYREM in a safe place, out of the reach of children and pets. Get emergency medical help (call 911) right away if a child drinks your XYREM

HOW DO I PROPERLY DISPOSE OF XYREM?

To properly dispose of XYREM, pour any unused XYREM down the sink or toilet drain. Mark out all personal information on the prescription label, including the XYREM name, to make it unreadable before putting the empty bottle in the trash.

XYREM patients have the option to return unused or expired drug. Please ask the Certified Pharmacy for more details.

If you misplace, lose, or damage your XYREM dosing syringe, contact the Certified Pharmacy to have it replaced. Do not use a different syringe or try to guess the correct dose.

XYREM® (sodium oxybate) oral solution

XYWAV AND XYREM TAKEBACK PROGRAM

XYWAV or XYREM patients have an option to return any unused, leftover or expired XYWAV or XYREM product through a drug takeback program, upon request. Patients can request a shipper from the Certified Pharmacy. Once you receive the shipper, remember to mark out or remove your personal information from the bottle(s) and place the bottle(s) in the shipper. For more information, please ask the Certified Pharmacy for more details.

WHAT IF I HAVE CONCERNS ABOUT HAVING XYREM IN MY HOME?

- If your XYREM is lost or stolen, report the incident right away to the local police and to the Certified Pharmacy
- Use XYREM only as your healthcare provider tells you. Remember that use of your XYREM by others is illegal
- If you have any questions or concerns, or if you need advice about XYREM, call your healthcare provider or the Certified Pharmacy

INSURANCE COVERAGE

WILL INSURANCE PAY FOR MY XYREM?

In most cases, YES. A staff member from the Certified Pharmacy will call and work with your insurance company to help you get coverage for XYREM. In the unlikely event your insurance does not cover XYREM or you can't afford the out-of-pocket costs, ask the Certified Pharmacy about available financial assistance programs.

WHAT IS THE PHARMACY'S ROLE WITH MY INSURANCE?

An experienced staff member will:

- Call you to go over your prescription benefits and coverage
- Tell you what your co-pay is, if applicable
- Tell you about any XYREM prescription savings plans for which you may qualify
- Work with your healthcare provider on prior authorizations, if required by your insurance company
- Provide information about any financial help that may be available to you

The Certified Pharmacy's attempt to get coverage from a third-party payer does not guarantee that you will get coverage.

XYREM® (sodium oxybate) oral solution

GETTING MORE INFORMATION

WHERE CAN I GET MORE INFORMATION ABOUT XYREM?

For more information about XYREM, contact the REMS:

- **Phone:** 1-866-997-3688
- **Fax:** 1-866-470-1744 (toll free)
- **Outside the US:** +314-475-6000, ext 361 587
- **Website:** www.XYWAVXYREMREMS.com

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KEEP THIS BOOKLET AS A HELPFUL REMINDER

If you have questions or need information, contact the XYWAV and XYREM REMS.

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

Jazz Pharmaceuticals®

XYREM® (sodium oxybate) oral solution

3001 v3 Rev0721

The pharmacy may ask you to measure how much XYREM is left in your bottle. Please use this ruler to give them this information.

XYWAV and XYREM REMS

BROCHURE FOR PEDIATRIC PATIENTS AND THEIR CAREGIVERS

Important information about the safe use and handling of XYREM

Reference ID: 4840646

XYREM®
(sodium oxybate) oral solution

XYWAV and XYREM REMS

Dear Caregiver,

Welcome to the XYWAV and XYREM REMS You are receiving these materials because your child's healthcare provider has prescribed **XYREM**® (sodium oxybate) oral solution, 0.5 g/mL, for your child. XYREM is a medicine used to treat cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. XYREM may only be given to patients enrolled in the REMS.

Because of the serious risks associated with XYREM, the Food and Drug Administration (FDA) has required a special program called a Risk Evaluation and Mitigation Strategy (REMS). The purpose of this REMS is to make sure the benefits of XYREM outweigh the risks. All patients must be enrolled in the REMS to receive XYREM. Each pediatric patient must have a caregiver who is counseled on the serious risks and safe use of XYREM. This brochure contains information you need to know about XYREM and will help you give XYREM to your child correctly. Read this brochure before you start giving your child XYREM.

After your child's healthcare provider sends in your child's enrollment form and first prescription for XYREM, you will receive a call from the Certified Pharmacy from the XYWAV and XYREM REMS to counsel you on the serious risks and safe use of Xyrem, to tell you about the XYWAV and XYREM REMS requirements, and to answer any questions you or your child may have about XYREM.

A few things must happen before you receive your child's first shipment of XYREM:

- The Certified Pharmacy will call to:
  - Ask if your child's healthcare provider reviewed the XYREM Brochure for Pediatric Patients and Their Caregivers with you
  - Explain that you will receive this brochure with your child's first shipment, and that all drug shipments will include the XYREM Medication Guide
  - Ask you about your child's medical history and other medications he or she may be taking
  - Give you advice on how to prepare and give XYREM to your child and how to store it safely
  - Go over your child's insurance information
- **You must take this call before you can get your child's XYREM**

XYREM® (sodium oxybate) oral solution

If you have any additional questions about XYREM, please call your child's healthcare provider, or you can contact the XYWAV and XYREM REMS toll free at 1-866-997-3688. You can reach a pharmacist at this number 24 hours a day, 7 days a week with any questions. We hope you find this information and the XYWAV and XYREM REMS helpful.

Sincerely,

Jazz Pharmaceuticals

WARNING: XYREM can cause serious side effects.
Your child should not drink alcohol or take other medicines that cause sleepiness

XYREM is a prescription medicine used to treat patients 7 years of age and older with narcolepsy to reduce too much daytime sleepiness and to reduce cataplexy (suddenly weak or paralyzed muscles).

IMPORTANT INFORMATION ABOUT XYREM INCLUDES THE FOLLOWING:

- When taking XYREM, your child should not drink alcohol or take other medicines that may slow his or her breathing or mental activity or make him or her sleepy. Your child could have serious side effects
- XYREM can cause serious side effects, including slow breathing or changes in alertness. Call your child's doctor right away if your child has any of these serious side effects
- Abuse of XYREM can lead to dependence (a physical need to take the drug), craving for the medicine, and severe withdrawal symptoms (symptoms that start when the drug is stopped, especially when it is stopped suddenly)

XYREM® (sodium oxybate) oral solution

- Patients usually fall asleep in about 5 to 15 minutes, although some patients have reported falling asleep more quickly (without first feeling drowsy) and others take more time. The time that it takes to fall asleep might be different from night to night. You should give each dose of XYREM while your child is sitting up in bed and have your child lie down immediately after. Give the first dose at the time prescribed by your child's healthcare provider, and the second dose 2½ to 4 hours later. You may need to set an alarm to awaken to give the second dose
- Your child should not do anything that requires him or her to be fully alert for the first 6 hours after taking XYREM. When your child first starts taking XYREM, you and your child will need to be careful until you know how XYREM affects him or her.
- Keep XYREM out of the reach of children and pets. Get emergency medical help right away if a child who has not been prescribed XYREM drinks XYREM
- Report all side effects to your child's healthcare provider

WHAT WILL YOU FIND IN THIS BROCHURE?

This brochure provides information on the serious risks and safe use of XYREM, answers important questions about how to use XYREM properly, how to store it safely, and how to get your child's XYREM.

WHAT IS THE XYWAV AND XYREM REMS PROGRAM?

Because of the serious risks associated with XYREM, the FDA has required a special program called REMS for XYWAV and XYREM. Enrollment in the REMS by prescribers and patients is required by the FDA to ensure the benefits of XYREM outweigh the risks associated with XYREM. Your child is enrolled when your child's healthcare provider sends in your signed enrollment form. At that time, your child's healthcare provider also will send your child's prescription for XYREM to the Certified Pharmacy.

The Certified Pharmacy staff will review important information about XYREM with you. They will also answer any questions you and your child may have about XYREM.

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XYREM® (sodium oxybate) oral solution

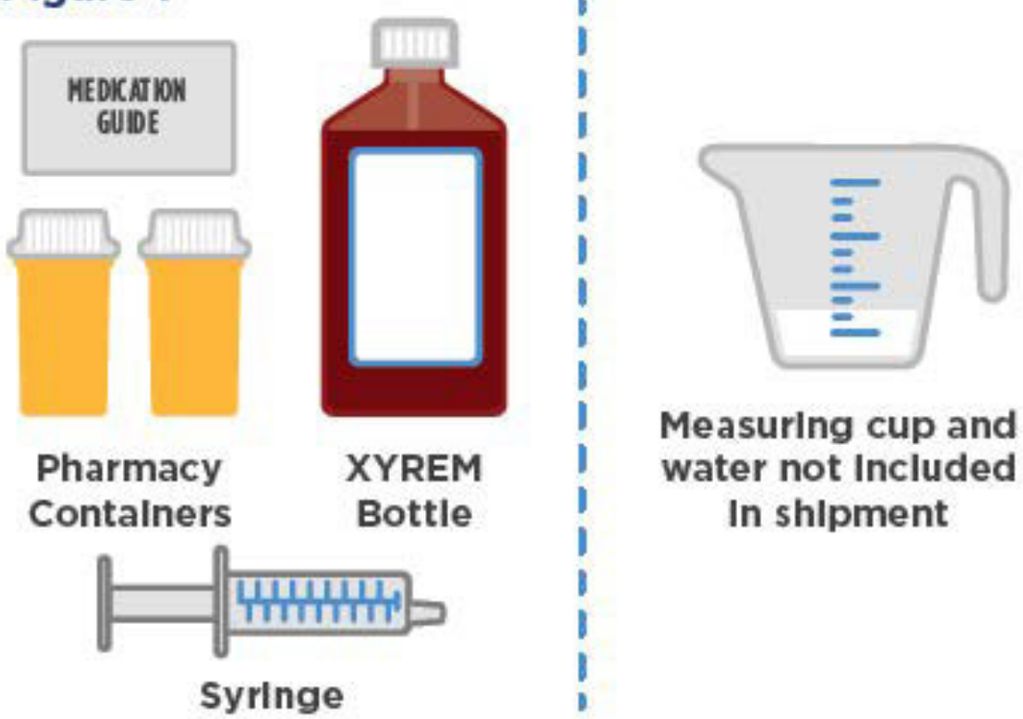
Preparation and Administration of XYREM

XYREM should be prepared and taken only as prescribed by your child's healthcare provider.

WHAT WILL I GET WITH MY CHILD'S XYREM PRESCRIPTION?

With each prescription, you will get 1 or more bottles of XYREM (each bottle, whether full or partial, contains the concentrated medicine), a dosing syringe for drawing up your child's XYREM dose, 2 **empty** pharmacy containers with child-resistant caps, and a printed Medication Guide (Figure 1).

Figure 1

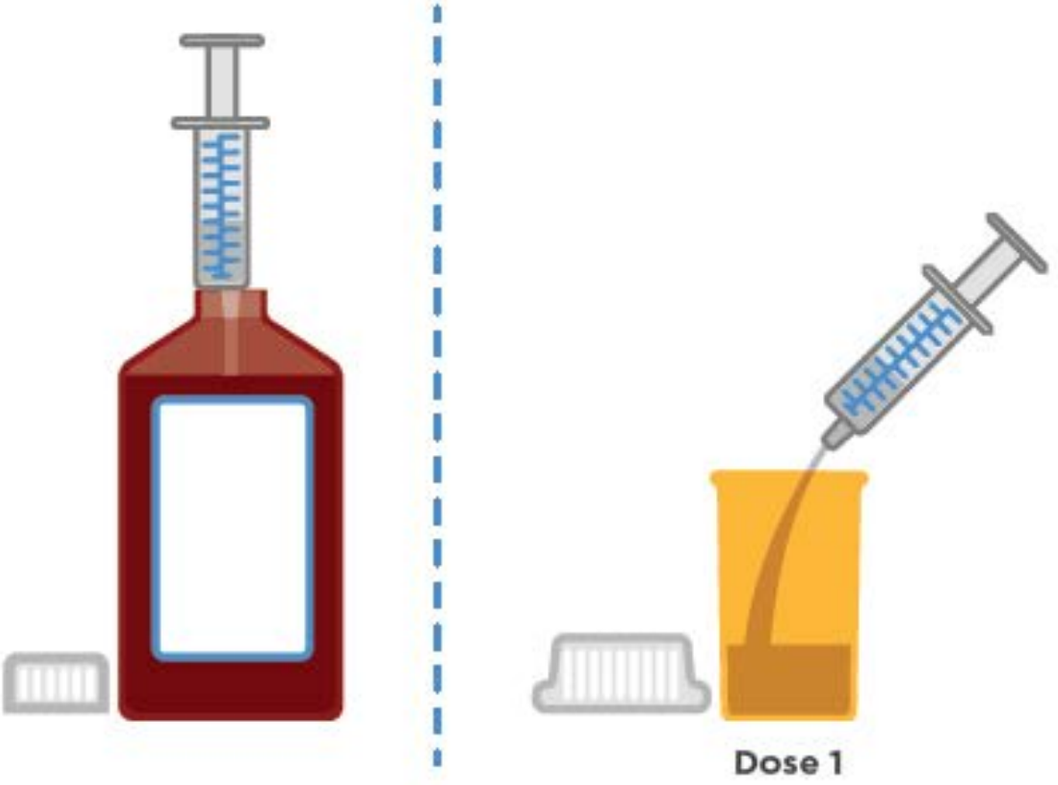


XYREM® (sodium oxybate) oral solution

HOW DO I PREPARE MY CHILD'S DOSES?

Place the bottle on a hard, flat surface and grip the bottle with one hand and firmly press the syringe into the center opening of the bottle with the other. Pull back on the plunger until the medication flows into the syringe and the liquid level is aligned with the corresponding tick mark for your child's dose. After you draw up the first XYREM dose, remove the syringe from the opening of the XYREM bottle. Empty all of the medicine from the syringe into 1 of the provided **empty** pharmacy containers by pushing down on the plunger until it stops (Figure 2).

Figure 2



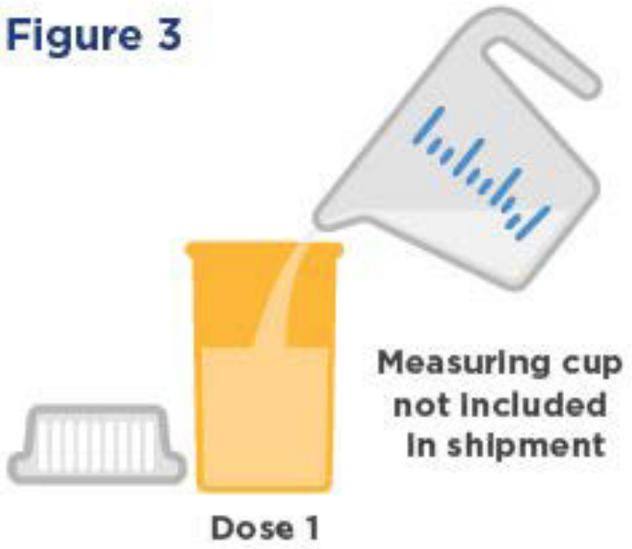
Any questions? Please call the XYWAV and XYREM REMS at 1-866-997-3688.
Please see the Medication Guide for more-detailed information about XYREM.

Using a measuring cup, pour about ¼ cup of water into the pharmacy container. **Be careful to add only water to the pharmacy container and not more XYREM.** Place the child-resistant cap provided on the filled pharmacy container and turn the cap clockwise (to the right) until it clicks and locks in its child-resistant position.

Repeat the steps described above by drawing up the amount of medicine prescribed for your child's second dose; emptying the syringe into the second pharmacy container, adding about ¼ cup of water, and closing the pharmacy container.

Put the cap back on the XYREM bottle and store the XYREM bottle and both prepared doses in a safe and secure place. Store in a locked place if needed. Keep the XYREM bottle and both prepared XYREM doses out of the reach of children and pets.

Figure 3



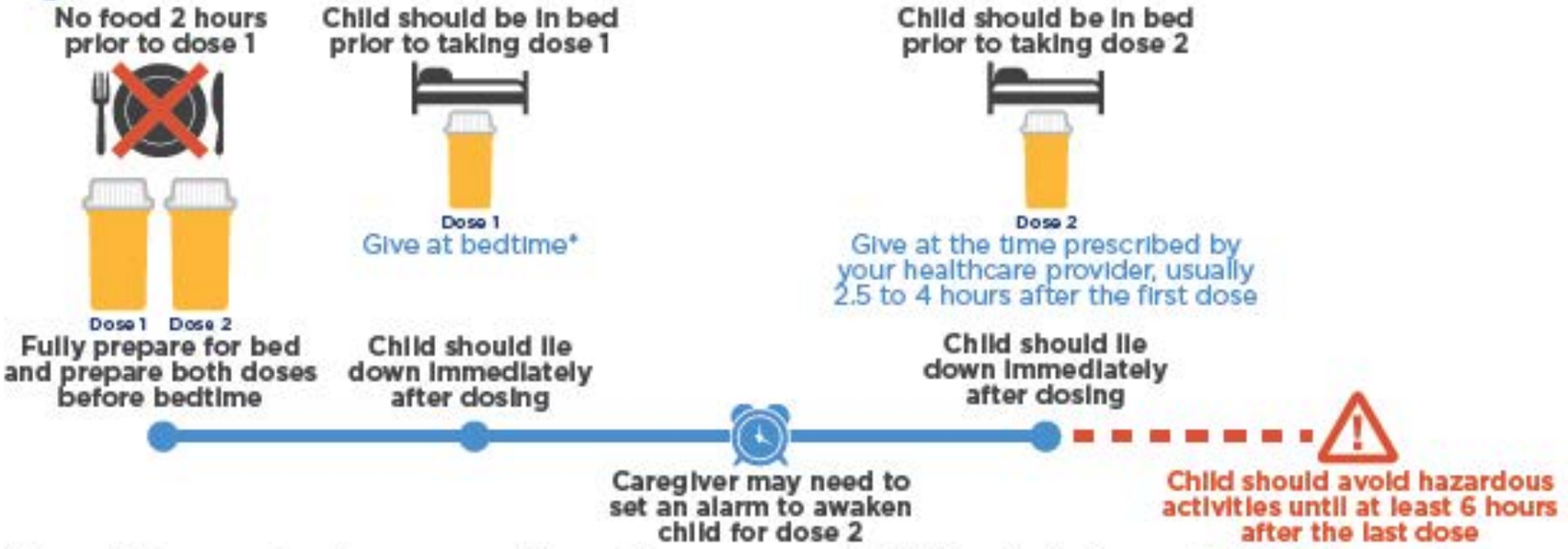
Rinse out the syringe and pharmacy containers with water after each use. Please refer to the Instructions for Use within the Medication Guide for additional details.

HOW DO I GIVE MY CHILD'S DOSES?

Wait at least 2 hours after your child eats before giving XYREM.

XYREM is a medicine that can make your child sleepy quickly; therefore, give your child's doses while he or she is sitting up in bed and have your child lie down immediately after dosing and remain in bed. Ensure your child is fully prepared for bed prior to taking the first nightly dose of XYREM (for example, has brushed teeth, gone to the bathroom). Give the first dose at the time prescribed by your child's healthcare provider, and the second dose 2½ to 4 hours later. Ensure that all XYREM doses are kept in a safe place until given. If your child continues evening activities after taking his or her dose, such as watching television or walking around, your child may experience light-headedness, dizziness, nausea, confusion, or other unpleasant feelings. Have the child lie down immediately after dosing and remain in bed (Figure 4).

Figure 4



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

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

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

WHAT DO I DO IF MY CHILD MISSES A DOSE?

- It is very important to give both doses of XYREM each night as prescribed. If the second dose is missed, skip that dose
  - Do not give your child XYREM again until the next night
  - Never give your child both XYREM doses at the same time
- Any unused XYREM doses that you prepared but didn't give to your child must be thrown away within 24 hours from the time you first prepared your child's doses

HOW SOON WILL WE SEE A CHANGE IN SYMPTOMS?

After starting XYREM, it may take a few weeks or longer to see your child's symptoms improve. It may also take time to find the right dose that works for your child. It is important that you talk with your child's healthcare provider often when your child first starts taking XYREM.

Tell your child's healthcare provider if you or your child do not see any improvements.

WHAT ARE THE SIDE EFFECTS OF XYREM?

XYREM can cause serious side effects, including breathing problems (slower breathing, trouble breathing, and short periods of no breathing while asleep), mental health problems (confusion, seeing or hearing things that are not real, unusual or disturbing thoughts, feeling anxious or upset, depression, thoughts of suicide), and sleepwalking. If your child has any of these side effects, call your child's healthcare provider right away.

XYREM® (sodium oxybate) oral solution

The most common side effects of XYREM in children are nausea, bedwetting, throwing up, headache, weight loss, decreased appetite, dizziness, and sleepwalking. Side effects may increase with higher doses.

These are not the only possible side effects with XYREM. If you or your child are worried about any possible side effects with XYREM, talk with your child's healthcare provider or the pharmacist at the XYWAV and XYREM REMS.

You should report all side effects by contacting your child's healthcare provider, Jazz Pharmaceuticals at 1-800-520-5568, or the FDA at 1-800-FDA-1088.

ARE THERE ANY PRECAUTIONS THAT SHOULD BE TAKEN WHILE MY CHILD IS ON XYREM?

- While taking XYREM, your child should not drink alcohol or take medicines that cause sleepiness
- Your child should not do anything that requires him or her to be fully alert for the first 6 hours after taking XYREM. When your child first starts taking XYREM, you and your child will need to be careful until you know how XYREM affects him or her.
- Before starting XYREM, tell your child's healthcare provider if your child is pregnant, or plans to become pregnant, or is breastfeeding. XYREM passes into breast milk. You and your child's healthcare provider should decide if your child will take XYREM or breastfeed.
- Keep XYREM in a safe place, out of the reach of children
- Give XYREM to your child while he or she is sitting up in bed and have your child lie down immediately and remain in bed after dosing

Tell your child's healthcare provider and pharmacist about any other medicines he or she is taking, including if your child begins a new medicine while taking XYREM. This would include prescription and non-prescription medicines, vitamins, and supplements.

It is also important to tell other healthcare providers, including pharmacists, that your child is taking XYREM before your child starts or changes any medications.

How Often Should My Child's Healthcare Provider Check on My Child's Progress On XYREM?

When your child first starts taking XYREM, you may need to talk to his or her healthcare provider often until he or she has determined the best dose for your child. You can expect that your child's dose may need to be adjusted. After your child's dose has been established, his or her healthcare provider should check on your child every 3 months while taking XYREM.

What do I need to do if my child is taking XYWAV® and their doctor prescribes XYREM for them?

- **Your child should never take both XYREM and XYWAV at the same time, it can lead to serious side effects**
- XYREM contains the same medicine as XYWAV, which is called oxybate, but with more sodium
- Your child should take their XYREM exactly as instructed by their doctor
- Prepare your child's XYREM the same way you prepared XYWAV

XYREM® (sodium oxybate) oral solution

- Do not mix XYREM and XYWAV together. If you have unused XYWAV, dispose of it before your child starts XYREM. Refer to "HOW DO I PROPERLY DISPOSE OF XYREM?" for further instructions
- The Certified Pharmacy will contact you to talk to you about how to make this change
- XYREM contains a large amount of sodium (salt) and may not be right for your child, especially if they are on a salt-restricted diet or have had heart failure, high blood pressure (hypertension), or kidney problems. Make sure to tell your child's doctor if your child has any of these conditions before they start XYREM.

Storage and Safety Tips at Home

HOW DO I STORE XYREM?

- Always store XYREM in its original bottle
- Store XYREM at room temperature. Do not refrigerate XYREM
- Keep XYREM in a safe place, out of the reach of children and pets. Get emergency medical help (call 911) right away if a child not prescribed XYREM drinks XYREM

HOW DO I PROPERLY DISPOSE OF XYREM?

To properly dispose of XYREM, pour any unused XYREM down the sink or toilet drain. Mark out all personal information on the prescription label, including the XYREM name, to make it unreadable before putting the empty bottle in the trash.

XYREM patients have the option to return unused or expired drug. Please ask the Certified Pharmacy for more details.

If you misplace, lose, or damage your child's XYREM dosing syringe, contact the Certified Pharmacy to have it replaced. Do not use a different syringe or try to guess the correct dose.

XYWAV AND XYREM TAKEBACK PROGRAM

XYWAV or XYREM patients have an option to return any unused, leftover or expired XYWAV or XYREM product through a drug takeback program, upon request. Patients can request a shipper from the Certified Pharmacy. Once you receive the shipper, remember to mark out or remove your personal information from the bottle(s) and place the bottles in the shipper. For more information, please ask the Certified Pharmacy for more details.

WHAT IF I HAVE CONCERNS ABOUT HAVING XYREM IN MY HOME?

- If your child's XYREM is lost or stolen, report the incident right away to the local police and to the Certified Pharmacy
- Give XYREM only as your child's healthcare provider tells you. Remember that use of your child's XYREM by others is illegal
- If you have any questions or concerns, or if you need advice about XYREM, call your child's healthcare provider or the Certified Pharmacy

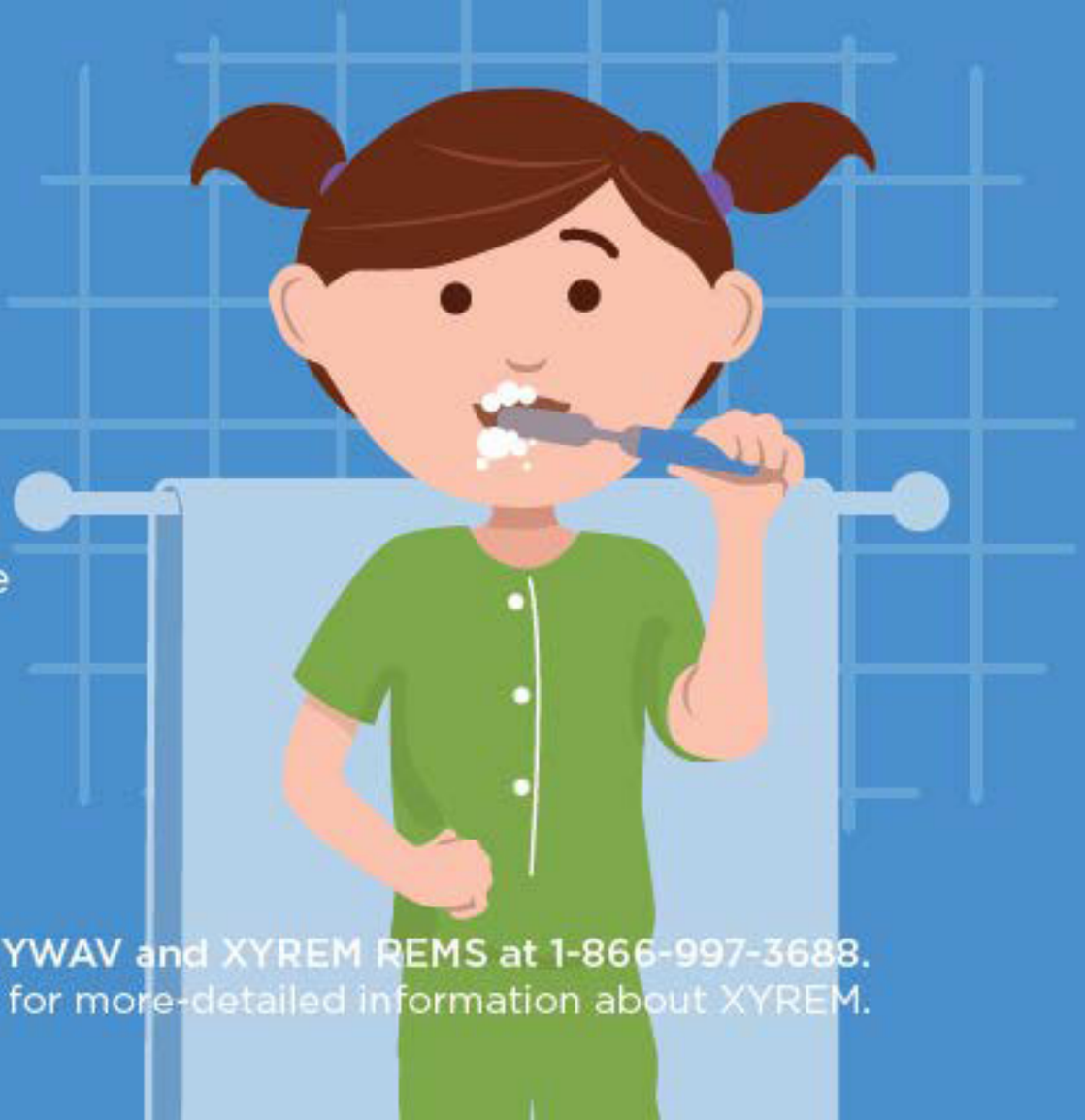
XYREM® (sodium oxybate) oral solution

XYWAV and XYREM REMS

Important Information Your Child Must Know About Taking XYREM

You can use these pages to help teach your young child what they need to know about taking their XYREM.

WHAT SHOULD MY CHILD KNOW ABOUT TAKING XYREM?



Get Ready

- Get ready for bed before you drink your XYREM
- Finish your bedtime routine before you get in bed and drink your XYREM

Any questions? Please call the XYWAV and XYREM REMS at 1-866-997-3688.
Please see the Medication Guide for more-detailed information about XYREM.

Reference ID: 4840646

Stay In Bed

- Drink your XYREM while sitting up in bed. Lie down right away after you drink it and stay in bed
- Call for a grown-up if you want to get out of bed after taking XYREM
- It may take a while, or you may fall asleep quickly after taking XYREM

XYREM®
(sodium oxybate) oral solution

Reference ID: 4840648

XYWAV and **XYREM** REMS

Be Careful

- Be careful in the morning
- Call for a grown-up to help you if you still feel sleepy in the morning

Any questions? Please call the XYWAV and XYREM REMS at 1-866-997-3688.
Please see the Medication Guide for more-detailed information about XYREM.

Reference ID: 4840646

Always Remember!

- Don't share your XYREM with anyone else
  - This medicine is only for you!
- Don't drink too much XYREM
  - Never drink more than 1 of your XYREM cups at a time
  - Only drink XYREM from your XYREM cup
- Tell a grown-up how you are feeling and about any changes in how you are feeling

XYREM®
(sodium oxybate) oral solution

Reference ID: 4840646

Including Your Child in His or Her Care

HOW CAN I PREPARE MY CHILD TO BE ABLE TO CARRY OUT ONE OR MORE SAFE USE ACTIVITIES?

It is important for your child to take an active part in the safe use of his or her XYREM. This is especially true for teenagers and those going to college. This brochure can help you talk with your child about taking XYREM.

Before your child moves away from your home (for example, going away to college), talk with your healthcare provider and the Certified Pharmacy about additional ways to ensure safe use, handling, and storage. To help prepare your child for this transition, make sure that he or she is counseled about the serious risks and safe use of XYREM by a member of your child's XYREM healthcare team (for example, your child's healthcare provider or the Certified Pharmacy). Your child should also read this brochure and ask his or her healthcare provider any questions he or she may have.

Enrolling Your Child in the XYWAV and XYREM REMS

DOES MY CHILD HAVE TO ENROLL IN THE XYWAV AND XYREM REMS?

Yes. In order for your child to receive XYREM, your healthcare provider will have you sign an enrollment form and will send the form to the REMS. You must verify that you have been counseled by your child's healthcare provider on the serious risks and safe use of XYREM and that you were able to ask your child's healthcare provider any questions you have about XYREM. You may choose to have your child also receive counseling from your healthcare provider on the serious risks and safe use of XYREM.

WHAT IS MY ROLE AS A CAREGIVER?

As a caregiver of a pediatric patient who is in the REMS, you are required to:

- Read this brochure and ask your child's healthcare provider any questions you have about XYREM.
- Ensure that XYREM is prepared and given only as prescribed
- Ensure that XYREM is kept in a safe place, away from children and pets, and protected from theft

XYREM® (sodium oxybate) oral solution

- Notify your child's healthcare provider right away if you notice any serious side effects while your child is taking XYREM

Also be sure to let your child's healthcare provider know if your child is taking other medicines or if your child has any medical conditions that might affect his or her breathing.

If you need to give your responsibilities as your child's caregiver to someone else, please notify your child's healthcare provider. You also can contact the REMS toll free at 1-866-997-3688 to make sure that the new caregiver is counseled on the risks and safe use of XYREM.

Filling Your Child's XYREM Prescription

HOW IS MY CHILD'S PRESCRIPTION FILLED?

All XYREM prescriptions are filled and shipped directly to your home only by the REMS Certified Pharmacy.

WHAT ELSE DOES THE CERTIFIED PHARMACY DO?

Your child's healthcare provider sends your child's XYREM prescription directly to the Certified Pharmacy.

You will then receive a call from the Certified Pharmacy to counsel you on the serious risks and safe use of XYREM, to tell you how to get your child started on XYREM and to answer any questions about XYREM. A staff member from the Certified Pharmacy will call you to complete a counseling checklist. The counseling checklist will include information about other medicines that your child is taking and other medical conditions that might increase your child's risk of serious side effects. The Certified Pharmacy will go over the information about how to use XYREM safely and provide a copy of the Medication Guide with each XYREM shipment.

XYREM® (sodium oxybate) oral solution

The Certified Pharmacy will always ask you where and when you would like your child's XYREM delivered and who will sign for the shipment. XYREM will be shipped by an overnight service. You may be able to have your child's XYREM shipped to your place of work or to a local overnight carrier hub for pickup. Saturday deliveries may also be an option for you. The Certified Pharmacy will work with you to find the best options available. When the courier arrives, you or another adult you previously named must sign for your child's XYREM.

Finally, the Certified Pharmacy will call you soon after you receive your child's first XYREM shipment to confirm receipt and answer any questions you may have about your child's first few days taking XYREM.

HOW DO I GET XYREM REFILLS FOR MY CHILD?

The Certified Pharmacy will contact you when it is close to your child's refill time. You may opt-in to receive text, e-mail, or automated voice reminders for refills. You may also call the Certified Pharmacy at 1-866-997-3688 to schedule your child's refills.

CAN MY LOCAL PHARMACY PROVIDE XYREM FOR MY CHILD?

No. You can get your child's XYREM only from the XYWAV and XYREM REMS Certified Pharmacy.

Insurance Coverage

WILL INSURANCE PAY FOR MY CHILD'S XYREM?

In most cases, YES. A staff member from the Certified Pharmacy will call and work with your child's insurance company to help you get coverage for your child's XYREM. In the unlikely event your child's insurance does not cover XYREM or you can't afford the out-of-pocket costs, ask the Certified Pharmacy about available financial assistance programs.

WHAT IS THE PHARMACY'S ROLE WITH MY CHILD'S INSURANCE?

An experienced staff member will:

- Call you to go over your child's prescription benefits and coverage
- Tell you what your co-pay is, if applicable
- Tell you about any XYREM prescription savings plans for which you may qualify
- Work with your child's healthcare provider on prior authorizations, if required by the insurance company
- Provide information about any financial help that may be available to you

The Certified Pharmacy's attempt to get coverage from a third-party payer does not guarantee that you will get coverage.

XYREM® (sodium oxybate) oral solution

Contact Information

WHOM SHOULD I CONTACT WITH CONCERNS OR FOR MORE INFORMATION ABOUT XYREM?

FOR QUESTIONS ABOUT SIDE EFFECTS OR FOR MORE INFORMATION ABOUT XYREM, CONTACT YOUR CHILD'S HEALTHCARE PROVIDER:

Name: _____

Phone: _____

Email: _____

FOR MORE INFORMATION ABOUT XYREM, CONTACT THE CERTIFIED PHARMACY:

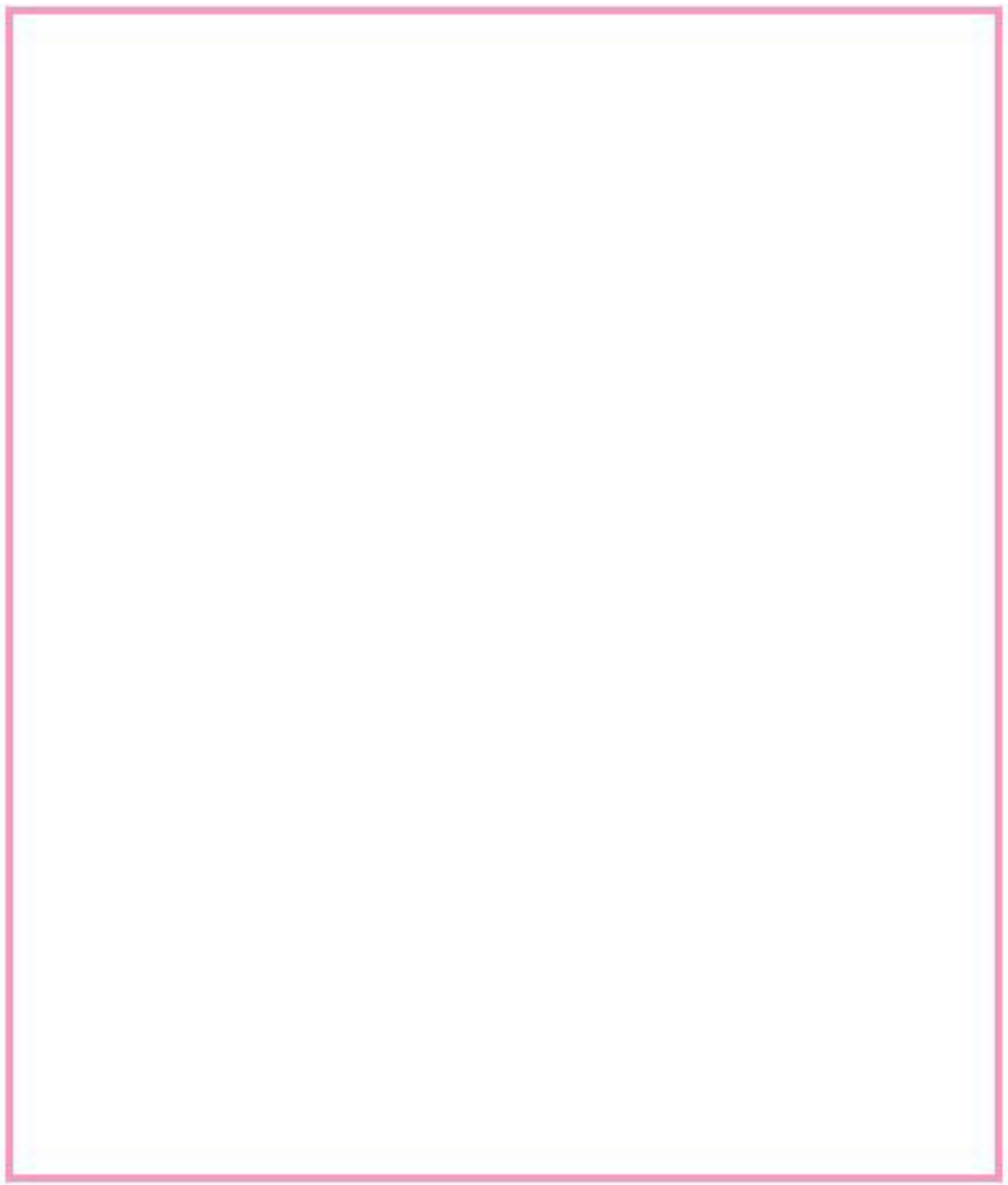
- **Phone:** 1-866-997-3688
- **Fax:** 1-866-470-1744 (toll free)
- **Outside the US:** +314-475-6000, ext. 361 587
- **Website:** www.XYWAVXYREMREMS.com

TO REPORT ALL SIDE EFFECTS, YOU CAN CONTACT:

- Jazz Pharmaceuticals at 1-800-520-5568
- The FDA at 1-800-FDA-1088

FOR EMERGENCIES:

- Call 911



KEEP THIS BOOKLET AS A HELPFUL REMINDER

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

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

Jazz Pharmaceuticals®

XYREM® (sodium oxybate) oral solution

3002 v3 Rev0721

The pharmacy may ask you to measure how much XYREM is left in your bottle. Please use this ruler to give them this information.

XYWAV and XYREM REMS

PATIENT QUICK START GUIDE

Important information about the safe use and handling of XYWAV

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

Reference ID: 4840646

Dear Patient,

Welcome to the XYWAV and XYREM REMS. You are receiving these materials because your healthcare provider has prescribed XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL, for you. 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 also indicated for the treatment of idiopathic hypersomnia in adults. *If you are the caregiver of a pediatric patient receiving XYWAV, please refer to the XYWAV Brochure for Pediatric Patients and Their Caregivers instead of this guide for important information about helping your child get started with XYWAV.*

Because of the serious risks associated with XYWAV, the Food and Drug Administration (FDA) has required a special program called a Risk Evaluation and Mitigation Strategy (REMS) for XYWAV. The purpose of this REMS is to make sure the benefits of XYWAV outweigh the risks. All patients must be enrolled in the REMS to receive XYWAV. This Quick Start Guide contains information you need to know about XYWAV and will help you to use XYWAV correctly. Read this Quick Start Guide before you start taking XYWAV.

After your healthcare provider sends in your enrollment form and first prescription for XYWAV, you will receive a call from the Certified Pharmacy of the REMS to tell you how the REMS helps you get started with taking XYWAV and to answer any questions you may have about XYWAV.

Reference ID: 4840646

You will also speak with appropriate staff at the Certified Pharmacy, who will go over your insurance information with you. Before you can receive your first shipment of XYWAV, a pharmacist at the Certified Pharmacy will ask if your healthcare provider reviewed the XYWAV Patient Quick Start Guide with you and explain that you will receive this guide with your first shipment, and that all drug shipments will include the XYWAV Medication Guide. The pharmacist will also ask you about your medical history and other medications you may be taking, and give you advice on how to prepare and take your XYWAV and how to store it safely. **You must take this call before you can get your XYWAV.**

Please call your healthcare provider if you have questions about XYWAV, or you can contact the REMS toll free at 1-866-997-3688. You can reach a pharmacist at this number 24 hours a day, 7 days a week with any questions.

We hope you find this information and the REMS services helpful.

Sincerely,

Jazz Pharmaceuticals

XYWAV and XYREM REMS

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

XYWAV is a prescription medicine used to treat patients 7 years of age and older with narcolepsy to reduce too much daytime sleepiness and to reduce cataplexy (suddenly weak or paralyzed muscles). XYWAV is also used to treat idiopathic hypersomnia (IH) in adults.

IMPORTANT INFORMATION ABOUT XYWAV INCLUDES THE FOLLOWING:

- When taking XYWAV, do not drink alcohol or take other medicines that slow your breathing or mental activity or make you sleepy. You could have serious side effects
- XYWAV can cause serious side effects, including trouble breathing while asleep, confusion, unusual or disturbing thoughts, depression, and passing out, even at recommended doses. Tell your healthcare provider if you have any of these problems while taking XYWAV
- Abuse of XYWAV can lead to dependence (a physical need to take the drug), craving for the medicine, and severe withdrawal symptoms (symptoms that start when the drug is stopped, especially when it is stopped suddenly)
- Patients usually fall asleep in about 5 to 15 minutes, although some patients have reported falling asleep more quickly (without first feeling drowsy) and others take more time. The time that it takes to fall asleep might be different from night to night. You should take each dose of XYWAV while in bed. Lie down immediately after taking XYWAV and remain in bed afterwards.

Any questions? Please call the XYWAV and XYREM REMS at 1-866-997-3688.
Please see the Medication Guide for more detailed information about XYWAV.

- XYWAV can be taken 1 or 2 times a night as prescribed by your doctor. Take the first dose at bedtime and the second 2½ to 4 hours later. You may need to set an alarm to awaken for the second dose
- Do not drive a car, use heavy machinery, fly an airplane, or do anything that is dangerous or that requires you to be alert for the first 6 hours after taking XYWAV. When you first start taking XYWAV, be careful until you know how XYWAV affects you
- Keep XYWAV out of the reach of children and pets. Get emergency medical help right away if a child drinks your XYWAV
- Report all side effects to your healthcare provider

WHAT WILL YOU FIND IN THIS BOOKLET?

This booklet answers important questions about how to get your XYWAV, how to use XYWAV properly, and how to store it safely. It also gives you important information about XYWAV.

WHAT IS THE XYWAV AND XYREM REMS PROGRAM?

Because of the serious risks associated with XYWAV, the FDA has required a special program called REMS for XYWAV and XYREM. Enrollment in the REMS by prescribers and patients is required by the FDA to ensure the benefits of XYWAV outweigh the risks associated with XYWAV. You are enrolled in the program when your healthcare provider sends in the enrollment form you signed. At that time, your healthcare provider also sent your prescription for XYWAV to the Certified Pharmacy.

The Certified Pharmacy staff will review important information about XYWAV with you. They will also answer any questions you may have about XYWAV.

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

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ENROLLING IN THE XYWAV AND XYREM REMS

WHAT AM I REQUIRED TO DO IN THE XYWAV AND XYREM REMS PROGRAM?

As a patient, your responsibility is to discuss the safe use of XYWAV with your healthcare provider and to read this XYWAV Patient Quick Start Guide before you begin taking XYWAV. Be sure to let your healthcare provider know if you are taking other medications or if you have any conditions that might affect your breathing.

DO I HAVE TO ENROLL IN THIS PROGRAM?

Yes. In order for you to receive XYWAV, your healthcare provider will have you sign an enrollment form and will send the form to the REMS. You must verify that you have been counseled by your healthcare provider on the serious risks and safe use of XYWAV and that you were able to ask your healthcare provider any questions you have about XYWAV.

FILLING YOUR XYWAV PRESCRIPTION

HOW IS MY PRESCRIPTION FILLED?

All XYWAV prescriptions are filled only by the REMS Certified Pharmacy.

WHAT DOES THE CERTIFIED PHARMACY DO?

Your healthcare provider sends your XYWAV prescription directly to the Certified Pharmacy.

After your healthcare provider sends in your first prescription of XYWAV, you will receive a call from the Certified Pharmacy to tell you how the REMS helps you get started with taking XYWAV and to answer any questions you may have about XYWAV. A staff member from the Certified Pharmacy will call you to complete a Patient Counseling Checklist. The Patient Counseling Checklist will include information about other medications that you are taking and other medical conditions which might increase your risk of serious side effects. The Certified Pharmacy will go over the information about how to use XYWAV safely and provide a copy of the Medication Guide with each XYWAV shipment.

The Certified Pharmacy will always ask you where and when you would like your XYWAV delivered and who will sign for the shipment. XYWAV will be shipped by an overnight service. When the courier arrives, you or an adult you name must sign for your XYWAV.

WHAT WILL I GET WITH MY XYWAV PRESCRIPTION?

With each prescription, you will get 1 or more bottles of XYWAV (each bottle, whether full or partial, has the concentrated medicine), a dosing syringe for drawing up your XYWAV dose, 2 **empty** pharmacy containers with child-resistant caps, and a printed Medication Guide.

HOW DO I GET MY XYWAV REFILLS?

The Certified Pharmacy will contact you when it is close to your refill time. You may opt-in to receive text, e-mail, or automated voice reminders. You may also call the Certified Pharmacy at 1-866-997-3688 to schedule your refills.

CAN MY LOCAL PHARMACY PROVIDE XYWAV?

No. You can get your XYWAV only from the REMS central Certified Pharmacy. You may be able to have your XYWAV shipped to your place of work or to a local overnight carrier hub for pickup. Saturday deliveries may also be an option for you. The Certified Pharmacy will work with you on the best options available.

HOW DO I TAKE MY XYWAV?

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

HOW DO I PREPARE MY DOSES?

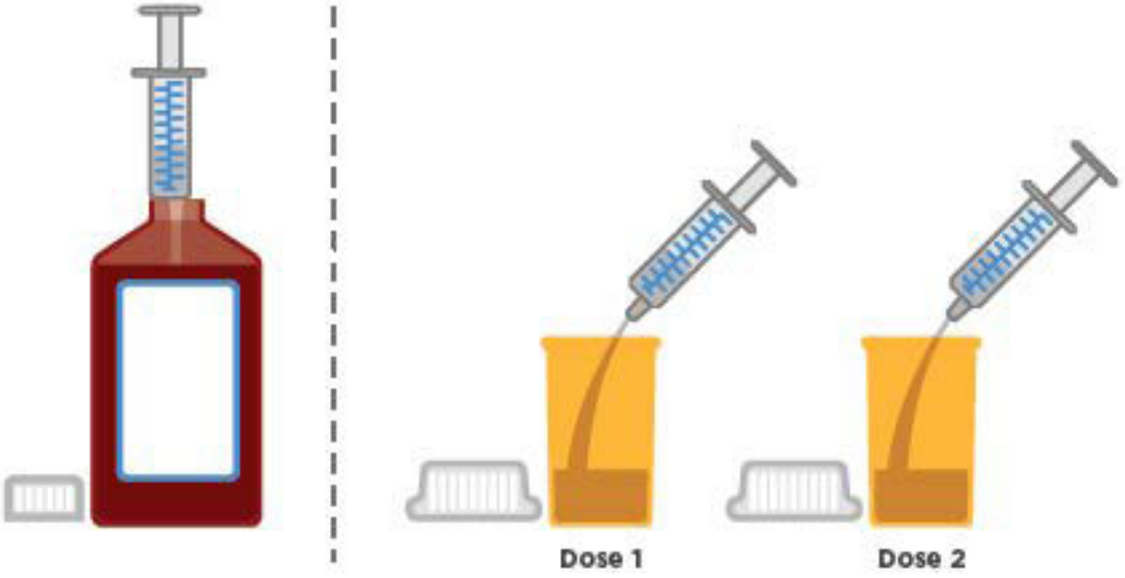
Your doctor and pharmacist will provide instructions to take XYWAV 1 time a night or 2 times a night.

- For 1 time a night, you will use the dosing syringe to draw up your prescribed XYWAV dose and empty the dose into 1 pharmacy container for mixing. You will only need1 pharmacy container to prepare your dose.
- For 2 times a night, you will need to split your prescribed XYWAV dose into 2 separate pharmacy containers for mixing. If prescribed 2 times a night, repeat the steps described above for each dose.

2 Times a Night Dosing

Place the bottle on a hard, flat surface and grip the bottle with one hand and firmly press the syringe into the center opening of the bottle with the other. Pull back on the plunger until the medicine flows into the syringe and the liquid level is lined up with the marking on the syringe that matches your dose.

After you draw up the first XYWAV dose, remove the syringe from the opening of the XYWAV bottle. Empty all of the medicine from the syringe into 1 of the provided **empty** pharmacy containers by pushing down on the plunger until it stops.



Using a measuring cup, pour about ¼ cup of water into the pharmacy container. **Be careful to add only water to the pharmacy container and not more XYWAV.** Place the child-resistant cap provided on the filled pharmacy container and turn the cap clockwise (to the right) until it clicks and locks in its child-resistant position.

Repeat the steps described above by drawing up the amount of medicine prescribed for your second dose; emptying the syringe into the second pharmacy container, adding about ¼ cup of water, and closing the

Any questions? Please call the XYWAV and XYREM REMS at 1-866-997-3688.
Please see the Medication Guide for more detailed information about XYWAV.

pharmacy container. Put the cap back on the XYWAV bottle and store the XYWAV bottle and both prepared doses in a safe and secure place. Store in a locked place if needed. Keep the XYWAV bottle and both prepared XYWAV doses out of the reach of children and pets.

Rinse out the syringe and pharmacy containers with water after each use. Please refer to the Instructions for Use within the Medication Guide for additional details.

1 Time a Night Dosing (for use in adults with Idiopathic Hypersomnia)

Place the bottle on a hard, flat surface and grip the bottle with one hand and firmly press the syringe into the center opening of the bottle with the other. Pull back on the plunger until the medicine flows into the syringe and the liquid level is lined up with the marking on the syringe that matches your dose.

After you draw up the prescribed XYWAV dose, remove the syringe from the opening of the XYWAV bottle. Empty all of the medicine from the syringe into 1 of the provided **empty** pharmacy containers by pushing down on the plunger until it stops. You may need to draw up the medicine a second time to make up your total prescribed dose. For doses requiring 2 draws from the XYWAV bottle, empty the second draw into the same pharmacy container.

Dose Preparation

xywav®

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

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Using a measuring cup, pour about ¼ cup of water into the pharmacy container. **Be careful to add only water to the pharmacy container and not more XYWAV.** Place the child-resistant cap provided on the filled pharmacy container and turn the cap clockwise (to the right) until it clicks and locks in its child-resistant position.

Dose Preparation

Put the cap back on the XYWAV bottle and store the XYWAV bottle and prepared dose in a safe and secure place. Store in a locked place if needed. Keep the XYWAV bottle and prepared XYWAV dose out of the reach of children and pets.

Rinse out the syringe and pharmacy container with water after each use. Please refer to the Instructions for Use within the Medication Guide for additional details.

HOW DO I TAKE MY DOSE(S)?

Wait at least 2 hours after eating before taking XYWAV.

XYWAV is a medicine that can make you sleepy quickly; therefore, take your dose(s) while you are in bed. Lie down immediately after taking XYWAV and remain in bed afterwards. Doses may be divided equally or unequally and the first dose taken at bedtime and the second dose taken 2½ to 4 hours later. If you continue evening activities after taking your dose, such as watching television or walking around, you may experience light-headedness, dizziness, nausea, confusion, or other unpleasant feelings.

WHAT SHOULD I DO IF I MISS A XYWAV DOSE?

- It is very important to take XYWAV each night, as prescribed.
- If you are prescribed 2 times a night dosing and you missed the second dose, skip that dose
  - Do not take XYWAV again until the next night
  - Never take both XYWAV doses at the same time
- Any unused XYWAV doses that you prepared but didn't take must be thrown away within 24 hours from the time you first prepared your doses

HOW SOON WILL I SEE A CHANGE IN MY SYMPTOMS?

After starting XYWAV, it may take a few weeks or longer to see your symptoms improve. It may also take time to find the right dose that works for you. It is important that you talk with your healthcare provider often when you first start taking XYWAV.

Tell your healthcare provider if you don't feel any improvements while taking XYWAV. XYWAV may not be right for you.

WHAT ARE THE SIDE EFFECTS OF XYWAV?

XYWAV can cause serious side effects, including breathing problems (slower breathing, trouble breathing, and short periods of no breathing while asleep), mental health problems (confusion, seeing or hearing things that are not real, unusual or disturbing thoughts, feeling anxious or upset, depression, thoughts of suicide), and sleepwalking. If you have any of these side effects, call your healthcare provider right away.

The most common side effects of XYWAV are nausea, headache, dizziness, anxiety, insomnia, decreased appetite, excessive sweating, vomiting, diarrhea, dry mouth, sleep walking, sleepiness, fatigue, and tremor. Side effects may increase with higher doses.

These are not the only possible side effects with XYWAV. If you are worried about any possible side effects with XYWAV, talk with your healthcare provider or the pharmacist at the REMS.

You should report all side effects by contacting your healthcare provider, Jazz Pharmaceuticals at 1-800-520-5568, or the FDA at 1-800-FDA-1088.

ARE THERE ANY PRECAUTIONS I SHOULD TAKE WHILE ON XYWAV?

- While taking XYWAV, do not drink alcohol or take medicines that cause sleepiness
- Do not drive a car, use heavy machinery, or do anything that is dangerous or requires you to be alert, for the first 6 hours after taking XYWAV. When you first start taking XYWAV, be careful until you know how it will affect you
- Before starting XYWAV, tell your healthcare provider if you are pregnant, or plan to become pregnant, or if you are breastfeeding. XYWAV passes into breast milk. You and your doctor should decide if you will take XYWAV or breastfeed.
- Keep your XYWAV in a safe place, out of the reach of children
- Take XYWAV while in bed

Tell your healthcare provider and pharmacist about any other medicines you are taking, including prescription and non-prescription medicines, vitamins, and supplements.

It is also important to tell other healthcare providers, including pharmacists, that you are taking XYWAV before you start or change any medications.

HOW OFTEN SHOULD MY HEALTHCARE PROVIDER CHECK MY PROGRESS WITH XYWAV?

When you first start taking XYWAV, you may need to talk to your healthcare provider often until he or she has determined the best dose for you. You can expect that your dose may need to be adjusted. After your dose has been established, your healthcare provider should check on you every 3 months while you are taking XYWAV.

WHAT DO I NEED TO DO IF I AM TAKING XYREM AND MY DOCTOR PRESCRIBES XYWAV FOR ME?

- **Never take both XYREM and XYWAV at the same time, it can lead to serious side effects**
- XYWAV contains the same medication as XYREM, which is called oxybate, but with less sodium
- Take XYWAV exactly as instructed by your doctor
- Prepare your XYWAV the same way you prepared XYREM
- Do not mix XYREM and XYWAV together. If you have unused XYREM, dispose of it before starting XYWAV. Refer to “HOW DO I PROPERLY DISPOSE OF XYWAV?” for further instructions
- The Certified Pharmacy will contact you to talk to you about how to make this change

STORAGE AND SAFETY TIPS AT HOME

HOW DO I STORE XYWAV?

- Always store XYWAV in its original bottle
- Store XYWAV at room temperature. Do not refrigerate XYWAV
- Keep XYWAV in a safe place, out of the reach of children and pets. Get emergency medical help (call 911) right away if a child drinks your XYWAV

HOW DO I PROPERLY DISPOSE OF XYWAV?

To properly dispose of XYWAV, pour any unused XYWAV down the sink or toilet drain. Mark out all personal information on the prescription label, including the XYWAV name, to make it unreadable before putting the empty bottle in the trash.

XYWAV patients have the option to return unused or expired drug. Please ask the Certified Pharmacy for more details.

If you misplace, lose, or damage your XYWAV dosing syringe, contact the Certified Pharmacy to have it replaced. Do not use a different syringe or try to guess the correct dose.

XYWAV AND XYREM TAKEBACK PROGRAM

XYWAV or XYREM patients have an option to return any unused, leftover or expired XYWAV or XYREM product through a drug takeback program, upon request. Patients can request a shipper from the Certified Pharmacy. Once you receive the shipper, remember to mark out or remove your personal information from the bottle(s) and place the bottles in the shipper. For more information, please ask the Certified Pharmacy for more details.

WHAT IF I HAVE CONCERNS ABOUT HAVING XYWAV IN MY HOME?

- If your XYWAV is lost or stolen, report the incident right away to the local police and to the Certified Pharmacy
- Use XYWAV only as your healthcare provider tells you. Remember that use of your XYWAV by others is illegal
- If you have any questions or concerns, or if you need advice about XYWAV, call your healthcare provider or the Certified Pharmacy

INSURANCE COVERAGE

WILL INSURANCE PAY FOR MY XYWAV?

In most cases, YES. A staff member from the Certified Pharmacy will call and work with your insurance company to help you get coverage for XYWAV. In the unlikely event your insurance does not cover XYWAV or you can't afford the out-of-pocket costs, ask the Certified Pharmacy about available financial assistance programs.

WHAT IS THE PHARMACY'S ROLE WITH MY INSURANCE?

An experienced staff member will:

- Call you to go over your prescription benefits and coverage
- Tell you what your co-pay is, if applicable
- Tell you about any XYWAV prescription savings plans for which you may qualify
- Work with your healthcare provider on prior authorizations, if required by your insurance company
- Provide information about any financial help that may be available to you

The Certified Pharmacy's attempt to get coverage from a third-party payer does not guarantee that you will get coverage.

GETTING MORE INFORMATION

WHERE CAN I GET MORE INFORMATION ABOUT XYWAV?

For more information about XYWAV, contact the REMS:

- **Phone:** 1-866-997-3688
- **Fax:** 1-866-470-1744 (toll free)
- **Outside the US:** +314-475-6000, ext 361 587
- **Website:** www.XYWAVXYREMREMS.com

NOTES

KEEP THIS BOOKLET AS A HELPFUL REMINDER

If you have questions or need information, contact the XYWAV and XYREM REMS.

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

Jazz Pharmaceuticals®

xywav®

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

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3102 v2 Rev0721

The pharmacy may ask you to measure how much XYWAV is left in your bottle. Please use this ruler to give them this information.

XYWAV and XYREM REMS

BROCHURE FOR PEDIATRIC PATIENTS AND THEIR CAREGIVERS

Important information about the safe use and handling of XYWAV

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

Reference ID: 4840646

XYWAV and XYREM REMS

Dear Caregiver,

Welcome to the XYWAV and XYREM REMS. You are receiving these materials because your child's healthcare provider has prescribed **XYWAV**® (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL, for your child. XYWAV is a medicine used to treat cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. XYWAV may only be given to patients enrolled in the REMS.

Because of the serious risks associated with XYWAV, the Food and Drug Administration (FDA) has required a special program called a Risk Evaluation and Mitigation Strategy (REMS). The purpose of this REMS is to make sure the benefits of XYWAV outweigh the risks. All patients must be enrolled in the REMS to receive XYWAV. Each pediatric patient must have a caregiver who is counseled on the serious risks and safe use of XYWAV. This brochure contains information you need to know about XYWAV and will help you give XYWAV to your child correctly. Read this brochure before you start giving your child XYWAV.

After your child's healthcare provider sends in your child's enrollment form and first prescription for XYWAV, you will receive a call from the Certified Pharmacy of the XYWAV and XYREM REMS to counsel you on the serious risks and safe use of XYWAV, to tell you about the REMS requirements, and to answer any questions you or your child may have about XYWAV.

A few things must happen before you receive your child's first shipment of XYWAV:

- The Certified Pharmacy will call to:
  - Ask if your child's healthcare provider reviewed the XYWAV Brochure for Pediatric Patients and Their Caregivers with you
  - Explain that you will receive this brochure with your child's first shipment, and that all drug shipments will include the XYWAV Medication Guide
  - Ask you about your child's medical history and other medications he or she may be taking
  - Give you advice on how to prepare and give XYWAV to your child and how to store it safely
  - Go over your child's insurance information
- **You must take this call before you can get your child's XYWAV**

If you have any additional questions about XYWAV, please call your child's healthcare provider, or you can contact the REMS toll free at 1-866-997-3688. You can reach a pharmacist at this number 24 hours a day, 7 days a week with any questions. We hope you find this information and the REMS helpful.

Sincerely,

Jazz Pharmaceuticals

WARNING: XYWAV can cause serious side effects.
Your child should not drink alcohol or take other medicines that cause sleepiness

XYWAV is a prescription medicine used to treat patients 7 years of age and older with narcolepsy to reduce too much daytime sleepiness and to reduce cataplexy (suddenly weak or paralyzed muscles).

IMPORTANT INFORMATION ABOUT XYWAV INCLUDES THE FOLLOWING:

- When taking XYWAV, your child should not drink alcohol or take other medicines that may slow his or her breathing or mental activity or make him or her sleepy. Your child could have serious side effects
- XYWAV can cause serious side effects, including slow breathing or changes in alertness. Call your child's doctor right away if your child has any of these serious side effects
- Abuse of XYWAV can lead to dependence (a physical need to take the drug), craving for the medicine, and severe withdrawal symptoms (symptoms that start when the drug is stopped, especially when it is stopped suddenly)

- Patients usually fall asleep in about 5 to 15 minutes, although some patients have reported falling asleep more quickly (without first feeling drowsy) and others take more time. The time that it takes to fall asleep might be different from night to night. You should give each dose of XYWAV while your child is sitting up in bed and have your child lie down immediately after. Give the first dose at the time prescribed by your child's healthcare provider, and the second dose 2½ to 4 hours later. You may need to set an alarm to awaken to give the second dose
- Your child should not do anything that requires him or her to be fully alert for the first 6 hours after taking XYWAV. When your child first starts taking XYWAV, you and your child will need to be careful until you know how XYWAV affects him or her.
- Keep XYWAV out of the reach of children and pets. Get emergency medical help right away if a child who has not been prescribed XYWAV drinks XYWAV
- Report all side effects to your child's healthcare provider

WHAT WILL YOU FIND IN THIS BROCHURE?

This brochure provides information on the serious risks and safe use of XYWAV, answers important questions about how to use XYWAV properly, how to store it safely, and how to get your child's XYWAV.

Reference ID: 4840646

WHAT IS THE XYWAV AND XYREM REMS PROGRAM?

Because of the serious risks associated with XYWAV, the FDA has required a special program called REMS for XYWAV and XYREM. Enrollment in the REMS by prescribers and patients is required by the FDA to ensure the benefits of XYWAV outweigh the risks associated with XYWAV. Your child is enrolled in the program when your child's healthcare provider sends in your signed enrollment form. At that time, your child's healthcare provider also will send your child's prescription for XYWAV to the Certified Pharmacy.

The Certified Pharmacy staff will review important information about XYWAV with you. They will also answer any questions you and your child may have about XYWAV.

Table of Contents

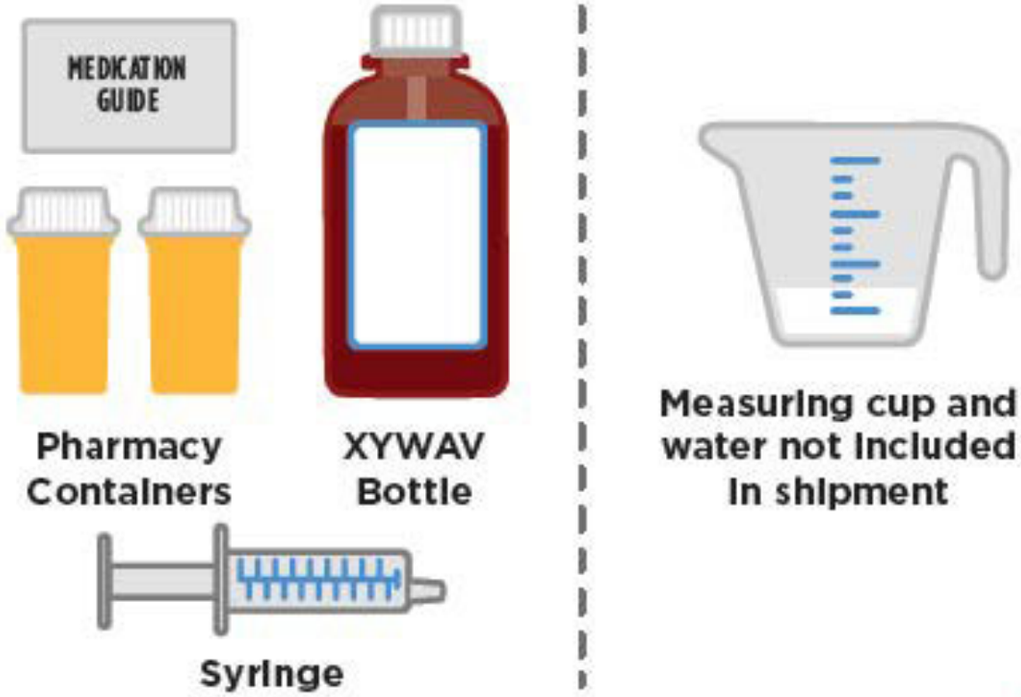
Preparation and Administration of XYWAV

XYWAV should be prepared and taken only as prescribed by your child's healthcare provider.

WHAT WILL I GET WITH MY CHILD'S XYWAV PRESCRIPTION?

With each prescription, you will get 1 or more bottles of XYWAV (each bottle, whether full or partial, contains the concentrated medicine), a dosing syringe for drawing up your child's XYWAV dose, 2 **empty** pharmacy containers with child-resistant caps, and a printed Medication Guide (Figure 1).

Figure 1



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

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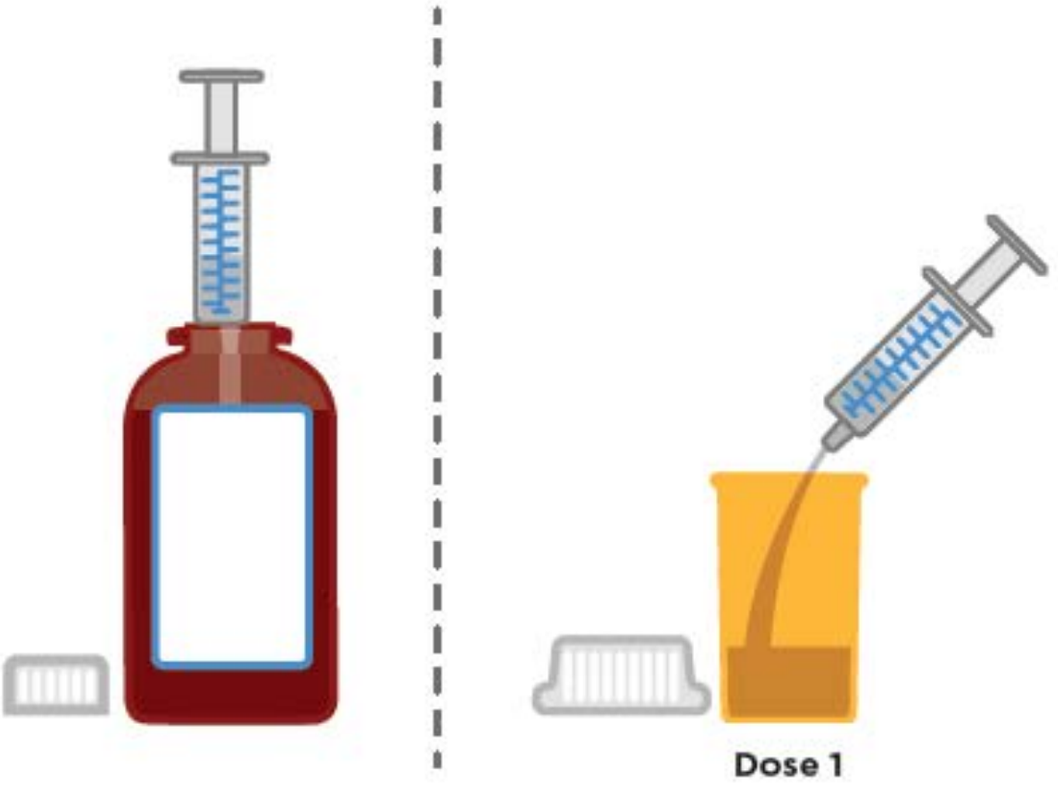
HOW DO I PREPARE MY CHILD'S DOSES?

Place the bottle on a hard, flat surface and grip the bottle with one hand and firmly press the syringe into the center opening of the bottle with the other. Pull back on the plunger until the medication flows into the syringe and the liquid level is aligned with the corresponding tick mark for your child's dose. After you draw up the first XYWAV dose, remove the syringe from the opening of the XYWAV bottle. Empty all of the medicine from the syringe into 1 of the provided **empty** pharmacy containers by pushing down on the plunger until it stops (Figure 2).

Figure 2



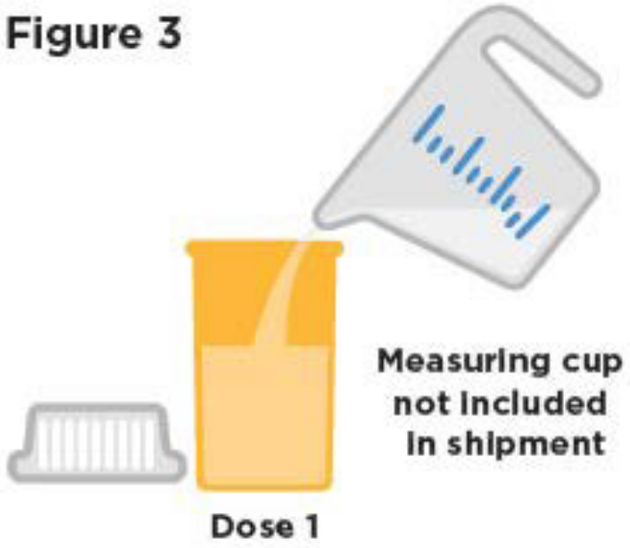
Any questions? Please call the XYWAV and XYREM REMS at 1-866-997-3688.
Please see the Medication Guide for more-detailed information about XYWAV.

Using a measuring cup, pour about ¼ cup of water into the pharmacy container. **Be careful to add only water to the pharmacy container and not more XYWAV.** Place the child-resistant cap provided on the filled pharmacy container and turn the cap clockwise (to the right) until it clicks and locks in its child-resistant position.

Repeat the steps described above by drawing up the amount of medicine prescribed for your child's second dose; emptying the syringe into the second pharmacy container, adding about ¼ cup of water, and closing the pharmacy container.

Put the cap back on the XYWAV bottle and store the XYWAV bottle and both prepared doses in a safe and secure place. Store in a locked place if needed. Keep the XYWAV bottle and both prepared XYWAV doses out of the reach of children and pets.

Figure 3



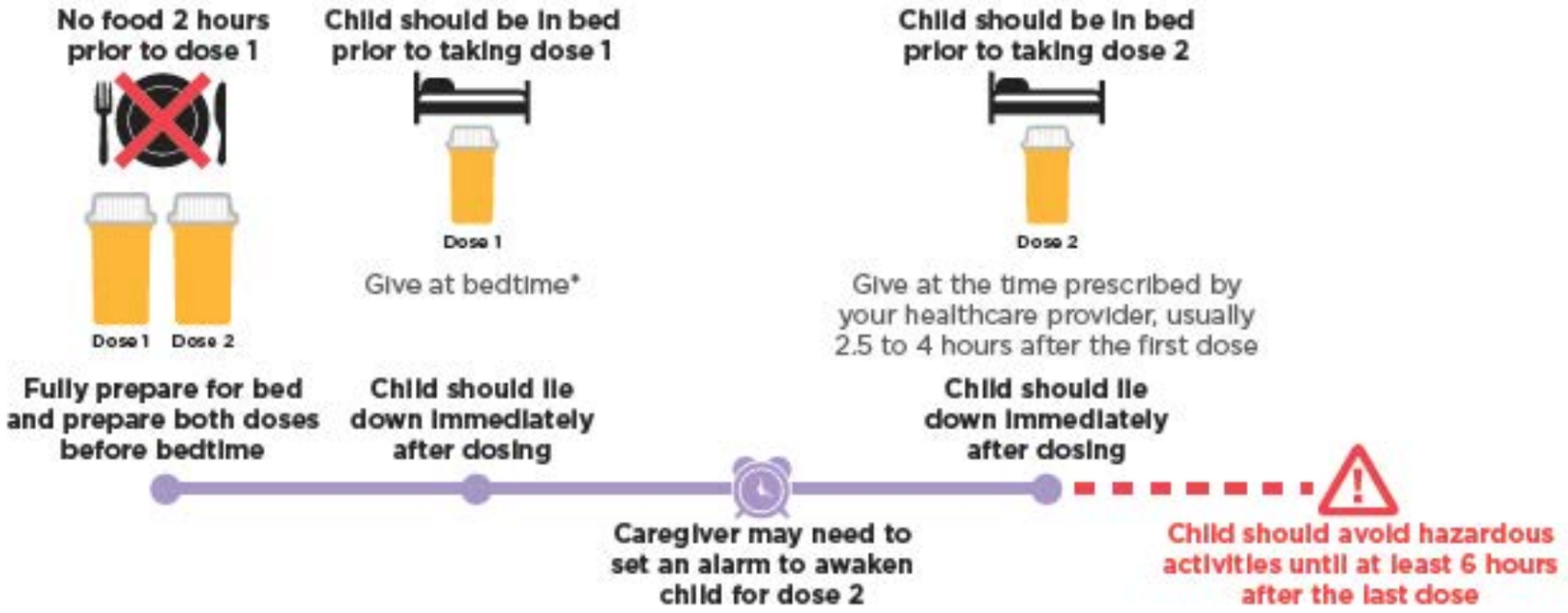
Rinse out the syringe and pharmacy containers with water after each use. Please refer to the Instructions for Use within the Medication Guide for additional details.

HOW DO I GIVE MY CHILD'S DOSES?

Wait at least 2 hours after your child eats before giving XYWAV.

XYWAV is a medicine that can make your child sleepy quickly; therefore, give your child's doses while he or she is sitting up in bed and have your child lie down immediately after dosing and remain in bed. Ensure your child is fully prepared for bed prior to taking the first nightly dose of XYWAV (for example, has brushed teeth, gone to the bathroom). Give the first dose at the time prescribed by your child's healthcare provider, and the second dose 2½ to 4 hours later. Ensure that all XYWAV doses are kept in a safe place until given. If your child continues evening activities after taking his or her dose, such as watching television or walking around, your child may experience light-headedness, dizziness, nausea, confusion, or other unpleasant feelings. Have the child lie down immediately after dosing and remain in bed (Figure 4).

Figure 4



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

WHAT DO I DO IF MY CHILD MISSES A DOSE?

- It is very important to give both doses of XYWAV each night as prescribed. If the second dose is missed, skip that dose
  - Do not give your child XYWAV again until the next night
  - Never give your child both XYWAV doses at the same time
- Any unused XYWAV doses that you prepared but didn't give to your child must be thrown away within 24 hours from the time you first prepared your child's doses

HOW SOON WILL WE SEE A CHANGE IN SYMPTOMS?

After starting XYWAV, it may take a few weeks or longer to see your child's symptoms improve. It may also take time to find the right dose that works for your child. It is important that you talk with your child's healthcare provider often when your child first starts taking XYWAV.

Tell your child's healthcare provider if you or your child do not see any improvements.

WHAT ARE THE SIDE EFFECTS OF XYWAV?

XYWAV can cause serious side effects, including breathing problems (slower breathing, trouble breathing, and short periods of no breathing while asleep), mental health problems (confusion, seeing or hearing things that are not real, unusual or disturbing thoughts, feeling anxious or upset, depression, thoughts of suicide), and sleepwalking. If your child has any of these side effects, call your child's healthcare provider right away.

The most common side effects with XYWAV in pediatric patients are nausea, bedwetting, throwing up, headache, weight loss, decreased appetite, dizziness, and sleepwalking. Side effects may increase with higher doses.

These are not the only possible side effects with XYWAV. If you or your child are worried about any possible side effects with XYWAV, talk with your child's healthcare provider or the pharmacist at the REMS.

You should report all side effects by contacting your child's healthcare provider, Jazz Pharmaceuticals at 1-800-520-5568, or the FDA at 1-800-FDA-1088.

ARE THERE ANY PRECAUTIONS THAT SHOULD BE TAKEN WHILE MY CHILD IS ON XYWAV?

- While taking XYWAV, your child should not drink alcohol or take medicines that cause sleepiness

Reference ID: 4840646

- Your child should not do anything that requires him or her to be fully alert for the first 6 hours after taking XYWAV. When your child first starts taking XYWAV, you and your child will need to be careful until you know how XYWAV affects him or her.
- Before starting XYWAV, tell your child's healthcare provider if your child is pregnant, or plans to become pregnant, or is breastfeeding. XYWAV passes into breast milk. You and your child's healthcare provider should decide if your child will take XYWAV or breastfeed.
- Keep XYWAV in a safe place, out of the reach of children
- Give XYWAV to your child while he or she is sitting up in bed and have your child lie down immediately and remain in bed after dosing

Tell your child's healthcare provider and pharmacist about any other medicines he or she is taking, including if your child begins a new medicine while taking XYWAV. This would include prescription and non-prescription medicines, vitamins, and supplements.

It is also important to tell other healthcare providers, including pharmacists, that your child is taking XYWAV before your child starts or changes any medications.

How Often Should My Child's Healthcare Provider Check on My Child's Progress On XYWAV?

When your child first starts taking XYWAV, you may need to talk to his or her healthcare provider often until he or she has determined the best dose for your child. You can expect that your child's dose may need to be adjusted. After your child's dose has been established, his or her healthcare provider should check on your child every 3 months while taking XYWAV.

What do I need to do if my child is taking XYREM and their doctor prescribes XYWAV FOR THEM?

- **Your child should never take both XYWAV and XYREM at the same time, it can lead to serious side effects**
- XYWAV contains the same medication as XYREM, which is called oxybate, but with less sodium
- Your child should take their XYWAV exactly as instructed by their doctor
- Prepare your child's XYWAV the same way you prepared XYREM
- Do not mix XYREM and XYWAV together. If you have unused XYREM, dispose of it before starting XYWAV. Refer to "HOW DO I PROPERLY DISPOSE OF XYWAV?" for further instructions
- The Certified Pharmacy will contact you to talk to you about how to make this change

Storage and Safety Tips at Home

HOW DO I STORE XYWAV?

- Always store XYWAV in its original bottle
- Store XYWAV at room temperature. Do not refrigerate XYWAV
- Keep XYWAV in a safe place, out of the reach of children and pets. Get emergency medical help (call 911) right away if a child not prescribed XYWAV drinks XYWAV

HOW DO I PROPERLY DISPOSE OF XYWAV?

To properly dispose of XYWAV, pour any unused XYWAV down the sink or toilet drain. Mark out all personal information on the prescription label, including the XYWAV name, to make it unreadable before putting the empty bottle in the trash.

XYWAV patients have the option to return unused or expired drug. Please ask the Certified Pharmacy for more details.

If you misplace, lose, or damage your child's XYWAV dosing syringe, contact the Certified Pharmacy to have it replaced. Do not use a different syringe or try to guess the correct dose.

XYWAV AND XYREM TAKEBACK PROGRAM

XYWAV or XYREM patients have an option to return any unused, leftover or expired XYWAV or XYREM product through a drug takeback program, upon request. Patients can request a shipper from the Certified Pharmacy. Once you receive the shipper, remember to mark out or remove your personal information from the bottle(s) and place the bottle(s) in the shipper. For more information, please ask the Certified Pharmacy for more details.

WHAT IF I HAVE CONCERNS ABOUT HAVING XYWAV IN MY HOME?

- If your child's XYWAV is lost or stolen, report the incident right away to the local police and to the Certified Pharmacy
- Give XYWAV only as your child's healthcare provider tells you. Remember that use of your child's XYWAV by others is illegal
- If you have any questions or concerns, or if you need advice about XYWAV, call your child's healthcare provider or the Certified Pharmacy

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XYWAV and **XYREM** REMS

Important Information Your Child Must Know About Taking XYWAV

You can use these pages to help teach your young child what he or she needs to know about taking his or her XYWAV.

WHAT SHOULD MY CHILD KNOW ABOUT TAKING XYWAV?

Get Ready

- Get ready for bed before you drink your XYWAV
- Finish your bedtime routine before you get in bed and drink your XYWAV

Any questions? Please call the XYWAV and XYREM REMS at 1-866-997-3688.
Please see the Medication Guide for more-detailed information about XYWAV.

Reference ID: 4840646

Stay In Bed

- Drink your XYWAV while sitting up in bed. Lie down right away after you drink it and stay in bed
- Call for a grown-up if you want to get out of bed after taking XYWAV
- It may take a while, or you may fall asleep quickly after taking XYWAV

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XYWAV and XYREM REMS

Be Careful

- Be careful in the morning
- Call for a grown-up to help you if you still feel sleepy in the morning

Any questions? Please call the XYWAV and XYREM REMS at 1-866-997-3688.
Please see the Medication Guide for more-detailed information about XYWAV.

Reference ID: 4840646

Always Remember!

- Don't share your XYWAV with anyone else
  - This medicine is only for you!
- Don't drink too much XYWAV
  - Never drink more than 1 of your XYWAV cups at a time
  - Only drink XYWAV from your XYWAV cup
- Tell a grown-up how you are feeling and about any changes in how you are feeling

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Reference ID: 4840646

Including Your Child in His or Her Care

HOW CAN I PREPARE MY CHILD TO BE ABLE TO CARRY OUT ONE OR MORE SAFE USE ACTIVITIES?

It is important for your child to take an active part in the safe use of his or her XYWAV. This is especially true for teenagers and those going to college. This brochure can help you talk with your child about taking XYWAV.

Before your child moves away from your home (for example, going away to college), talk with your healthcare provider and the Certified Pharmacy about additional ways to ensure safe use, handling, and storage. To help prepare your child for this transition, make sure that he or she is counseled about the serious risks and safe use of XYWAV by a member of your child's XYWAV healthcare team (for example, your child's healthcare provider or the Certified Pharmacy). Your child should also read this brochure and ask his or her healthcare provider any questions he or she may have.

Enrolling Your Child in the XYWAV and XYREM REMS

DOES MY CHILD HAVE TO ENROLL IN THE XYWAV AND XYREM PROGRAM?

Yes. In order for your child to receive XYWAV, your healthcare provider will have you sign an enrollment form and will send the form to the REMS. You must verify that you have been counseled by your child's healthcare provider on the serious risks and safe use of XYWAV and that you were able to ask your child's healthcare provider any questions you have about XYWAV. You may choose to have your child also receive counseling from your healthcare provider on the serious risks and safe use of XYWAV.

WHAT IS MY ROLE AS A CAREGIVER?

As a caregiver of a pediatric patient who is in the REMS, you are required to:

- Read this brochure and ask your child's healthcare provider any questions you have about XYWAV.
- Ensure that XYWAV is prepared and given only as prescribed
- Ensure that XYWAV is kept in a safe place, away from children and pets, and protected from theft
- Notify your child's healthcare provider right away if you notice any serious side effects while your child is taking XYWAV

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C III

Also be sure to let your child's healthcare provider know if your child is taking other medicines or if your child has any medical conditions that might affect his or her breathing.

If you need to give your responsibilities as your child's caregiver to someone else, please notify your child's healthcare provider. You also can contact the REMS toll free at 1-866-997-3688 to make sure that the new caregiver is counseled on the risks and safe use of XYWAV.

Filling Your Child's XYWAV Prescription

HOW IS MY CHILD'S PRESCRIPTION FILLED?

All XYWAV prescriptions are filled and shipped directly to your home only by the REMS Certified Pharmacy.

WHAT ELSE DOES THE CERTIFIED PHARMACY DO?

Your child's healthcare provider sends your child's XYWAV prescription directly to the Certified Pharmacy.

You will then receive a call from the Certified Pharmacy to counsel you on the serious risks and safe use of XYWAV, to tell you how to get your child started on XYWAV and to answer any questions about XYWAV. A staff member from the Certified Pharmacy will call you to complete a counseling checklist. The counseling checklist will include information about other medicines that your child is taking and other medical conditions that might increase your child's risk of serious side effects. The Certified Pharmacy will go over the information about how to use XYWAV safely and provide a copy of the Medication Guide with each XYWAV shipment.

The Certified Pharmacy will always ask you where and when you would like your child's XYWAV delivered and who will sign for the shipment. XYWAV will be shipped by an overnight service. You may be able to have your child's XYWAV shipped to your place of work or to a local overnight carrier hub for pickup. Saturday deliveries may also be an option for you. The Certified Pharmacy will work with you to find the best options available. When the courier arrives, you or another adult you previously named must sign for your child's XYWAV.

Finally, the Certified Pharmacy will call you soon after you receive your child's first XYWAV shipment to confirm receipt and answer any questions you may have about your child's first few days taking XYWAV.

HOW DO I GET XYWAV REFILLS FOR MY CHILD?

The Certified Pharmacy will contact you when it is close to your child's refill time. You may opt-in to receive text, e-mail, or automated voice reminders for refills. You may also call the Certified Pharmacy at 1-866-997-3688 to schedule your child's refills.

CAN MY LOCAL PHARMACY PROVIDE XYWAV FOR MY CHILD?

No. You can get your child's XYWAV only from the REMS Certified Pharmacy.

Insurance Coverage

WILL INSURANCE PAY FOR MY CHILD'S XYWAV?

In most cases, YES. A staff member from the Certified Pharmacy will call and work with your child's insurance company to help you get coverage for your child's XYWAV. In the unlikely event your child's insurance does not cover XYWAV or you can't afford the out-of-pocket costs, ask the Certified Pharmacy about available financial assistance programs.

WHAT IS THE PHARMACY'S ROLE WITH MY CHILD'S INSURANCE?

An experienced staff member will:

- Call you to go over your child's prescription benefits and coverage
- Tell you what your co-pay is, if applicable
- Tell you about any XYWAV prescription savings plans for which you may qualify
- Work with your child's healthcare provider on prior authorizations, if required by the insurance company
- Provide information about any financial help that may be available to you

The Certified Pharmacy's attempt to get coverage from a third-party payer does not guarantee that you will get coverage.

Contact Information

WHOM SHOULD I CONTACT WITH CONCERNS OR FOR MORE INFORMATION ABOUT XYWAV?

FOR QUESTIONS ABOUT SIDE EFFECTS OR FOR MORE INFORMATION ABOUT XYWAV, CONTACT YOUR CHILD'S HEALTHCARE PROVIDER:

Name: _____

Phone: _____

Email: _____

FOR MORE INFORMATION ABOUT XYWAV, CONTACT THE CERTIFIED PHARMACY:

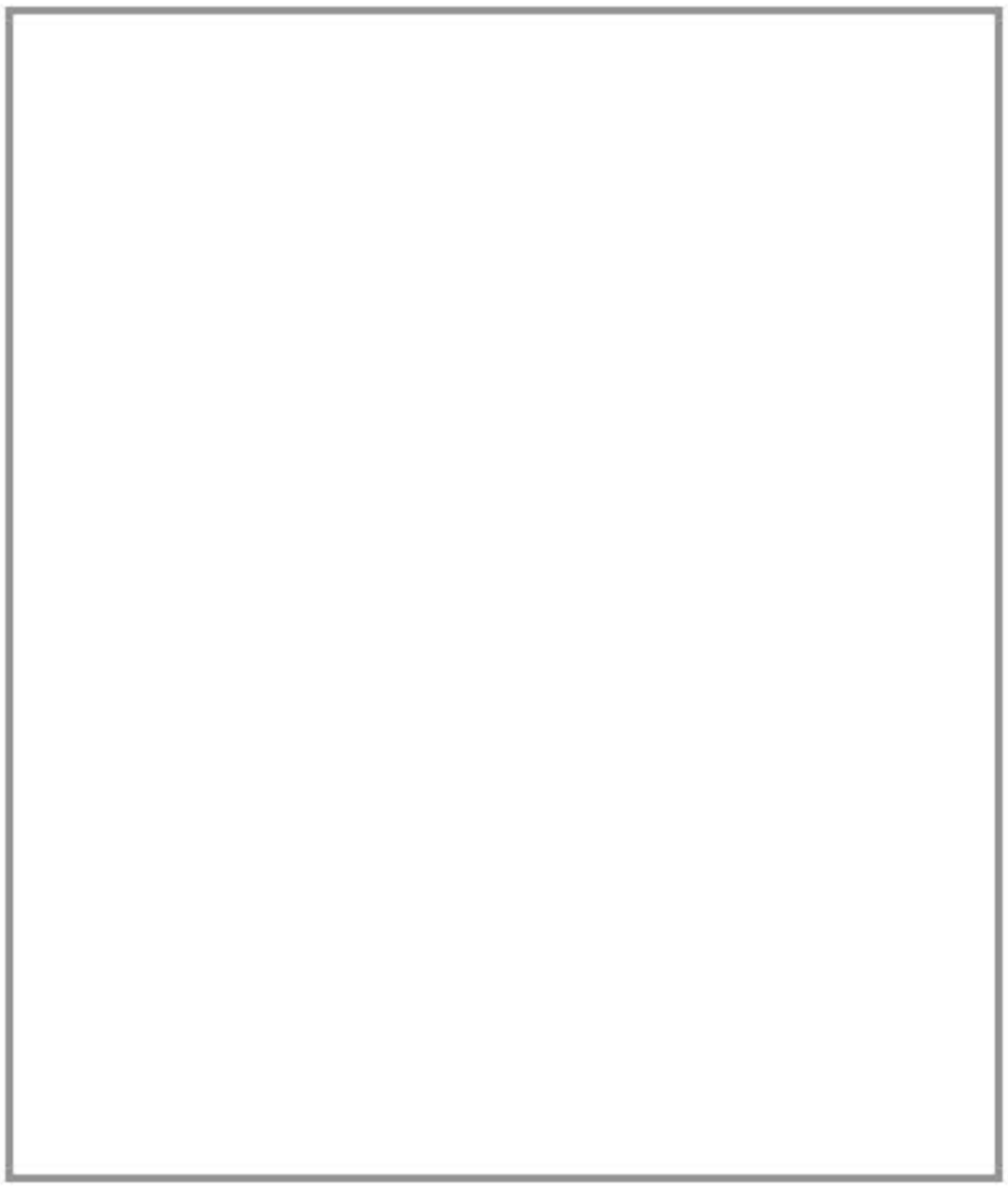
- **Phone:** 1-866-997-3688
- **Fax:** 1-866-470-1744 (toll free)
- **Outside the US:** +314 475-6000, ext. 361 587
- **Website:** www.XYWAVXYREMREMS.com

TO REPORT ALL SIDE EFFECTS, YOU CAN CONTACT:

- Jazz Pharmaceuticals at 1-800-520-5568
- The FDA at 1-800-FDA-1088

FOR EMERGENCIES:

- Call 911



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KEEP THIS BOOKLET AS A HELPFUL REMINDER

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

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

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The pharmacy may ask you to measure how much XYWAV is left in your bottle. Please use this ruler to give them this information.

XYWAV and XYREM REMS

Certified Pharmacy Training

MODULES A AND B

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

Dear 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 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 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.

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

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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 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 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.

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 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 and idiopathic hypersomnia were receiving central nervous system stimulants *[see Clinical Trials (14.1, 14.2, 14.3)]*.
- 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 Program *[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 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).
- 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
    - Indication for Use
    - 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.

Pharmacy Staff Information

Name: _____

Job Title: _____

Knowledge Assessment: Module A

XYWAV and XYREM REMS Overview

1. XYWAV® (calcium, magnesium potassium, and sodium oxybates) oral solution, 0.5 g/mL, 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 in adults. XYREM® (sodium oxybate) oral solution, 0.5 g/mL, is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.
   - **A.** True
   - **B.** False

   (Answer: A)

2. Both XYWAV and XYREM contain GHB, and are controlled substances because:
   - **A.** It must be administered twice nightly
   - **B.** It has abuse potential
   - **C.** It requires dilution before dosing
   - **D.** It is a central nervous system (CNS) depressant

   (Answer: B)

3. XYWAV and XYREM are contraindicated in patients:
   - **A.** Who take sedative hypnotics
   - **B.** Who drink alcohol while using XYWAV or XYREM
   - **C.** Who have succinic semialdehyde dehydrogenase deficiency, a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia
   - **D.** A, B, and C

   (Answer: D)

4. XYWAV and XYREM are CNS depressants. Which of the following is NOT a warning related to CNS depression?
   - **A.** Concurrent use with other CNS depressants may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death
   - **B.** 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
   - **C.** All surgeries and procedures must be reported as adverse events
   - **D.** 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

   (Answer: C)

5. The XYWAV and XYREM REMS has which of the following requirements?
   - **A.** Use of the central Certified Pharmacy
   - **B.** Healthcare providers who prescribe XYWAV or XYREM must have completed the XYWAV and XYREM REMS Prescriber Enrollment Form and must comply with the requirements of the XYWAV and XYREM REMS
   - **C.** For adult patients to receive XYWAV or XYREM, they must be enrolled in the XYWAV and XYREM REMS and be counseled on the serious risks and safe use of XYWAV and XYREM treatment
   - **D.** For pediatric patients to receive XYWAV or XYREM, they must be enrolled in the XYWAV and XYREM REMS and their caregiver must be counseled on the serious risks and safe use of XYWAV and XYREM
   - **E.** All of the above

   (Answer: E)

6. In processing enrollment information, the XYWAV and XYREM REMS requires all of the following EXCEPT:
   - **A.** 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-related attestations
   - **B.** Prescribers are notified when they are enrolled in the XYWAV and XYREM REMS and can prescribe XYWAV and XYREM
   - **C.** When a patient enrollment form is received, the Central Database is searched to determine if a patient is already enrolled (duplicate patient)
   - **D.** The Certified Pharmacy will ensure that refill orders are shipped when a patient has approximately 10 days of therapy remaining from the previous shipment
   - **E.** A patient or prescriber may be disenrolled for noncompliance with the XYWAV and XYREM REMS

   (Answer: D)

7. Which of the following is NOT true of caregivers of pediatric patients within the XYWAV and XYREM REMS?
   - **A.** A caregiver for a pediatric patient can be changed
   - **B.** They must complete a separate enrollment form
   - **C.** They must sign the patient enrollment form attesting that they have been counseled
   - **D.** They must be counseled on the serious risks and safe use of XYWAV and XYREM

   (Answer: B)

8. Which of the following is NOT entered in the Central Database in the XYWAV and XYREM REMS?
   - **A.** Patient and prescriber enrollment information
   - **B.** Patient medical history
   - **C.** Interactions with patients, caregivers and prescribers
   - **D.** Prescription information
   - **E.** Shipment information
   - **F.** All of the above are entered

   (Answer: F)

9. In validating a prescription for XYWAV or XYREM, the Certified Pharmacy will verify that:
- The XYWAV Prescription Form or the XYREM Prescription Form was received from the prescriber's office, is complete and signed by the prescriber, and is dated within the last 6 months;
- 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;
- The prescription is for only a one-month supply (first fill) or no more than a 3-month supply (refills).

A. True
B. False
(Answer: A)

10. When must a healthcare provider complete and submit a XYWAV Prescription Form to the pharmacy (select all that apply)?
A. For a patient's initial prescription of XYWAV
B. For patients who are restarting XYWAV after a lapse in therapy of 6-months or longer
C. For all refills and renewals of XYWAV
D. If a patient changes from XYREM to XYWAV and has never had a previous prescription for XYWAV
(Answer: A, B and D)

11. In monitoring patients and prescribers for signs of inappropriate prescribing, abuse, misuse, and diversion, the pharmacy will:
A. Document early refill requests and instances of patient and prescriber behavior that suggest potential abuse, misuse, or diversion by completing a XYWAV and XYREM REMS Risk Management Report
B. Place an alert 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
C. Inform a XYWAV and XYREM REMS pharmacist immediately if pharmacy staff suspects a patient or prescriber of abuse, misuse, or diversion
D. A and B only
E. A, B, and C
(Answer: E)

12. All potential adverse events must be reported to Jazz Pharmaceuticals within one business day.
A. True
B. False
(Answer: A)

Pharmacy Staff Information

Name: _____

Job Title: _____

Knowledge Assessment: Module B

In-Depth Pharmacy Training for the XYWAV and XYREM REMS

1. Upon completion of formal training, a new pharmacist will perform which of the following assigned duties under the observation of a senior pharmacy mentor?
   - **A.** Execution of the XYWAV and XYREM REMS Patient Counseling Checklist with new patients (or their caregiver for pediatric patients) and patients (or their caregiver for pediatric patients) who have not received either XYWAV® or XYREM® for 6 months or longer
   - **B.** Detailed monitoring, including completion of a XYWAV and XYREM REMS Risk Management Report (RMR)
   - **C.** Follow-up interactions with patients, caregivers (for pediatric patients), and prescribers
   - **D.** A, B, and C

   (Answer: D)

2. The Central Pharmacy certified through the XYWAV and XYREM REMS will:
   - **A.** Limit the patient's first shipment of any oxybate-containing product within the XYWAV and XYREM REMS to a one-month supply and subsequent shipments to a three-month supply
   - **B.** Report potential adverse events to Jazz Pharmaceuticals
   - **C.** Notify prescribers when patients are taking sedative hypnotics, other CNS depressants, or other potentially interacting agents of which the prescriber is not already aware or there are signs of potential abuse or misuse
   - **D.** A, B, and C

   (Answer: D)

3. The XYWAV and XYREM REMS Central Database will contain the following information that must be available for ongoing review to ensure XYWAV and XYREM are dispensed to enrolled patients only after completion and documentation of safe use conditions:
   - **A.** Complete patient and prescriber enrollment information
   - **B.** Patient information, including two additional identifiers, current and previous prescribers, comorbid conditions and concomitant medications reported by the patient or caregiver (for pediatric patients), and prescription history
   - **C.** Caregiver information (for pediatric patients)
   - **D.** Prescription information, including whether the prescription is for XYWAV or XYREM, date, dose, titration instructions, number of refills, and total quantity
   - **E.** RMRs, shipment information, and documentation of interactions with patients, caregivers, and prescribers
   - **F.** All of the above

   (Answer: F)

4. XYWAV and XYREM contain the same amount of the active moiety, oxybate, per milliliter of solution.
   A. True
   B. False
   (Answer: A)

5. Prior to shipment of XYWAV or XYREM, the XYWAV and XYREM REMS Patient Counseling Checklist must be completed as follows (not all possible scenarios triggering use of the Patient Counseling Checklist are noted):
   - For initial prescriptions of XYWAV or XYREM and for patients restarting XYWAV or XYREM after not receiving either XYWAV or XYREM for 6 months or more, complete the entire checklist
   - For prescription renewals and refills, if the patient or caregiver indicates a change in the patient's health or medications, transfer the patient or caregiver to the pharmacist to determine if further counseling and prescriber outreach 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 that is listed in Step 4 of the XYWAV and XYREM REMS Patient Counseling Checklist.
   - For new caregivers of already enrolled pediatric patients, complete the entire checklist

   A. True
   B. False
   (Answer: A)

6. When the patient is transitioning from XYWAV to XYREM and is on a salt-restricted diet or has comorbidities such as high blood pressure, heart failure, or kidney problems, the certified pharmacy will have to counsel the patient utilizing the XYWAV and XYREM REMS Patient Counseling Checklist.
   A. True
   B. False
   (Answer: A)

7. If patient use of a contraindicated medication (e.g. sedative hypnotics or alcohol) is confirmed and the prescriber has not indicated prior knowledge, the pharmacist will contact and consult the prescriber prior to shipping XYWAV or XYREM.
   A. True
   B. False
   (Answer: A)

8. If there are any clinical usage clarifications needed for a prescription, the pharmacist will:
   A. Refuse to fill the prescription
   B. Notify and consult the prescriber
   C. Fill out an RMR
   D. Disenroll the prescriber
   (Answer: B)

9. Which of the following is NOT true for the prescription refill process?
   A. Up to 5 refills are allowed on a XYWAV or XYREM prescription
   B. Refill prescriptions can be submitted electronically
   C. Refill orders are opened when the patient has approximately 10 days of therapy remaining from the previous prescription
   D. All refills must be countersigned by the prescriber
   (Answer: D)

10. As part of processing a prescription refill, the pharmacist may discuss the following with the patient or caregiver (for pediatric patients) EXCEPT:
- **A.** Use of sedative hypnotics (e.g., diazepam, phenobarbital, or zolpidem)
- **B.** Use of alcohol
- **C.** History of sleep apnea
- **D.** Choice of prescriber
- **E.** History of asthma, COPD, or other conditions affecting breathing

(Answer: D)

11. If the pharmacist identifies that the patient is taking a potentially interacting agent that may present a risk to the patient, the pharmacist should consider which of the following actions before filling the prescription?
- **A.** Notifying law enforcement
- **B.** Taking no action
- **C.** Consulting the prescriber
- **D.** Consulting the insurance provider

(Answer: C)

12. In monitoring and assessing for signs of abuse, misuse, or diversion, a pharmacist must document risk management events in the Central Database by completing a Risk Management Report. Events that should generate an RMR include, but are not limited to (choose BEST answer):
- **A.** Early refill requests (excluding requests to accommodate shipment logistics)
- **B.** Lost, stolen, destroyed, or spilled drug
- **C.** Patient or caregiver claims that product was not delivered while carrier shows receipt of delivery
- **D.** Counterfeit or contaminated product
- **E.** All of the above

(Answer: E)

13. When is weight required on the prescription form?
- **A.** For all patients on every prescription form
- **B.** For all patients on initial and restart fills only
- **C.** For adult patients on every prescription form
- **D.** For adult patients on initial and restart fills only
- **E.** For pediatric patients on every prescription form
- **F.** For pediatric patients on initial and restart fills only

(Answer: F)

XYWAV and XYREM REMS

XYREM PRESCRIPTION FORM

XYREM® (sodium oxybate) oral solution 0.5 g/mL

Form available online at www.XYWAVXYREMREMS.com. Print, sign, and:
Fax to XYWAV and XYREM REMS: 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)

Please Print (*denotes required field; †denotes required field for pediatric patients on initial fill and restarts)

Prescriber Information

*First Name: _____ M.I.: _____ *Last Name: _____

*Street Address: _____ *Phone: _____

*City: _____ *State: _____ *Zip Code: _____ *Fax: _____

*DEA No.: _____ *NPI No.: _____

Office Contact: _____ Office Contact Phone: _____ *State License No.: _____

Patient Information

*Indication for Use (required for initial prescription and any change in diagnosis) Select one: ☐ Narcolepsy with Cataplexy and/or EDS OR ☐ Other

*First Name: _____ M.I.: _____ *Last Name: _____ *Primary Phone: _____

*Date of Birth (MM/DD/YYYY): _____ † Weight (if under age 18): _____ kg *Gender: ☐ M ☐ F Cell Phone: _____

*Address: _____ Work Phone: _____

*City: _____ *State: _____ *Zip Code: _____ E-mail: _____

*MEDICATIONS: (list all known current prescription and non-prescription medications and dosages or submit as a separate page)	COMORBIDITIES: (list known comorbidities or submit as a separate page)

*Total Quantity	Refills:
1 2 3 month(s) supply (circle one)	0 1 2 3 4 5 (circle one)

Dispensing Instructions
Directions: Take first dose p.o., diluted in ¼ cup of water, at bedtime. Take second dose p.o., diluted in ¼ cup of water 2.5 to 4 hours later.
Note: Prepare both doses at the same time prior to bedtime. The XYREM shipment does not include water for dilution.

Initial prescription fill cannot exceed 1 month of therapy. Refills cannot exceed 3 months supply.
Please complete EITHER the titrated dosing OR fixed dosing section.
Please see the Prescriber Brochure and the Prescribing Information for additional dosing instructions.

Titrated XYREM Dosing: Titrate to Effect

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

First dose is ordinarily taken at bedtime; second dose is taken 2.5 to 4 hours later.
***For pediatric patients who sleep more than 8 hours per night, the first dose of XYREM may be given at bedtime or after an initial period of sleep.**
****If XYREM is used in patients 7 years of age and older who weigh less than 20 kg, a lower starting dosage, lower maximum weekly dosage increases, and lower total maximum nightly dosage should be considered. Some patients may achieve better responses with unequal doses at bedtime and 2.5 to 4 hours later.**

Fixed XYREM Dosing

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

Special Dosing Instructions

Prescriber Verification—My signature below signifies that: I understand the statements and agree to the REMS requirements, which are found on the back of this form; XYREM is medically appropriate for this patient; and I have informed the patient and/or caregiver that the XYWAV and XYREM REMS will send him or her the appropriate educational material (XYREM Patient Quick Start Guide for adult patients and XYREM Brochure for Pediatric Patients and their Caregivers for pediatric patients) with the first prescription fill.

*Prescriber's signature (sign below)

Dispense as Written: _____ Date: _____ Substitution Allowed: _____ Date: _____

Supervising Physician Signature: _____ Date: _____
(If required by state law)

XYREM® (sodium oxybate) oral solution

Reference ID: 4840646

XYWAV and XYREM REMS

XYREM PRESCRIPTION FORM

XYREM® (sodium oxybate) oral solution 0.5 g/mL

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

I 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.

I understand that:

- XYREM is a CNS depressant and can cause obtundation and clinically significant respiratory depression at recommended doses
- Alcohol and sedative hypnotics are contraindicated in patients who are using XYREM
- Concurrent use of XYREM with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptics, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death
  - If use of these CNS depressants in combination with XYREM is required, dose reduction or discontinuation of one or more CNS depressants (including XYREM) should be considered
  - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with XYREM should be considered
- Patients who have sleep apnea or compromised respiratory function (e.g., asthma, COPD, etc.) may be at higher risk of developing respiratory depression, loss of consciousness, coma, and death with XYREM use
- XYREM is a Schedule III controlled substance with potential for abuse and misuse
- Safe use and handling by patients is important in order to prevent abuse/misuse and accidental exposure to family/friends, including children
- XYREM is to be prescribed only to patients enrolled in the XYWAV and XYREM REMS

I have read and understand the Prescribing Information and XYWAV and XYREM REMS Prescriber Brochure.

I have screened this patient for:

- History of alcohol or substance abuse
- History of sleep-related breathing disorders
- History of compromised respiratory function
- Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
- History of depression or suicidality

I have counseled this patient and/or caregiver on:

- The serious risks associated with XYREM
- Contraindications (alcohol and sedative hypnotics)
- Risk of concomitant use of XYREM with alcohol, other CNS depressants, or other potentially interacting agents
- Preparation and dosing instructions for XYREM
- Risk of abuse and misuse associated with use of XYREM
- Risk of operating hazardous machinery, including automobiles or airplanes, for the first 6 hours after taking a dose of XYREM
- Preparation and dosing instructions for XYREM
- Safe use, handling, and storage of XYREM

XYREM® (sodium oxybate) oral solution

XYWAV and XYREM REMS

XYWAV PRESCRIPTION FORM

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

Form available online at www. XYWAVXYREMREMS.com. Print, sign, and:
Fax to XYWAV and XYREM REMS: 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)

Please Print (*denotes required field; †denotes required field for pediatric patients on initial fill and restarts)

Prescriber Information

*First Name: _____ M.I.: _____ *Last Name: _____

*Street Address: _____ *Phone: _____

*City: _____ *State: _____ *Zip Code: _____ *Fax: _____

*DEA No.: _____ *NPI No.: _____

Office Contact: _____ Office Contact Phone: _____ *State License No.: _____

Patient Information

*Indication for Use (required for initial prescription and any change in diagnosis) Select one: ☐ Narcolepsy with Cataplexy and/or EDS OR ☐ Idiopathic Hypersomnia OR ☐ Other

*First Name: _____ M.I.: _____ *Last Name: _____ *Primary Phone: _____

*Date of Birth (MM/DD/YYYY): _____ †Weight (if under age 18): _____ kg *Gender: ☐ M ☐ F Cell Phone: _____

*Address: _____ Work Phone: _____

*City: _____ *State: _____ *Zip Code: _____ E-mail: _____

*MEDICATIONS: (list all known current prescription and non-prescription medications and dosages or submit as a separate page)	COMORBIDITIES: (list known comorbidities or submit as a separate page)

*Total Quantity 1 2 3 month(s) supply (circle one)	Refills: 0 1 2 3 4 5 (circle one)

Dispensing Instructions
Directions For 1 Time a Night Dosing (IH Patients): Take the dose p.o., diluted in ¼ cup of water, at bedtime
Directions For 2 Times a Night Dosing (For Narcolepsy and IH): Take first dose p.o., diluted in ¼ cup of water, at bedtime. Take second dose p.o., diluted in ¼ cup of water 2.5 to 4 hours later.
Note: Prepare both doses at the same time prior to bedtime. The XYWAV shipment does not include water for dilution.

Initial prescription fill cannot exceed 1 month of therapy. Refills cannot exceed 3 months supply.
Please complete EITHER the titrated dosing OR fixed dosing section.
Please see the Prescriber Brochure and the Prescribing Information for additional dosing instructions.

Titrated XYWAV Dosing: Titrate to Effect

1 time a night dosing (IH patients)		2 times a night dosing (For Narcolepsy and IH)						
Starting Dose:	Dose: _____ g	Starting Dose:	First dose: _____ g	+	Second dose: _____ g	=	_____ g	Total Nightly Dose for _____ days
1st Titration:	Dose: _____ g	1st Titration:	First dose: _____ g	+	Second dose: _____ g	=	_____ g	Total Nightly Dose for _____ days
2nd Titration:	Dose: _____ g	2nd Titration:	First dose: _____ g	+	Second dose: _____ g	=	_____ g	Total Nightly Dose for _____ days
3rd Titration:	Dose: _____ g	3rd Titration:	First dose: _____ g	+	Second dose: _____ g	=	_____ g	Total Nightly Dose for _____ days

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

Fixed XYWAV Dosing

1 time a night dosing (IH patients)	2 times a night dosing (For Narcolepsy and IH)
Dose: _____ g	First dose: _____ g + Second dose: _____ g = _____ g Total Nightly Dose for _____ days

Special Dosing Instructions

Prescriber Verification—My signature below signifies that: I understand the statements and agree to the REMS requirements, which are found on the back of this form; XYWAV is medically appropriate for this patient; and I have informed the patient and/or caregiver that the XYWAV and XYREM REMS will send him or her the appropriate educational material XYWAV Patient Quick Start Guide for adult patients and XYWAV Brochure for Pediatric Patients and their Caregivers for pediatric patients) with the first prescription fill.

*Prescriber Signature: _____ *Date: _____

Supervising Physician Signature: _____ Date: _____
(If required by state law)

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

Reference ID: 4840646

XYWAV and XYREM REMS

XYWAV PRESCRIPTION FORM

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

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

I understand that XYWAV is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. I understand that XYWAV is indicated for the treatment of idiopathic hypersomnia in adults.

I understand that:

- XYWAV is a CNS depressant and can cause obtundation and clinically significant respiratory depression at recommended doses
- Alcohol and sedative hypnotics are contraindicated in patients who are using XYWAV
- Concurrent use of XYWAV with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptics, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death
  - If use of these CNS depressants in combination with XYWAV is required, dose reduction or discontinuation of one or more CNS depressants (including XYWAV) should be considered
  - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with XYWAV should be considered
- Patients who have sleep apnea or compromised respiratory function (e.g., asthma, COPD, etc.) may be at higher risk of developing respiratory depression, loss of consciousness, coma, and death with XYWAV use
- XYWAV is a Schedule III controlled substance with potential for abuse and misuse
- Safe use and handling by patients is important in order to prevent abuse/misuse and accidental exposure to family/friends, including children
- XYWAV is to be prescribed only to patients enrolled in the XYWAV and XYREM REMS

I have read and understand the Prescribing Information and XYWAV and XYREM REMS Prescriber Brochure.

I have screened this patient for:

- History of alcohol or substance abuse
- History of sleep-related breathing disorders
- History of compromised respiratory function
- Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
- History of depression or suicidality

I have counseled this patient and/or caregiver on:

- The serious risks associated with XYWAV
- Contraindications (alcohol and sedative hypnotics)
- Risk of concomitant use of XYWAV with alcohol, other CNS depressants, or other potentially interacting agents
- Preparation and dosing instructions for XYWAV
- Risk of abuse and misuse associated with use of XYWAV
- Risk of operating hazardous machinery, including automobiles or airplanes, for the first 6 hours after taking a dose of XYWAV
- Preparation and dosing instructions for XYWAV
- Safe use, handling, and storage of XYWAV

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

XYWAV and XYREM REMS Patient Counseling Checklist

(Prior to dispensing XYWAV® or XYREM®, the XYWAV and XYREM REMS Certified Pharmacy ensures the completion of the checklist and its requirements and documents the information received in the XYWAV and XYREM REMS Central Database. Include additional requirements (if any) per federal or state requirements that need to be collected as part of the patient counseling process.)

STEP 1: PATIENT INFORMATION

Prescription for:

- ☐ XYWAV
- ☐ XYREM

(Complete this section for new patients [first shipment of any oxybate-containing product within the XYWAV and XYREM REMS], existing patients who are restarting XYWAV or XYREM treatment after not receiving either of the drug products for 6 months or longer, and patients who report a new medication or new comorbid medical condition listed in Step 4 of this checklist)

- ☐ New/restart
- ☐ Scheduled refill
- ☐ Early refill approved through RMR process
- ☐ Change of care responsibility

Patient Name: _____ **Patient ID Number:** _____

Prescriber Name: _____ **Prescriber ID Number:** _____

For pediatric patients, include caregiver information below.

Caregiver Name: _____ **Caregiver ID Number:** _____

Include Pharmacist name and date time stamp for each section completed.

STEP 2: COUNSELING

(Complete this section ONLY for new patients and existing patients who are restarting XYWAV or XYREM treatment after not receiving XYWAV or XYREM for 6 months or longer)

☐ Ask if the prescriber reviewed the appropriate XYWAV and XYREM REMS material with the patient/caregiver (XYWAV or XYREM Patient Quick Start Guide for adult patients, XYWAV or XYREM Brochure for Pediatric Patients and Their Caregivers for pediatric patients) and explain that this material will be included with the first shipment.

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

☐ Verify that the patient/caregiver has been counseled on **Therapy Expectations** below

- During clinical trials with XYWAV and XYREM, some patients with narcolepsy experienced improvement inexcessive daytime sleepiness and/or cataplexy in the first weeks after beginning therapy. However, the response varies from patient to patient. It may also take time to find the right dose that works for the patient. The prescriber will determine the dose that is appropriate.

- During a clinical trial with XYWAV, some patients with idiopathic hypersomnia experienced improvement in symptoms of idiopathic hypersomnia in the first few weeks of therapy. However, the response varies from patient to patient. It may also take time to find the right dose that works for the patient. The prescriber will determine the dose that is appropriate.
- The patient/caregiver should talk to the prescriber about any troubling side effects or if the patient does not feel any benefits while taking XYWAV or XYREM.
- For any prescription changes, the prescriber should call or fax the new prescription change to the pharmacy; patients or caregivers should NEVER attempt to change the dose themselves.

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

☐ Verify that the patient/caregiver has been counseled on **Preparation and Administration** information below

- If the patient is prescribed 2 times a night dosing regimen, XYWAV/XYREM should be prepared and taken only as directed by the prescriber (review prescriber's instructions with patient/caregiver).
  - Prepare the first dose by placing _____ grams of XYWAV/XYREM into 1 of the provided pharmacy containers.
    - Add 1/4 cup of water to the container and turn the cap clockwise (to the right) until it clicks and locks into its child-resistant position.
  - Then, prepare the second dose by placing grams of XYWAV/XYREM into the second pharmacy container, adding about 1/4 cup of water, and closing the pharmacy container.
  - A single dose administration greater than 4.5 g will require 2 draws from the bottle.
    - For doses requiring 2 draws from the bottle, the second draw must be emptied into the same pharmacy container.
  - The water does not come with XYWAV/XYREM. The patient/caregiver can use either tap or bottled water. The solution should remain clear.
  - XYREM will taste salty. For patients switching from XYREM to XYWAV, the XYWAV solution will taste differently.
  - Place the containers in a safe place, out of the reach of children or pets.
    - For adult patients, the recommended location for the second dose is a safe place near the patient's bed.
    - For pediatric patients, it is recommended that the caregiver ensure that all XYWAV/XYREM doses are kept in a safe place until given.
- If the patient is prescribed 1 time a night dosing regimen, XYWAV should be prepared and taken only as directed by the prescriber (review prescriber's instructions with patient/caregiver).
  - Prepare the XYWAV dose by placing _____ grams of XYWAV into a single pharmacy container.
  - A single dose greater than 4.5 g will require 2 draws from the bottle.
    - For doses requiring 2 draws from the bottle, the second draw must be emptied into the same pharmacy container.
    - Add 1/4 cup of water to the container and turn the cap clockwise (to the right) until it clicks and locks into its child-resistant position.
  - The water does not come with XYWAV/XYREM. The patient/caregiver can use either tap or bottled water. The solution should remain clear.
  - Place the container in a safe place out of reach of children or pets.

- The patient/caregiver should call the XYWAV and XYREM REMS with any questions regarding how XYWAV/XYREM is to be prepared or taken. The pharmacy is available Monday through Friday, from 7 AM to 8 PM Central Time, at 1-866-997-3688, and a pharmacist is always available, 24 hours a day, 7 days a week, if needed.
- The patient/caregiver should refer to the product Medication Guide for additional information on preparation of doses.
- When the patient is ready to go to sleep, the first dose of XYWAV/XYREM should be taken while sitting in bed and the patient should lie down immediately after dosing.
  - XYWAV and XYREM doses should be taken at least 2 hours after eating.
  - The time that it takes to fall asleep might be different from night to night. The patient may fall asleep quickly, in about 5 to 15 minutes, although some patients have reported falling asleep more quickly (without first feeling drowsy) and others may take longer to fall asleep.
  - The patient/caregiver may want to set an alarm to make sure the patient wakes up to take the second dose. The second dose of XYWAV/XYREM should be taken 2.5 to 4 hours after the first dose of XYWAV/XYREM is taken.
  - If a dose is missed, the patient should NEVER take 2 doses of XYWAV/XYREM at the same time.
- The diluted medication MUST be used within 24 hours of preparation. Discard any unused medication down the sink or toilet drain.
- When XYWAV/XYREM can no longer be drawn out of the bottle with the dispensing device, the patient/caregiver should dispose of the bottle. Remind the patient/caregiver to mark out information on the prescription label, including all personal information and the XYWAV/XYREM name, to make it unreadable before throwing out the empty bottle or other empty medicine packaging.
- The patient/caregiver should be sure to store both the XYWAV/XYREM bottle and all prepared doses in a safe and secure place out of the reach of children and pets. Emergency medical help should be sought right away if a child who has not been prescribed XYWAV/XYREM drinks XYWAV/XYREM.
- XYWAV/XYREM should be stored at room temperature.

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

☐ Verify that the patient/caregiver has been counseled on **Precautions Needed for XYWAV/XYREM Use**

- XYWAV/XYREM is classified as a controlled substance medication. XYWAV/XYREM must be used only by the person for whom it is prescribed and as directed by the physician. All lost or stolen medication must be reported.
- Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.
- XYWAV/XYREM contains oxybate, which is a form of gamma-hydroxybutyrate (GHB). GHB has been used as a substance of abuse and has been associated with drug-facilitated sexual assault (date rape).
- Abuse of GHB can lead to dependence (a physical need to take the drug), craving for the medicine, and severe withdrawal symptoms (symptoms that start when the drug is stopped, especially when it is stopped suddenly). Abuse of GHB, with or without other central nervous system (CNS) depressants (e.g., nortriptyline, oxycodone, or heroin), including alcohol, can lead to seizure, trouble breathing, decreases in the level of consciousness, coma, and death.

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

☐ Verify that the patient/caregiver has been counseled on **Side Effects**

- In clinical trials:
  - in adult patients, the most commonly observed side effects associated with the use of XYWAV included: nausea, headache, dizziness, anxiety, insomnia, decreased appetite, hyperhidrosis, vomiting, diarrhea, dry mouth, sleep walking, sleepiness, fatigue, and tremor.
  - in adult patients, the most commonly observed side effects associated with the use of XYREM included: nausea, dizziness, vomiting, somnolence, enuresis, and tremor.
  - in pediatric patients, the most commonly observed side effects associated with the use of XYWAV/XYREM included: nausea, enuresis, vomiting, headache, weight decreased, decreased appetite, dizziness, and sleepwalking.
  - Some side effects may be more likely to be observed with higher doses of XYWAV/XYREM.
- XYWAV/XYREM can cause serious side effects, including trouble breathing while asleep, confusion, unusual or disturbing thoughts, depression, and passing out, even at recommended doses. The patient/caregiver should consult with the prescriber if the patient has any of these problems while taking XYWAV/XYREM.
- Patients should not participate in hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that XYWAV/XYREM does not affect them adversely.
- When taking XYWAV/XYREM, patients should not drink alcohol or take medicines that make them sleepy, including antidepressants, antipsychotics, anti-epileptics, opioids, general anesthetics, muscle relaxants, and/or illicit CNS depressants (e.g., heroin or GHB).
- These are not all of the side effects that patients may experience. The patient/caregiver should contact the prescriber if there are concerns about any possible side effects. Refer to the product Medication Guide for additional information on possible side effects.

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

☐ Instruct patients/caregivers to call the prescriber if:

- Patient is pregnant or plans to become pregnant. It is not known if XYWAV/XYREM can affect an unborn baby.
- Patient is breastfeeding. XYWAV/XYREM passes into breast milk. The patient/caregiver should talk to the prescriber to decide if the patient will take XYWAV/XYREM or breastfeed.
- Patient has or has had depression or tried to harm him- or herself. Patients should be watched for new signs of depression.
- Patient has liver problems. The dose may need to be adjusted.
- Patient has sleep apnea (short periods of not breathing while asleep), snoring, or breathing or lung problems. Patients with these may have a higher chance of serious breathing problems with XYWAV/XYREM.
- Patient has mental health problems.
- Patient walks during sleep.
- For patients taking XYREM: Patient is on a salt-restricted diet, has high blood pressure, heart failure, or kidney problems. XYREM is a drug with a high sodium (salt) content and may not be right for patients with these conditions.

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

☐ For situations involving a change of care responsibility:
- Inform caregiver/patient that this completes this section of the checklist. Confirm that the caregiver/patient has asked any questions he or she has about XYWAV/XYREM.

STEP 3: SCREENING

(Complete this section for new patients, existing patients who are restarting XYWAV or XYREM treatment after not receiving either of the drug products for 6 months or longer, and patients who report a new medication or new comorbid medical condition listed in Step 4 of this checklist)

1. Is the patient taking sedative hypnotics (e.g., eszopiclone, zaleplon, zolpidem, temazepam, suvorexant, quazepam, estazolam, flurazepam, triazolam, tasimelteon, ramelteon)?
☐ Yes ☐ Counseled Patient/Caregiver
☐ No
Please list the drug(s) and dose of each: _____

_____

_____

2. Is the patient taking sedating antidepressants, antipsychotics, or anti-epileptics such as divalproex sodium (Depakote); benzodiazepines (e.g., diazepam, alprazolam or any not listed in question 1), general anesthetics; muscle relaxants; opioid analgesics; or illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB])?
☐ Yes ☐ Counseled Patient/Caregiver
☐ No
Please list the drug(s) and dose of each: _____

_____

_____

3. What other prescription and non-prescription medications is the patient taking?
Please list the drug(s) and dose of each: _____

_____

_____

4. Does the patient drink alcohol?
☐ Yes ☐ Counseled Patient/Caregiver
☐ No

5. Has the patient been diagnosed with sleep apnea (short periods of not breathing while asleep)?
☐ Yes ☐ Counseled Patient/Caregiver
☐ No

6. Does the patient have a diagnosis of or suffer from asthma, chronic obstructive pulmonary disease (COPD), or other conditions affecting his/her breathing (slower breathing, trouble breathing)?
☐ Yes ☐ Counseled Patient/Caregiver
☐ No

Please list the drug(s) used to treat, and dose of each, if known:

_____

_____

7. Does the patient have any other current medical conditions for which the patient is under a healthcare provider's care?
- ☐ Yes ☐ Counseled Patient/Caregiver
- ☐ No

Please list the conditions(s) if known: _____

_____

_____

8. Does the patient/caregiver have any clinical questions about XYWAV and/or XYREM?
- ☐ Yes ☐ Counseled Patient/Caregiver
- ☐ No ☐ Referred Patient/Caregiver to Prescriber

Please list the question(s): _____

_____

_____

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

STEP 4: CONCOMITANT MEDICATION & COMORBIDITY SUMMARY

(Complete this section for new patients, existing patients who are restarting XYWAV or XYREM treatment after not receiving either of the drug products for 6 months or longer, and patients who report a new medication or new comorbid medical condition listed in Step 4 of this checklist)

Medication Type
- ☐ Sedative hypnotics
- ☐ Benzodiazepines
- ☐ Alcohol
- ☐ Other potentially interacting agents:
  - ☐ Sedating antidepressants, antipsychotics, or anti-epileptics
  - ☐ General anesthetics
  - ☐ Muscle relaxants
  - ☐ Opioid analgesics
  - ☐ Divalproex sodium or other valproate drug (e.g., valproic acid)
  - ☐ Illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB])

Medical Conditions
- ☐ Sleep apnea
- ☐ Asthma
- ☐ COPD
- ☐ Other conditions affecting the patient's breathing
- ☐ History of depression or suicidality
- ☐ History of drug or alcohol abuse
- ☐ Seizure disorders
- ☐ Hepatic impairment
- ☐ High blood pressure, heart problems, kidney problems, or a salt-restricted diet [Prescriber consult may be required for patients taking XYREM]

If any medication types or medical conditions listed on previous page are checked, or any questions in Step 3 were answered yes and there is no confirmation of prior prescriber knowledge, call the prescriber to consult:

Is a prescriber consult required?
- ☐ Yes
- ☐ No

If no, please provide reason: _____

If yes, action(s) taken (check all that apply and document details in prescriber consult outcome section below):
- ☐ Called prescriber: _____ / _____ / _____
- ☐ Other: _____ / _____ / _____

Is prescriber consult due to concomitant sedative hypnotics or benzodiazepines? If yes, complete all of the following questions at the conclusion of the consult. If no, complete step 5 only.
- ☐ No
- ☐ Yes

Is treatment with XYWAV or XYREM to be continued?
- ☐ No
- ☐ Yes

  If yes, what action will be taken?
  - ☐ Concomitant medication will be discontinued
  - ☐ Dosage of concomitant medication has been/will be reduced
  - ☐ No action (continue concomitant medication with Xywav or Xyrem) -
    - Prescriber's rationale for continuing concomitant medication with Xywav or Xyrem:
      - ☐ Medication will not be taken at the same time as Xywav/Xyrem
      - ☐ Medication will be taken at the same time as Xywav/Xyrem
        - ☐ Medication will be taken as a sleep aid
        - ☐ Medication will be taken for a different indication per medical need
        - ☐ Information unavailable
      - ☐ Xywav/Xyrem dose regimen changed
      - ☐ No rationale provided or Information unavailable

Overall prescriber consult outcome: _____

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

STEP 5: COMPLETION SUMMARY

(Complete this section for new patients, existing patients who are restarting XYWAV or XYREM treatment after not receiving either of the drug products for 6 months, and patients who report a new medication or new comorbid medical condition listed in Step 4 of this checklist)

Checklist Completed
- ☐ Yes
- ☐ No (XYWAV or XYREM is not shipped until checklist is completed.)

If yes, date checklist completed: _____ / _____ / _____ (Date Time)

If no, reason for non-completion: _____

_____

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

XYWAV and XYREM REMS Risk Management Report

Risk Management Reports (RMRs) are filled out by the central Certified Pharmacy to document and report events that give rise to a reasonable suspicion of abuse, misuse, diversion, or any behavior or information that may indicate the drug is not being used according to the prescriber's instructions. The RMR history of a patient allows for the review of prior events of suspected abuse, misuse, or diversion and gives the pharmacist a more complete picture of the patient's history. The availability of individual patient RMRs enables the pharmacist to track and monitor for trends suggesting abuse, misuse, or diversion in individual patients. A trend or pattern of behavior in a patient's RMR history can be an indicator of abuse, misuse, or diversion and identifies patients who may require additional scrutiny when another event, such as an early refill request, occurs. In these cases, the RMR history informs actions of the pharmacist.

Examples of events that would require completion of an RMR under the XYWAV and XYREM REMS include, but are not limited to, the following:

- Patient requests for early refills.
- Patient's loss/misuse of the product.
- Patient claim that he or she did not receive the product but the delivery service shows receipt of delivery, or that the shipment was lost or stolen or delivered to an incorrect address and was not returned.
- Tampering with or counterfeiting or contaminating the product.
- Inquiries and/or arrests by law and regulatory enforcement agencies associated with the misuse or diversion of the product, or crimes related to the product.
- Prescribers whose DEA and/or state license numbers cannot be validated and the prescriber is submitting a REMS Prescriber Enrollment Form, REMS Patient Enrollment Form, XYWAV Prescription Form, or XYREM Prescription Form.

To complete an RMR:

- Assign a unique Control Number to each report in the Central Database.
- Complete investigation of the event, which may include contacting the patient, prescriber, law enforcement agency, or other parties.
- Attach any additional documentation required to support the investigation, including but not limited to the following: DEA 106 Form, police or fire report, or report from the shipping service.
- Complete review, follow up, and sign-off on the RMR.
  - When the event involves suspected abuse, misuse, or diversion, the prescriber will be contacted and an alert may be placed in the prescriber or patient profile of the Central Database to ensure prescriber and pharmacist awareness.
  - The Certified Pharmacy will monitor any associated patient or prescriber activity in the XYWAV and XYREM REMS during the course of the investigation and for a period after the investigation, where appropriate.
  - The Certified Pharmacy will work with Jazz Pharmaceuticals to determine the need to notify local, state, or federal agencies.
- Ensure that the information contained in the RMR is maintained in the Central Database.
- Send the RMR to Jazz Pharmaceuticals within one business day.

If the RMR includes a potential adverse event, the potential adverse event is reported through the Jazz Pharmaceuticals adverse event reporting system. If the RMR includes a product complaint, the event is also reported through the Jazz Pharmaceuticals product complaint system.

XYWAV and XYREM REMS Risk Management Report

Date: _____ **Control No.:** JRM- _____
Addendum: Yes ☐ No ☐

Type of reporter (e.g., patient, pharmacist, physician): _____

If not patient, name of reporter: _____

Nature of report (e.g., early refill request, lost or stolen bottle, package not received, other):

_____

Identification number(s) (patient and/or prescriber ID associated with RMR): _____

Date enrolled in program (from patient or prescriber record): _____

Reviewed alerts and RMR history for individual? Yes ☐ No ☐

RMR event (please provide detail): _____

_____

Date(s) of RMR event: Start: _____ End: _____

Early refill requested? Yes ☐ No ☐
If yes, reason for early refill request (e.g., dose increase, spilled medication, lost/stolen product):

_____

Prescriber contacted? Yes ☐ No ☐
If yes, outcome: _____ If no, reason: _____

Early refill status: Approved ☐ Denied ☐ Early refill status reason: _____

Potential adverse event associated with report? Yes ☐ No ☐ If yes, AE number: _____

Summary of investigation: _____

_____

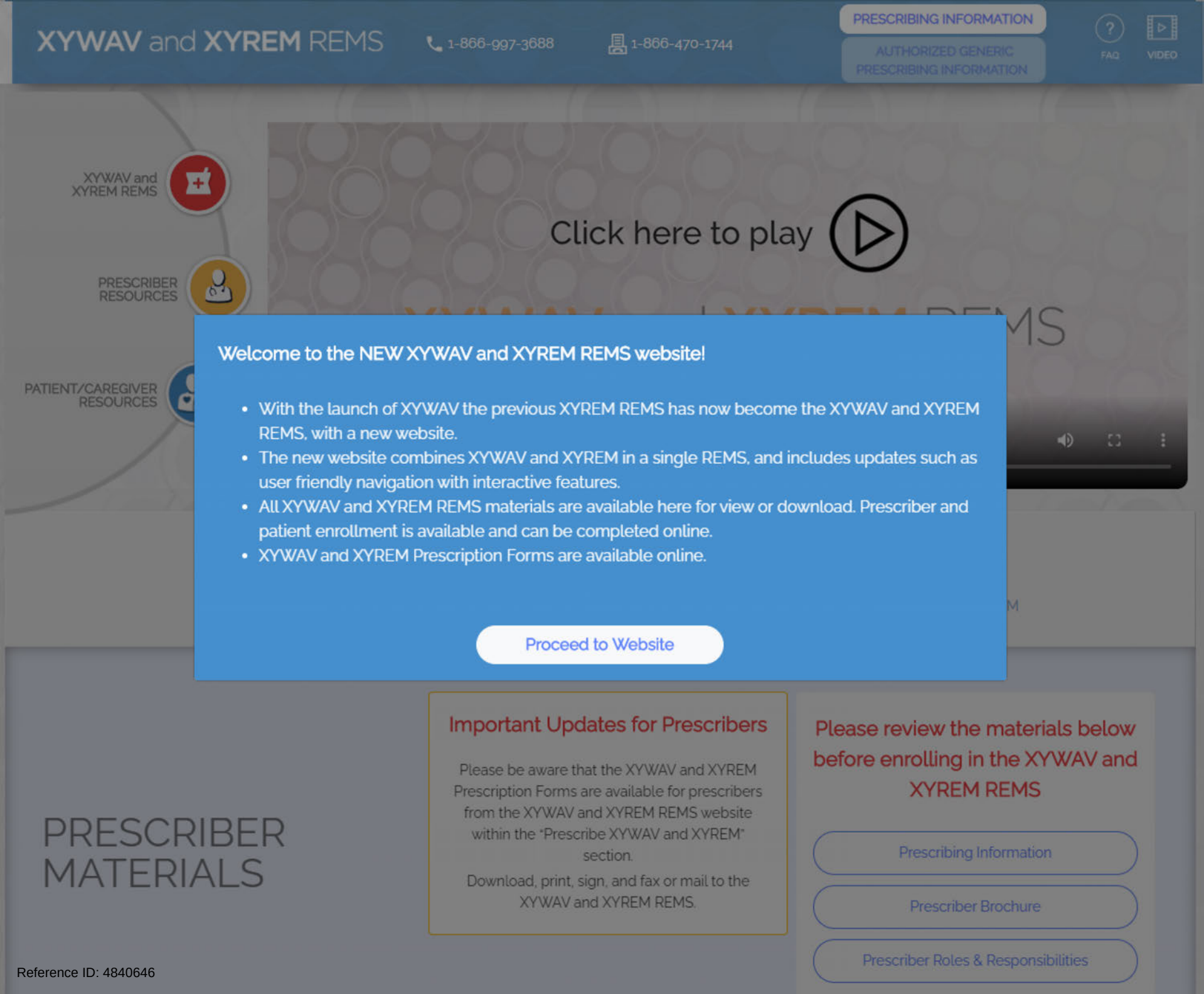
Attachments (check all that apply):
DEA 106 Form ☐ Police/Fire Report ☐ Shipping Service Report ☐
Other ☐ (specify) _____

Monitor (alert placed): Yes ☐ No ☐ N/A ☐

Report closed: Yes ☐ No ☐

Operations Director (or designee): _____ Signature (date/time) _____

Pharmacist in Charge (or designee): _____ Signature (date/time) _____



Reference ID: 4840646

XYWAV and XYREM REMS
PRESCRIBER RESOURCES
PATIENT/CAREGIVER RESOURCES

Prescriber Materials
Patient Materials
Prescriber Enrollment
Patient Enrollment
Prescribe XYWAV and XYREM

PRESCRIBER MATERIALS

Important Updates for Prescribers

Please be aware that the XYWAV and XYREM Prescription Forms are available for prescribers from the XYWAV and XYREM REMS website within the "Prescribe XYWAV and XYREM" section.

Download, print, sign, and fax or mail to the XYWAV and XYREM REMS.

Please review the materials below before enrolling in the XYWAV and XYREM REMS

- Prescribing Information
- Prescriber Brochure
- Prescriber Roles & Responsibilities

XYWAV and XYREM REMS
PRESCRIBER RESOURCES
PATIENT/CAREGIVER RESOURCES

Overview

The REMS Program

A REMS (Risk Evaluation and Mitigation Strategy) is a program 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 program ensures that XYWAV® (calcium, magnesium, potassium, and sodium oxybates) and XYREM® (sodium oxybate) are dispensed only from the Certified Pharmacy.

The XYWAV and XYREM REMS is designed to ensure that prescribers and patients are educated on and understand the risks and safe use conditions of XYWAV and XYREM and agree to follow the requirements of the XYWAV and XYREM REMS. XYWAV and XYREM may only be dispensed to patients enrolled in the XYWAV and XYREM REMS.

What are XYWAV and XYREM?

XYWAV and XYREM are central nervous system depressants.

- 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 (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.

Prescriber Materials
Patient Materials
Prescriber Enrollment
Patient Enrollment
Prescribe XYWAV and XYREM

Important Updates for Prescribers

Please be aware that the XYWAV and XYREM Prescription Forms are available for prescribers from the XYWAV and XYREM REMS website

Please review the materials below before enrolling in the XYWAV and XYREM REMS

XYWAV and XYREM REMS
PRESCRIBER RESOURCES
PATIENT/CAREGIVER RESOURCES

Prescriber Resources

Select the buttons below to view or download.

Enrollment

Prescriber Enrollment Form

Patient Enrollment Form

Prescribing Information

For XYWAV

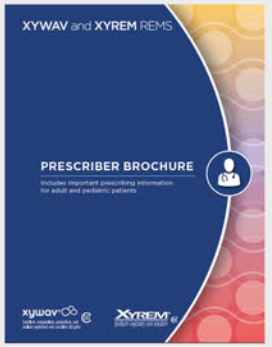
For XYREM

Prescription Forms

For XYWAV

For XYREM

XYWAV and XYREM Prescriber Brochure



Download

Prescriber Materials
Patient Materials
Prescriber Enrollment
Patient Enrollment
Prescribe XYWAV and XYREM

PRESCRIBER MATERIALS

Important Updates for Prescribers

Please be aware that the XYWAV and XYREM Prescription Forms are available for prescribers from the XYWAV and XYREM REMS website within the "Prescribe XYWAV and XYREM" section.

Please review the materials below before enrolling in the XYWAV and XYREM REMS

Prescribing Information

XYWAV and XYREM REMS

PRESCRIBER RESOURCES

PATIENT/CAREGIVER RESOURCES

Patient/Caregiver Resources

Patient
Quick Start Guide

For XYWAV

For XYREM

Brochure for Pediatric Patients and their Caregiver

For XYWAV

For XYREM

What You Should Know

- All patients must be enrolled in the XYWAV and XYREM REMS by the patient's heathcare provider.
- Prescriptions for XYWAV and XYREM are only dispensed and shipped to patients who are enrolled in the REMS with documentation of safe use conditions.
- Each pediatric patient must have a caregiver who is counseled by the healthcare provider.
- XYWAV and XYREM will be dispensed only by the REMS Certified Pharmacy.

PRESCRIBER MATERIALS

Important Updates for Prescribers

Please be aware that the XYWAV and XYREM Prescription Forms are available for prescribers from the XYWAV and XYREM REMS website within the "Prescribe XYWAV and XYREM" section.

Download, print, sign, and fax or mail to the XYWAV and XYREM REMS.

Please review the materials below before enrolling in the XYWAV and XYREM REMS

Prescribing Information

Prescriber Brochure

Prescriber Roles & Responsibilities

PRESCRIBER MATERIALS

Important Updates for Prescribers

Please be aware that the XYWAV and XYREM Prescription Forms are available for prescribers from the XYWAV and XYREM REMS website within the "Prescribe XYWAV and XYREM" section.

Download, print, sign, and fax or mail to the XYWAV and XYREM REMS.

Please review the materials below before enrolling in the XYWAV and XYREM REMS

- Prescribing Information
- Prescriber Brochure
- Prescriber Roles & Responsibilities

Prescriber Materials

- XYWAV Prescription Form
- XYREM Prescription Form
- XYWAV and XYREM REMS Prescriber Enrollment Form
- XYWAV and XYREM REMS Patient Enrollment Form
- XYWAV and XYREM REMS Prescriber Brochure

Patient Materials

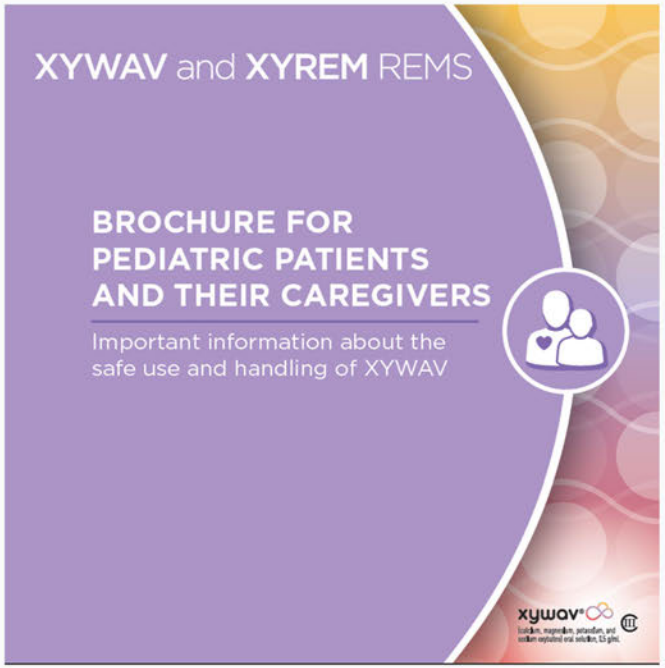
- XYREM Patient Quick Start Guide
- XYREM Brochure for Pediatric Patients and their Caregivers
- XYWAV Brochure for Pediatric Patients and their Caregivers
- XYWAV Patient Quick Start Guide

XYWAV and **XYREM** REMS

Jazz Pharmaceuticals

PATIENT MATERIALS

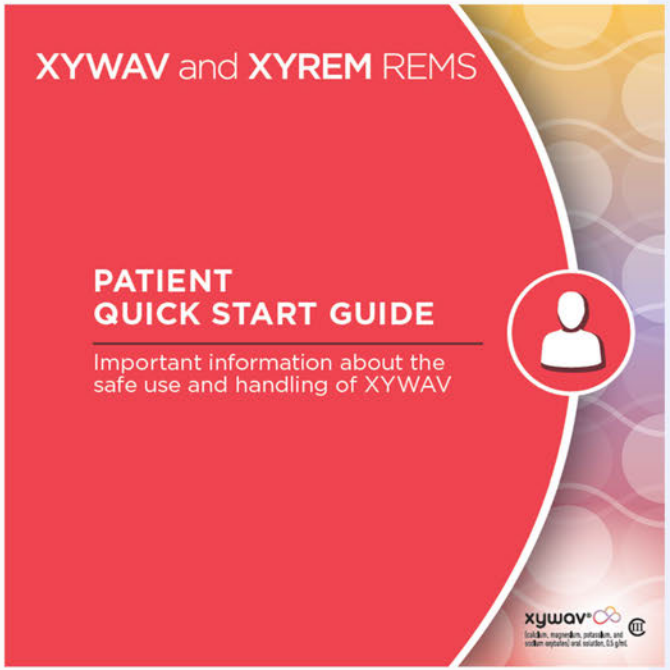
Before enrolling, patients can use the Quick Start Guide and Brochure for Pediatric Patients and Their Caregivers on the right to find out more concerning the use of XYWAV and XYREM.



Brochure for Pediatric Patients And their Caregivers

Use the Caregiver Brochure to counsel caregivers of pediatric patients.

For XYWAV | For XYREM



Patient Quick Start Guide

Click below to read the Patient Quick Start Guide for counseling adult patients.

For XYWAV | For XYREM

Prescriber Materials

- XYWAV Prescription Form
- XYREM Prescription Form
- XYWAV and XYREM REMS Prescriber

Patient Materials

- XYREM Patient Quick Start Guide
- XYREM Brochure for Pediatric Patients and their Caregivers

XYWAV and XYREM REMS

For Prescriber Use Only

PRESCRIBER ENROLLMENT

To become certified, each prescriber must complete a XYWAV and XYREM REMS Prescriber Enrollment Form once and submit it to the XYWAV and XYREM REMS via the options shown on the right.

Before enrolling in the XYWAV and XYREM REMS, ensure you're familiar by reading the XYWAV and XYREM Prescribing Information, Prescriber Roles & Responsibilities and the XYWAV and XYREM Prescriber Brochure.

The enrollment process for prescribers is quick, easy, and secure. Choose one of the two methods described below. Complete your enrollment form and submit it to the Certified Pharmacy for processing. For best results please use **Adobe Acrobat** to fill out the forms.

Option 1

Download:
Prescriber Enrollment Form

Scan and Email to:
ESSDSPrescribers@express-scripts.com

OR

Fax to:
XYWAV and XYREM REMS
1-866-470-1744 (toll free)

OR

Mail to:
XYWAV and XYREM REMS
PO Box 66589
St. Louis, MO 63166-6589

Option 2

Submit using DocuSign

By using DocuSign, the XYWAV and XYREM REMS can ensure that your personal information can stay safe, secure, and protected.

ACCESS ONLINE PRESCRIBER ENROLLMENT FORM

For Prescriber Use Only

PATIENT ENROLLMENT

If you begin patient enrollment online, your patient will receive an e-mail to complete his/her portions of the form, including an e-signature. Then, you will submit the form to the Certified Pharmacy. Both you and your patient will be notified when enrollment in the program is successful.

If you choose Option 1, have your patient sign the enrollment form in your office. You will then submit it to the Certified Pharmacy by e-mail, fax, or mail. For best results please use **Adobe Acrobat** to fill out the forms.

Option 1

Download:
Patient Enrollment Form

Scan and Email to:
ESSDSPrescribers@express-scripts.com

OR

Fax to:
XYWAV and XYREM REMS
1-866-470-1744 (toll free)

OR

Mail to:
XYWAV and XYREM REMS
PO Box 66589
St. Louis, MO 63166-6589

Option 2

Submit using DocuSign
By using DocuSign, the XYWAV and XYREM REMS can ensure that your personal information can stay safe, secure, and protected.

ACCESS ONLINE PATIENT ENROLLMENT FORM

Prescriber Materials

- XYWAV Prescription Form
- XYREM Prescription Form

Patient Materials

- XYREM Patient Quick Start Guide
- XYREM Brochure for Pediatric Patients and their Caregivers

XYWAV and **XYREM** REMS

PRESCRIBE XYWAV and XYREM

Utilize the resources here to understand the benefits and risks of XYWAV and XYREM and to prescribe XYWAV and XYREM. For more information please call the XYWAV and XYREM REMS toll free at 1-866-997-3688.

To prescribe XYWAV and XYREM, both prescriber and patient must be enrolled in the XYWAV and XYREM REMS.

VIEW PRESCRIBING INFORMATION

Please submit the signed form to the Certified Pharmacy by e-mail, fax, or mail. Online submission is coming soon. For best results please use **Adobe Acrobat** to fill out the forms.

Download Prescription Forms

Download the XYWAV Prescription Form

Download the XYREM Prescription Form

Print and Sign the completed XYWAV or XYREM Prescription Form for your Patient

Fax to:
XYWAV and XYREM REMS
1-866-470-1744 (toll free)

Mail to:
XYWAV and XYREM REMS
PO Box 66589
St. Louis, MO 63166-6589

Online Prescription Forms

Complete the XYWAV Prescription Form Online For Your Patient

Complete the XYREM Prescription Form Online For Your Patient

Print and Sign the completed XYWAV or XYREM Prescription Form for your Patient

COMING SOON

Print and Sign the completed XYWAV or XYREM Prescription Form for your Patient

Prescriber Materials

- XYWAV Prescription Form
- XYREM Prescription Form
- XYWAV and XYREM REMS Prescriber Enrollment Form

Patient Materials

- XYREM Patient Quick Start Guide
- XYREM Brochure for Pediatric Patients and their Caregivers
- XYWAV Brochure for Pediatric Patients

XYWAV and XYREM REMS

FAQ

Is it still possible to enroll offline?
Yes, you can still enroll offline. Please download the PDF version of this form and follow the submission instructions.

How do I add my signature to an online enrollment?
This is done securely and easily through DocuSign.

Do I need a DocuSign account to complete the online enrollment process?
No. You do not need a DocuSign account to complete the online enrollment process.

Do I need to complete the online version of the prescriber enrollment form if I am already enrolled into the XYWAV and XYREM REMS?
No. If you are already enrolled into the newly approved XYWAV and XYREM REMS or the Xyrem REMS or have completed the prescriber enrollment process offline and faxed it to the Certified Pharmacy, you do not need to complete the online version of the prescriber enrollment form.

You can still use the online enrollment form to enroll your patients.

How long does it take to process my enrollment so I can enroll patients?
Generally, the Certified Pharmacy will process your enrollment within 2 to 3 business days.

How will patients be notified that they need to complete their portion of the enrollment form?
Once you initiate the patient enrollment form, an email notification will be sent to your patient. The email will include a link to the enrollment form on DocuSign, where your patient can securely complete their portion of the enrollment process.

If your patient does not complete their portion of the enrollment form, we will send them a series of notification reminder emails.

How can I help my patient complete their portion of the enrollment form?
Due to security and privacy reasons, patients must fill out the entire portion of their form. If additional assistance is needed, we recommend you assist them with the process through a phone call.

Will a patient be able to include a copy of their insurance identification card?
If a patient confirms that they have prescription coverage on the enrollment form, they will be able to include a copy of their insurance identification card as an attachment.

If patients are completing the enrollment form on a mobile device, they will be able to use the camera to take a picture of their identification card.

How do I know my patient's information is safe?
DocuSign provides full document encryption to ensure the security and privacy of your data. Documents stored in their ISO 27001 and SSAE 16 data centers are encrypted with the highest levels of encryption.

Will my or my patient's information be shared with any third parties?
No. Your or your patient's information will be kept strictly confidential and never be shared or sold to third parties

Prescriber Roles & Responsibilities

Prescribers enrolled in the XYWAV and XYREM REMS agree to perform the following:

1. Review the Prescribing Information (PI) and the XYWAV and XYREM REMS Prescriber Brochure.
2. Screen each patient for:
   - History of alcohol or substance abuse
   - History of sleep-related breathing disorders
   - History of compromised respiratory function
   - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
   - History of depression or suicidality
3. Counsel each patient prior to initiating therapy with XYWAV and XYREM on the serious risks and safe use and handling of XYWAV and XYREM using the XYWAV and XYREM REMS Quick Start Guide.
4. Enroll each patient in the XYWAV and XYREM REMS by completing the XYWAV and XYREM REMS Patient Enrollment Form and submitting the form to the XYWAV and XYREM REMS.
5. Evaluate each patient within the first 3 months of starting XYWAV and XYREM therapy, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while taking XYWAV and XYREM.
   - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
   - Serious adverse events
   - Signs of abuse and misuse, including:
     1. an increase in dose or frequency of dosing
     2. reports of lost, stolen, or spilled medication
     3. drug-seeking behavior
6. 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.

Each time a new prescription is written the prescriber will complete the XYWAV and XYREM REMS Prescription Form and submit it to the XYWAV and XYREM REMS. By completing and signing this form, the prescriber acknowledges:

1. Having an understanding of:

   The approved indications for XYWAV:

   - Treatment of cataplexy in narcolepsy or treatment of excessive daytime sleepiness in narcolepsy in patients 7 years and older
   - Treatment of idiopathic hypersomnia in adults

   The approved indications for XYREM:

   - Treatment of cataplexy in narcolepsy or treatment of excessive daytime sleepiness in narcolepsy in patients 7 years and older
2. Having screened the patient for the following:
   - History of alcohol or substance abuse
   - History of sleep-related breathing disorders
   - History of compromised respiratory function
   - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
   - History of depression or suicidality
3. Having counseled the patient on:
   - The serious risks associated with XYWAV and XYREM Contraindications (alcohol and sedative hypnotics) and implications of concomitant use of XYWAV and XYREM with other potentially interacting agents
   - Preparation and dosing instructions for XYWAV and XYREM
   - Risk of abuse and misuse associated with XYWAV and XYREM
   - Risk of operating hazardous machinery including automobiles or airplanes for the first 6 hours after taking a dose of XYWAV and XYREM
   - Safe use, handling, and storage of XYWAV and XYREM
4. That XYWAV and XYREM is medically appropriate for the patient
5. Having listed all known prescription and nonprescription medications and doses on the XYWAV or XYREM Prescription Forms

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERESA J BURACCHIO on behalf of ERIC P BASTINGS
08/12/2021 01:15:04 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s006

CLINICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA (Serial Number)	**212690 (S-006)**
Sponsor:	**Jazz Pharmaceuticals, Inc.**
Product:	**Xywav (JZP-258)**
Proposed Indication:	**Idiopathic Hypersomnia**
Material Submitted:	**Supplemental New Drug Application**
Correspondence Date:	**2/12/21**
Date Received By Reviewer:	**2/12/21**
Date Review Completed:	**8/11/21**
Reviewer:	**Ranjit B. Mani, M.D.**

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EXECUTIVE SUMMARY

Recommendation

I recommend that Xywav™ (JZP-258) be approved for the treatment of idiopathic hypersomnia in adults, under New Drug Application #212690, Supplement #6.

Proposed Indication

The proposed new indication for Xywav™ as stated in the original submission to this application is as follows:

"XYWAV is indicated for the treatment of adult patients with idiopathic hypersomnia (IH)."

Currently Approved Indication

The currently-approved indication for Xywav™ as stated in the Prescribing Information for that product is as follows:

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

Background To Application

Idiopathic hypersomnia is an uncommon chronic disorder, distinct from narcolepsy, that is characterized by an uncontrollable daytime need to sleep or daytime lapses into sleep; however, daytime naps and longer periods of sleep are unrefreshing. Other sleep-related symptoms occur together with distinctive findings on the multiple sleep latency test. This disorder may be severely disruptive of daily activities. Current criteria for the diagnosis of idiopathic hypersomnia are included under the International Classification of Sleep Disorders, 3rd Edition (ICSD-3).

No treatment has previously been approved for idiopathic hypersomnia.

Xywav™ (a low-sodium oxybate oral solution formulation containing a mixture of calcium, magnesium, potassium, and sodium oxybates), also named JZP-258, is currently approved for the treatment of cataplexy or excessive daytime sleepiness, in patients 7 years or older with narcolepsy. Xywav™ was originally approved for that indication on July 21, 2020. Xyrem® (sodium oxybate oral solution [500 mg/mL]) is currently approved for the same indication as Xywav™.

The development of Xywav™ for the treatment of idiopathic hypersomnia was earlier discussed with the Agency on several occasions. Those discussions extended to the design of a single efficacy and safety study (JZP080-301) which the Agency indicated would be sufficient in form to support the approval of Xywav™ (then known as JZP-258 alone) for the treatment of idiopathic

hypersomnia provided Xywav™ was already approved for the treatment of narcolepsy at that time

Xywav™ has been granted Fast Track Designation for the treatment of idiopathic hypersomnia and this application has been granted Priority Review.

Summary Of Main Clinical Findings

A single efficacy and safety study (JZP080-301) was the only clinical study of JZP-258 that was conducted in support of the proposed indication of idiopathic hypersomnia.

Study Design

The main features of Study JZP080-301 were as follows.

- The primary objective of the study was to evaluate the efficacy of JZP-258 in the treatment of idiopathic hypersomnia.

- This was to be a double-blind, placebo-controlled, randomized withdrawal, multicenter study of the efficacy and safety of JZP-258. Patients enrolled in the study were to include those whose prior treatment status was in any of the following 2 categories:

    - Treatment with a stable dose of Xyrem®.
    - No prior treatment with Xyrem®.

- The study was to consist of the following consecutive periods: screening; open-label titration and treatment optimization (of variable duration up to a maximum of 14 weeks, depending on prior treatment status); open-label stable dose treatment (2 weeks); double-blind, randomized withdrawal (2 weeks); and safety follow-up (2 weeks). All study patients were to be titrated (during the variable-duration open-label titration period) to a dose of JZP-258 that was deemed both effective and tolerable and was maintained for at least 2 weeks prior to entering the two-week, open-label, stable-dose period. An open-label extension of 24 weeks was to follow the double-blind treatment period.

- A total of about 140 patients were planned to be enrolled in the study of whom about 112 patients were expected to enter the randomized double-blind withdrawal period during which they were to be randomly assigned 1:1 to either continuing the same dose of JZP-258 taken during the stable dose period or to placebo.

- The main inclusion criteria for this study were to be as follows: men and women, aged 18 to 70 years; a primary diagnosis of idiopathic hypersomnia that met the ICSD–2 or -3 criteria; a history of an average

total nightly treatment ≥ 7 hours; treatment status prior to study entry consisting of one of the aforementioned 2 categories; if not treated with Xyrem®, must have an Epworth Sleepiness Scale scores ≥ 11; and if treated with a stimulant for narcolepsy must have been at an unchanged dose for at least 2 months prior to dosing or must not have been treated at all with a stimulant.

- The primary efficacy parameter was to be the change in Epworth Sleepiness Scale score from the end of the 2-week stable dose period to the end of the 2-week double-blind treatment period. Key secondary efficacy endpoints were to be the Patient Global Impression of Change and the Idiopathic Hypersomnia Sleepiness Scale score, extending over the same period as the primary efficacy parameter. Safety measures were to include adverse events, vital signs, weight, physical examinations, 12-lead electrocardiograms, safety laboratory tests (hematology, clinical chemistry, and urinalysis), and the Columbia-Suicide Severity Rating Scale (for assessing suicidality). Plasma samples for pharmacokinetic analysis were drawn from a subset of patients over a single night.

- The analyses of the primary efficacy parameter and key secondary efficacy parameters were to employ a fixed sequential testing strategy in which the initial step was to involve a comparison of JZP-258 with placebo for the primary efficacy parameter; if the initial comparison was statistically significant, the treatment groups were then to be compared on the key secondary efficacy parameters in the following sequence: Patient Global Impression of Change followed by Idiopathic Hypersomnia Sleepiness Scale scores. An analysis of covariance model was to be used for the primary efficacy analysis and for the analysis of one of the key secondary efficacy measures, the Idiopathic Hypersomnia Sleepiness Scale. The Cochran-Mantel-Haenszel test was to be used for the analysis of the Patient Global Impression of Change. An optional interim analysis was planned when about 60% of the 112 planned randomized patients had completed or were terminated early from the double-blind randomized withdrawal period, and incorporated a plan for controlling familywise Type 1 error.

Study Results

Study JZP080-301 was conducted in a manner consistent with the study protocol. No interim analysis was conducted.

154 patients were enrolled in the study and entered the optimized treatment and titration period (up to 14 weeks). They consisted of the following: 2 patients who were receiving Xyrem only; 4 patients who were receiving a combination of Xyrem and a stimulant; 82 patients who were receiving a stimulant only; and 66

patients who were drug-naïve at study entry. 123 patients then entered the stable-dose period (2 weeks).

113 patients who completed the stable-dose period were then randomized, and entered the randomized, double-blind, placebo-controlled, withdrawal period (2 weeks). At the beginning of that period, 57 patients were randomized to continuing JZP-258 and 59 patients were randomized to placebo; 56 patients randomized to JZP-258 and 57 patients randomized to placebo completed that period of the study.

The primary efficacy analysis (based on an analysis of covariance) indicated that the median change from baseline over the two-week randomized withdrawal period in Epworth Sleepiness Scale score was an increase of 8.0 points for the placebo group and 0.0 points for the group that continued to take JZP-258. This difference was statistically significant ($p < 0.0001$). Statistically significant treatment differences favoring JZP-258 over placebo were seen on both key secondary efficacy parameters analyzed in the prespecified sequence. On the Patient Global Impression of Change, the percentage of subjects with minimally, much, or very much worse scores on the Patient Global Impression of Change at the end of the double-blind randomized withdrawal period was 88.1% in the placebo group and 21.4% in the JZP-258 group; that difference was statistically significant based on the Cochran-Mantel-Haenszel test ($p < 0.0001$). On the Idiopathic Hypersomnia Sleepiness Scale, an increase in median score of 14 points was seen in the placebo group over the double-blind randomized withdrawal period as opposed to no change on that measure in the JZP-258 group; this difference was statistically significant based on an analysis of covariance ($p < 0.0001$).

106 patients then entered the open-label phase of the study, with 95 patients completing that phase.

The adverse event profile of JZP-258 as seen across this study was not substantially different from that seen with JZP-258 or Xyrem® when used for the treatment of narcolepsy. The other safety outcomes did not reveal any data of concern.

Conclusion

Substantial evidence of the efficacy of Xywav™ (JZP-258) in the treatment of idiopathic hypersomnia in adults was demonstrated by the results of a single adequate and well-controlled clinical study JZP080-301.

The safety profile of Xywav™ (JZP-258) in the treatment of idiopathic hypersomnia as seen in Study JZP080-301 is acceptable and not substantially different from that of Xywav™ (or Xyrem®) in the treatment of narcolepsy.

1. Background

This review is of a Supplemental New Drug Application (sNDA) for Xywav™ (calcium, magnesium, potassium, and sodium oxybates) oral solution 0.5 g/mL, submitted under New Drug Application (NDA) 212690.

Under the current sNDA, the sponsor is seeking the approval of Xywav™ for the treatment of idiopathic hypersomnia in adults. Sections of this application were submitted early (i.e., as a "rolling" submission), with the Agency's agreement, on December 18, 2020.

Xywav™ (a low-sodium oxybate oral solution formulation containing a mixture of calcium, magnesium, potassium, and sodium oxybates) is currently approved for the treatment of cataplexy or excessive daytime sleepiness, in patients 7 years or older with narcolepsy; it was originally approved for that indication on July 21, 2020.

Xywav™ was originally named "JZP-258," a name that is used interchangeably with "Xywav™" in this submission.

The report of a single clinical efficacy and safety study of Xywav™ (JZP080-301) has been submitted in this application. This study forms the main basis for seeking the approval of Xywav™ for the treatment of idiopathic hypersomnia.

Another product currently approved for the treatment the treatment of cataplexy or excessive daytime sleepiness, in patients 7 years or older with narcolepsy is Xyrem® (sodium oxybate oral solution [500 mg/mL]); Xyrem® was initially approved under NDA 21196 on July 17, 2002. Xywav™ and Xyrem® have a common sponsor: Jazz Pharmaceuticals, Inc,.

A common Xywav™ and Xyrem® Risk Evaluation and Mitigation Strategy (REMS) is currently in place for both Xyrem® and Xywav™. A set of changes to that REMS has been proposed in accompaniment of the current sNDA and has been submitted to both NDA 212690 and 21196.

This sNDA has been assigned Priority Review status after a request from the applicant was included in the main submission to this sNDA. That request was on the grounds that there is currently no approved treatment for idiopathic hypersomnia.

In addition, the Agency has granted:

- Orphan Drug designation for gamma-hydroxybutyrate as a treatment for idiopathic hypersomnia on July 31, 2019.

- Fast Track Designation for Xywav™ in the treatment of idiopathic hypersomnia on September 18, 2020.

Xywav™ has been developed for the treatment of idiopathic hypersomnia under IND

2. Contents Of Submission

The following are the main items in each of the 3 main components of this application.

- The pre-submission of December 18, 2020 (under "rolling" review), which has been submitted in electronic Common Technical Document format. This component has two main components, enumerated and headed as follows:

    - Module 1: Administrative Information and Prescribing Information.
    - Module 5: The report of Study JZP080-301, the main clinical efficacy study supporting this application, dated December 14, 2020. Analysis datasets for the above study.

- The Original sNDA submission of February 12, 2021, which has been submitted in electronic Common Technical Document format. This component has three main components, enumerated and headed as follows:

    - Module 1: Administrative Information and Prescribing Information
    - Module 2: Common Technical Document Summaries.
    - Module 5. Clinical Study Reports (The report of Study JZP080-301, the main clinical efficacy study supporting this application, dated December 14, 2020, submitted a second time).

- 120-Day Safety Update, dated April 23, 2021, which has been submitted in electronic Common Technical Document format. This component has three main components, enumerated and headed as follows:

    - Module 1: Administrative Information and Prescribing Information.
    - Module 5. Clinical Study Reports (containing the final report of Study JZP080-301, dated March 30, 2021). Note that a minor information amendment to this report was submitted on May 28, 2021.

3. Contents Of Review

The contents of this sNDA will be reviewed under the following headings and in the same consecutive order as below.

- Idiopathic hypersomnia
- Outline of main clinical study (JZP080-301) supporting this application.
- 120-Day Safety Update.
- Review of proposed Prescribing Information and related documents.
- Summary of Office of Surveillance and Epidemiology review.
- Summary of Division of Medical Policy Programs/Office of Prescription Drug Promotion Reviews.
- Controlled Substances Staff review.
- Financial disclosure information.
- Site inspection.
- Overall conclusions.
- Recommendation.

4. Idiopathic Hypersomnia

The following summary was created from several sources.

Idiopathic hypersomnia, a central disorder of hypersomnolence, is an uncommon condition that is distinct from narcolepsy.

The prevalence of idiopathic hypersomnia is estimated at 20 to 50 patients per million.

The core criteria for idiopathic hypersomnia according to the International Classification of Sleep Disorders, 3rd Edition (ICSD-3) are as follows.

- Daily periods of an irrepressible need to sleep or daytime lapses into sleep present for at least 3 months.
- Fewer that two sleep-onset rapid eye movement periods (SOREMPS) on the multiple sleep latency test (or less than one period if nocturnal rapid eye movement [REM] latency was ≤ 15 minutes).
- No cataplexy.

- Either 1 or 2 below.

    1. Mean sleep latency ≤ 8 minutes on the multiple sleep latency test.

    2. Total 24-hour sleep time ≥ 660 minutes on 24-hour polysomnography monitoring or wrist actigraphy, averaged over ≥ 7 days.

- Exclusion of insufficient sleep syndrome.

- The hypersomnolence and/or multiple sleep latency test findings are not better explained by other causes.

Idiopathic hypersomnia usually has its onset in adolescence or early adulthood, and is usually lifelong, although its severity can fluctuate over time. Men are affected more than women. Daytime naps are generally long (> 1 hour) and are unrefreshing. Patients may also sleep for longer periods (e.g., ≥ 9 hours or more in 24 hours; these periods are also unrefreshing. “Sleep drunkenness” (sleep inertia) may also occur with extreme and prolonged difficulty awakening fully and an uncontrollable desire to get back to sleep, accompanied by automatic behavior and confusion. Other symptoms such as sleep hallucinations and sleep paralysis may also occur, as may postural hypotension and other manifestations of an autonomic disturbance

Idiopathic hypersomnia may be severely disruptive of most daily activities.

The pathophysiology of idiopathic hypersomnia is not understood but is different from that of narcolepsy type 1 which is due to a hypocretin deficiency.

A review of idiopathic hypersomnia is available at the link below.

https://www.uptodate.com/contents/idiopathic-hypersomnia

Currently, no medications have been approved by this Agency for the treatment of idiopathic hypersomnia. However, medications that are commonly used to treat excessive daytime sleepiness in narcolepsy are commonly used to treat idiopathic hypersomnia.

The following table which I have copied from a submission under IND 49641 summarizes the differences between the two types of narcolepsy and idiopathic hypersomnia.

Feature	Narcolepsy Type 1	Narcolepsy Type 2	Idiopathic Hypersomnia
EDS	Present	Present	Present
Cataplexy	Generally present (cataplexy plus characteristic MSLT features, or hypocretin deficiency are necessary for diagnosis)	Absent (by definition)	Absent (by definition)
Sleep paralysis[a]	Present in 69%	Present in 35%	Present in 20%
Sleep hallucinations[a]	Present in 77%	Present in 42%	Present in 25%
Tetrad of all 4 of the above symptoms	Present in 42% (although not all present initially)	Absent	Absent
Fragmented nocturnal sleep	Significantly lower sleep efficiency than narcolepsy without cataplexy or IH	May be common	Not typical
REM sleep behavior disorder	Present in 45-61%; significantly more PSG-measured REM sleep without atonia than in IH	Significantly more PSG-measured REM sleep without atonia than in IH	Rate of REM sleep behavior disorder not studied
Sleep drunkenness	Rare, but occasionally reported	May be common	Common
Long nocturnal sleep times	Present in 18% of patients with narcolepsy with or without cataplexy	Present in 18% of patients with narcolepsy with or without cataplexy	Common
Effect and duration of naps	Refreshing, short		Unrefreshing (compared with either patients with narcolepsy with cataplexy or normal control subjects), long

[a] Frequency estimates for sleep paralysis and hypnagogic hallucinations are compilations from case series reporting on at least 2 of the groups outlined in this table.
Source: Khan and Trotti 2015.

5. Main Regulatory Interactions Regarding The Development of Xywav™ For The Treatment Of Idiopathic Hypersomnia

The following in sequence is a list of the main regulatory interactions between the Agency and sponsor regarding the development of Xywav™ for the treatment of idiopathic hypersomnia. These interactions all occurred under IND 49641.

- The development of Xywav™ for the treatment of idiopathic hypersomnia was first discussed with the Agency in a Type C meeting package submitted on May 29, 2018, under Serial #304, to which the Agency provided a Written Response on July 17, 2018. The discussion extended to an earlier version of Protocol JZP080-301 (i.e., a version earlier than that described further in this review) which the Agency stated would be sufficient in form to support the approval of Xywav™ (then known as JZP-258 alone) for the treatment of idiopathic hypersomnia provided Xywav™ was already approved for the treatment of narcolepsy at that time. Clinical pharmacology-related responses were also provided in the meeting package. Please note that the protocol for Study JZP080-301 was originally submitted as Serial #301 on May 3, 2018.

- The last formal amendment to Protocol JZP080-301 (Amendment #2) was submitted on April 1, 2019, under Serial #335.

- In a submission dated May 22, 2020 (under Serial #363), a request for comments and advice, the sponsor proposed methods of collecting efficacy and safety data remotely, and of delivering study medication to the patient in the context of the COVID-19 pandemic. This submission was reviewed by Agency Biometrics staff and a response provided to the sponsor on June 24, 2020; additional analyses were recommended by the Agency at that time.

- A revised Statistical Analysis plan was submitted by the sponsor on July 8, 2020 (Serial #364), to which the Agency responded on August 21, 2020.

- A Fast Track Designation request for Xywav™ in the treatment of idiopathic hypersomnia was submitted on August 7, 2020, under Serial #365, and was granted in a letter dated September 18, 2020.

- The final Statistical Analysis Plan was submitted to the Agency on September 3, 2020 (Serial #367).

- A Pre-sNDA meeting package was submitted on November 5, 2020 (Serial #370). Preliminary responses to the sponsor's questions were then conveyed to the sponsor on December 4, 2020. After receiving the above preliminary responses, the sponsor canceled the planned meeting (teleconference) that was scheduled for December 8, 2020.

Please see the full text of the above submissions and Agency letters for further details.

6. Outline Of Main Clinical Study (JZP080-301) Supporting This Application

As previously outlined in this review, the report of a single clinical efficacy and safety study of Xywav™ (JZP080-301) has been submitted in this application. This study is the basis for seeking the approval of Xywav™ for the treatment of idiopathic hypersomnia.

As also previously outlined in this review, the Agency had previously concurred that a single adequate and well-controlled efficacy trial of JZP-258 (as Xywav™ was then known) would be needed to support the approval of that drug for the treatment of idiopathic hypersomnia if JZP-258 has by then already been approved for the treatment of narcolepsy.

The protocol and key results for Study JZP080-301 are summarized below.

Please note the name "JZP-258" has been used interchangeably with "Xywav™" in that summary.

6.1 Study Protocol

The version of the protocol for JZP080-301 summarized before is the final version, containing Amendment #2, and dated February 20, 2019. Note that the final statistical analysis plan for this study (Version 2.0 of the statistical analysis plan) was dated August 31, 2020.

6.1.1 Objectives

6.1.1.1 Primary Objective

To evaluate the efficacy of JZP-258 in the treatment of idiopathic hypersomnia.

6.1.1.2 Secondary Objectives

- To evaluate the safety of JZP-258 in the treatment of idiopathic hypersomnia.

- To characterize oxybate pharmacokinetics when administering JZP-258 to patients with idiopathic hypersomnia.

6.1.2 Design, Dose, Sample Size, And Duration

This was to be a double-blind, placebo-controlled, randomized withdrawal multicenter study of the efficacy and safety of JZP-258 in idiopathic hypersomnia.

The study was to have the following consecutive periods.

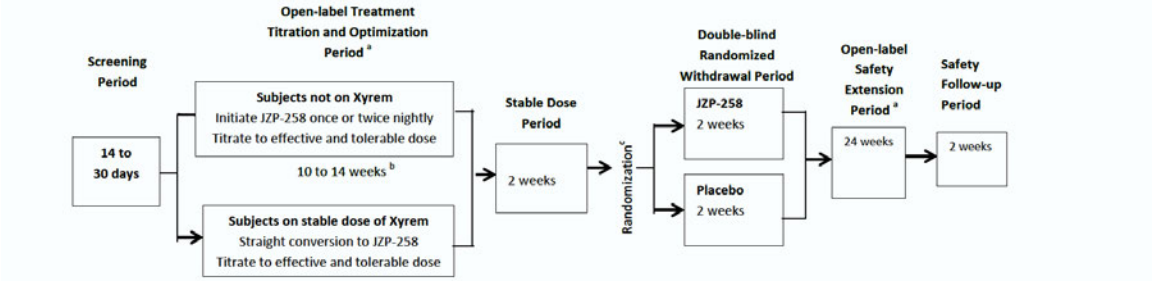
- Screening period of 14 to 30 days.
- Open-label titration and optimization period of 10 to 14 weeks.
- Stable dose period of 2 weeks.
- Double-blind randomized withdrawal period of 2 weeks.
- Open-label safety extension period of 24 weeks.
- Safety follow-up period of 2 weeks.

Those enrolled in the study were to include those whose prior treatment status was in any of the following categories:

- Treatment with stable dose of Xyrem®.

- No prior treatment with Xyrem®.

A schematic of the study design is copied below from the study protocol.



NOTE: Randomized Withdrawal Period may stop. All subjects who have not already been randomized would then receive open-label JZP-258 during the Double-blind Randomized Withdrawal Period. All subjects who have already entered the Double-blind Randomized Withdrawal Period will complete that period as planned.

[a] A subset of up to 30 subjects will participate in a single overnight PK evaluation during either the Open-label Treatment Titration and Optimization Period or the Open-label Safety Extension Period. The PK evaluation night may occur on any night during 1 of the 2 periods, but preferably during 1 of the scheduled in-clinic visits.

[b] The Open-label Treatment Titration and Optimization Period will occur over a period of 10 to 14 weeks. Every effort should be made to titrate to an optimally effective and tolerable dose and regimen within the first 10 weeks. For subjects requiring additional titration, with approval from the Medical Monitor, up to an additional 4 weeks of titration/adjustment may be performed. See Sec. 5.3 for dosing details.

[c] If the optional IA is conducted and the predefined efficacy stopping rule is met, enrollment and randomization to placebo treatment during the Double-blind

PK= pharmacokinetic

The study was to enroll about 140 patients so that a total of 112 patients would enter the double-blind randomized withdrawal period and would then be randomized 1:1 to the two treatment group (56 patients per treatment group).

Subjects entering the study were to be dosed with JZP-258 as follows.

- Those taking a stable dose of Xyrem® at entry were to continue the same dosing regimen, but using JZP-258. The dose of JZP-258 could then be adjusted until an optimal dosing regimen was achieved in regard to both efficacy and tolerability.

- Those not taking Xyrem® at entry were to be begin JZP-258 as either a twice nightly or once nightly regimen at the discretion of the investigator, with a proportion of patients needing a thrice nightly regimen to control symptoms. The dosing regimen for these patients is summarized in the next table copied from the submission.

Dosing Regimen	Starting Nightly Dose	Titration Increments[a]	Maximum Nightly Dose
Once Nightly	≤3 g	≤1.5 g/night per week	6 g[b]
Twice Nightly	≤4.5 g (divided)	≤1.5 g/night per week	9 g
Thrice Nightly (*titration only, not a starting dose*)	Not applicable	≤ 1.5 g/night per week	9 g

NOTE: the aim of JZP-258 dose titration and optimization is to maximize efficacy (reduced IH symptoms, e.g.. EDS, sleep inertia, and sleep duration) while ensuring adequate nocturnal sleep and minimizing risks associated with safety and tolerability.

[a] The weekly increase in dose of ≤1.5 g/night may be made incrementally every few days as tolerated.

[b] The maximum single dose should not exceed 6 g and the maximum nightly dose should not exceed 9 g at twice or thrice nightly dosing

EDS= excessive daytime sleepiness; IH=idiopathic hypersomnia

A subset of 30 patients were to participate in a pharmacokinetic substudy undergoing overnight pharmacokinetic sampling during a single night, either during the open-label titration and optimization period or during the open-label extension.

6.1.3 Key Inclusion Criteria

These criteria are listed below.

- Male or female. Age 18 to 75 years.
- Primary diagnosis of idiopathic hypersomnia that meets the International Classification of Sleep Disorders (ICSD) – 2 or ICSD-3 criteria.
- Treatment status prior to study entry consisting of <u>one</u> the following:
    - Taking Xyrem® at a stable dose.
    - Not receiving Xyrem®.
- If not taking Xyrem® at entry, must have Epworth Sleepiness Scale scores ≥ 11 (as assessed with a look-back period of 1 week). However, any subjects washing out of any medication (such as a stimulant not taken at a stable dose) that could impact the Epworth Sleepiness score during the screening period would only need to have an Epworth Sleepiness Scale score ≥ 11 at the baseline visit.
- Average total nightly sleep time ≥ 7 hours, per subject history. Total sleep time may be confirmed by the investigator's review of sleep diaries collected during the final two weeks of the screening period.
- If currently treated with stimulants and/or alerting agents or nicotine replacement therapy must have been taking the same regimen and dose for at least 2 months prior to screening and must continue to take the same dose leading up and throughout the double-blind dosing period.
- Using a medically-acceptable means of contraception for at least 2 months prior to the first dose of study drug and consent to use a medically acceptable method of contraception throughout the entire study period and for 90 days after the study is completed.
- Informed consent.

6.1.4 Key Exclusion Criteria

Subjects meeting any of the following exclusion criteria were to be excluded from the study. The list below has been copied from the study protocol,

- Hypersomnia due to another medical, behavioral, or psychiatric disorder condition (e.g., narcolepsy, multiple sclerosis, Parkinson's disease, stroke).
- Evidence of untreated or inadequately treated sleep-disordered breathing including:
  a. Presence of clinically significant and untreated obstructive or central sleep apnea as determined by the Investigator or documented previously

  or documentation of 1 of the following:

  b. Apnea Index (>10) on any historical test (unless a subsequent apneal index≤ 10 was reported after treatment), and the subject agrees to use this treatment throughout the duration of the study) or during the Screening PSG (if done) while on obstructive sleep apnea treatment or untreated
  c. Clinically significant hypoventilation
  d. Noncompliance with primary obstructive sleep apnea therapy (compliance defined as positive airway pressure use of ≥4 hours per night on ≥70% of nights [≥5 of 7 nights / week], historical report [with Investigator concurrence] of use of an oral appliance on ≥70% of nights [≥5 of 7 nights/week], or receipt of an effective surgical intervention for obstructive sleep apnea symptoms)
- Clinically significant parasomnias (e.g., sleep walking, rapid eye movement [REM] sleep behavior disorder, etc.).
- Current or past (within 1 year) major depressive episode according to DSM-5 criteria. Subjects with depression under control are allowed per the judgment of the Investigator or the treating physician and the antidepressant treatment has to be stable for at least 6 months prior to Screening and remain stable for the duration of the study.
- Current suicidal risk as determined from history, by presence of active suicidal ideation as indicated by positive response to item No.4 or No.5 on the Columbia Suicide Severity Rating Scale (C-SSRS), or any history of suicide attempt.
- Occupation requiring nighttime shift work or variable shift work with early work start times or other occupations that could affect the safety of the subject per the judgment of the Investigator.
- Treatment or planned treatment with any central nervous system (CNS) sedating agents, including but not limited to benzodiazepines or other sedating anxiolytics, sedating antidepressants, hypnotics, sedatives, neuroleptics, opioids, barbiturates, phenytoin, ethosuximide, medications containing valproic acid or its sodium salt (e.g., depakene and Depakote™), or other sedating antiseizure medications, melatonin, muscle relaxants, general anesthetics, or any other medication in which the subject experiences sedation are prohibited during the study. Treatment must have been discontinued for at least 2 weeks or 5 half-lives prior to enrollment (whichever is longer). Discontinuation for the purpose of study enrollment is permitted only if considered safe and medically appropriate by the Investigator, and approved by the Medical Monitor. The Investigator must ensure that discontinuation from these medications is medically supervised. Subjects must abstain from these medications during the study.
- Current or past substance use disorder (including alcohol) according to DSM-5 criteria or the subject is unwilling to refrain from consuming alcohol, cannabinoids, or prohibited medications during the study.

6.1.5 Concomitant Medications

6.1.5.1 Prohibited Medications

These are listed below; the list has been copied from the study protocol.

a. Treatment or planned treatment with any CNS sedating agent, including but not limited to benzodiazepines, or other sedating anxiolytics, sedating antidepressants, hypnotics, sedatives, neuroleptics, opioids, barbiturates, phenytoin, ethosuximide, medications containing valproate acid or its sodium salt (e.g., depakene and Depakote), or other sedating antiseizure medications, melatonin, muscle relaxants, general anesthetics, or any other medication in which the subject experiences sedation are prohibited during the study. Treatment must have been discontinued for at least 2 weeks or 5 half-lives prior to enrollment (whichever is longer). (Discontinuation for the purpose of study enrollment is permitted only if considered safe and medically appropriate by the Investigator, and approved by the Medical Monitor.) The Investigator must ensure that discontinuation from these medications is medically supervised. Subjects must abstain from these medications during the study. If a subject undergoes a procedure during the study and requires general anesthetics, opioids or benzodiazepine use, study drug may be held while these medications are given if approved by the Medical Monitor. JZP-258 administration is not allowed to continue during treatment with any CNS sedating agent. If opioid or benzodiazepine use is required for a prolonged period of time, the subject should be discontinued from the study.
b. Investigational drugs other than study drug are prohibited during the study.
c. Stimulants or alerting agents are prohibited during the study for subjects who have not been on a stable dose of these medications during and prior to participation in the study (including but not limited to pseudoephedrine, methylphenidate, amphetamines, modafinil, and armodafinil). Treatment must have been discontinued for at least 2 weeks or 5 half-lives prior to enrollment (whichever is longer). (Discontinuation for the purpose of study enrollment is only permitted if considered safe and medically appropriate by the Investigator, and approved by the Medical Monitor.) The Investigator must ensure that discontinuation from these medications is medically supervised. The exception will be short-term use of decongestant medications to treat AEs such as upper respiratory infections during the open-label treatment titration and optimization period and safety extension and follow-up periods.
d. Drugs of abuse (cannabis, opioids, etc.) are prohibited during the study, except for prescribed medication allowed by the protocol. However, cannabis products will not be allowed under any circumstances.

6.1.5.2 Permitted Medications

These are listed below; the list has been copied from the study protocol.

a. Stimulants or alerting agents or nicotine replacement therapy may be continued during the study provided doses were unchanged for 2 months prior to Screening and stimulant doses remain unchanged throughout the Double-blind Randomized Withdrawal Period.
b. Nonsedating antidepressant medications may be continued during the study if doses were unchanged for 6 months prior to dosing with JZP-258 and doses remain unchanged throughout the study.
c. Vitamins in normal doses may be continued (herbal supplements are prohibited).
d. Birth control pills, patches, injections, or implants (all hormonal contraceptives) may be continued.
e. Nicotine may be continued if there is no dependence that has an effect on sleep (e.g., a subject must not routinely awaken at night to smoke).
f. Local topical anesthetic agent before any blood draws.
g. Nonsedating antihistamines.
h. Antiinflammatories for pain.
i. Paracetamol (acetaminophen) for pain
j. Chronic topical or oral antibiotics for acne.

6.1.6 Schedule

The study schedule of events is summarized below in three tables that I have copied from the study protocol.

- The first table covers the screening visit, open-label treatment titration optimization period, the stable-dose period, and the double-blind randomized withdrawal period.

- The second table covers the open-label safety extension period and safety follow-up period.

- The third table covers the single night of pharmacokinetic sampling for the pharmacokinetic substudy.

The tables below are self-explanatory.

6.1.6.1 Schedule Until End Of Double-Blind, Randomized Withdrawal Period

Events	Screening (14 to 30 d)	OL Treatment Titration and Optimization Period (10 to 14 weeks) [a]							Stable Dose Period (2 weeks)	DBRW Period (2 weeks)	
	Study entry	Switch to / start JZP-258	Titration Treatment [b]					End Titration/ Begin Stable Dose	End Stable Dose/ Begin DBRW		End DBRW
Visits [c]	**Screening Visit**	**Baseline Visit**	**W1**	**W2, W3 Call**	**W4**	**W6 Call**	**W8**	**Ext Titration 1** [d] **Ext Titration 2** [d]	**End Titration**[e]	**End of Stable Dose**	**DBRW W1 Call**	**End DBRW** [f]**/ ET Visit**
Window (Days)	-30 to -2	Day 1	7-10	14-17; 21-24	28-31	35-49	49-63	63-77; 77-91	63-98	14-17	4-10	14-17
Window Relative to	Baseline		Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	End Titration	End Stable Dose	End Stable Dose
Collect / review sleep diary and VAS for Sleep inertia [l]		X								X		X
PSG /MSLT, if necessary [m]	X											
ESS	X	X	X		X		X	X	X	X		X
CGIs		X										
CGIc			X		X		X	X	X	X		X [n]
PGIc			X		X		X	X	X	X		X [o]
IHSS		X	X		X		X	X	X	X		X
FOSQ-10		X								X		X
WPAI:SHP		X								X		X
C-SSRS Baseline/ Screening Version	X											

Events	Screening (14 to 30 d)	OL Treatment Titration and Optimization Period (10 to 14 weeks) [a]							Stable Dose Period (2 weeks)	DBRW Period (2 weeks)	
	Study entry	Switch to / start JZP-258	Titration Treatment [b]					End Titration/ Begin Stable Dose	End Stable Dose/ Begin DBRW		End DBRW
Visits [c]	**Screening Visit**	**Baseline Visit**	**W1**	**W2, W3 Call**	**W4**	**W6 Call**	**W8**	**Ext Titration 1** [d] **Ext Titration 2** [d]	**End Titration**[e]	**End of Stable Dose**	**DBRW W1 Call**	**End DBRW** [f]**/ ET Visit**
Window (Days)	-30 to -2	Day 1	7-10	14-17; 21-24	28-31	35-49	49-63	63-77; 77-91	63-98	14-17	4-10	14-17
Window Relative to	Baseline		Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	End Titration	End Stable Dose	End Stable Dose
C-SSRS Since Last Visit Version		X	X	X	X	X	X	X	X	X	X	X
Dispense Study Drug Dosing Diary		X	X		X		X	X	X	X		X
Review Study Drug Dosing Diary for completeness and compliance			X	X	X	X	X	X	X	X	X	X
Assess subject and determine if additional dose titration is necessary			X	X	X	X	X	X				
Dispense Study Drug		X	X		X		X	X	X	X [p]		X

Events	Screening (14 to 30 d)	OL Treatment Titration and Optimization Period (10 to 14 weeks) [a]							Stable Dose Period (2 weeks)	DBRW Period (2 weeks)	
	Study entry	Switch to / start JZP-258	Titration Treatment [b]					End Titration/ Begin Stable Dose	End Stable Dose/ Begin DBRW		End DBRW
Visits [c]	**Screening Visit**	**Baseline Visit**	**W1**	**W2, W3 Call**	**W4**	**W6 Call**	**W8**	**Ext Titration 1** [d] **Ext Titration 2** [d]	**End Titration**[e]	**End of Stable Dose**	**DBRW W1 Call**	**End DBRW** [f]/ **ET Visit**
Window (Days)	-30 to -2	Day 1	7-10	14-17; 21-24	28-31	35-49	49-63	63-77; 77-91	63-98	14-17	4-10	14-17
Window Relative to	Baseline		Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	Bsl	End Titration	End Stable Dose	End Stable Dose
Collect Study Drug, Measure compliance			X		X		X	X	X	X		X
Randomize subjects										X		
AE Reporting	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
PK Study [q]					X							

AE = adverse event; Bsl = baseline; d = days; DB = double-blind; CGIs = Clinical Global Impression of severity; CGIc = Clinical Global Impression of change; C-SSRS = Columbia-Suicide Severity Rating Scale; DBRW= double-blind randomized withdrawal; DMC= data monitoring committee; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; FOSQ-10 = Functional Outcomes of Sleep Questionnaire, short form; IHSS = Idiopathic Hypersomnia Severity Scale; IH = idiopathic hypersomnia; MSLT = multiple sleep latency test; OL = open-label; PE= physical exam; PGIc = Patient Global Impression of change; PSG = polysomnogram; PK = pharmacokinetic; RW = randomized withdrawal; SOREMP=sleep onset rapid eye movement periods; TSH = Thyroid Stimulating hormone; VAS = Visual analog scale; W = week; WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

[a] The Open-label Treatment Titration and Optimization Period will occur over a period of 10 to 14 weeks. Every effort should be made to titrate to an optimally effective and tolerable dose and regimen within the first 10 weeks. For subjects requiring additional titration, with approval from the Medical Monitor, up to an additional 4 weeks of titration/adjustment may be performed.

[b] All subjects will begin JZP-258 treatment at the beginning of this period and continue through the End of Titration Visit. Every effort should be made to titrate to an effective and tolerable dose and regimen within the first 8 weeks, and maintain on an unchanged dose and regimen of JZP-258 for at least 2 weeks prior to entering the Stable Dose Period.

[c] Visits conducted by phone call are shaded in grey.

[d] Extension Titration 1 and Extension Titration 2 are visits required when titration/adjustment extends beyond 10 and 12 weeks, respectively.

[e] At the End Titration Visit subjects should begin taking a stable dose of JZP-258.

[f] For all subjects who prematurely discontinue during the Double-blind Randomized Withdrawal Period, an attempt should be made to perform all procedures associated with the End of Double-blind Randomized Withdrawal Visit. For all subjects who prematurely discontinue during periods other than the Double-blind Randomized Withdrawal Period, an attempt should be made to perform all procedures associated with the End of Open-label Extension Visit. A 12-lead ECG is needed for subjects who prematurely discontinue treatment due to an AE only.

[g] Medical History includes IH history, usual bedtime and awakening time.

[h] The Physical Exam includes a brief neurological exam, excludes genitourinary. Weight should be taken with the subject in indoor clothes without shoes.

[i] Vital signs include blood pressure, pulse/heart rate, body temperature, and respiratory rate. BP should be measured after the subject has been resting for at least 5 minutes.

[j] Pulse oximetry should be performed on room air while fully awake.

[k] Serum pregnancy tests (screening and end of stable dose) and urine pregnancy tests will be performed in women of childbearing potential.

[l] The daily sleep diary will require subjects to respond to questions about their sleep (including time of bedtime, number of hours slept each night, number of naps taken daily, approximate duration of sleep across all naps each day). A daily sleep diary will be completed for at least 2 weeks during the Screening Period, immediately prior to the Baseline Visit.

[m] A PSG followed by an MSLT will be performed, when necessary, for diagnosis of IH during the Screening Period. If the Investigator suspects a subject with a previous diagnosis of narcolepsy type 2 actually has IH, providing their previous PSG and MSLT did not have >2 SOREMPs on an MSLT or any nighttime SOREMPs, a Screening PSG and MSLT can be done to confirm an IH diagnosis. A PSG may also be performed, when necessary, to evaluate the subject for evidence of sleep disordered breathing, if the subject has not been adequately evaluated prior to study entry. The PSG and MSLT will be performed according to the study center's standard procedures.

[n] The CGIc taken at the end of the Double-blind Treatment Period will be compared to status at the end of the Stable Dose Period. All other CGIc measures taken throughout the study will be compared to status at Baseline.

[o] The PGIc taken at the end of the Double-blind Treatment Period will be compared to status at the end of the Stable Dose Period. All other PGIc measures taken throughout the study will be compared to status at Baseline.

[p] At the time of the interim analysis, if the predefined efficacy stopping rule is met, per DMC communication, enrollment and randomization to placebo treatment may stop. All subjects who have not already been randomized would then receive open-label JZP-258 during the Double-blind Randomized Withdrawal Period. All subjects who have already entered the Double-blind Randomized Withdrawal Period will complete that period as planned. The interim analysis may not be performed due to administrative or operational considerations.

[q] A PK sub-study for subjects during either the Open-label Treatment Titration and Optimization Period or Open-label Safety Extension Period (Appendix 1.3, 1.4 and Section 7.7).

[r] PE not required unless the subject is discontinuing due to early termination.

6.1.6.2 Schedule For Open-Label Safety Period And Safety Follow-Up Period

Events	OL Safety Extension Period (24 weeks)							Safety Follow-up Period (2 weeks)
	OL Treatment							
Weeks (W)[a]	**OLE W2**	**OLE W6**	**OLE W10** In Clinic or Call[b]	**OLE W14**	**OLE W18** In Clinic or Call[b]	**OLE W22** In Clinic or Call[b]	**End OLE / ET Visit[c]**	**Safety FU**
Window (Days)	7-21	35-49	63-77	91-105	119-133	147-161	161-175	175-189
Window Relative to	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW
Physical Exam [d]							X	X
Weight	X	X	X	X	X[a]	X[a]	X	X
Vital Signs [e]	X	X	X	X	X[a]	X[a]	X	X
Hematology, Chemistry							X	
Urinalysis							X	
Urine drug screen	X	X	X	X	X[a]	X[a]	X	
Breath alcohol test	X	X	X	X	X[a]	X[a]	X	
Urine/Serum pregnancy test [f]	X	X	X[b]	X	X[ab]	X[ab]	X[f]	X
12-lead ECG							X	
ESS	X	X		X			X	
CGIc	X	X		X			X	
PGIc	X	X		X			X	
IHSS	X	X		X			X	
FOSQ-10		X		X			X	
WPAI:SHP		X		X			X	
C-SSRS Since Last Visit Version	X	X	X	X	X	X	X	X

Events	OL Safety Extension Period (24 weeks)							Safety Follow-up Period (2 weeks)
	OL Treatment							
Weeks (W)[a]	**OLE W2**	**OLE W6**	**OLE W10** In Clinic or Call[b]	**OLE W14**	**OLE W18** In Clinic or Call[b]	**OLE W22** In Clinic or Call[b]	**End OLE / ET Visit[c]**	**Safety FU**
Window (Days)	7-21	35-49	63-77	91-105	119-133	147-161	161-175	175-189
Window Relative to	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW	End DBRW
Assess subject and determine if additional dose titration is necessary	X	X						
Assess tolerability to current dose			X	X	X	X		
Dispense Study Drug [g]	X	X	X[b]	X	X[b]	X[b]		
Collect Study Drug, Measure compliance	X	X		X			X	
AE Reporting	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
PK Study [h]		X						

AE = adverse event; CGIc = Clinical Global Impression of change; C-SSRS = Columbia-Suicide Severity Rating Scale; DBRW= double-blind randomized withdrawal; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; FOSQ-10 = Functional Outcomes of Sleep Questionnaire, short form; FU= follow up; IHSS = Idiopathic Hypersomnia Severity Scale; OL = open-label; OLE= open label extension; PGIc = Patient Global Impression of change; PK = pharmacokinetics; WOCBP = Women of Child Bearing Potential; W = week; WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

[a] Visits conducted by phone call are shaded in grey. If a phone visit is conducted in clinic, assessments noted should be performed.

[b] Phone visit may be converted to a clinic visit if required due to local regulations. If these visits are in-clinic visits, dispensing of JZP-258 may occur and urine pregnancy testing should be completed for WOCBP.

[c] For all subjects who prematurely discontinue during the Double-blind Randomized Withdrawal Period, an attempt should be made to perform all procedures associated with the End of Double-blind Randomized Withdrawal Visit. For all subjects who prematurely discontinue during periods other than the Double-blind Randomized Withdrawal Period, an attempt should be made to perform all procedures associated with the End of Open-label Extension Visit.

[d] The Physical Exam includes a brief neurological exam, excludes genitourinary.

[e] Vital signs include blood pressure, pulse/heart rate, body temperature, and respiratory rate. BP should be measured after the subject has been resting at least 5 minutes. On PK Nights, vital signs will be measured at the times specified in the schedule of events for the PK substudy (see Appendix 1.3 and Appendix 1.4).

[f] Serum pregnancy tests (end of open-label extension/early termination visit only) and urine pregnancy tests will be performed in WOCBP if the visit is performed in clinic.

[g] Subjects will start the Open-label Safety Extension Period at a dose no higher than the dose they received at the end of the Stable Dose Period. A lower starting dose will be allowed at the discretion of the Investigator. If further titration is required, it will proceed at a rate of ≤1.5 g per night per week during this period, not to exceed a maximum total dose of 9 g/night.

[h] A PK substudy for subjects during either the Open-label Treatment Titration and Optimization Period or Open-label Safety Extension Period (Appendix 1.3 and Section 7.7).

6.1.6.3 Schedule For Night Of Pharmacokinetic Sampling

Procedure	Prior to PK dosing	PK Night timepoints (hours) All timepoints post-dose unless specified											Prior to discharge	Notes
		First Dose					Second Dose					8 h ± 15 min after first dose		
		Pre Dose	0.5h ± 5 min	0.75h ± 5 min	1h ± 5 min	1.5h± 15 min	PreDose	0.5 h ± 5 min	0.75h ± 5 min	1h ± 5 min	1.5h ± 15 min			
Informed consent	X													
Record meal time/content in the eCRF [a]	X													
Vital Signs [b] Includes supine BP, pulse/heart rate, and respiratory rate	X (include body temp)	X	X		X	X	X	X		X	X	X (include body temp)	X	Subject should be supine for ≥5 min prior to BP measurement; vital signs should be taken prior to PK blood draws
Concomitant Medications	X													Unscheduled visit only
Pulse Oximetry [c]	X	X	X		X	X	X	X		X	X	X	X	Continuous monitoring through 8 hours after the first dose with recorded times at predose, 0.5, 1, 1.5 hours after each dose and 8 hours after the first dose.

Procedure	Prior to PK dosing	PK Night timepoints (hours) All timepoints post-dose unless specified											Prior to discharge	Notes
		First Dose					Second Dose					8 h ± 15 min after first dose		
		Pre Dose	0.5h ± 5 min	0.75h ± 5 min	1h ± 5 min	1.5h± 15 min	PreDose	0.5 h ± 5 min	0.75h ± 5 min	1h ± 5 min	1.5h ± 15 min			
Urine drug screen	X													
Breath alcohol test	X													
Urine pregnancy test (WOCBP)[d]	X													
Efficacy Assessments (pre dose)[e] : ESS, CGIc, PGIc, IHSS, FOSQ-10, WPAI:SHP, C-SSRS Since Last Visit Version	X[e]													Assessments only to be performed if the visit is unscheduled. All assessments to be completed prior to first dose of JZP-258
Administer/supervise JZP-258 dose from subject's study drug supply or Dispense Study Drug (if applicable)[f]	X													
Record time of dose(s) [g]		X					X							
Blood samples for twice nightly dosing (per dose)[h]		X	X	X	X	X	X	X	X	X	X	X		8 hour sample refers to after the first dose only
Record any AEs		----------Continuous monitoring----------												

Procedure	Prior to PK dosing	PK Night timepoints (hours) All timepoints post-dose unless specified										Prior to discharge	Notes
		First Dose					Second Dose					8 h ± 15 min after first dose	
		Pre Dose	0.5h ± 5 min	0.75h ± 5 min	1h ± 5 min	1.5h± 15 min	PreDose	0.5 h ± 5 min	0.75h ± 5 min	1h ± 5 min	1.5h ± 15 min		
Brief neurological exam [i]												X	Assessment should occur the morning after PK assessment to assess for sleepiness

BP= blood pressure; CGIc= Clinical global impression of change; C-SSRS= Columbia suicide severity rating scale; eCRF = electronic case report form; ESS= Epworth Sleepiness Scale; FOSQ-10= Functional Outcome of Sleep Questionnaire short version; h= hours; IHSS = Idiopathic Hypersomnia Severity Scale; IxRS: interactive web/voice response technology;PGIc= patient global impression of change; PK = pharmacokinetics; WOCBP= women of childbearing potential; WPAI:SHP= work productivity and activity impairment questionnaire: specific health problem[a] Subjects are instructed to take their usual meal at their normal time. The meal may be taken at the clinic or at home, without regard to dosing.

[b] Vital signs include supine blood pressure, pulse/heart rate, body temperature (prior to dosing and 8 hours postdose only), and respiratory rate. Obtain vital signs after subject has been resting for ≥5 min. If vital signs are taken at the same timepoints as PK blood draws, vital signs should be measured prior to blood draws.

[c] Pulse oximetry is monitored continuously from immediately before first dose through 8 hours after the first dose with recorded measurements as noted. An additional measurement will be taken while the subject is awake and before release from the study center.

[d] Urine pregnancy tests will be performed in women of childbearing potential.

[e] Assessments to be performed only if the visit is unscheduled. All assessments to be completed prior to first dose of JZP-258.

[f] Subjects are instructed to bring their nightly dose of JZP-258 to the clinic. In the event they do not bring their dose, dosing is allowed via IWRS.

[g] Administer the subject's nightly dose of JZP-258 as per their usual dosing and regimen and record time.

[h] Blood samples (2 mL at each time point) will be collected depending on the dose frequency. Blood samples for the twice nightly dosing regimen will be collected at 0 (predose), and 0.5, 0.75, 1 and 1.5 hours after dosing for each dose administered, with the last sample collected at 8 h after the first dose. Blood samples must be collected within ± 5 minutes of the protocol-specified time points for those time points ≤1 hour after dosing and within ± 15 minutes of the protocol-specified time points for those longer than 1 hour after dosing (e.g., 4 and 8 hours postdose).

[i] Brief neurological exam before discharge on the morning after PK assessment to assess for sleepiness.

6.1.7 Outcome Measures

6.1.7.1 Primary Efficacy Endpoint

Change in Epworth Sleepiness Scale score from the end of the 2-week stable dose period to the end of the 2-week double-blind randomized withdrawal treatment period.

The Epworth Sleepiness Scale is a self-administered questionnaire asking study subjects how likely they would be to fall asleep in specific situations. It is intended to be a measure of a patient's daytime sleep propensity. The scale has 8 questions with each question having responses ranging from 0 to 3 as follows:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Higher total scores are indicative of a greater propensity to sleep.

A copy of the Epworth Sleepiness Scale questionnaire is at the link below.

https://nasemso.org/wp-content/uploads/neuro-epworthsleepscale.pdf

6.1.7.2 Key Secondary Efficacy Endpoints

- Patient Global Impression of Change: proportion of patients reported as worse (minimally, much, or very much) on this measure at the end of the double-blind randomized withdrawal period, compared with the end of the stable-dose period.

The Patient Global Impression of Change is a patient-rated assessment. It uses a 7-point Likert scale use the change in the patient's overall condition since a previous study timepoint. The scale is rated from 1 ("very much improved") to 7 ("very much worse").

- Idiopathic Hypersomnia Severity Scale: Change in score from the end of the 2-week stable dose period to the end of the 2-week double-blind randomized withdrawal treatment period.

  The Idiopathic Hypersomnia Severity Scale is a 14-item patient-rated questionnaire that is intended to evaluate the severity of idiopathic hypersomnia. The questions that form are directed at evaluating excessive sleepiness, sleep inertia, and sleep duration. Total scores on this instrument range from 0 to 50 with higher scores indicating a greater severity of symptoms.

  The Idiopathic Hypersomnia Severity Scale questionnaire is available at the link below.

  https://cdn-links.lww.com/permalink/wnl/a/wnl_2019_02_08_dauvilliers_1_sdc1.pdf

6.1.7.3 Other Secondary Efficacy Endpoints

- Clinical Global Impression of Change: proportion of patients reported as worse (minimally, much, or very much) on this measure at the end of the double-blind randomized withdrawal period.

- Functional Outcomes of Sleep Questionnaire (FOSQ)-10: Change in total score from the end of the stable-dose period to the end of the double-blind withdrawal period.

6.1.7.4 Exploratory Efficacy Endpoints

These are copied below from the submission.

- Sleep Inertia Endpoints:
  - VAS for Sleep Inertia: Change in the mean daily score from the last week of the Stable Dose Period to the last week of the Double-blind Randomized Withdrawal Period
  - Sleep Inertia Questionnaire (SIQ): Change in total score from the end of the Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period

    For each domain of the SIQ (cognitive, behavioral, emotional, and physiological), the change from the end of the Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period will be analyzed as separate exploratory endpoints.
- Hypersomnolence Severity Scale (HSS): Change in total score from the end of the Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period
- Total Sleep Time (TST) from daily sleep diary: Change in the mean of the daily 24-hour TST from the last week of Stable Dose Period to the last week of the Double-blind Randomized Withdrawal Period

6.1.7.5 Safety Measures

Adverse events, vital signs, weight, physical examinations, 12-lead electrocardiogram, safety laboratory tests (hematology, clinical chemistry, and urinalysis), and Columbia-Suicide Severity Rating Scale (for assessing suicidality).

6.1.7.6 Pharmacokinetic Measures

Plasma concentrations of oxybate.

Plasma samples for pharmacokinetic analysis were to be drawn in a subset of 30 patients over a single overnight pharmacokinetic evaluation to be conducted during either the open-label treatment titration and optimization period or during the open-label safety extension period.

6.1.8 Analysis Plan

6.1.8.1 Analysis Sets

The following analysis sets were to be used for this study.

- The Safety Analysis Set was to be comprised of all subjects who received at least one dose of study medication. This set was to be used for all safety analyses.

- The Modified Intent-to-Treat Analysis Set was to be comprised of all subjects who were randomized to JZP-258 or placebo, received at least one dose of study medication during the double-blind randomized withdrawal period and had at least one set of post-randomization assessments for the Epworth Sleepiness Scale or the Idiopathic Hypersomnia Sleepiness Scale, or a Patient Global Impression of Change score at the end of the double-blind, randomized withdrawal period. This set was to be used for the analysis of all efficacy endpoints.

- The Pharmacokinetic Analysis Set was to be comprised of all subjects who received JZP-258 and had any evaluable pharmacokinetic data from at least one post-dose sample. This dataset was to be used for summarizing all pharmacokinetic data.

6.1.8.2 Demographic and Other Baseline Characteristics

These characteristics were to be summarized descriptively for all analysis set. For the Modified Intent-to-Treat Analysis Set, results were to be provided by randomized group.

6.1.8.3 Main Efficacy Analyses

The following description addresses the analysis of the primary efficacy endpoint and the key secondary efficacy endpoints.

For comparisons between JZP-258 and placebo, those randomized to continue JZP-258 in the double-blind randomized withdrawal period were to be treated as a single group regardless of the dose of JZP-258 that was received.

A fixed sequential testing strategy was to be used to address multiplicity during hypothesis testing. A hierarchical group sequence testing approach was to be used to address the key endpoints (primary and key secondary endpoints) and the multiple timepoints at which each analysis was possibly to be performed, i.e., interim (if conducted) and final analysis. The sequence of testing at each timepoint was to be as follows: the analysis of the primary endpoint (the change in Epworth Sleepiness Scale score) was to be conducted first; if that analysis yielded a statistically significant result, a formal analysis of a key secondary efficacy endpoint (the Patient Global Impression of Change score) was to be conducted next; if that analysis too yielded a statistically significant result, the final analysis in this hierarchical sequence was to be that of the other secondary efficacy endpoint, the change in Idiopathic Hypersomnia Sleepiness Scale score. If the interim analysis (see below) was not performed, the primary and key secondary efficacy endpoints were to be tested in the same order as above at the final analysis with each step using a two-sided level of significance of 0.05.

6.1.8.3.1 Primary Efficacy Analysis

An analysis of covariance model was to be used to analyze the change in Epworth Sleepiness Scale score. The model was to include treatment group, randomization stratum, and the efficacy measurement at the end of the stable-dose period as fixed effects.

6.1.8.3.2 Key Secondary Efficacy Analyses

The analysis of the key secondary efficacy measure, the Patient Global Impression of Change, was to be made using the Cochran-Mantel-Haenszel test stratified by medication group.

The analysis of the other key secondary efficacy measure, the Idiopathic Hypersomnia Severity Scale was to be conducted using the same method as that used for the primary efficacy analysis.

6.1.8.3.3 Handling Of Dropouts And Missing Data

Sensitivity analyses describing the handling of missing data were included in the statistical analysis plan for this study.

6.1.8.3.4 Pooling Of Study Sites

Data for all investigational study sites were to be pooled.

6.1.8.3.5 Interim Efficacy Analysis

The study protocol states that an interim analysis was to be conducted optionally when about 60% of the 112 planned randomized subjects had completed or were terminated early from the double-blind randomized withdrawal period of this study. Such an analysis if conducted, was to be performed by an unblinded statistician not directly involved with the design and analysis of the results of the study. Efficacy and safety data pertinent to the interim analysis were to be reviewed by a Data Monitoring Committee.

The interim analysis, if eventually conducted, was to include the primary and key secondary efficacy endpoints. To maintain the studywise Type 1 error at 0.05 (two-sided), a hierarchical group testing approach was to be applied.

For the primary endpoint (change from baseline in Epworth Sleepiness Scale score) and a key secondary efficacy endpoint (the Patient Global Impression of Change), a Lan-Demets alpha spending function approach that approximated the O'Brien-Fleming boundaries for evaluating efficacy was to be used. For the other key secondary efficacy endpoint (the change in Idiopathic Hypersomnia Sleepiness Scale score), a Lan-Demets alpha spending function approach that approximated the Pocock boundaries for evaluating efficacy was to be used. The boundaries (based on p-values) for each of these spending functions are depicted in the sponsor table below, headed "*Boundary Crossing Probabilities*."

Endpoint	Analysis	Sample Size at Analysis	Superiority Boundary to Reject H_0 for Efficacy (p-value)[a]
ESS and PGIc	Interim Analysis	68	0.0075
	Final Analysis	112	0.0476
IHSS	Interim Analysis	68	0.0357
	Final Analysis	112	0.0256

[a] p-values are based on a 2-sided test

ESS= Epworth sleepiness scale; IHSS=idiopathic hypersomnia severity scale; PGIc= patient's global impression of change

With the hierarchical testing strategy referred to above, the key secondary endpoint, the Patient Global Impression of Change was to be subjected to formal statistical testing, only if the analysis of the primary efficacy endpoint (the change in Epworth Sleepiness Scale score) achieved statistical significance at the interim and/or final analysis. The other key secondary efficacy endpoint (the change from baseline in Idiopathic Hypersomnia Sleepiness Scale score) was to be subject to formal statistical testing only if the analysis of the primary efficacy endpoint and the key secondary efficacy endpoint reached statistical significance at the interim and/or final analysis.

If the interim analysis was not performed, the primary and key secondary efficacy endpoints were to be tested in the same order as above at the final analysis with each step using a two-sided level of significance of 0.05.

Other aspects of the interim analysis are described in the submission.

6.1.8.3.6 Sample Size Estimate

The sponsor had estimated that a sample size of 56 subjects randomized per treatment group will provide 91.8% to detect a difference of 3.5 points in the change in Epworth Sleepiness Scale score between JZP-258 and placebo from the end of the stable-dose period to the end of the double-blind, randomized withdrawal period. This sample size estimate was based on the following assumptions

- A two-sample Z-test with a group sequential design including one interim analysis at the 60% information fraction using a Lan-Demets alpha spending function approach that approximated the O'Brien-Fleming boundaries
- A common standard deviation of 5.5 points in the change in Epworth Sleepiness Scale score for both study arms.
- A two-sided significance level of 0.05.

Assuming a dropout rate of 20% prior to randomization, up to 140 patients were to be enrolled.

6.1.8.4 Other Efficacy Analyses

Analyses of the other secondary efficacy endpoints and the exploratory endpoints are described in the statistical analysis plan for this study, but do not require further elaboration in this review.

6.1.8.5 Safety Analyses

Safety analyses were to be performed on the safety analysis set.

Safety analyses were to be conducted for descriptive purposes only. These were to be conducted and data presented in the standard manner.

For the double-blind treatment period, safety data were to be summarized in a descriptive manner only.

Adverse events were to be mapped to System Organ Classes and Preferred Terms, using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent adverse events, adverse events related to study medication, serious adverse events, adverse events leading to discontinuation, and fatal adverse events were all to be described.

Summary statistics were to be provided for observed and change from baseline values for vital signs, weight, safety laboratory tests, and electrocardiographic intervals. Columbia-Suicide Severity Rating Scale parameters were to be summarized by study visit.

6.1.8.6 Pharmacokinetic Analyses

Plasma pharmacokinetic parameters to be estimated using oxybate concentrations were to include the following: C_{max}, T_{max}, $t_{1/2}$, and AUC.

The dosing regimen, oxybate concentration-time data, and pharmacokinetic parameters were to be listed by subject.

Descriptive statistics were to be used to summarize concentration data and pharmacokinetic parameters for subjects based on stable versus non-stable doses, and dosing regimens (once versus twice nightly) as appropriate.

Plasma oxybate concentration-time displays were to be displayed based on stable versus non-stable doses, and dosing regimens (once versus twice nightly) as appropriate.

6.2 Study Results

This study appears to have been conducted in a manner consistent with that described in the study protocol.

The study was conducted at 63 centers worldwide of whom 57 centers enrolled participants.

The data included in this review are based on the final report of this study dated March 30, 2021, and submitted on April 23, 2021.

6.2.1 Patient Disposition

This study was begun in November 2018, with enrollment being completed on March 6, 2020.

The last subject completed the randomized, double-blind, placebo-controlled withdrawal period on June 12, 2020. The last patient visit in this study occurred on December 18, 2020.

The efficacy database for this study was locked on September 28, 2020, to perform an analysis of all efficacy and pharmacokinetic data, and all available

safety data. Top-line efficacy results for this study were available on October 8, 2020.

The last patient visit in this study occurred on December 18, 2020.

244 patients were screened for this study, of whom 154 patients were enrolled and entered the initial open-label treatment titration and optimization period. Note that of the 154 enrolled patients:

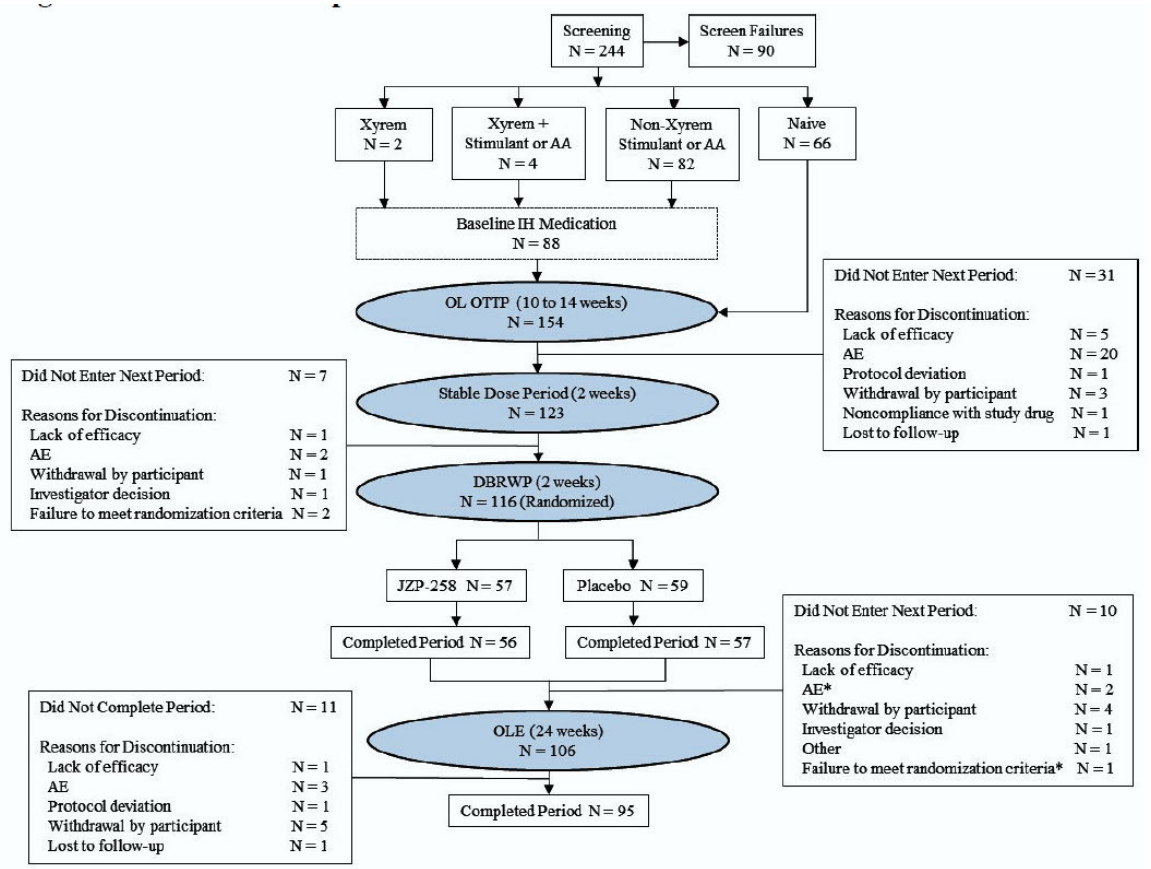
- 88 patients were on treatment at entry with one or more medications intended for the treatment of idiopathic hypersomnia. These 88 patients consisted of:
    - 2 patients who were receiving Xyrem® alone.
    - 4 patients who were receiving Xyrem® together with a stimulant.
    - 82 patients who were being treated with a stimulant, but not with Xyrem.
- 66 patients were treatment naïve, i.e., not receiving any treatment directed at idiopathic hypersomnia.

123 patients then entered the stable-dose period of whom 116 patient entered the double-blind, randomized withdrawal phase, with 113 patients completing that phase. At the beginning of the double-blind randomized withdrawal period, 57 patients were randomized to continue JZP-258 in the same dose and 59 patients were randomized to placebo; 56 patients in the JZP-258 group and 57 patients in the placebo group completed the double-blind, randomized withdrawal phase.

106 patients then continued into the open-label extension phase. 95 patients completed that phase of the study.

The details of patient disposition are summarized in the following schematic, which I have copied from the submission.

Note that at the time of initial submission of this application, 32 patients had completed the open-label extension, whereas that segment of the study was still ongoing in 65 subjects



Abbreviations: AA = alerting agent; AE = adverse event; DBRWP = Double-blind Randomized Withdrawal Period; OLE = Open-Label Extension Period; OL OTTP = Open-label Treatment Titration and Optimization Period
There were 10 randomized participants who did not enter the OLE (3 participants discontinued during the DBRWP and 7 participants discontinued after completing the DBRWP).
*Indicates cases who discontinued during the DBRWP.

6.2.2 Analysis Populations

Those enrolled in this study (n = 154) are referred to as the Enrolled Analysis Set. The analysis sets defined in the statistical analysis plan as well as other analysis sets are summarized in the following sponsor table, grouped according to whether medication for idiopathic hypersomnia was being administered at study baseline or not.

Study Period Analysis Set	Statistic	On Baseline IH Medication (N = 88)	Treatment Naïve (N = 66)	Total (N = 154)
Enrolled Analysis Set	n (%)	88 (100)	66 (100)	154 (100)
Safety Analysis Set	n (%)	88 (100)	66 (100)	154 (100)
PK Analysis Set	n (%)	14 (15.9)	14 (21.2)	28 (18.2)
SDP Safety Analysis Set	n (%)	71 (80.7)	52 (78.8)	123 (79.9)
Randomized Participants Analysis Set	n (%)	69 (78.4)	47 (71.2)	116 (75.3)
DBRWP Safety Analysis Set	n (%)	69 (78.4)	47 (71.2)	116 (75.3)
mITT Analysis Set	n (%)	68 (77.3)	47 (71.2)	115 (74.7)
OLE Safety Analysis Set	n (%)	65 (73.9)	41 (62.1)	106 (68.8)

Abbreviations: DBRWP = Double-blind Randomized Withdrawal Period; ENR = Enrolled Analysis Set; ESS = Epworth Sleepiness Scale; IH = idiopathic hypersomnia; IHSS = Idiopathic Hypersomnia Severity Scale; mITT = modified intent-to-treat; OL = Open-label; OLE = Open-label Extension Period; PGIc = Patient Global Impression of Change; PK = pharmacokinetics; SAF = Safety Analysis Set; SDP = Stable Dose Period
Percentages were based on the total number reported in each column (N).

The ENR was defined as all participants who provided a signed informed consent form for this study and were deemed as meeting the inclusion/exclusion criteria of this study by the investigator and were dispensed study drug.
The SAF included all participants who took at least one dose of study drug.
The PK Analysis Set included all participants who received JZP-258 and have any evaluable PK data from at least 1 post-dose sample.
The SDP Safety Analysis Set included all participants in the ENR who took at least one dose of OL study drug during the SDP.
The Randomized Analysis Set included all participants randomized.
The DBRWP Safety Analysis Set included all participants who received at least one dose of double-blind study drug.
The mITT Analysis Set included all randomized participants who received at least one dose of double-blind study drug and had at least one set of post-randomization efficacy assessment for ESS or IHSS, or a PGIc value at the end of the DBRWP.
The OLE Safety Analysis Set contained all participants in the ENR who took at least one dose of OL study drug during the OLE.
The On Baseline IH (Idiopathic Hypersomnia) Medication Group includes participants who were on Xyrem and/or a stimulant or alerting agent at study entry. The Treatment Naïve group includes participants not on Xyrem or a stimulant or alerting agent at study entry.

6.2.3 Major Protocol Deviations

Major protocol deviations for the enrolled population (enrolled analysis set) are summarized in the following sponsor table.

Major Protocol Deviation Category[a]	Baseline Medication Group		
	On Baseline Medication (N = 88)	Naïve (N = 66)	Total (N = 154)
Informed consent	8 (9.1), 8	0 (0), 0	8 (5.2), 8
Eligibility and entry criteria	1 (1.1), 1	5 (7.6), 6	6 (3.9), 7
Concomitant medications	7 (8.0), 8	1 (1.5), 1	8 (5.2), 9
Laboratory assessments	6 (6.8), 6	1 (1.5), 1	7 (4.5), 7
Study procedures	13 (14.8), 17	10 (15.2), 11	23 (14.9), 28
Visit schedule	7 (8.0), 7	2 (3.0), 2	9 (5.8), 9
Investigational product compliance	25 (28.4), 36	17 (25.8), 23	42 (27.3), 59
Efficacy criteria	3 (3.4), 4	6 (9.1), 7	9 (5.8), 11
Administrative	0 (0), 0	1 (1.5), 1	1 (0.6), 1
Total	45 (51.1), 87	31 (47.0), 52	76 (49.4), 139

Abbreviations: ICF = Informed Consent Form; IH = Idiopathic Hypersomnia
[a] A participant may have been reported in > 1 category.
The Enrolled Analysis Set is defined as all -participants who provided a signed ICF for this study and were deemed as meeting the inclusion/exclusion criteria of this study by the Investigator and were dispensed study drug.
Data is presented as the number of unique participants with deviation (percentage based on the total number of enrolled participants reported in each column [N]), and the total number of deviations.
The On Baseline IH Medication Group includes participants who were on Xyrem and/or a stimulant or alerting agent at study entry. The Treatment Naïve group includes participants not on Xyrem or a stimulant or alerting agent at study entry.

6.2.4 Demographic And Other Baseline Characteristics (Efficacy Population)

Demographic and other baseline characteristics for the efficacy population, i.e., for the Modified Intent-to-Treat Set, are in the following sponsor table.

	Randomized Treatment Group		
Characteristic	**JZP-258 (N = 56)**	**Placebo (N = 59)**	**Total (N = 115)**
Age (years)			
n	56	59	115
Mean (SD)	43.4 (14.44)	38.5 (13.01)	40.9 (13.88)
Median	43.0	35.0	39.0
Q1, Q3	31.0, 52.5	28.0, 44.0	29.0, 52.0
Min., Max.	19, 72	21, 75	19, 75
Gender			
Male	17 (30.4)	16 (27.1)	33 (28.7)
Female	39 (69.6)	43 (72.9)	82 (71.3)
Race			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	3 (5.4)	4 (6.8)	7 (6.1)
Native Hawaiian or Other Pacific Islander	0	1 (1.7)	1 (0.9)
White	48 (85.7)	45 (76.3)	93 (80.9)

	Randomized Treatment Group		
Characteristic	**JZP-258 (N = 56)**	**Placebo (N = 59)**	**Total (N = 115)**
Declined to state	5 (8.9)	8 (13.6)	13 (11.3)
Multiple[A]	0	1 (1.7)	1 (0.9)
Ethnicity			
Hispanic or Latino	8 (14.3)	4 (6.8)	12 (10.4)
Not Hispanic or Latino	44 (78.6)	47 (79.7)	91 (79.1)
Body Mass Index (kg/m2) at Baseline			
n	56	59	115
Mean (SD)	28.68 (9.694)	27.2 (6.135)	27.92 (8.065)
Median	26.63	26.3	26.3
Q1, Q3	23.37, 31.32	22.53, 30.25	22.98, 30.51
Min., Max.	18.1, 84.2	18.3, 46	18.1, 84.2
Region			
North America	35 (62.5)	42 (71.2)	77 (67.0)
Europe	21 (37.5)	17 (28.8)	38 (33.0)
Baseline Medication Group			
Xyrem	2 (3.6)	4 (6.8)	6 (5.2)
Xyrem only	1 (1.8)	1 (1.7)	2 (1.7)
Xyrem + Stimulant or AA	1 (1.8)	3 (5.1)	4 (3.5)
Non-Xyrem	54 (96.4)	55 (93.2)	109 (94.8)
Stimulant or AA	31 (55.4)	31 (52.5)	62 (53.9)
Treatment Naïve	23 (41.1)	24 (40.7)	47 (40.9)

Abbreviations: AA = alerting agent; DBRWP = Double-blind Randomized Withdrawal Period; ESS = Epworth Sleepiness Scale; IHSS = Idiopathic Hypersomnia Severity Scale; Max = maximum; Min = minimum; mITT = modified intent-to-treat; PGIc = Patient Global Impression of Change; Q1 = quarter 1; Q3 = quarter 3; SD = standard deviation

[A] Participants who reported more than one race.

The mITT Analysis Set included all randomized participants who received at least one dose of Double-Blind study drug and have at least one set of post-randomization efficacy assessment for ESS or IHSS, or a PGIc value at the end of the DBRWP.

Baseline was defined as the last non-missing assessment collected prior to or on the same day than the first dose of study drug, including unscheduled assessments.

Percentages were based on the total number of participants in the Analysis Set reported in each column.

6.2.5 Disease History And Baseline Disease Characteristics (Efficacy Population)

Disease history and baseline disease characteristics for the for the efficacy population, i.e., for the Modified Intent-to-Treat Set, are in the following sponsor

table. The difference between treatment groups on the more important of these measures does not appear to have been appreciable.

		Randomized Treatment Group		
		JZP-258 (N = 56)	**Placebo (N = 59)**	**Total (N = 115)**
Participant's IH diagnosis				
With Long Sleep	n (%)	13 (23.2)	11 (18.6)	24 (20.9)
Without Long Sleep	n (%)	43 (76.8)	48 (81.4)	91 (79.1)
Baseline CGI – severity				
Normal, not at all ill	n (%)	0	0	0
Borderline ill	n (%)	1 (1.8)	0	1 (0.9)
Mildly ill	n (%)	4 (7.1)	0	4 (3.5)
Moderately ill	n (%)	21 (37.5)	24 (40.7)	45 (39.1)
Markedly ill	n (%)	19 (33.9)	21 (35.6)	40 (34.8)

		Randomized Treatment Group		
		JZP-258 (N = 56)	**Placebo (N = 59)**	**Total (N = 115)**
Severely ill	n (%)	11 (19.6)	13 (22.0)	24 (20.9)
Among the most Extremely ill	n (%)	0	1 (1.7)	1 (0.9)
ESS at Study Entry (Baseline)				
	n	56	59	115
	Mean (SD)	15.61 (3.296)	15.88 (4.198)	15.75 (3.772)
	Median	16	17	16
	Q1, Q3	14, 17.5	14, 19	14, 18
	Min., Max.	3, 23	0, 22	0, 23
IHSS at Study Entry (Baseline)				
	n	56	59	115
	Mean (SD)	31.11 (8.17)	32.01 (8.548)	31.57 (8.342)
	Median	33	33	33
	Q1, Q3	26.5, 36	27, 39	27, 37
	Min., Max.	7, 48	5.3, 46	5.3, 48
24-Hour Total Sleep Time During Screening (Week 2)				
	n	50	50	100
	Mean (SD)	523.89 (98.644)	549.78 (153.593)	536.84 (129.08)
	Median	503.5	516.43	510.43
	Q1, Q3	458, 560	462.69, 597.5	460.72, 564.8
	Min., Max.	364, 812	323, 1232	323, 1232
VAS for sleep inertia During Screening (Week 2)				
	n	54	51	105
	Mean (SD)	51.45 (26.39)	57.56 (24.332)	54.42 (25.475)
	Median	54.79	57.75	56.43
	Q1, Q3	31.43, 73.14	38.57, 78.33	35.14, 74.75
	Min., Max.	3.6, 91.5	1.4, 100	1.4, 100

Abbreviations: CGI = clinical global impression; DBRWP = Double-blind Randomized Withdrawal Period; ESS = Epworth Sleepiness Scale; IH = idiopathic hypersomnia; IHSS = Idiopathic Hypersomnia Severity Scale; max = maximum; min = minimum; mITT = modified intent-to-treat; PGIc = Patient Global Impression of Change; Q1 = quarter 1; Q3 = quarter 3; SD = standard deviation; VAS = Visual analog scale
A diagnosis of IH with or without long sleep was determined by investigators per ICSD-2 or ICSD-3 criteria.
The mITT Analysis Set includes all randomized participants who received at least one dose of Double-Blind study drug and have at least one set of post-randomization efficacy assessment for ESS or IHSS, or a PGIc value at the end of the DBRWP.

6.2.6 Treatment Compliance (Efficacy Population)

Treatment compliance in the efficacy population, i.e., for the Modified Intent-to-Treat Set, are in the following sponsor table. The difference between treatment groups on the more important of these measures does not appear to have been noteworthy.

Compliance	JZP-258 (N = 57)	Placebo (N = 59)	DBRWP SAF (N = 116)
SDP	(N = 52)	(N = 54)	(N = 106)
<75%	3 (5.8)	1 (1.9)	4 (3.8)
75% to 125%	48 (92.3)	53 (98.1)	101 (95.3)
>125%	1 (1.9)	0	1 (0.9)
DBRWP	(N = 53)	(N = 53)	(N = 106)
<75%	3 (5.7)	0	3 (2.8)
75% to 125%	49 (92.5)	52 (98.1)	101 (95.3)
>125%	1 (1.9)	1 (1.9)	2 (1.9)

Abbreviations: DBRWP = Double-blind Randomized Withdrawal Period; SAF = Safety Analysis Set; SDP = Stable Dose Period
The DBRWP Safety Analysis Set includes all subjects who received at least one dose of double-blind study drug.
Compliance with study drug, inpercentage, was calculated as follows: volume of solution taken during the study period (ie, total dispensed –total returned) divided by the volume of solution that should have been taken by the participant during the study period and then, multiply by 100%. Percentages calculated only for those participants with returned bottles.
Percentages are based on the total number of participants in the Analysis Set for each period.

6.2.7 Overall Exposure Data (All Study Periods)

These are summarized in the following sponsor table, which is complex but self-explanatory.

Characteristic	On Baseline IH Medication (N = 88)	Treatment Naïve (N = 66)	SAF (N = 154)
Across all Study Periods			
Average of Total Nightly Dose of JZP-258 (g/night)			
n	88	66	154
Mean (SD)	6.351 (1.622)	5.704 (1.558)	6.074 (1.622)
Median	6.545	5.847	6.093
Q1, Q3	5.373, 7.341	4.5, 6.764	4.869, 7.251
Min., Max.	1.7, 9.0	2.3, 8.5	1.7, 9.0
Duration of Study Drug Exposure (days)			
n	88	66	154
Mean (SD)	210.0 (101.02)	195.0 (106.63)	203.6 (103.38)
Median	268.5	266.5	267.0
Q1, Q3	103.0, 278.5	91.0, 278.0	96.0, 278.0
Min., Max.	6, 326	4, 321	4, 326
Duration of Exposure to JZP-258 excluding time participants received Placebo in the DBRWP (days)			
n	88	66	154
Mean (SD)	204.18 (98.621)	190.09 (103.356)	198.14 (100.587)
Median	259	259	259
Q1, Q3	100.5, 274.5	90, 273	91, 273
Min., Max.	6, 311	4, 307	4, 311
Duration of Exposure to Single dose of JZP-258 > 4.5 g, excluding time participants received Placebo in the DBRWP (days)			
n	14	20	34
Mean (SD)	109.43 (109.565)	118.2 (103.119)	114.59 (104.262)
Median	66.5	75.5	75.5
Q1, Q3	8, 227	28.5, 241	14, 232
Min., Max.	1, 276	1, 281	1, 281

Characteristic	On Baseline IH Medication (N = 88)	Treatment Naïve (N = 66)	SAF (N = 154)
Open-label Titration and Optimization Period			
Total Nightly Starting Dose of JZP-258 (g/night)			
n	88	66	154
Mean (SD)	4.21 (1.27)	3.69 (1.048)	3.99 (1.204)
Median	4.5	4.5	4.5
Q1, Q3	4.5, 4.5	3, 4.5	3, 4.5
Min., Max.	1, 9	1, 4.5	1, 9
1 g/night	2 (2.3)	1 (1.5)	3 (1.9)
1.5 g/night	4 (4.5)	0	4 (2.6)
2 g/night	1 (1.1)	11 (16.7)	12 (7.8)
2.25 g/night	1 (1.1)	0	1 (0.6)
2.5 g/night	1 (1.1)	0	1 (0.6)
3 g/night	10 (11.4)	15 (22.7)	25 (16.2)
4.5 g/night	63 (71.6)	39 (59.1)	102 (66.2)
6 g/night	4 (4.5)	0	4 (2.6)
9 g/night	2 (2.3)	0	2 (1.3)
Starting Dosing Regimen of JZP-258			
Once Nightly JZP-258	14 (15.9)	26 (39.4)	40 (26.0)
Twice Nightly JZP-258	74 (84.1)	40 (60.6)	114 (74.0)
Average of Total Nightly Dose of JZP-258 (g/night)			
n	88	66	154
Mean (SD)	6.032 (1.441)	5.272 (1.324)	5.706 (1.438)
Median	6.217	5.461	5.932
Q1, Q3	5.271, 6.916	4.4, 6.269	4.846, 6.664
Min., Max.	1.667, 9	2.304, 7.497	1.667, 9
Number of Dose Adjustments			
0	6 (6.8)	6 (9.1)	12 (7.8)
1	4 (4.5)	5 (7.6)	9 (5.8)
2	13 (14.8)	14 (21.2)	27 (17.5)
3	19 (21.6)	15 (22.7)	34 (22.1)
4	18 (20.5)	10 (15.2)	28 (18.2)

Characteristic	On Baseline IH Medication (N = 88)	Treatment Naïve (N = 66)	SAF (N = 154)
5	7 (8.0)	7 (10.6)	14 (9.1)
6	7 (8.0)	3 (4.5)	10 (6.5)
7	9 (10.2)	0	9 (5.8)
8	4 (4.5)	1 (1.5)	5 (3.2)
9	1 (1.1)	3 (4.5)	4 (2.6)
11	0	1 (1.5)	1 (0.6)
14	0	1 (1.5)	1 (0.6)
Time to Get to Total Nightly Stable Dose (days)			
n	71	52	123
Mean (SD)	45.2 (23.72)	49.5 (23.72)	47.0 (23.72)
Median	43.0	57.0	49.0
Q1, Q3	29.0, 61.0	28.5, 64.0	29.0, 64.0
Min., Max.	1, 97	1, 90	1, 97
Duration of Exposure to JZP-258 (days)			
n	88	66	154
Mean (SD)	69.8 (20.65)	68.9 (23.08)	69.4 (21.66)
Median	71.0	70.0	70.5
Q1, Q3	65.5, 79.5	68.0, 80.0	67.0, 80.0
Min., Max.	6, 123	4, 107	4, 123
Open-label Stable Dose Period			
Average of Total Nightly Dose of JZP-258 (g/night)			
n	71	52	123
Mean (SD)	6.838 (1.723)	6.285 (1.819)	6.604 (1.778)
Median	7.429	6	7
Q1, Q3	6, 8	5, 7.75	5.25, 8
Min., Max.	2.5, 9	2.5, 9	2.5, 9
Dosing Information Among Twice and Thrice Nightly			
Equal Nighttime JZP-258 Dosages	45 (63.4)	26 (50.0)	71 (57.7)
Unequal Nighttime JZP-258 Dosages	15 (21.1)	8 (15.4)	23 (18.7)
Dosing Regimen of JZP-258			
Once Nightly JZP-258	11 (15.5)	18 (34.6)	29 (23.6)

Characteristic	On Baseline IH Medication (N = 88)	Treatment Naïve (N = 66)	SAF (N = 154)
Twice Nightly JZP-258	60 (84.5)	33 (63.5)	93 (75.6)
Thrice Nightly JZP-258	0	1 (1.9)	1 (0.8)
Duration of Exposure to JZP-258 (days)			
n	71	52	123
Mean (SD)	14.8 (1.86)	15.7 (7.40)	15.2 (5.01)
Median	14.0	14.0	14.0
Q1, Q3	14.0, 15.0	14.0, 15.5	14.0, 15.0
Min., Max.	11, 22	6, 61	6, 61
Double-blind Randomized Withdrawal Period			
Average of Total Nightly Dose (g/night)			
n	69	47	116
Mean (SD)	6.884 (1.651)	6.229 (1.832)	6.619 (1.749)
Median	7.5	6	7
Q1, Q3	6, 8	4.5, 8	5.25, 8
Min., Max.	3, 9	2.5, 9	2.5, 9
2.5 g/night	0	1 (2.1)	1 (0.9)
3 g/night	3 (4.3)	3 (6.4)	6 (5.2)
3.5 g/night	1 (1.4)	0	1 (0.9)
4 g/night	0	3 (6.4)	3 (2.6)
4.5 g/night	5 (7.2)	5 (10.6)	10 (8.6)
4.75 g/night	1 (1.4)	0	1 (0.9)
5 g/night	2 (2.9)	3 (6.4)	5 (4.3)
5.25 g/night	2 (2.9)	1 (2.1)	3 (2.6)
5.5 g/night	1 (1.4)	2 (4.3)	3 (2.6)
6 g/night	8 (11.6)	6 (12.8)	14 (12.1)
6.5 g/night	3 (4.3)	3 (6.4)	6 (5.2)
6.75 g/night	3 (4.3)	0	3 (2.6)
7 g/night	3 (4.3)	3 (6.4)	6 (5.2)
7.25 g/night	2 (2.9)	0	2 (1.7)
7.5 g/night	16 (23.2)	5 (10.6)	21 (18.1)
8 g/night	3 (4.3)	6 (12.8)	9 (7.8)

Characteristic	On Baseline IH Medication (N = 88)	Treatment Naïve (N = 66)	SAF (N = 154)
8.25 g/night	2 (2.9)	0	2 (1.7)
8.5 g/night	1 (1.4)	1 (2.1)	2 (1.7)
9 g/night	13 (18.8)	5 (10.6)	18 (15.5)
Duration of Study Drug Exposure (days)			
n	69	47	116
Mean (SD)	14.4 (2.97)	14.1 (2.31)	14.3 (2.71)
Median	14.0	14.0	14.0
Q1, Q3	14.0, 15.0	14.0, 15.0	14.0, 15.0
Min., Max.	2, 27	1, 18	1, 27
Open-label Safety Extension Period			
Average of Total Nightly Dose of JZP-258 (g/night)			
n	65	41	106
Mean (SD)	6.859 (1.535)	6.376 (1.755)	6.672 (1.633)
Median	7.419	6.159	6.895
Q1, Q3	6, 7.94	5, 7.719	5.555, 7.94
Min., Max.	3, 9	2.579, 9	2.579, 9
Duration of Exposure to JZP-258 (days)			
n	65	41	106
Mean (SD)	158.3 (42.16)	166.9 (31.53)	161.6 (38.47)
Median	172.0	172.0	172.0
Q1, Q3	166.0, 175.0	168.0, 176.0	167.0, 175.0
Min., Max.	4, 195	7, 194	4, 195

Abbreviations: DBRWP = Double-blind Randomized Withdrawal Period;; IH = idiopathic hypersomnia; max = maximum; min = inimum; OTTP = Open-label Treatment Titration and Optimization Period; Q1 = quarter 1; Q3 = quarter 3; SAF = Safety Analysis Set; SD = standard deviation
The SAF included all participants who received at least one dose of study drug.
Time to get to total nightly stable dose was calculated as follows: (The Study Drug Administration Date of the Stable Dose when it was first achieved in the OTTP based on total dose consideration – date of the first day of study drug in the OTTP) + 1.
Duration of exposure, in days, was calculated as follows: (date of last dose of study drug during the study period – date of first dose of study drug during the study period) + 1. With the following exception, interruptions were not taken into account for the duration of exposure.
Percentages were based on the total number of participants who took at least one dose of study drug within the indicated period.
The On Baseline IH Medication Group includes subjects who were on Xyrem and/or a stimulant or AA at study entry. The Treatment Naïve group includes subjects not on Xyrem or a stimulant or AA at study entry.

6.2.8 Efficacy Results

Note that the optional interim analysis described in the study protocol was not conducted.

6.2.8.1 Primary Efficacy Analysis

The results of the primary efficacy analysis compared the JZP-258 and placebo groups comparing the change in Epworth Sleepiness Scale score from the end of

the stable dose period to the end of the double-blind randomized withdrawal period are in the following table for the Modified Intent-to Treat Set (i.e., the efficacy population).

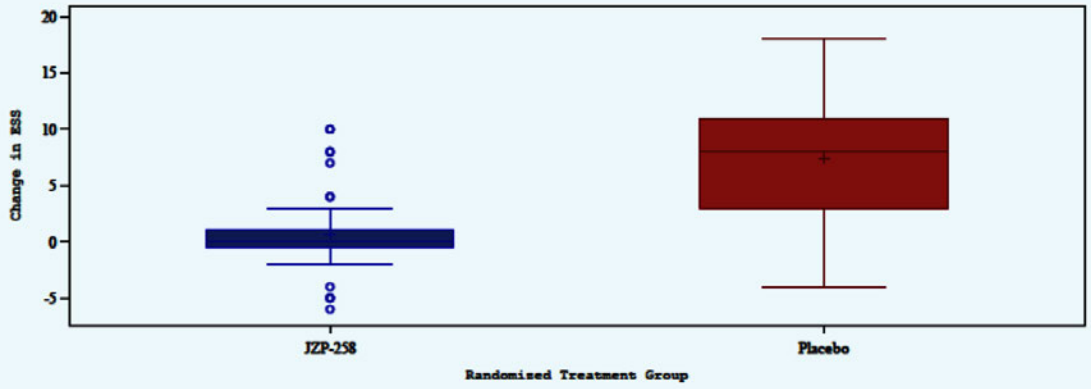
The analysis was conducted using the analysis of covariance model described in the statistical analysis plan.

	Randomized Treatment Group		
Timepoint	**JZP-258 (N=56)**	**Placebo (N=59)**	**Total (N=115)**
End of the Stable Dose Period			
n	56	59	115
Mean (SD)	6.3 (4.33)	5.8 (3.66)	6.1 (3.99)
Median	6.5	5.0	6.0
Q1, Q3	2.0, 9.5	3.0, 8.0	3.0, 8.0
Min., Max.	0, 15	0, 17	0, 17
End of the Double-Blind Randomized Withdrawal Period			
n	56	59	115
Mean (SD)	7.0 (5.03)	13.3 (4.06)	10.2 (5.52)
Median	7.0	14.0	10.0
Q1, Q3	3.0, 10.0	11.0, 16.0	6.0, 14.0
Min., Max.	0, 21	3, 21	0, 21
Change from the End of the Stable Dose Period to the End of the Double-Blind Randomized Withdrawal Period			
n	56	59	115
Mean (SD)	0.7 (3.22)	7.4 (5.16)	4.2 (5.47)
Median	0.0	8.0	2.0
Q1, Q3	-0.5, 1.0	3.0, 11.0	0.0, 9.0
Min., Max.	-6, 10	-4, 18	-6, 18

	Randomized Treatment Group		
Timepoint	**JZP-258 (N=56)**	**Placebo (N=59)**	**Total (N=115)**
LS Mean	0.8	7.3	
SE	0.54	0.53	
LS Mean Diff	-6.51		
SE	0.747		
95% CI	(-7.99, -5.03)		
p-value	<0.0001		

Abbreviations: CI = confidence interval; DBRWP = Double-blind Randomized Withdrawal Period; ESS = Epworth Sleepiness Scale; IHSS = Idiopathic Hypersomnia Severity Scale; LS = least squares; LS Mean Diff = LS mean difference; max = maximum; min = minimum; mITT = modified intent-to-treat; OL = Open label; PGIc = Patient Global Impression of Change; Q1 = quarter 1; Q3 = quarter 3; SD = standard deviation; SDP = Stable Dose Period; SE = standard error
The mITT Analysis Set included all randomized participants who received at least one dose of double-blind study drug and had at least one set of post-randomization efficacy assessment for ESS or IHSS, or a PGIc value at the end of the DBRWP.
The ESS total score is the sum of the 8 item-scores and ranges between 0 to 24. Higher scores indicated greater daytime sleepiness. If three or more item-scores were missing, the ESS total score was set to missing. If one or two ESS item-scores were missing at a specific time point, the mean of the remaining seven or six non-missing ESS item-scores at that time point was used to impute the missing ESS item-scores. The ESS total score was then calculated as the sum of the observed and imputed item-scores.
The LS mean, SE, LS Mean Diff, 95% CI and p-values have been obtained from an analysis of covariance (ANCOVA) model including the change in ESS total score from the end of the OL SDP to the end of the DBRWP as response variable. Covariates in the model included: Baseline Medication Group, treatment group and ESS total score at the end of the OL SDP.

The box plot for the above data is in the figure below which I have taken from the submission.

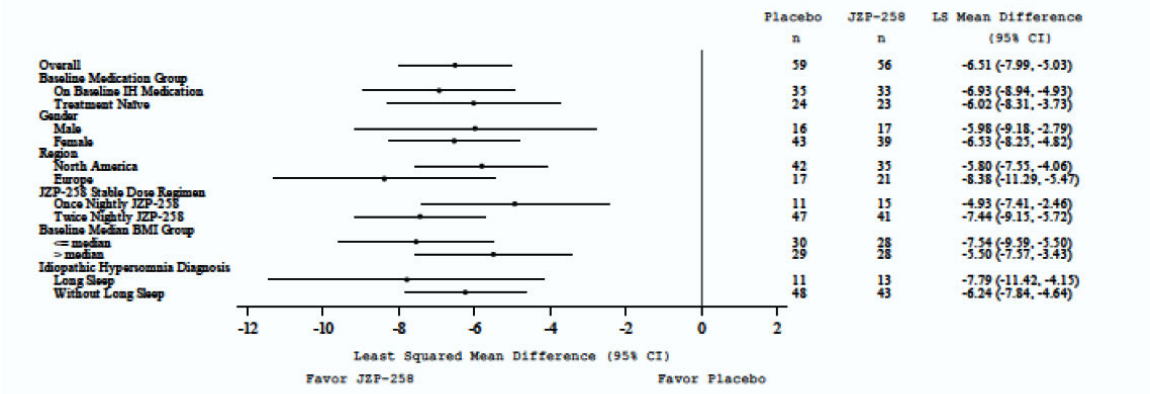


Abbreviations: DBRWP = Double-blind Randomized Withdrawal Period; ESS = Epworth Sleepiness Scale; IHSS = Idiopathic Hypersomnia Severity Scale; mITT = modified intent-to-treat; PGIc = Patient Global Impression of Change; Q1 = quartile 1; Q3 = quartile 3
The mITT Analysis Set included all randomized participants who received at least one dose of double-blind study drug and have at least one set of post-randomization efficacy assessment for ESS or IHSS, or a PGIc value at the end of the DBRWP.
The bottom and top edges of the box indicate the 1st and 3rd quartiles [Q1 and Q3]. The difference between Q3 and Q1 is the interquartile range (IQR). The line inside the box is the median and the marker inside the box is the mean. The upper and lower whisker extend Q3 + 1.5*IQR and Q1- 1.5*IQR, respectively. Any points that are a distance of more than 1.5*IQR from the box are considered outliers and are represented as a 'o'.

As the table and figure above indicate, a statistically significant superiority of JZP-258 over placebo ($p < 0.0001$) was seen on this measure, with a greater

increase in Epworth Sleepiness Scale score in those administered placebo than in those continuing JZP-258 during the randomized, double-blind, placebo-controlled withdrawal period.

Similar trends were also observed in subgroups defined by baseline medication groups, gender, region, once-nightly versus twice-nightly stable dose regimen, baseline median Body Mass Index group, and idiopathic hypersomnia diagnosis (long sleep versus without long sleep). These are depicted in the following sponsor figure.



Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; DBRWP = Double-blind Randomized Withdrawal Period; ESS = Epworth Sleepiness Scale; IH = Idiopathic Hypersomnia; IHSS = Idiopathic Hypersomnia Severity Scale; LS = least square; LS Mean Diff = LS mean difference; min = minimum; mITT = modified intent-to-treat; OL SDP = Open-label Stable Dose Period; PGIc = Patient Global Impression of Change

The mITT Analysis Set included all randomized participants who received at least one dose of double-blind study drug and had at least one set of post-randomization efficacy assessment for ESS or IHSS, or a PGIc value at the end of the DBRWP.

The ESS total score was the sum of the 8 item-scores and ranged between 0 to 24. Higher scores indicated greater daytime sleepiness. If three or more item-scores were missing, the ESS total score was set to missing. If one or two ESS item-scores were missing at a specific time point, the mean of the remaining seven or six non-missing ESS item-scores at that time point was used to impute the missing ESS item-scores. The ESS total score was then calculated as the sum of the observed and imputed item-scores.

The LS Mean Diff and 95% CI was obtained from an ANCOVA model including the change in ESS total score from the end of the OL SDP to the end of the DBRWP as response variable. Covariates in the model included: Baseline Medication group, treatment group, and ESS total score at the end of the OL SDP. Baseline medication group was not included in the model for the subgroup analysis by baseline medication group.

No sensitivity analyses of this measure were conducted.

6.2.8.2 Analysis Of Key Secondary Efficacy Endpoints

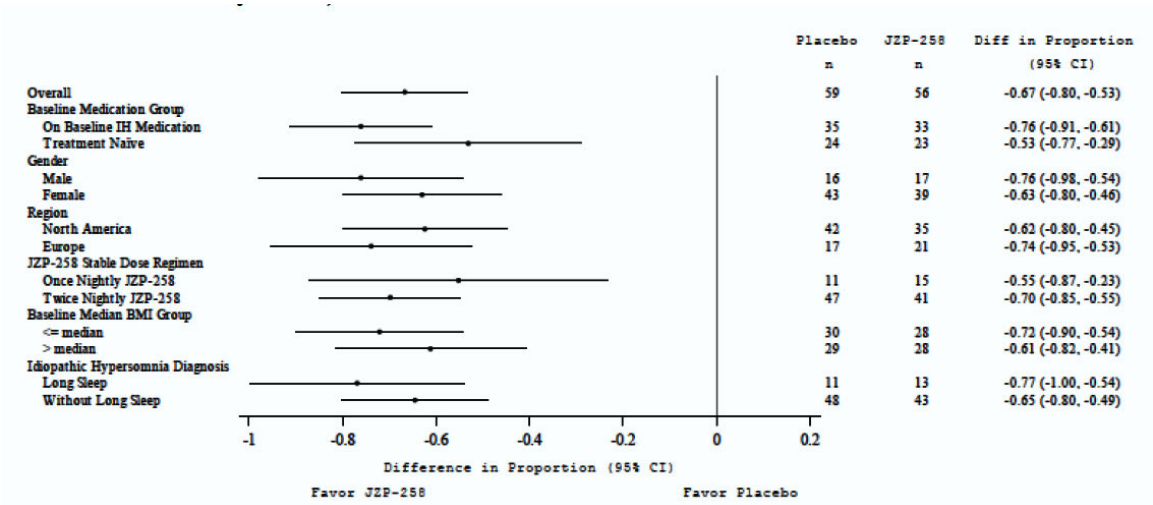
6.2.8.2.1 Patient Global Impression of Change

The results of the analysis of this measure at the end of the double-blind randomized withdrawal period are in the following table. The measure assesses the change seen from the end of the stable dose period to the end of the double-blind, randomized withdrawal period.

	Randomized Treatment Group		
Variable Category	**JZP-258 (N=56)**	**Placebo (N=59)**	**Total (N=115)**
PGIc at the End of the Double-Blind Randomized Withdrawal Period			
Participants with at Least One Survey	56	59	115
Very much improved	5 (8.9)	0	5 (4.3)
Much improved	13 (23.2)	3 (5.1)	16 (13.9)
Minimally improved	3 (5.4)	1 (1.7)	4 (3.5)
No change	23 (41.1)	3 (5.1)	26 (22.6)
Minimally worse	9 (16.1)	14 (23.7)	23 (20.0)
Much worse	2 (3.6)	22 (37.3)	24 (20.9)
Very much worse	1 (1.8)	16 (27.1)	17 (14.8)
Proportion Worsened (minimally, much or very much worse)	12 (21.4)	52 (88.1)	64 (55.7)
Difference in Proportion	-0.67		
95% CI	(-0.80, -0.53)		
p-value	<0.0001		

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; DBRWP = Double-blind Randomized Withdrawal Period; ESS = Epworth Sleepiness Scale; IHSS = Idiopathic Hypersomnia Severity Scale; mITT = modified intent-to-treat; OL SDP = Open label Stable Dose Period
; PGIc = Patient Global Impression of Change
The mITT Analysis Set included all randomized participants who received at least one dose of double-blind study drug and have at least one set of post-randomization efficacy assessment for ESS or IHSS, or a PGIc value at the end of the DBRWP.
At the end of the DBRWP/ early termination visit, participants rated the change in their condition compared with the end of the OL SDP.
Continuity corrected Wilson's 95% CI as modified by Newcombe were presented for the difference in proportion.
The p-value for comparing the proportion worsened on the PGIc between treatments is from a CMH test stratified by baseline medication group.
Percentages and p-values were based on the total number of participants with at least one survey in each treatment column.

The changes in the table above are also depicted in the Forest plot below.



Abbreviations: CI = Confidence Interval; DBRWP = Double-blind Randomized Withdrawal Period; ESS = Epworth Sleepiness Scale; IH = Idiopathic Hypersomnia; IHSS = Idiopathic Hypersomnia Severity Scale; mITT = modified intent-to-treat; OL SDP = Open-label Stable Dose Period; PGIc = Patient Global Impression of Change;
The mITT Analysis Set included all randomized participants who received at least one dose of Double-Blind study drug and have at least one set of post-randomization efficacy assessment for ESS or IHSS, or a PGIc value at the end of the DBRWP.
At the end of the DBRWP/ early termination visit, participants rated the change in their condition compared with the end of the OL SDP.
Continuity corrected Wilson's 95% CI as modified by Newcombe are presented for the difference in proportion.

As the table above indicates, the percentage of subjects with minimally, much, or very much worse scores on the Patient Global Impression of Change was statistically significantly greater in the placebo group than in the JZP-258 group ($p < 0.0001$).

The above trends were confirmed in subgroup analyses (subgroups analyzed were similar to those for which the change in Epworth Sleepiness Scale was analyzed).

No sensitivity analyses of this measure were conducted.

6.2.8.2.2 Idiopathic Hypersomnia Sleepiness Scale

An increase in median Idiopathic Hypersomnia Sleepiness Scale score was seen in the placebo group over the double-blind randomized withdrawal period as opposed to no change on that measure in the JZP-258 group; this difference was statistically significant ($p < 0.0001$). The further details of that analysis are depicted in the next sponsor figure.

	Randomized Treatment Group		
Timepoint	**JZP-258 (N=56)**	**Placebo (N=59)**	**Total (N=115)**
End of the Stable Dose Period			
n	56	59	115
Mean (SD)	15.5 (9.20)	15.2 (7.78)	15.3 (8.46)
Median	14.0	14.0	14.0
Q1, Q3	7.0, 22.0	10.0, 21.0	8.0, 21.0
Min., Max.	1, 39	2, 37	1, 39
End of the Double-Blind Randomized Withdrawal Period			
n	56	59	115
Mean (SD)	16.9 (8.09)	28.5 (8.96)	22.9 (10.30)
Median	16.0	29.0	23.0
Q1, Q3	11.0, 23.0	23.0, 34.0	15.0, 30.0
Min., Max.	1, 34	8, 49	1, 49
Change from the End of the SDP to the End of the DBRWP			
n	56	59	115
Mean (SD)	1.5 (5.82)	13.3 (9.29)	7.5 (9.76)
Median	0.0	14.0	4.0
Q1, Q3	-2.0, 2.5	4.0, 19.0	0.0, 15.0
Min., Max.	-8, 24	-2, 38	-8, 38
Estimated median difference	-12.00		
95% CI	(-15.00, -8.00)		
p-value	<0.0001		

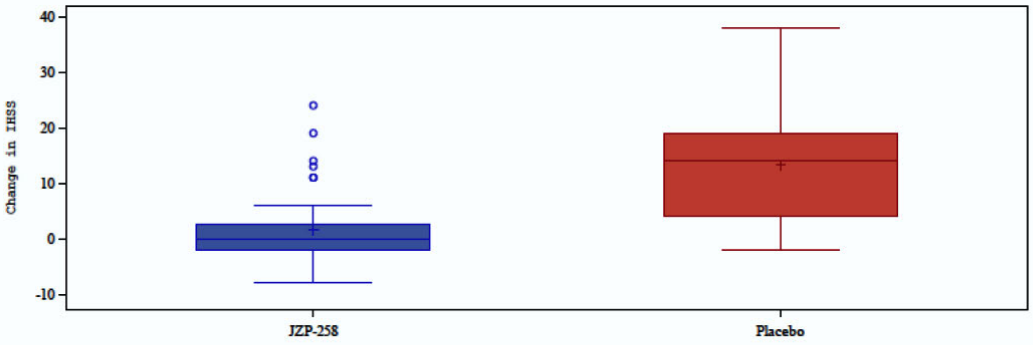
Abbreviations: CI = confidence interval; DBRWP = Double-blind Randomized Withdrawal Period; ESS = Epworth Sleepiness Scale; IHSS = Idiopathic Hypersomnia Severity Scale; max = maximum; min = minimum; mITT = modified intent-to-treat; PGIc = Patient Global Impression of Change; SD = standard deviation; SDP = Stable Dose Period

The mITT Analysis Set includes all randomized participants who received at least one dose of Double-Blind study drug and have at least one set of post-randomization efficacy assessment for ESS or IHSS, or a PGIc value at the end of the DBRWP.

The IHSS total score was the sum of the 14 item-scores. Scores range from 0 to 50; higher scores indicate more severe and frequent symptoms. If four or more item-scores are missing at a specific time point, the IHSS total score was set to missing. If less than four IHSS item-scores were missing at a specific time point, then missing items are imputed by multiplying the missing item's maximum response value by the average of the remaining non-missing items proportion of maximum response. The IHSS total score was then calculated as the sum of the observed and imputed item-scores.

The estimated median difference between two treatment groups and 95% asymptotic CI are from Hodges-Lehmann estimate. The p-value has been obtained from a rank based analysis of covariance (ANCOVA) model including the rank change in IHSS from the end of the Open-Label SDP to the end of the DBRWP as the response variable; Covariates in the model included: Baseline Medication Group, treatment group and ranked IHSS total score at the end of the Open-Label SDP.

A box plot provided in this application depicting the above is copied below.



Abbreviations: DBRWP = Double-blind Randomized Withdrawal Period; ESS = Epworth Sleepiness Scale; IHSS = Idiopathic Hypersomnia Severity Scale; IQR = interquartile range; mITT = modified intent-to-treat; PGIc = Patient Global Impression of Change
The mITT Analysis Set included all randomized participants who received at least one dose of Double-Blind study drug and have at least one set of post-randomization efficacy assessment for ESS or IHSS, or a PGIc value at the end of the DBRWP.
The bottom and top edges of the box indicate the 1st and 3rd quartiles [Q1 and Q3]. The difference between Q3 and Q1 is the IQR. The line inside the box is the median and the marker inside the box is the mean. The upper and lower whisker extend Q3 + 1.5*IQR and Q1- 1.5*IQR, respectively. Any points that are a distance of more than 1.5*IQR from the box are considered outliers and are represented as a 'o'.

The above trends were confirmed in subgroup analyses (subgroups analyzed were similar to those for which the change in Epworth Sleepiness Scale was analyzed).

No sensitivity analyses of this measure were conducted.

6.2.8.3 Analysis Of Other Secondary Endpoints And Exploratory Endpoints

Trends in the following secondary and exploratory outcomes showed the same trends over the double-blind, randomized withdrawal period as would have been expected from the results of the analysis of the primary and key secondary efficacy outcomes: Clinical Global Impression of Change; Functional Outcomes of Sleep Questionnaire; Night/Inertia and Day/Performance Components of the Idiopathic Hypersomnia Sleepiness Scale; Total Sleep Time (from daily sleep diary); and Work Productivity and Activity Impairment Questionnaire.

6.2.9 Safety Results

Please note that the safety results summarized below are for all phases of the study, including those in the 120-Day Safety Update which was submitted after the study was completed and all data for the study included.

6.2.9.1 Adverse Events

6.2.9.1.1 Overall Summary Of Adverse Events

The following table presents a summary of all adverse events that occurred during this study, excluding placebo data, for all study periods.

Category, n (%)	On Baseline IH Medication (N = 88)	Treatment Naïve (N = 66)	SAF (N = 154)
Number of Participants with at Least One TEAE	73 (83.0)	50 (75.8)	123 (79.9)
Number of Participants with at Least One Related TEAE	54 (61.4)	38 (57.6)	92 (59.7)
Number of Participants with at Least One Serious TEAE	2 (2.3)	2 (3.0)	4 (2.6)
Number of Participants with at Least One TEAE			
Mild	68 (77.3)	46 (69.7)	114 (74.0)
Moderate	45 (51.1)	32 (48.5)	77 (50.0)
Severe	0	1 (1.5)	1 (0.6)
Life-threatening	0	0	0
Fatal	0	0	0
Number of Participants with an AE Outcome of Death	0	0	0
Number of Participants with at Least One TEAE Leading to Discontinuation of Study Drug	16 (18.2)	10 (15.2)	26 (16.9)
Number Of Participants With At Least One TEAE Leading To Study Drug Dose Reduction	25 (28.4)	17 (25.8)	42 (27.3)
Number Of Participants With At Least One TEAE Leading To Study Drug Dose Increase	5 (5.7)	5 (7.6)	10 (6.5)
Number Of Participants With At Least One TEAE Leading To Study Drug Dose Interruption	10 (11.4)	6 (9.1)	16 (10.4)

Abbreviations: AE = adverse event; DBRWP = Double-blind Randomized Withdrawal Period; IH = idiopathic hypersomnia; OLE = Open-label Extension Period; SAF = Safety Analysis Set; TEAEs = treatment-emergent adverse events
The SAF included all participants who received at least one dose of study drug.
TEAEs for participants randomized to placebo during the DBRWP plus the minimum of up to 30 days after completion of the DBRWP or the start of the OLE, whichever was earlier, were excluded from this summary.
TEAEs were defined as any AEs that started or worsened in severity on or after the first dose of study drug, including adverse events that occurred until 30 days after the last dose date.
A Related AE was defined as an AE with a relationship to study drug of 'related' per the investigator. AE with a missing relationship to study drug was classified as related.
Participants reporting more than one AE under a category were counted only once within that category.
Percentages were based on the total number of participants in the Analysis Set reported in each column.
The On Baseline IH (Idiopathic Hypersomnia) Medication Group includes subjects who were on Xyrem and/or a stimulant or alerting agent at study entry. The Treatment Naïve group includes subjects not on Xyrem or a stimulant or alerting agent at study entry.

6.2.9.1.2 Treatment-Emergent Adverse Events

The following table presents the frequency of individual adverse events, by Preferred Term, that occurred during this study, excluding placebo data, for all study periods. These were adverse events with a frequency ≥ 5% in all patients enrolled. The table is self-explanatory, and needs no further elaboration in this review.

Preferred Term, n (%)	On Baseline IH Medication (N = 88)	Treatment Naïve (N = 66)	SAF (N = 154)
Number of Particpants with at Least One TEAE	**73 (83.0)**	**50 (75.8)**	**123 (79.9)**
Nausea	21 (23.9)	13 (19.7)	34 (22.1)
Headache	15 (17.0)	12 (18.2)	27 (17.5)
Dizziness	8 (9.1)	11 (16.7)	19 (12.3)
Anxiety	10 (11.4)	7 (10.6)	17 (11.0)
Vomiting	14 (15.9)	3 (4.5)	17 (11.0)
Decreased appetite	7 (8.0)	7 (10.6)	14 (9.1)
Diarrhoea	9 (10.2)	3 (4.5)	12 (7.8)
Nasopharyngitis	6 (6.8)	6 (9.1)	12 (7.8)
Upper respiratory tract infection	7 (8.0)	5 (7.6)	12 (7.8)
Urinary tract infection	6 (6.8)	6 (9.1)	12 (7.8)
Fatigue	7 (8.0)	4 (6.1)	11 (7.1)
Insomnia	9 (10.2)	2 (3.0)	11 (7.1)
Dry mouth	8 (9.1)	2 (3.0)	10 (6.5)
Night sweats	7 (8.0)	2 (3.0)	9 (5.8)
Tremor	9 (10.2)	0	9 (5.8)
Muscle spasms	7 (8.0)	1 (1.5)	8 (5.2)

Abbreviations: AE = adverse event; DBRWP: Double-blind Randomized Withdrawal Period; IH = idiopathic hypersomnia; OLE = Open-label Extension Period; PT = preferred term; SAF = Safety Analysis Set; TEAEs = treatment-emergent adverse events.
The SAF included all participants who received at least one dose of study drug.
TEAEs for participants randomized to placebo during the DBRWP plus the minimum of up to 30 days after completion of the DBRWP or the start of the OLE, whichever was earlier were excluded from this summary.
TEAEs were defined as any AEs that started or worsened in severity on or after the first dose of study drug, including adverse events that occur until 30 days after the last dose date.
AEs were coded using the MedDRA dictionary, version 19.1.
Participants reporting an AE more than once within a PT were counted only once within that preferred term. PTs were sorted in descending order of participant incidence.
Percentages were based on the total number of participants in the Analysis Set reported in each column.
The On Baseline IH Medication Group includes subjects who were on Xyrem and/or a stimulant or alerting agent at study entry.
The Treatment Naïve group includes subjects not on Xyrem or a stimulant or alerting agent at study entry.

6.2.9.1.3 Deaths, Serious Adverse Events, And Discontinuations Due To Adverse Events

6.2.9.1.3.1 Deaths

There were no deaths during this study.

6.2.9.1.3.2 Serious Adverse Events

9 treatment-emergent serious adverse events occurred in 4 patients across all periods of the study. These are summarized in the following table. On reviewing the narratives for the individual adverse events listed in that table, none appear likely to be due to study medication.

	Treatment at TEAE Onset	AE Onset Period	Severe TEAE(s) by SOC/PT	Severity Grade/ Relationship to Study Drug	Action Taken with Study Drug	Outcome
SAE Participant	JZP-258	OLE	General disorders and administration site conditions/ Non-cardiac chest pain	Mild/ Not related	Drug withdrawn	Recovered
SAE Participant	JZP-258	OTTP	Musculoskeletal and connective tissue disorders/ Rhabdomyolysis	Moderate/ Not related	Drug interrupted	Recovered
SAE Participant	Not reported	SFU	Nervous system disorders/ Syncope	Moderate/ Not related	Not applicable	Recovered
SAE Participant	JZP-258	OTTP	Renal and urinary disorders/ Nephrolithiasis	Mild/ Not related	Dose not changed	Recovered
	JZP-258	OTTP	Renal and urinary disorders/ Nephrolithiasis	Moderate/ Not related	Drug interrupted	Recovered
	JZP-258	OTTP	Renal and urinary disorders/ Nephrolithiasis	Moderate/ Not related	Drug interrupted	Recovered
	JZP-258	OLE	Renal and urinary disorders/ Nephrolithiasis	Moderate/ Not related	Drug Interrupted	Recovered
	JZP-258	OLE	Renal and urinary disorders/ Nephrolithiasis	Moderate/ Not related	Drug interrupted	Recovered
	JZP-258	OLE	Infections and infestations/ Pyelonephritis	Moderate/ Not related	Drug interrupted	Recovered

Abbreviations: AE = adverse event; OLE = Open-label Extension Period; OTTP = Optimization Period; PT = preferred term; SAE = serious adverse event; SFU = Safety Follow-ip; SOC = system organ class; TEAEs = treatment-emergent adverse events
AE Start and End Study Days have been calculated based on the date of the first dose of Open-label study drug.
The Safety Analysis Set includes all subjects who received at least one dose of study drug.
TEAEs are defined as any AEs that started or worsened in severity on or after the first dose of study drug, including adverse events that occur until 30 days after the last dose date.
AEs have been coded using the MedDRA dictionary, version 19.1.
AE Onset and End Study Days have been calculated based on the date of the first dose of Open-label Optimized Treatment and Titration Period study drug.
Dose presented as Total Nightly Dose (g/night)/ Dosing Regimen defined as once nightly (1x) or twice nightly (2x) or thrice nightly (3x) along with the each administered dose/night (first dose/ second dose/ third dose)
A total of 4 participants reported 9 treatment emergent SAEs.
Narrative links in blue.

6.2.9.1.3.3 Discontinuations Due To Adverse Events

Adverse events leading to treatment discontinuation across all study periods are summarized in the following sponsor table, which is self-explanatory. These

adverse events need no further discussion, based on my review of the details of each.

System Organ Class Preferred Term	On Baseline IH Medication (N = 88)	Treatment Naïve (N = 66)	SAF (N = 154)
Number of Participants with at Least One TEAE	16 (18.2)	10 (15.2)	26 (16.9)
Ear and labyrinth disorders	1 (1.1)	0	1 (0.6)
Vertigo	1 (1.1)	0	1 (0.6)
Gastrointestinal disorders	3 (3.4)	1 (1.5)	4 (2.6)
Nausea	3 (3.4)	0	3 (1.9)
Vomiting	0	1 (1.5)	1 (0.6)
General disorders and administration site conditions	3 (3.4)	0	3 (1.9)
Fatigue	1 (1.1)	0	1 (0.6)
Feeling abnormal	1 (1.1)	0	1 (0.6)
Non-cardiac chest pain	1 (1.1)	0	1 (0.6)
Infections and infestations	0	2 (3.0)	2 (1.3)
Corona virus infection	0	1 (1.5)	1 (0.6)
Oral fungal infection	0	1 (1.5)	1 (0.6)
Injury, poisoning and procedural complications	2 (2.3)	0	2 (1.3)
Fall	1 (1.1)	0	1 (0.6)
Limb injury	1 (1.1)	0	1 (0.6)
Metabolism and nutrition disorders	0	1 (1.5)	1 (0.6)

System Organ Class Preferred Term	On Baseline IH Medication (N = 88)	Treatment Naïve (N = 66)	SAF (N = 154)
Decreased appetite	0	1 (1.5)	1 (0.6)
Musculoskeletal and connective tissue disorders	1 (1.1)	0	1 (0.6)
Arthralgia	1 (1.1)	0	1 (0.6)
Nervous system disorders	3 (3.4)	1 (1.5)	4 (2.6)
Anterograde amnesia	0	1 (1.5)	1 (0.6)
Dizziness	1 (1.1)	0	1 (0.6)
Paraesthesia	1 (1.1)	0	1 (0.6)
Tremor	1 (1.1)	0	1 (0.6)
Psychiatric disorders	9 (10.2)	4 (6.1)	13 (8.4)
Anxiety	2 (2.3)	2 (3.0)	4 (2.6)
Insomnia	3 (3.4)	0	3 (1.9)
Apathy	0	1 (1.5)	1 (0.6)
Confusional arousal	0	1 (1.5)	1 (0.6)
Confusional state	1 (1.1)	0	1 (0.6)
Decreased interest	1 (1.1)	0	1 (0.6)
Hallucination, visual	1 (1.1)	0	1 (0.6)
Irritability	1 (1.1)	0	1 (0.6)
Panic attack	1 (1.1)	0	1 (0.6)
Somnambulism	0	1 (1.5)	1 (0.6)
Renal and urinary disorders	1 (1.1)	0	1 (0.6)
Pollakiuria	1 (1.1)	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders	0	1 (1.5)	1 (0.6)
Obstructive airways disorder	0	1 (1.5)	1 (0.6)

Abbreviations: IH = idiopathic hypersomnia; DBRWP = Double-blind Randomized Withdrawal Period; OLE = Open-label Extension Period; PT = preferred term; SAF = Safety Analysis Set; SOC = system organ class; TEAE = treatment-emergent adverse event
The Safety Analysis Set included all participants who received at least one dose of study drug.
TEAEs for participants randomized to placebo during the DBRWP plus the minimum of up to 30 days after completion of the DBRWP or the start of the OLE, whichever was earlier, were excluded from this summary.
TEAEs were defined as any AEs that started or worsened in severity on or after the first dose of study drug, including adverse events that occur until 30 days after the last dose date.
AEs were coded using the MedDRA dictionary, version 19.1.
Participants reporting an AE more than once within an SOC/PT have been counted only once within that SOC/PT. SOCs were sortedalphabetically. PTs within SOC were sorted in descending order of participant incidence.
A participant may have had more than one preferred term under a given system organ class.
Percentages were based on the total number of participants in the Analysis Set reported in each column.
The On Baseline IH Medication Group includes subjects who were on Xyrem and/or a stimulant or alerting agent at study entry.
The Treatment Naïve group includes subjects not on Xyrem or a stimulant or alerting agent at study entry.

6.2.9.1.4 Adverse Events During Randomized Withdrawal Phase

6.2.9.1.4.1 Serious Adverse Events

No serious adverse events occurred during the randomized withdrawal phase.

6.2.9.1.4.2 Adverse Events Leading To Treatment Discontinuation

A single placebo-treated patient developed insomnia and dysphoria during the randomized withdrawal phase resulting in placebo being withdrawn.

6.2.9.1.4.3 Incidence Of Individual Adverse Events

The incidence of individual adverse events reported by ≥ 2% of patients in both treatment groups combined during the double-blind randomized withdrawal period are summarized in the following table, which I have copied from the submission.

System Organ Class Preferred Term	Randomized Treatment Group JZP-258 (N = 57) n (%)	 Placebo (N = 59) n (%)	 SAF (N = 116) n (%)
Gastrointestinal disorders	5 (8.8)	3 (5.1)	8 (6.9)
Vomiting	2 (3.5)	2 (3.4)	4 (3.4)
Diarrhoea	1 (1.8)	2 (3.4)	3 (2.6)
Psychiatric disorders	2 (3.5)	9 (15.3)	11 (9.5)
Insomnia	0	6 (10.2)	6 (5.2)

Abbreviations: SAF = Safety Analysis Set; TEAEs = Treatment Emergent Adverse Events
The Double-Blind Randomized-Withdrawal Safety Analysis Set includes all subjects who received at least one dose of double-blind study drug.

6.2.9.2 Safety Laboratory Tests

There are no items of special concern in regard to Xywav in the sponsor's display and analysis of the data from standard hematology, clinical chemistry, and urinalysis parameters observed during this study. As has been the case for other safety data presented above, the sponsor's presentation has compared those who were not on treatment for idiopathic hypersomnia at study entry with those who were receiving such treatment.

6.2.9.3 Vital Signs

The changes observed in blood pressure, pulse rate, respiratory rate, and temperature during this study were unremarkable and did not appear to be of clinical significance. Again, the sponsor's presentation has compared patients who were not on treatment for idiopathic hypersomnia at study entry with those who were receiving such treatment.

6.2.9.4 Body Weight

The sponsor has presented an analysis of changes in body weight across the course of the study. There were no findings of concern in these analyses which compared the same two groups compared on other safety parameters.

6.2.9.5 Electrocardiograms

No clinically significant findings were noted in the sponsor's analysis of electrocardiographic data obtained during this study. The groups compared have been the same as those compared on other safety data.

6.2.9.6 Columbia-Suicide Severity Rating Scale

There was no evidence of suicidality on the Columbia-Suicide Severity Rating Scale. No adverse event of suicidal ideation or behavior was noted either.

6.2.9.7 Adverse Events Of Special Interest Across Study

Adverse events of special interest during this study included the following: anxiety, confusion, convulsions, depressed consciousness, depression and suicidality, psychotic and dissociative disorders, impaired attention or cognitions, parasomnias, respiratory failure and respiratory depression, drug abuse, and accidents and injuries. Their incidence across all study periods is summarized in the following sponsor table.

Special Interest Category Preferred Term, n (%)	On Baseline IH Medication (N=88)	Treatment Naïve (N=66)	SAF (N=154)
Number of Participants with at Least One AESI	39 (44.3)	27 (40.9)	66 (42.9)
Accidents and Injuries	7 (8.0)	2 (3.0)	9 (5.8)
Fall	5 (5.7)	1 (1.5)	6 (3.9)
Contusion	3 (3.4)	1 (1.5)	4 (2.6)
Limb injury	2 (2.3)	0	2 (1.3)
Muscle strain	2 (2.3)	0	2 (1.3)
Clumsiness	0	1 (1.5)	1 (0.6)
Laceration	1 (1.1)	0	1 (0.6)
Post-traumatic neck syndrome	1 (1.1)	0	1 (0.6)
Road traffic accident	1 (1.1)	0	1 (0.6)
Tendon injury	0	1 (1.5)	1 (0.6)
Anxiety	18 (20.5)	11 (16.7)	29 (18.8)
Anxiety	10 (11.4)	7 (10.6)	17 (11.0)
Irritability	4 (4.5)	1 (1.5)	5 (3.2)
Nervousness	2 (2.3)	3 (4.5)	5 (3.2)
Feeling jittery	2 (2.3)	0	2 (1.3)
Agitation	1 (1.1)	0	1 (0.6)
Panic attack	1 (1.1)	0	1 (0.6)
Social anxiety disorder	0	1 (1.5)	1 (0.6)

Special Interest Category Preferred Term, n (%)	On Baseline IH Medication (N=88)	Treatment Naïve (N=66)	SAF (N=154)
Confusion	3 (3.4)	1 (1.5)	4 (2.6)
Confusional state	3 (3.4)	1 (1.5)	4 (2.6)
Depressed Consciousness	3 (3.4)	7 (10.6)	10 (6.5)
Somnolence	3 (3.4)	4 (6.1)	7 (4.5)
Syncope	0	2 (3.0)	2 (1.3)
Sedation	0	1 (1.5)	1 (0.6)
Depression and Suicidality	7 (8.0)	8 (12.1)	15 (9.7)
Depressed mood	3 (3.4)	2 (3.0)	5 (3.2)
Affect lability	1 (1.1)	1 (1.5)	2 (1.3)
Dysphoria	0	2 (3.0)	2 (1.3)
Anhedonia	0	1 (1.5)	1 (0.6)
Apathy	0	1 (1.5)	1 (0.6)
Blunted affect	0	1 (1.5)	1 (0.6)
Crying	0	1 (1.5)	1 (0.6)
Decreased interest	1 (1.1)	0	1 (0.6)
Depression	1 (1.1)	0	1 (0.6)
Major depression	0	1 (1.5)	1 (0.6)
Mood altered	1 (1.1)	0	1 (0.6)
Mood swings	0	1 (1.5)	1 (0.6)
Drug abuse	14 (15.9)	13 (19.7)	27 (17.5)
Dizziness	8 (9.1)	11 (16.7)	19 (12.3)
Feeling drunk	2 (2.3)	3 (4.5)	5 (3.2)
Feeling abnormal	4 (4.5)	0	4 (2.6)
Euphoric mood	0	1 (1.5)	1 (0.6)
Impaired Attention or Cognition	1 (1.1)	2 (3.0)	3 (1.9)
Amnesia	1 (1.1)	0	1 (0.6)
Anterograde amnesia	0	1 (1.5)	1 (0.6)
Disturbance in attention	0	1 (1.5)	1 (0.6)
Parasomnias	4 (4.5)	2 (3.0)	6 (3.9)
Confusional arousal	1 (1.1)	1 (1.5)	2 (1.3)
Sleep paralysis	1 (1.1)	1 (1.5)	2 (1.3)
Nightmare	1 (1.1)	0	1 (0.6)
Sleep talking	1 (1.1)	0	1 (0.6)

Special Interest Category Preferred Term, n (%)	On Baseline IH Medication (N=88)	Treatment Naïve (N=66)	SAF (N=154)
Somnambulism	0	1 (1.5)	1 (0.6)
Psychotic and dissociative disorders	9 (10.2)	6 (9.1)	15 (9.7)
Irritability	4 (4.5)	1 (1.5)	5 (3.2)
Affect lability	1 (1.1)	1 (1.5)	2 (1.3)
Hallucination, visual	2 (2.3)	0	2 (1.3)
Apathy	0	1 (1.5)	1 (0.6)
Blunted affect	0	1 (1.5)	1 (0.6)
Dissociation	1 (1.1)	0	1 (0.6)
Flat affect	1 (1.1)	0	1 (0.6)
Hallucination, auditory	1 (1.1)	0	1 (0.6)
Hypnopompic hallucination	0	1 (1.5)	1 (0.6)
Hypomania	1 (1.1)	0	1 (0.6)
Mood swings	0	1 (1.5)	1 (0.6)
Respiratory Failure and Respiratory Depression	1 (1.1)	1 (1.5)	2 (1.3)
Apnoea	1 (1.1)	0	1 (0.6)
Obstructive airways disorder	0	1 (1.5)	1 (0.6)

Abbreviations: AE = Adverse Event; DBRWP: Double-blind Randomized Withdrawal Period; IH = Idiopathic Hypersomnia; PT = preferred term; SAF = Safety Analysis Set; SOC = system organ class; TEAE = treatment-emergent adverse event; OLE = Open-label Extension Period
The SAF included all participants who received at least one dose of study drug.
Treatment-emergent adverse events for participants randomized to placebo during the DBRWP plus the minimum of up to 30 days after completion of the DBRWP or the start of the OLE, whichever was earlier, were excluded from this summary.
Treatment-emergent adverse events were defined as any AEs that started or worsened in severity on or after the first dose of study drug, including adverse events that occur until 30 days after the last dose date.
AEs were coded using the MedDRA dictionary, version 19.1.
Participants reporting an AE more than once within a category/ PT were counted only once within that SOC/PT. Special interest category were sorted alphabetically. Preferred term within the category were sorted in descending order of participant incidence. A participant may have had more than one PT under a given category/ SOC.
Percentages were based on the total number of participants in the Analysis Set reported in each column.
The On Baseline IH (IH) Medication Group included participants who were on Xyrem and/or a stimulant or alerting agent at study entry. The Treatment Naïve group includes participants not on Xyrem or a stimulant or alerting agent at study entry.
*In addition, the TEAE of "Worsening of obstructive breathing" was identified by manual review

6.2.9.8 Potential Abuse And Misuse Of JZP-258 Across Study

No study subjects with evidence of drug abuse or misuse were identified, despite the measures that the sponsor took to identify such subjects.

6.2.10 Pharmacokinetic Results

28 patients participated in the pharmacokinetic substudy: 9 of these participants received a once-nightly regimen of Xywav™ and 19 of these participants received a twice nightly regimen of Xywav™.

The sponsor states that across all study periods, the distribution in dose range and dose frequency in the pharmacokinetic substudy was similar to the distribution in dose range and frequency in the efficacy and safety datasets.

Additional observations made by the sponsor after analyzing pharmacokinetic data for this substudy were as follows:

- For those receiving a once-nightly regimen, descriptive statistics were reported for the concentration-time data and pharmacokinetic parameters for those participants (n = 7) whose stable dose ranged from 3 to 6 grams/night. For those 7 patients, the T_{max} ranged from 0.75 to 2.0 hours, the C_{max} ranged from 39.7 to 110 µg/mL, and the $AUC_{0\text{-}tlast}$ ranged from 79.47 to 421.84 µg.hr/mL.

- For those receiving a stable twice nightly regimen (total dose ranging from 5.25 grams to 9 grams/night; n = 13), the C_{max} ranged from 57.1 to 188 µg/mL and the $AUC_{0\text{-}tlast}$ ranged from 190.19 to 1032.99 µg.hr/mL. However, data for the entire cohort that received a twice-nightly regimen were not entirely conducive to summarizing concentration-time data or pharmacokinetic parameters as each participant had a dosing regimen that was individualized with a different first or second dose or a different interval between doses.

- There was a greater than dose-proportional relationship between total nightly dose and $AUC_{0\text{-}tlast}$.

- There was an almost dose-proportional relationship between total nightly dose and C_{max}.

A population pharmacokinetic analysis has also been performed by the sponsor using data from Study JZP258-301 and two previously completed clinical pharmacology (relative bioavailability and bioequivalence) studies of JZP-258, Studies 13-010 and JZP258-101. The results of the latter clinical pharmacology studies were first reviewed under the original NDA (212690) submission for JZP-258 seeking the approval of that drug for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy.

6.3 Changes In Conduct Of Study Due To COVID-19 Pandemic

In accordance with various guidance documents issued by regulatory bodies, the sponsor implemented the following alternative approaches as needed to maintain the continuity of the study, access to study drug, continued safety of participants, and integrity of study data.

- Delivery of study medication directly to the residence of a subject or to a pharmacy near that residence.

- Introducing remote assessments that may have included the following:.
    - Adaptation of efficacy assessments.
    - Alternative methods of safety assessment.
    - Alternative measures for study monitoring and oversight.

The study report includes a detailed description of the above alternative approaches and assessing their impact on the evaluation of efficacy and safety.

The alternative measures described above were introduced relatively late during the study and about one-third of the patients enrolled in the study were affected.

The sponsor has concluded that the COVID-19-related restrictions had no significant impact on either the safety or the efficacy results for this study.

6.4 Sponsor's Conclusions

The sponsor's salient conclusions based on the results of this study were as follows.

- JZP-258 had efficacy in the treatment of idiopathic hypersomnia. The results of this study were robust and clinically meaningful across the main analyses of primary and key secondary endpoints, supported by the results subgroup analyses of the same endpoints.
- JZP-258 was well-tolerated by patients with idiopathic hypersomnia. The safety profile of JZP-258 in this study was consistent with that of this drug in narcolepsy. It was also consistent with the safety profile of Xyrem® in narcolepsy.

6.5 Reviewer's Summary Comments

A single efficacy and safety study (JZP080-301) was the only clinical study of JZP-258 that was conducted in support of the proposed indication of idiopathic hypersomnia.

6.5.1 Study Design

The main features of Study JZP080-301 were as follows.

- The primary objective of the study was to evaluate the efficacy of JZP-258 in the treatment of idiopathic hypersomnia.
- This was to be a double-blind, placebo-controlled, randomized withdrawal, multicenter study of the efficacy and safety of JZP-258. Patients enrolled

in the study were to include those whose prior treatment status was in any of the following 2 categories:

- Treatment with a stable dose of Xyrem®.
- No prior treatment with Xyrem®.

- The study was to consist of the following consecutive periods: screening; open-label titration and treatment optimization (of variable duration up to a maximum of 14 weeks, depending on prior treatment status); open-label stable dose treatment (2 weeks); double-blind, randomized withdrawal (2 weeks); and safety follow-up (2 weeks). All study patients were to be titrated (during the variable-duration open-label titration period) to a dose of JZP-258 that was deemed both effective and tolerable and was maintained for at least 2 weeks prior to entering the two-week, open-label, stable-dose period. An open-label extension of 24 weeks was to follow the double-blind treatment period.

- A total of about 140 patients were planned to be enrolled in the study of whom about 112 patients were expected to enter the randomized double-blind withdrawal period during which they were to be randomly assigned 1:1 to either continuing the same dose of JZP-258 taken during the stable dose period or to placebo.

- The main inclusion criteria for this study were to be as follows: men and women, aged 18 to 70 years; a primary diagnosis of idiopathic hypersomnia that met the ICSD–2 or -3 criteria; a history of an average total nightly treatment ≥ 7 hours; treatment status prior to study entry consisting of one of the aforementioned 2 categories; if not treated with Xyrem®, must have an Epworth Sleepiness Scale scores ≥ 11; and if treated with a stimulant for narcolepsy must have been at an unchanged dose for at least 2 months prior to dosing or must not have been treated at all with a stimulant.

- The primary efficacy parameter was to be the change in Epworth Sleepiness Scale score from the end of the 2-week stable dose period to the end of the 2-week double-blind treatment period. Key secondary efficacy endpoints were to be the Patient Global Impression of Change and the Idiopathic Hypersomnia Sleepiness Scale score, extending over the same period as the primary efficacy parameter. Safety measures were to include adverse events, vital signs, weight, physical examinations, 12-lead electrocardiograms, safety laboratory tests (hematology, clinical chemistry, and urinalysis), and the Columbia-Suicide Severity Rating

Scale (for assessing suicidality). Plasma samples for pharmacokinetic analysis were drawn from a subset of patients over a single night.

- The analyses of the primary efficacy parameter and key secondary efficacy parameters were to employ a fixed sequential testing strategy in which the initial step was to involve a comparison of JZP-258 with placebo for the primary efficacy parameter; if the initial comparison was statistically significant, the treatment groups were then to be compared on the key secondary efficacy parameters in the following sequence: Patient Global Impression of Change followed by Idiopathic Hypersomnia Sleepiness Scale scores. An analysis of covariance model was to be used for the primary efficacy analysis and for the analysis of one of the key secondary efficacy measures, the Idiopathic Hypersomnia Sleepiness Scale. The Cochran-Mantel-Haenszel test was to be used for the analysis of the Patient Global Impression of Change. An optional interim analysis was planned when about 60% of the 112 planned randomized patients had completed or were terminated early from the double-blind randomized withdrawal period, and incorporated a plan for controlling familywise Type 1 error.

6.5.2 Study Results

Study JZP080-301 was conducted in a manner consistent with the study protocol.

154 patients were enrolled in the study and entered the optimized treatment and titration period (up to 14 weeks). They consisted of the following: 2 patients who were receiving Xyrem only; 4 patients who were receiving a combination of Xyrem and a stimulant; 82 patients who were receiving a stimulant only; and 66 patients who were drug-naïve at study entry. 123 patients then entered the stable-dose period (2 weeks).

113 patients who completed the stable-dose period were then randomized, and entered the randomized, double-blind, placebo-controlled, withdrawal period (2 weeks). At the beginning of that period, 57 patients were randomized to continuing JZP-258 and 59 patients were randomized to placebo; 56 patients randomized to JZP-258 and 57 patients randomized to placebo completed that period of the study.

The primary efficacy analysis (based on an analysis of covariance) indicated that the median change from baseline over the two-week randomized withdrawal period in Epworth Sleepiness Scale score was an increase of 8.0 points for the placebo group and 0.0 points for the group that continued to take JZP-258. This difference was statistically significant ($p < 0.0001$). Statistically significant treatment differences favoring JZP-258 over placebo were seen on both key secondary efficacy parameters analyzed in the prespecified sequence. On the

Patient Global Impression of Change, the percentage of subjects with minimally, much, or very much worse scores on the Patient Global Impression of Change at the end of the double-blind randomized withdrawal period was 88.1% in the placebo group and 21.4% in the JZP-258 group; that difference was statistically significant based on the Cochran-Mantel-Haenszel test ($p < 0.0001$). On the Idiopathic Hypersomnia Sleepiness Scale, an increase in median score of 14 points was seen in the placebo group over the double-blind randomized withdrawal period as opposed to no change on that measure in the JZP-258 group; this difference was statistically significant based on an analysis of covariance ($p < 0.0001$).

106 patients then entered the open-label phase of the study, with 95 patients completing that phase.

The adverse event profile of JZP-258 as seen across this study was not substantially different from that seen with JZP-258 or Xyrem® when used for the treatment of narcolepsy . The other safety outcomes did not reveal any data of concern.

7. 120-Day Safety Update

The key elements of the 120-Day Safety Update were included in the safety data summarized in Section 6.

8. Review Of Proposed Prescribing Information And Related Documents

I have reviewed the Prescribing Information proposed by the sponsor together with the sponsor proposals for a number of linked documents, namely the Medication Guide, Instructions for Use, and, to a limited extent, the Risk Evaluation and Mitigation Strategy (REMS).

That review has been assisted by the input of several other disciplines within the Agency, most of which are listed later in this review.

While I have participated in Agency deliberations regarding all the documents listed above, my own review has been primarily directed at the following sections of the Prescribing Information, proper.

Highlights of Prescribing Information.
Boxed Warning.
Section 1. Indications and Usage.
Section 2. Dosage and Administration.
Section 5. Warnings and Precautions.
Section 6. Adverse Reactions.
Section 8. Use in Special Populations.
Section 14. Clinical Studies.

Section 17. Patient Counseling Information.

As this component of my review has been complex and iterative, it is not possible to summarize here the basis for every recommendation that I have made regarding the Prescribing Information and related documents.

I am however in agreement with the finalized versions of the documents listed above that are to accompany the approval letter for this application.

Dr. Tracy Peters, who is affiliated with this Division as an Associate Director, has had played a primary role in drafting both the Prescribing Information and related documents.

9. Summary Of Statistical Review

The primary statistical review of this sNDA has been performed by Dr. Minjeong Park of the Division of Biometrics I.

Her review has been directed at the efficacy results of the randomized, double-blind, placebo-controlled, withdrawal phase of Study JZP080-301, based on the analysis of the primary and key secondary efficacy endpoints for that study.

She has substantiated the results of the sponsor's main analyses of the primary efficacy endpoint and the key secondary efficacy endpoints.

Please see the full text of Dr. Park's review for more details.

10. Summary Of Clinical Pharmacology Review

An integrated primary clinical pharmacology review of this submission was completed by Drs. Gopichand Gottipatti, Mike Bewernitz, Atul Bhattaram, and Bilal AbuAsal.

They reviewed the clinical pharmacology and other data submitted with this application and recommended the approval of Xywav™ for the proposed indication.

While the sponsor had proposed that JZP-258 be administered without regard to food in patients with idiopathic hypersomnia, the clinical pharmacology reviewers have recommended otherwise; they have recommended, instead, that JZP-258 be administered at least 2 hours after food for the treatment of both idiopathic hypersomnia and narcolepsy. The basis for that recommendation is in their review and will not be repeated here.

The clinical pharmacology staff have also made other recommendations in regard to the Prescribing Information for Xyrem®.

Please see the full text of the clinical pharmacology review for more information.

11. Summary Of Office Of Surveillance And Epidemiology Reviews

11.1 Division Of Risk Management Review

The Risk Evaluation and Mitigation Strategy (REMS) accompanying this application (a combined REMS for both Xyrem® and Xywav™) was reviewed by Donella Fitzgerald, PharmD, of the Division of Risk Management.

In a series of communications with the sponsor, changes were made to the text of the proposed REMS, and were finalized with the mutual agreement of both the Agency and the sponsor. Please see Dr. Fitzgerald's review for further details.

11.2 Division Of Medical Error Prevention And Analysis Review

The labeling accompanying this application was reviewed by Justine Kalonia, PharmD, of the Division of Medical Error Prevention and Analysis.

This review was directed at the following: Prescribing Information, Medication Guide, and Instructions for Use.

Dr. Kalonia made a number of recommendations regarding the above components of the label. Those recommendations were taken into consideration when finalizing the label..

Please see the text of her review for further details.

12. Summary Of Division Of Medical Policy Programs/Office Of Prescription Drug Promotion Reviews

12.1 Office Of Prescription Drug Promotion Review

Dhara Shah, Regulatory Review Officer, reviewed the proposed Prescribing Information that accompanied this application. He recommended changes to the text of the proposed Prescribing Information.

Those recommendations have been taken into consideration when finalizing the Prescribing Information for Xywav™.

Please see the text of that review for full details.

12.2 Division Of Medical Policy Programs/Office Of Prescription Drug Programs Collaborative Review

This review was completed by Maria Nguyen, RN, and Aline Moukhtara, RN.

These staff reviewed the Medication Guide and Instructions for Use components of the proposed label and recommended changes to the text of those items. Those recommendations were taken into consideration when finalizing the Prescribing Information for Xywav™.

Please see the text of that review for further details.

13. Controlled Substances Staff Review

This sNDA was reviewed by James M. Tolliver, PhD, Senior Pharmacologist of the Controlled Substances Staff. Among his key observations and conclusions are the following.

- Xywav™ (JZP-258) is already included in Schedule III of the Controlled Substances Act (as is Xyrem®).

- The proposed new indication for Xywav™, i.e., the treatment of idiopathic hypersomnia in adults, and a description of the prescribing and dispensing of Xywav™ should be described in a revised version of the existing Risk Evaluation and Mitigation Strategy (REMS) that combines both Xyrem® and Xywav™, if Xywav™ is approved for that indication.

- No major issues related to the abuse potential of Xywav™ were identified in Study JZP080-301.

The Controlled Substances Staff did not have any additional recommendations for this Division.

14. Financial Disclosure Information

Financial disclosure information has been collected only for the single clinical efficacy trial, JZP080-301, included in this submission. That information is summarized below.

14.1 Components Of Certification

14.1.1 Certification Pertinent To Investigators/Sub-Investigators Who Declared That They Did Not Have Any Relevant Financial Interests (FDA Form 3454)

The sponsor has supplied a list of all such investigators and sub-investigators who were involved in this study. In regard to this list the sponsor has:

- Certified that it has not entered into any financial agreement with the clinical investigators listed in the application, whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)

- Certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements

- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f).

14.1.2 Certification Pertinent To Investigators/Sub-Investigators With Disclosable Financial Interests (FDA Form 3455)

The sponsor has listed a single investigator to whom such certification applied: (b) (4) Further, the sponsor has cited a number of reasons why that investigator was cleared for participation in Study JZP080-301 and why his participation in that study was appropriate and was unlikely to have introduced significant bias into the results of the study.

14.2 Reviewer's Comments

It appears unlikely that the financial arrangements disclosed above introduced significant bias into the results of the single clinical study (JZP080-301) that were submitted with this application.

15. Site Inspections

After internal discussion, it was concluded that an inspection of study sites participating in Study JZP080-301 was not necessary. Thus, no site inspections were conducted

16. Overall Conclusion

Substantial evidence of the efficacy of Xywav™ (JZP-258) in the treatment of idiopathic hypersomnia in adults was demonstrated by the results of a single adequate and well-controlled clinical study, JZP080-301.

The safety profile of Xywav™ (JZP-258) in the treatment of idiopathic hypersomnia as seen in Study JZP080-301 is acceptable and not substantially different from that of Xywav™ (or Xyrem®) in the treatment of narcolepsy.

17. Recommendation

I recommend that Xywav™ (JZP-258) be approved for the treatment of idiopathic hypersomnia in adults, under the current Supplemental New Drug Application.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm
cc:
HFD-120
IND

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RANJIT B MANI
08/12/2021 09:44:21 AM

TERESA J BURACCHIO on behalf of ERIC P BASTINGS
08/12/2021 09:50:08 AM
I concur with Dr. Mani's recommendation for approval and will issue an approval letter.

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 20, 2021

To: Eric Bastings, M.D., Acting Director
Division of Neurology I

Through: Dominic Chiapperino, Ph.D., Director
Silvia Calderon, Ph.D., Pharmacologist
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Senior Pharmacologist
Controlled Substance Staff

Subject: XYWAV (Calcium, Magnesium, Potassium, and Sodium Oxybates), Code Name JZP-258, NDA 212-690, (b) (4) Efficacy Supplement 006
Trade Name, dosages, formulations, routes: Oral Solution, 0.5 mg/mL, equivalent to an active moiety concentration of 0.413 g/mL oxybate
IND Number: 049641
Indication(s): Currently approved for the treatment of cataplexy or excessive daytime sleepiness, in patients 7 years or older with narcolepsy.
Proposed New Indication: Treatment of adult patients with idiopathic hypersomnia (IH)
Sponsor: Jazz Pharmaceuticals

Materials Reviewed:

Clinical study JZP080-301 Amendment 2 submitted in support of efficacy supplement 006 of NDA 212690.

Table of Contents

I. SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Neurology I dated February 19, 2021, for CSS to review and provide any comments from an abuse potential perspective concerning efficacy supplement 006 under NDA 212-690 for XYWAV oral solution, developed by Jazz Pharmaceuticals. This product was initially approved on July 21, 2020 for treatment of cataplexy or excessive daytime sleepiness, in patients 7 years or older with narcolepsy. Via letter dated December 18, 2020, Sponsor submitted to the NDA, efficacy supplement 006 to expand the indicated uses for XYWAV to include treatment of adult patients with idiopathic hypersomnia (IH).

IH is a rare disorder of central nervous system hypersomnolence. The primary manifestation is severe excessive daytime sleepiness (EDS). According to the International Classification of Sleep Disorders (ICSD), third Edition (ICSD-3), the primary symptom of IH is EDS occurring almost daily for at least 3 months, despite normal quality, quantity and timing of sleep (American Academy of Sleep Medicine ICSD-3 2014). Additional symptoms include sleep inertia, known as “sleep drunkenness”, and prolonged nighttime sleep exceeding 11 hours per night. There are no medications approved for the treatment of IH. Current treatments are based on expert opinion and utilize regimens similar to those for narcolepsy.

Sodium oxybate is a central nervous system depressant having an abuse potential. The substance is in Schedule I of the federal Controlled Substances Act (CSA). Two products, namely XYREM and XYWAV, each containing oxybate salts and approved for medical use, are in Schedule III of the CSA.

To support efficacy supplement 006 under NDA 212-690, the Sponsor has submitted clinical study JZP080-301, entitled “A Double-Blind, Placebo-Control, Randomized Withdrawal, Multicenter Study of the Efficacy and Safety of JZP-258 in the Treatment of IH with an Open-Label Safety Extension” Amendment 2. CSS has examined this study from an abuse potential perspective. In this study XYWAV is referred to under the code name JZP-258.

2. Conclusions

1. The intent of efficacy supplement 006 under NDA 212-690 is to obtain approval for XYWAV for the treatment of a rare disorder, idiopathic hypersomnia (IH). XYWAV was initially approved on July 21, 2020 for the treatment of cataplexy or excessive daytime sleepiness, in patients 7 years or older with narcolepsy.

2. XYWAV is a mixture of calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate (gamma hydroxybutyrate [GHB]). XYWAV is in Schedule III of the federal Controlled Substances Act (CSA) due to it being a product containing salts of oxybate (also known as gamma hydroxybutyrate) that is approved for medical use in the United States.

3. Clinical study JZP080-301 was provided under efficacy supplement 006 to support extending the approved indication of XYWAV oral solution to include treatment of IH. Study JZP080-301 is a phase 3, double-blind, placebo-controlled, randomized withdrawal, multicenter study with an open-label safety extension period. The study was designed to evaluate the efficacy, safety, and PK of JZP-258 oral solution in adult participants with IH. Individuals with a history of substance abuse disorder or alcohol abuse were excluded from the study. Overall, no major issues regarding abuse potential of JZP-258 were identified in this study. From the standpoint of abuse potential assessment, the following specific findings are noted:

    a. From the safety population consisting of 156 subjects, only five treatment emergent adverse events possibly related to abuse potential were documented. "Euphoric Mood" and "Hypnopompic Hallucination" were each reported by one subject within the treatment naïve group. One subject each from the baseline IH medication group reported "Hallucination Visual", "Mood Altered", and "Dissociation." (See DISCUSSION, Section 4.2)
    b. Although compliance issues were documented and assessed from an abuse potential perspective, no compliance issues were found to be related to possible abuse during the study. (See DISCUSSION, Section 2.2)

4. In order to mitigate the specific risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of sodium oxybate, XYWAV was added to the Xyrem Risk Evaluation and Mitigation Strategy (REMS) following approval of XYWAV in July 2020. However, if approved the use of XYWAV for the new indication should be added to the "XYWAV and XYREM REMS," so the product will be subject to same REMS requirements than that of the same product approved for the treatment of cataplexy or excessive daytime sleepiness and XYREM. The current REMS program requires distribution of the product by a certified pharmacy that directly ships the product to patients, and a central database of longitudinal patient and prescriber information to track drug shipments, prevent multiple prescriptions, ensure that patients are monitored for suspected abuse or misuse (and the adverse events that could result), mitigate risks associated with CNS depression (including the risks associated with use of contraindicated drugs and other CNS depressants), and protect the public from the risks associated with potential illicit use of the drug. The Sponsor is working with the Division to add the indication of idiopathic hypersomnia (IH) for XYWAV to the "XYWAV and XYREM REMS."

3. Recommendations

There are no scheduling issues. XYWAV is in Schedule III of the CSA due to its containing oxybate salts and being a product approved for medical use in the United States.

CSS does not have specific recommendations to the Division or the Sponsor, but does agree with the Sponsor and the Division that the current XYREM/XYWAV REMS should be revised to accommodate the prescribing and dispensing of XYWAV to patients with idiopathic hypersomnia.

II. DISCUSSION

1. Chemistry

1.1 Product Information

XYWAV™ (Project code: JZP-258) is a mixture of calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate (gamma hydroxybutyrate [GHB]). These correspond to an active ingredient concentration of 0.5 g/mL, equivalent to an active moiety concentration of 0.413 g/mL oxybate.

2. Clinical Studies

A single clinical study, namely study JZP080-301, was provided under efficacy supplement 006 to support extending the approved indication of XYWAV for treatment of IH.

Study JZP080-301 is a phase 3, double-blind, placebo-controlled, randomized withdrawal, multicenter study with an open-label safety extension period. The study was designed to evaluate the efficacy, safety, and PK of JZP-258 oral solution in adult participants with IH. All individuals who participated in the study had HI according to the International Classification of Sleep Disorders (ICSD)-2 or ICSD-3 criteria. Participants included those being treated at study entry with or without Xyrem and treated with or without stimulants/ alerting agents (AAs). Excluded from the study were individuals with current or past substance use disorder, including alcohol, according to DSM-5 criteria. The study comprised 6 periods as designated below.

- Screening Period for 14 to 30 days, with the option to rescreen once.
- All subjects were switched to JZP-258 during the Open-label Treatment Titration and Optimization Period (OTTP) for 10 to 14 weeks. Flexible dosing was allowed with starting doses of JZP-258 in Xyrem naïve participants of no greater than 3 g once or 4.5 g total divided twice nightly; and titrated to a tolerable and effective dose not to exceed a single dose of 6 g and maximum total nightly dose of 9 g divided equally or unequally twice or thrice nightly.
- Stable Dose Period (SDP) for 2 weeks. All subjects were stabilized at a tolerable JZP-258 dose
- Double-blind Randomized Withdrawal (DBRW) Period for 2 weeks. Participants were randomized 1:1 to either JZP-258 at the stable dose and regimen or placebo at a volume and regimen equivalent to the JZP-258 dose and regimen.

- Open-label Safety Extension (OLE) Period for 24 weeks. During this period all subjects are on JZP-258. Those subjects who were randomized to placebo during the DBRW period were placed back on JZP-258.
- Safety Follow-up Period for 2 weeks.

2.1 Adverse Event Profile Through all Phases of Development

Treatment emergent adverse events were monitored throughout study JZP080-301 and documented in the safety population consisting of 154 subjects total. The most common TEAEs by preferred term (PT) were nausea, headache, dizziness, anxiety and vomiting.

Sponsor used the 2017 FDA Guidance on the Assessment of Abuse Potential to identify TEAEs possibly related to abuse potential. The only TEAEs possibly related to abuse potential observed in the study are listed below. None of these TEAEs occurred during the brief 2 weeks that half of the subjects were placed on placebo during the DBRW period. All were taking JZP080-301.

- "Euphoric Mood" – 1 subject – Treatment Naïve
- "Hallucination Visual" – 1 subject – Baseline IH Medication
- "Hypnopompic Hallucination" – 1 Subject – Treatment Naïve
- "Mood Altered" – 1 Subject - Baseline IH Medication
- "Dissociation" – 1 Subject - Baseline IH Medication

2.2 Evidence of Abuse, Misuse, and Diversion in Clinical Trials

Under Section 5.3.5.1 of NDA 212-690 (SN0105), Sponsor provided document "JZP080-301 – 8.12 Abuse Potential" detailing instances of during which study staff evaluated 24 participants of study JZP080-301 for potential abuse based on compliance >125% and/or participants who did not return all study drug bottles. For all cases, investigators at the study sites ruled out abuse as a reason for the compliance issues.

3. Regulatory Issues and Assessment

There are no scheduling issues. XYWAV is controlled in Schedule III of the CSA, as it contains salts of oxybate (gamma hydroxybutyrate) and is a product approved for medical use in the United States.

In order to mitigate the specific risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of sodium oxybate, XYWAV was added to the Xyrem Risk Evaluation and Mitigation Strategy (REMS) following approval of XYWAV in July 2020. This program uses a certified pharmacy, direct shipment to patients, and a central database of longitudinal patient and prescriber information to track drug shipments, prevent multiple prescriptions, ensure that patients are monitored for suspected abuse or misuse (and the adverse events that could result), mitigate risks associated with CNS depression (including the risks associated with use of contraindicated drugs

and other CNS depressants), and protect the public from the risks associated with potential illicit use of the drug. The Sponsor is working with the Division to add the indication of idiopathic hypersomnia (IH) for XYWAV to the REMS for XYWAV and XYREM.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAMES M TOLLIVER
07/20/2021 01:07:49 PM

SILVIA N CALDERON
07/20/2021 01:29:03 PM

DOMINIC CHIAPPERINO
07/20/2021 01:53:16 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s006

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA 212690 / S-006**

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original	PAS (Efficacy)	2/12/2021	2/12/2021	2/18/2021	8/12/2020	7/15/2021

3. **Provides For:** an expansion of the indication of Xywav™ oral solution to include the treatment of adult patients with idiopathic hypersomnia (IH) and modifications to the Risk Evaluation and Mitigation Strategy (REMS) for Xywav and Xyrem (a drug product not approved under this NDA) considering this proposed new indication of use.

4. **Review #:** 1

5. **Clinical Review Division:** CDER/ON/DN1

6. **Name and Address of Applicant**:

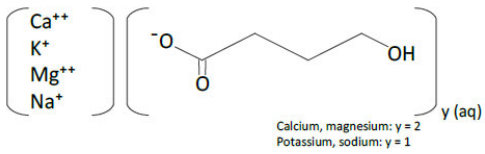
Jazz Pharmaceuticals Ireland Limited
Fifth Floor, Waterloo Exchange
Waterloo Road
Dublin, Dublin / Ireland D04 E5W7

Authorized U.S. Agent Name
Jazz Pharmaceuticals, Inc.
3170 Porter Drive
Palo Alto, California 94304

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Xywav™ (calcium, magnesium, potassium, and sodium oxybates) oral solution	Solution	0.5 g/mL	Oral	Rx	No

8. **Chemical Name and Structure of Drug Substance**:

	**Chemical name:** Calcium, magnesium, potassium, and sodium oxybates **Molecular formula**: $Ca(C_4H_7O_3)_2 + Mg(C_4H_7O_3)_2 + K(C_4H_7O_3) + Na(C_4H_7O_3)$ **MW:** 246.3 g/mol for calcium oxybate, 230.5 g/mol for magnesium oxybate, 142.2 g/mol for potassium oxybate, and 126.1 g/mol for sodium oxybate

9. **Indication**: for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

10. Supporting/Relating Documents: See pages 3-4.

11. Consults: None

12. Executive Summary:

OND Managed: In this supplemental submission, the applicant proposes to expand the indication of Xywav™ oral solution to include the treatment of adult patients with idiopathic hypersomnia (IH) and to modify the Risk Evaluation and Mitigation Strategy (REMS) for Xywav and Xyrem (a drug product not approved under this NDA) considering this proposed new indication of use.

No changes have been made to the CMC sections of the application and the applicant has provided a categorical exclusion for Environmental Assessment. The applicant claims categorical exclusion under 21 CFR 25.31(b) from the requirement to prepare an Environmental Assessment because approval of this supplemental submission will not increase the estimated concentration of the drug substance at the point of entry into the aquatic environment above 1 part per billion. Based upon the calculations provided (see details in the body of the review), the claim of categorical exclusion appears to be warranted.

The submitted draft USPI (annotated, tracked-changes) showed no changes to the currently approved CMC-related information included in Section "2 DOSAGE AND ADMINISTRATION". All CMC-related information included in this section appears to be correct. The submitted draft USPI (annotated, tracked-changes) showed no changes at all to Sections "3 DOSAGE FORMS AND STRENGTHS", "11 DESCRIPTION", and "16 HOW SUPPLIED/STORAGE AND HANDLING"; all CMC-related information proposes no changes to the currently approved.

13. Conclusions & Recommendations:

This supplemental submission is recommended for approval from a CMC standpoint.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Richard T. Matsuoka, Ph.D., CMC reviewer, Branch 3, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:

Gurpreet Gill-Sangha, Ph.D., Branch Chief, Branch 3, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

CMC ASSESSMENT

I BACKGROUND INFORMATION

Xywav™ (calcium, magnesium, potassium, and sodium oxybates) oral solution was approved on 07/21/2020 for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. Xywav oral solution "contains a mixture of calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate equivalent to 0.5 g/mL"; this mixture "corresponds to 0.413 g/mL oxybate". Each mL of Xywav contains the following mixture of oxybates: 0.234 g of calcium oxybate, $Ca(C_4H_7O_3)_2$; 0.096 g of magnesium oxybate, $Mg(C_4H_7O_3)_2$; 0.13 g of potassium oxybate, $K(C_4H_7O_3)$; and 0.04 g of sodium oxybate, $Na(C_4H_7O_3)$ in dissociated form in the solution. The molecular weights of each oxybate are as follows: calcium oxybate is 246.3 g/mol, magnesium oxybate is 230.5 g/mol, potassium oxybate is 142.2 g/mol, and sodium oxybate is 126.1 g/mol. The drug product also contains the following inactive ingredients: "purified water and sucralose". The maximum daily dose (MDD) is 9 grams.

II PROPOSED CHANGES

The applicant proposes to expand the indication of Xywav™ oral solution to include the treatment of adult patients with idiopathic hypersomnia (IH) and to modify the Risk Evaluation and Mitigation Strategy (REMS) for Xywav and Xyrem (a drug product not approved under this NDA) considering this proposed new indication of use.

III DATA SUBMITTED TO SUPPORT THE PROPOSED CHANGES

1. OTHER CORRESPONDENCE (1.12)

A. Environmental Analysis (1.12.14)

Comments: The applicant claims categorical exclusion from the requirement to prepare an Environmental Assessment for this supplemental submission because approval of this action would result in a concentration of the active moiety (calcium, magnesium, potassium, and sodium oxybates) in the aquatic environment of the United States below 1 part per billion (ppb); this claim is in accordance with the categorical exclusion criteria of 21 CFR 25.31(b). More specifically, the applicant states that this claim is based on a maximum yearly usage estimate for the drug substance, namely "30,720 kg/year", based on the 5-year forecast information. Based on this estimate, the expected introduction concentration (EIC) of an active moiety into the aquatic environment is "0.694 ppb". Moreover, the applicant certifies that "no extraordinary circumstances exist that may cause this action to have a significant effect on the quality of the human environment."

☑ **Reviewer Evaluation: Acceptable**

2. LABELING (1.14)

A. Draft Labeling (1.14.1)

A(i) Annoted Draft Labeling Text (1.14.1.2)

Comments: The submitted draft "United States Prescribing Information" (USPI) (annotated, tracked-changes) showed no changes to the CMC-related information included in Section "2 DOSAGE AND ADMINISTRATION". The submitted draft USPI (annotated, tracked-changes) showed no changes at all to Sections "3 DOSAGE FORMS AND STRENGTHS", "11 DESCRIPTION", and "16 HOW

SUPPLIED/STORAGE AND HANDLING"; all CMC-related information is same as the currently approved..

☑ **Reviewer Evaluation: Acceptable**

IV RISK ASSOCIATED WITH THE PROPOSED CHANGES AND IMPACT TO PRODUCT QUALITY AND PATIENT SAFETY

Low

Richard Matsuoka

Digitally signed by Richard Matsuoka
Date: 7/15/2021 04:49:54PM
GUID: 58405a2d00b8e6d18c2b669521269752

Gurpreet Gill Sangha

Digitally signed by Gurpreet Gill Sangha
Date: 7/15/2021 04:53:48PM
GUID: 5135f2ad000117842392c50c36c7f28a

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s006

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	212,690
Supplement #:	006
Drug Name:	XYWAV™ (JZP-258)
Indication(s):	Treatment of Idiopathic Hypersomnia (IH)
Applicant:	Jazz Pharmaceuticals
Date(s):	Submission date: 02/12/2021, PDUFA date: 08/12/2021
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Minjeong Park, Ph.D., Primary Reviewer
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader
	H.M. James Hung, Ph.D., Division Director
Medical Division:	Division of Neurology I
Clinical Team:	Mani Ranjit, M.D.
Project Manager:	Teresa Wheelous, PharmD.

Keywords: ANCOVA, CMH, Nonparametric ANCOVA

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1 EXECUTIVE SUMMARY

Jazz Pharmaceuticals submitted one phase 3 study (JZP080-301) to support the claim of the efficacy, safety and PK of JZP-258 oral solution in adult subjects aged 19-75 years having a primary diagnosis of idiopathic hypersomnia. In the primary analysis on the change in ESS from the end of stable dose period (SDP) to the end of double-blind withdrawal period (DBRWP), the least square (LS) mean difference between JZP-258 versus placebo was statistically significant (-6.51, 95% CI: [-7.99, -5.03], p-value < 0.0001), indicating a greater treatment effect in JZP-258 compared to the placebo. Both key secondary analyses also showed statistically significantly greater treatment effects in JZP-258 compared to the placebo (p-value < 0.0001 for both). Findings from efficacy evaluation in the phase 3 confirmatory study (JZP080-301) support a greater treatment effect of JZP-258 compared to the placebo in ESS, PGIc and IHSS.

2 INTRODUCTION

2.1 Overview

This application contains one phase 3 confirmatory study. It is a double-blind, placebo-controlled, randomized withdrawal, multicenter study to investigate the efficacy, safety and PK of JZP-258 oral solution with an open-label safety extension period.

Table 1. Summary of study included in analysis

Protocol No.	Phase and Design	Treatment Period	# of Subjects randomized per Arm	Study Population
JZP080-301	DB, PC, RW, MC	Open-label Treatment Titration and Optimization Period: 10-14 weeks Stable Dose Period: 2 weeks Double-blind Randomized Withdrawal Period: 2 weeks	JZP-258: 57 Placebo: 59	Subjects aged 19-75 years, having a primary diagnosis of IH according to the ICSD-2 or ICSD-3 criteria. Subjects who are not on Xyrem at the study entry must have Epworth Sleepiness Scale (ESS) scores ≥11 and those who are treated with Xyrem must have documented clinical improvement of excessive daytime sleepiness (EDS) after the initiation of Xyrem. Subjects who have average nightly total sleep time (TST) of ≥7 hours, per subject history.

** DB: double-blind, PC: placebo-controlled, RW: randomized withdrawal, MC: multi-center*

2.2 Data Sources

All documents reviewed for this supplement submission are in electronic form.
The electronic location of the submission is \\CDSESUB1\evsprod\NDA212690\0085\m5 .

SDTM located at: \\CDSESUB1\evsprod\NDA212690\0085\m5\datasets\jzp080-301\tabulations\sdtm
ADaM located at: \\CDSESUB1\evsprod\NDA212690\0085\m5\datasets\jzp080-301\analysis\adam\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

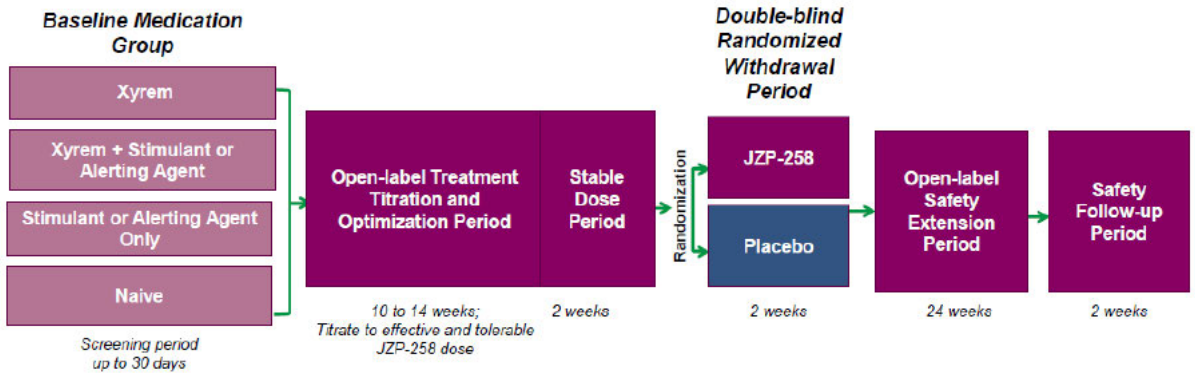
The sponsor submitted all necessary analysis datasets and SAS programs. This reviewer found the datasets acceptable. With these, this reviewer verified the analysis datasets and the primary results from the clinical study report.

3.2 Evaluation of Efficacy in JZP080-301

3.2.1 Study Design and Endpoints

Study JZP080-301 is a phase 3, double-blind, placebo-controlled, randomized withdrawal, multicenter study with an open-label safety extension period. The study was designed to evaluate the efficacy, safety and PK of JZP-258 oral solution in adult subjects with idiopathic hypersomnia (IH). Subjects included those being treated at study entry with or without Xyrem and treated with or without stimulants/alerting agents (AAs). The study comprised 6 periods, screening for 14-30 days (with the option to rescreen once), open-label treatment titration and optimization period (OTTP) for 10-14 weeks to maximize efficacy while ensuring adequate nocturnal sleep and minimizing risk associated with safety and tolerability, stable dose period for 2 weeks, double-blind randomized withdrawal for 2 weeks, open-label safety extension (OLE) for 24 weeks, safety follow-up for 2 weeks (Figure 1).

Figure 1. Study design



Abbreviations: OL = Open-label; OTTP = Open-label Treatment Titration and Optimization Period; PK = Pharmacokinetics
A subset of 28 participants participated in a single overnight PK evaluation during either the OTTP or the OL Safety Extension Period. The PK evaluation night occurred on any night during one of the two periods, but preferably during one of the scheduled in-clinic visits.
The OTTP occurred over a period of 10 to 14 weeks. Every effort was made to titrate to an optimally effective and tolerable dose and regimen within the first 10 weeks. For participants requiring additional titration, with approval from the Medical Monitor, up to an additional 4 weeks of titration/adjustment was performed.
Source: Figure 2 on page 25 of Clinical Study Report.

The primary efficacy endpoint is the change in Epworth Sleepiness Scale (ESS) score from the end of stable dose period (SDP) to the end of double-blind randomized withdrawal period (DBRWP). The ESS is a self-administered questionnaire with 8 questions asking the subjects how likely they would be to doze off or fall asleep in different situations. Responses range from

0 (would never doze) to 3 (high chance of dozing). The ESS total score is the sum of the 8 item-scores and can range between 0 and 24. Higher scores indicate greater daytime sleepiness. The key secondary endpoints are 1) proportion of subjects reported as worse (minimally, much or very much) on the patient global impression of change (PGIc) at the end of DBRWP and 2) change in total score of idiopathic hypersomnia severity scale (IHSS) from the end of the SDP to the end of the DBRWP. The PGIc is a 7-point Likert-type rating scale ranging from 1 (very much improved) to 7 (very much worse), and subjects rated the change in their condition at the end of the DBRWP compared to the end of the SDP. The IHSS is a 14-item self-reported questionnaire that assesses the severity of IH. Questions capture symptoms of excessive sleepiness, sleep inertia, and sleep duration. Symptom frequency, intensity, and consequences are rated using a 3- or 4-point Likert scale, providing total score that range from 0 to 50. Higher scores indicate more severe and frequent symptoms. Other secondary endpoints are the proportion of subjects reported as worse (minimally, much or very much) on clinical global impression of change (CGIc) at the end of the DBRWP and the change in total score of functional outcomes of sleep questionnaire (FOSQ-10) from the end of the SDP to the end of the DBRWP.

3.2.2 Statistical Methodologies

Sponsor's Methods

Power and sample size considerations

A sample size of 56 subjects randomized per treatment group (total randomized sample size of 112 subjects) will provide 91.8% power to detect a difference of 3.5 points for the change in ESS between JZP-258 and placebo, from the end of the SDP to the end of the DBRW. This study was originally designed to include an optional interim analysis (IA) for efficacy; thus, calculations were based on the following: a 2-sample Z test with a group-sequential design including one IA at 60% information fraction using Lan-Demets alpha spending function that approximates the O'Brien-Fleming boundaries, a common standard deviation (SD) of 5.5 points in the change in ESS for both arms, and a 2-sided significance level of 0.05. Assuming a 20% dropout rate prior to randomization, approximately 140 subjects will be enrolled. However, the Jazz study team decided not to perform the IA due to it not being operationally feasible, as full study recruitment has been achieved faster than originally anticipated.

Analysis sets

In this study, the safety evaluation set (SES) included all subjects who took at least one dose of study drug, the modified intent-to-treat (mITT) analysis set included all randomized subjects who received at least one dose of double-blind study drug and had at least one set of post-randomization efficacy assessment for ESS or IHSS, or a PGIc value at the end of the DBRWP. The mITT analysis set was used for analyzing efficacy endpoints (primary, secondary, and exploratory). This report only includes the results from primary and key secondary efficacy analyses.

Efficacy analyses

For the main analysis of the primary endpoint, an analysis of covariance (ANCOVA) was performed. The model included the change in ESS from the end of the SDP to the end of the

DBRWP as the dependent variable; the treatment group and baseline medication group as fixed effects as well as the ESS score at the end of SDP (baseline) as a covariate. If one or two ESS item scores are missing at a specific time point, the mean of the remaining seven or six non-missing ESS item scores (no more than 3 missings) at that time point was used to impute the missing ESS item value. If the ESS total score at the SDP and/or DBRWP is still missing after the imputation of ESS item values as specified, the subject was excluded from the primary analysis. All group comparisons from the ANCOVA model was based on Type III sum of squares. Least square (LS) mean and standard error (SE) was provided for each treatment group. The difference between these two LS means along with the SE of the difference, 95% confidence interval (CI) and associated p-value corresponding to testing the hypothesis of no difference between the treatment groups was provided. The normality assumption of the ANCOVA model was examined by residual analysis using the Shapiro-Wilk test at a 0.05 significance level.

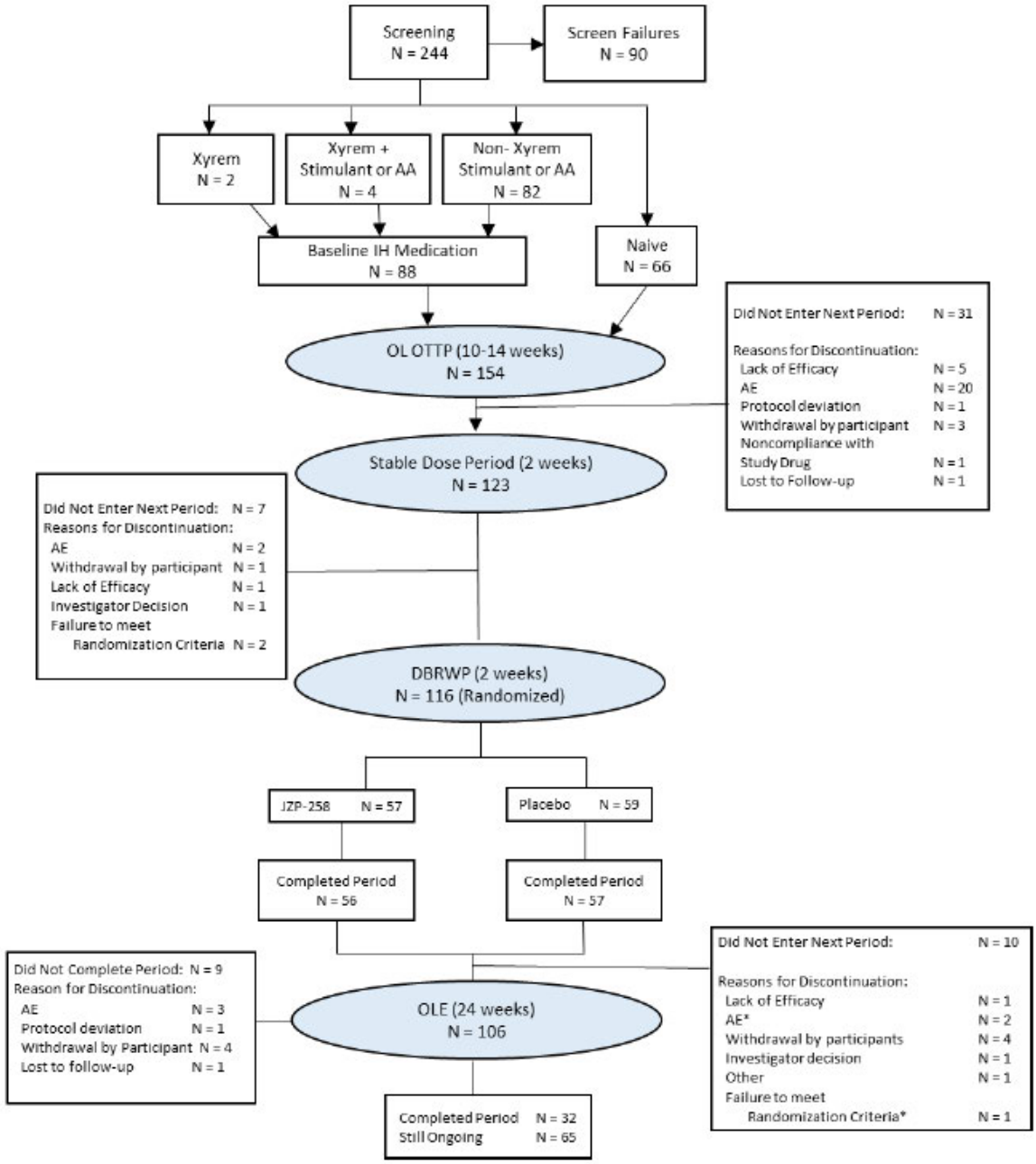
The first key secondary efficacy endpoint is defined as the proportion of subjects reporting worsening of symptoms (minimally, much or very much worse) on PGIc at the end of the DBRW. The proportion of subjects reporting worsening of symptoms on PGIc was compared between groups using the Cochran-Mantel-Haenszel (CMH) test (based on the PGIc binary endpoint) stratified by baseline medication group. The point estimate and continuity corrected Wilson's 95% CI (as modified by Newcombe) for the difference of the proportion were provided.

The other key secondary efficacy endpoint is the change in total IHSS score from the end of the SDP to the end of the DBRW. The IHSS total score is the sum of the 14 item-scores. Item 14 was scored as "0" (no problem) for subjects who indicate they do not drive. If four or more item scores were missing at a specific time point, the IHSS total score was set to missing. If less than four IHSS item scores were missing at a specific time point, then impute each missing item by multiplying the missing item's maximum response value by the average of the remaining non-missing items proportion of maximum response. This is described as follows:
Let Q_i be the score and M_i be the maximum possible score for each of the observed response for 14 items ($i \in \Psi = \{1,2,\ldots, 14\}$). If the total number of items missing were less than 4 and M_j represents the maximum score for the missing item, then the score for each missing item Q_j, ($j \in \Omega = \{l_1, l_2, \ldots, l_N\}$), was imputed as $Q_j = M_j * (\sum_{i \in \Psi} \frac{Q_i}{M_i}) / (14 - N), j \in \Omega$. Note that the maximum possible score can be either 3 or 4 depending on the specific question. The IHSS total score was then calculated as the sum of the observed and imputed item scores as follows: $S = \sum_{i \in \Psi \setminus \Omega} Q_i + \sum_{j \in \Omega} Q_j$. The change in IHSS total score was attempted to be analyzed similarly to the primary efficacy endpoint which used the ANCOVA, however, a non-parametric ANCOVA with the covariate and response variable replaced by their ranks was used in the final analysis since the normality assumption was considered violated. The ranks were used in the ANCOVA with the rank for the change from baseline as the dependent variable, treatment and baseline medication group as fixed effects, and the rank for ESS score at the end of SDP as a covariate. The estimated median difference between the change in IHSS between the two treatment groups and asymptotic 95% confidence intervals were presented using Hodges-Lehman estimator. P-value was from the rank-based ANCOVA.

3.2.3 Patient Disposition, Demographic

Among 244 subjects screened, 154 subjects were entered open-label OTTP. A total of 116 subjects of whom entered SDP (N=123) were randomized to treatment in the DBRWP; 57 subjects to JZP-258, 59 subjects to placebo. Among subjects who completed the DBRWP, 106 entered OLE period and 32 subjects were completed and 65 subjects were still ongoing at the moment of this document reported.

Figure 2. Patient disposition



Abbreviations: AA=alerting agent; AE=adverse event; DBRWP=Double-blind Randomized Withdrawal Period; OLE=Open-Label Extension Period; OL OTTP=Open-label Treatment Titration and Optimization Period

There were 10 randomized subjects who did not enter the OLE (3 subjects discontinued during the DBRWP and 7 subjects discontinued after completing the DBRWP).
*Indicates cases who discontinued during the DBRWP.
Source: Figure 3 on page 34 of Clinical Study Report, verified by the reviewer using sponsor's data (ds.xpt)

There was a total of 8 analysis sets, and the number of subjects included in each analysis set is summarized by the baseline medication group in Table 2.

Table 2. Analysis sets by Baseline Medication Group (Enrolled Analysis Set)

Study Period Analysis Set	Statistic	On Baseline IH Medication at Study Entry (N = 88)	Naïve (N = 66)	Total (N = 154)
Enrolled Analysis Set	n (%)	88 (100)	66 (100)	154 (100)
Safety Analysis Set	n (%)	88 (100)	66 (100)	154 (100)
PK Analysis Set	n (%)	14 (15.9)	14 (21.2)	28 (18.2)
SDP Safety Analysis Set	n (%)	71 (80.7)	52 (78.8)	123 (79.9)
Randomized Participants Analysis Set	n (%)	69 (78.4)	47 (71.2)	116 (75.3)
DBRWP Safety Analysis Set	n (%)	69 (78.4)	47 (71.2)	116 (75.3)
mITT Analysis Set	n (%)	68 (77.3)	47 (71.2)	115 (74.7)
OLE Safety Analysis Set	n (%)	65 (73.9)	41 (62.1)	106 (68.8)

Abbreviations: DBRWP = Double-blind Randomized Withdrawal Period; ENR = Enrolled Analysis Set; ESS = Epworth Sleepiness Scale; IH = idiopathic hypersomnia; IHSS = Idiopathic Hypersomnia Severity Scale; mITT = modified intent-to-treat; OL = Open-Label; OLE = Open-Label Extension Period; PGIc = Patient Global Impression of Change; PK = pharmacokinetics; SAF = Safety Analysis Set; SDP = Stable Dose Period
Percentages were based on the total number reported in each column (N).
The ENR was defined as all participants who provided a signed informed consent form for this study and were deemed as meeting the inclusion/exclusion criteria of this study by the investigator and were dispensed study drug.
The SAF included all participants who took at least one dose of study drug.
The PK Analysis Set included all participants who received JZP-258 and have any evaluable PK data from at least 1 post-dose sample.
The SDP Safety Analysis Set included all participants in the ENR who took at least one dose of OL study drug during the SDP.
The Randomized Analysis Set included all participants randomized.
The DBRWP Safety Analysis Set included all participants who received at least one dose of double-blind study drug.
The mITT Analysis Set included all randomized participants who received at least one dose of double-blind study drug and had at least one set of post-randomization efficacy assessment for ESS or IHSS, or a PGIc value at the end of the DBRWP.
The OLE Safety Analysis Set contained all participants in the ENR who took at least one dose of OL study drug during the OLE.
The On Baseline IH (Idiopathic Hypersomnia) Medication Group includes participants who were on Xyrem and/or a stimulant or alerting agent at study entry. The Treatment Naïve group includes participants not on Xyrem or a stimulant or alerting agent at study entry.
Source: Table 7 on page 36 in Clinical Study Report, verified by the reviewer using data provided by sponsor (adsl.xpt)

The demographic results by treatment group for the mITT analysis set are shown in Table 3. A majority of subjects were White, were non-Hispanic and were female. Randomization was stratified by baseline medication group and this table shows that baseline medication groups were well-balanced between two treatment arms.

Table 3. Demographic and Other Baseline Characteristics by Randomized Treatment Group (mITT Analysis Set)

Characteristic	Randomized Treatment Group		
	JZP-258 (N=56)	Placebo (N=59)	Total (N=115)
Age (years)			
n	56	59	115
Mean (SD)	43.4 (14.44)	38.5 (13.01)	40.9 (13.88)
Median (Q1, Q3)	43.0 (31.0, 52.5)	35.0 (28.0, 44.0)	39.0 (29.0, 52.0)
Min., Max.	19, 72	21, 75	19, 75
Gender			
Male	17 (30.4)	16 (27.1)	33 (28.7)
Female	39 (69.6)	43 (72.9)	82 (71.3)
Race			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	3 (5.4)	4 (6.8)	7 (6.1)
Native Hawaiian or Other Pacific Islander	0	1 (1.7)	1 (0.9)
White	48 (85.7)	45 (76.3)	93 (80.9)
Decline to state	5 (8.9)	8 (13.6)	13 (11.3)
Multiple[A]	0	1 (1.7)	1 (0.9)
Ethnicity			
Hispanic or Latino	8 (14.3)	4 (6.8)	12 (10.4)
Not Hispanic or Latino	44 (78.6)	47 (79.7)	91 (79.1)
Decline to state	4 (7.1)	8 (13.5)	12 (10.5)
Body Mass Index (kg/m2) at Baseline			
n	56	59	115
Mean (SD)	28.7 (9.69)	27.2 (6.14)	27.9 (8.06)
Median (Q1, Q3)	26.6 (23.4, 31.3)	26.3 (22.5, 30.3)	26.3 (23.0, 30.5)
Min., Max.	18.1, 84.2	18.3, 46.0	18.1, 84.2
Region			
North America	35 (62.5)	42 (71.2)	77 (67.0)
Europe	21 (37.5)	17 (28.8)	38 (33.0)
Baseline Medication Group			
Xyrem	2 (3.6)	4 (6.8)	6 (5.2)
Xyrem only	1 (1.8)	1 (1.7)	2 (1.7)
Xyrem + Stimulant or AA	1 (1.8)	3 (5.1)	4 (3.5)
Non-Xyrem	54 (96.4)	55 (93.2)	109 (94.8)
Stimulant or AA	31 (55.4)	31 (52.5)	62 (53.9)
Treatment Naïve	23 (41.1)	24 (40.7)	47 (40.9)

Abbreviations: AA=alerting agent; DBRWP=Double-blind Randomized Withdrawal Period; ESS=Epworth Sleepiness Scale, IHSS=Idiopathic Hypersomnia Severity Scale; LS=lease square; max=maximum; min=minimum; mITT=modified intent-to-treat; OL=Open label; PGIc=Patient Global Impression of Change; Q1=quarter 1; Q3=quarter 3; SD=standard deviation;
[A] Subjects who reported more than on race.
Baseline was defined as the last non-missing assessment collected prior to or on the same day than the first dose of study drug, including unscheduled assessments.
Percentages were based on the total number of subjects in the Analysis Set reported in each column.
Source: Reviewer using data provided by sponsor (adsl.xpt)

3.2.4 Efficacy Results

3.2.4.1 Primary Endpoint

Change in ESS from the end of SDP to the end of DBRWP

Descriptive statistics of ESS total scores were summarized for each period by treatment group in Table 4. The mean and median ESS score at the end of the SDP were similar between the treatment groups with the difference of 0.5 in both mean and median. At the end of the DBRWP, subjects randomized to continue JZP-258 reported small mean increase (0.7), while those randomized to placebo reported a larger increase (7.4) in mean ESS score indicating worsening of excessive daytime sleepiness (also see Figure 3). Table 4 also shows LS mean, SE, LS mean difference between two treatment groups and its 95% confidence intervals which were obtained from the ANCOVA model including the change in ESS total score from the end of SDP to the end of DBRWP as a response variable, and baseline medication group, treatment group and ESS total score at the end of SDP as covariates. There was a statistically significant difference in the change in ESS scores between two treatment groups, indicating a greater treatment effect in JZP-258 compared to the placebo (p-value < 0.0001).

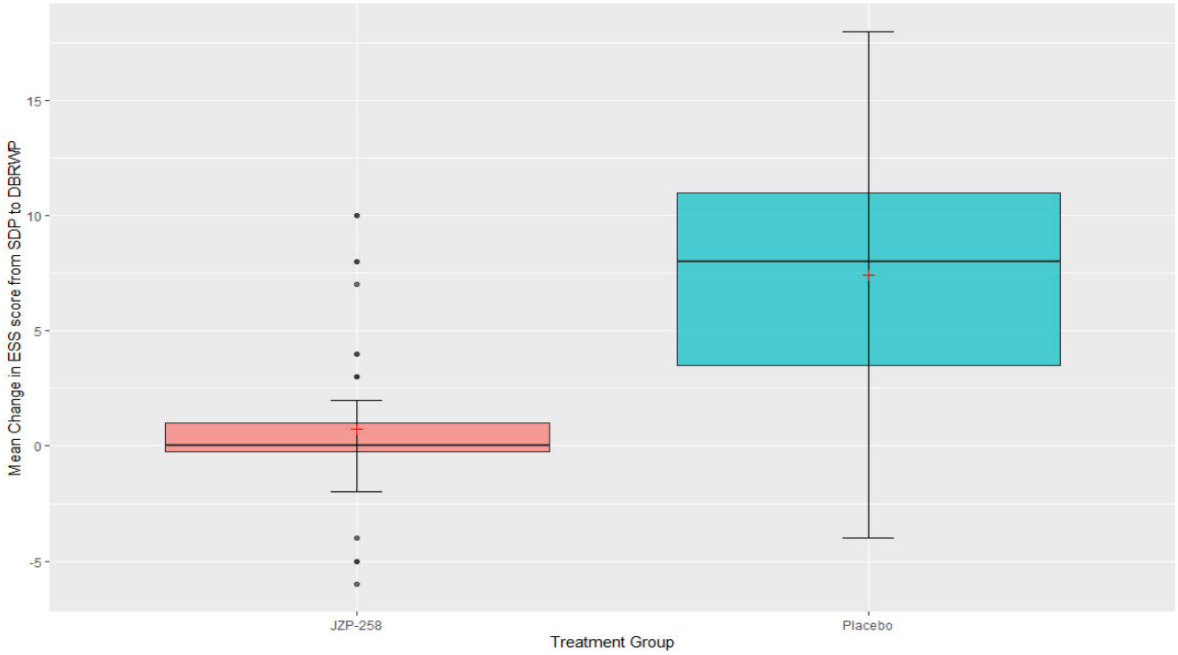
Table 4. Primary Efficacy Endpoint: Change in ESS from the end of SDP to the end of DBRWP by Randomized Treatment Group (mITT Analysis Set)

	Randomized Treatment Group		
Timepoint	**JZP-258 (N=56)**	**Placebo (N=59)**	**Total (N=115)**
End of the Stable Dose Period			
N	56	59	115
Mean (SD)	6.3 (4.33)	5.8 (3.66)	6.1 (3.99)
Median	6.5	5.0	6.0
Q1, Q3	2.0, 9.5	3.0, 8.0	3.0, 8.0
Min., Max.	0, 15	0, 17	0, 17
End of the Double-Blind Randomized Withdrawal Period			
N	56	59	115
Mean (SD)	7.0 (5.03)	13.3 (4.06)	10.2 (5.52)
Median	7.0	14.0	10.0
Q1, Q3	3.0, 10.0	11.0, 16.0	6.0, 14.0
Min., Max.	0, 21	3, 21	0, 21
Change from the End of the Stable Dose Period to the End of the Double-Blind Randomized Withdrawal Period			
N	56	59	115
Mean (SD)	0.7 (3.22)	7.4 (5.16)	4.2 (5.47)
Median	0	8.0	2.0
Q1, Q3	-0.5, 1.0	3.0, 11.0	0, 9.0
Min., Max.	-6, 10	-4, 18	-6, 18

LS Mean	0.83	7.34	
SE	0.538	0.526	
LS Mean Diff	-6.51		
SE	0.747		
95% CI	(-7.99, -5.03)		
p-value	< 0.0001		

Abbreviations: CI=confidence interval; DBRWP=Double-blind Randomized Withdrawal Period; ESS=Epworth Sleepiness Scale, LS=lease square; max=maximum; min=minimum; mITT=modified intent-to-treat; OL=Open label; Q1=quarter 1; Q3=quarter 3; SD=standard deviation; SDP=Stable Dose Period; SE=standard error
The LS mean, SE, LS Mean Difference, 95% CI and p-values have been obtained from an analysis of covariance model including the change in ESS total score from the end of the OL SDP to the end of the DBRWP as response variable. Covariates in the model included: baseline medication group, treatment group and ESS total score at the end of the OL SDP.
Source: Reviewer using data provided by sponsor (adqsess.xpt)

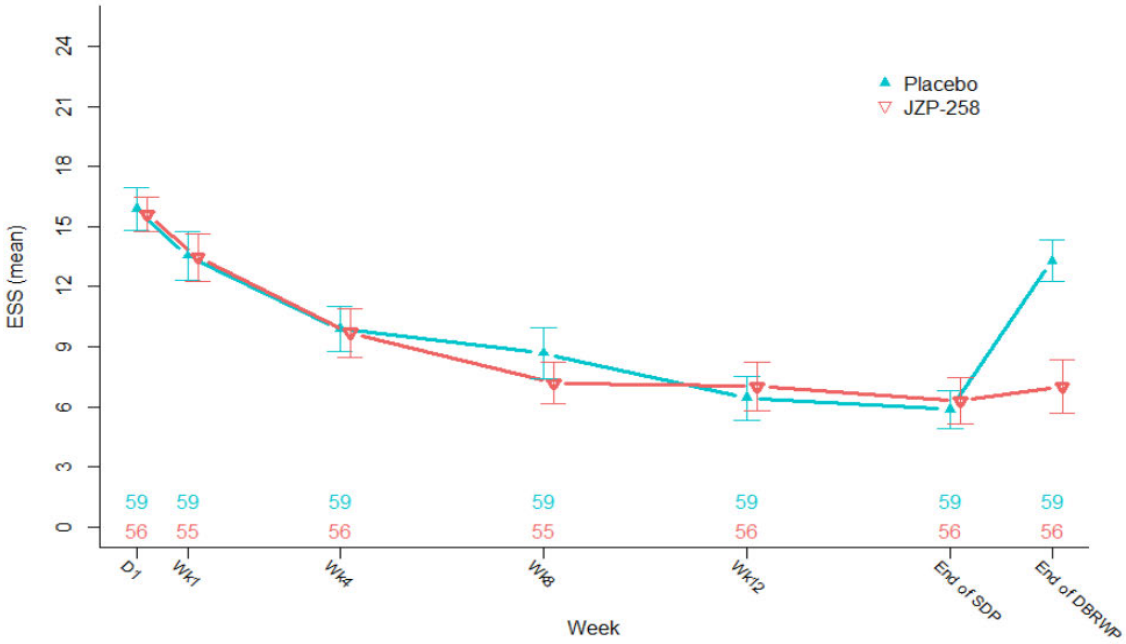
Figure 3. Primary Efficacy Endpoint: Box Plot of the Change in ESS from the end of SDP to the end of DBRWP by Randomized Treatment Group (mITT Analysis Set)



Abbreviations: DBRWP=Double-blind Randomized Withdrawal Period; ESS=Epworth Sleepiness Scale; mITT=modified intent-to-treat; Q1=quartile 1; Q3=quartile 3.
The bottom and top edges of the box indicate the 1st and 3rd quartiles [Q1 and Q3, IQR=Q3-Q1]. The line inside the box is the median and the marker inside the box is the mean. The upper and lower whisker extend Q3+1.5*IQR, Q1-1.5*IQR, respectively. Any points that are a distance of more than 1.5*IQR from the box are considered outliers.
Source: Reviewer using data provided by sponsor (adqsess.xpt)

Figure 4 shows the mean ESS score and its 95% CIs overtime from Day 1 of OTTP to the end of DBRWP by randomized treatment group. Mean ESS scores were similar at Day 1 of OTTP through the end of SDP between two groups, showing improvement over time. The placebo group showed increase (worsening) in mean ESS score during DBRWP, while JZP-258 group retained the mean ESS score which is similar to one at the end of SDP.

Figure 4. Mean ESS over time from Day 1 of OTTP to the end of DBRWP by Randomized Treatment Group (mITT Analysis Set)



Abbreviations: OTTP= Open-label treatment titration and optimization period; DBRWP=Double-blind Randomized Withdrawal Period; ESS=Epworth Sleepiness Scale; IHSS=Idiopathic Hypersomnia Severity Scale; mITT=modified intent-to-treat.
Source: Reviewer using data provided by sponsor (adqsess.xpt)

3.2.4.2 Key Secondary Endpoints

3.2.4.2.1 Patient Global Impression of Change for IH Overall

Table 5 shows the number and percentage of PGIc for each category and dichotomized category (worsened vs. the rest) at the end of the DBRWP. The percentage of subjects with worsened PGIc scores (minimally, much, or very much worse) was statistically significantly greater in placebo (88.1%), when compared to JZP-258 group (21.4%; p-value < 0.0001) (Table 5).

Table 5. Key Secondary Efficacy Endpoint: PGIc at the end of DBRWP by Randomized Treatment Group (mITT Analysis set)

	Randomized Treatment Group		
Variable Category	**JZP-258 (N=56)**	**Placebo (N=59)**	**Total (N=115)**
PGIc at the end of the Double-Blind Randomized Withdrawal Period (n (%))			
Very much improved	5 (8.9)	0	5 (4.3)
Much improved	13 (23.2)	3 (5.1)	16 (13.9)
Minimally improved	3 (5.4)	1 (1.7)	4 (3.5)
No change	23 (41.1)	3 (5.1)	26 (22.6)
Minimally worse	9 (16.1)	14 (23.7)	23 (20.0)
Much worse	2 (3.6)	22 (37.3)	24 (20.9)
Very much worse	1 (1.8)	16 (27.1)	17 (14.8)

Proportion Worsened (minimally, much or very much worse)	12 (21.4)	52 (88.1)	64 (55.7)
Difference in Proportion	-0.67		
95% CI	(-0.78, -0.49)		
p-value	< 0.0001		

Abbreviations: CI=confidence interval; CMH=Cochran-Mantel-Haenszel; DBRWP=Double-blind Randomized Withdrawal Period; mITT=modified intent-to-treat; PGIc=Patient Global Impression of Change; SDP=Stable Dose Period.
Continuity corrected Wilson's 95% CI as modified by Newcombe were presented for the difference in proportion.
The p-value for comparing the proportion worsened on the PGIc between treatment groups is from CMH test stratified by baseline medication group.
Source: Reviewer using data provided by sponsor (adqgi.xpt)

3.2.4.2.2 Idiopathic Hypersomnia Severity Scale

There were larger increases in total IHSS score from the end of the SDP to the end of the DBRWP in placebo compared to JZP-258 (13.3 vs 1.5 in means; 14.0 vs 0.0 in medians). It resulted in a statistically significant median difference between two groups (p-value <0.0001) (Table 6). Increases in IHSS score mean worsening of symptoms, hence, the results in Table 6 show a greater treatment effect of JZP-258 compared to placebo.

Table 6. Key Secondary Efficacy Endpoint: Change in IHSS from the end of SDP to the end of DBRWP by Randomized Treatment Group (mITT Analysis set)

	Randomized Treatment Group		
Timepoint	**JZP-258 (N=56)**	**Placebo (N=59)**	**Total (N=115)**
End of the Stable Dose Period			
N	56	59	115
Mean (SD)	15.5 (9.20)	15.2 (7.78)	15.3 (8.46)
Median	14.0	14.0	14.0
Q1, Q3	7.0, 22.0	10.0, 21.0	8.0, 21.0
Min., Max.	1, 39	2, 37	1, 39
End of the Double-Blind Randomized Withdrawal Period			
N	56	59	115
Mean (SD)	16.9 (8.09)	28.5 (8.96)	22.9 (10.30)
Median	16.0	29.0	23.0
Q1, Q3	11.0, 23.0	23.0, 34.0	15.0, 30.0
Min., Max.	1, 34	8, 49	1, 49
Change from the End of the Stable Dose Period to the End of the Double-Blind Randomized Withdrawal Period			
N	56	59	115
Mean (SD)	1.5 (5.82)	13.3 (9.29)	7.5 (9.768)
Median	0.0	14.0	4.0
Q1, Q3	-2.0, 2.5	4.0, 19.0	0.0, 15.0
Min., Max.	-8, 24	-2, 38	-8, 38

Estimated median difference	-12.0	
95% CI	(-15.0, -8.0)	
p-value	< 0.0001	

Abbreviations: CI=confidence interval; DBRWP=Double-blind Randomized Withdrawal Period; IHSS=Idiopathic Hypersomnia Severity Scale; max=maximum; min=minimum; mITT=modified intent-to-treat; OL=Open label; Q1=quarter 1; Q3=quarter 3; SD=standard deviation; SDP=Stable Dose Period.
The estimated median difference between two treatment groups and 95% asymptotic CI are from Hodges-Lehmann estimate. The p-value has been obtained from a rank based on analysis of covariance model including the rank change in IHSS from the end of the OL SDP to the end of the DBRWP as the response variable; Covariates in the model included: baseline medication group, treatment group and ranked IHSS total score at the end of the OL SDP.
Source: Reviewer using data provided by sponsor (adqsihss.xpt)

3.2.4.3 Sensitivity Analysis

No sensitivity analysis was performed since there was no dropout with missing assessment in the mITT analysis set population during the DBRWP.

3.3 Evaluation of Safety

This review does not evaluate safety. Please refer to the clinical review for an evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section contains the results of reviewer's subgroup analyses. Each subgroup analysis was analyzed similarly to the primary and key secondary efficacy analysis with the exception that for the baseline medication group analyses, the baseline medication group fixed effect was excluded from the ANCOVA models. Each subgroup result was also displayed in figures.

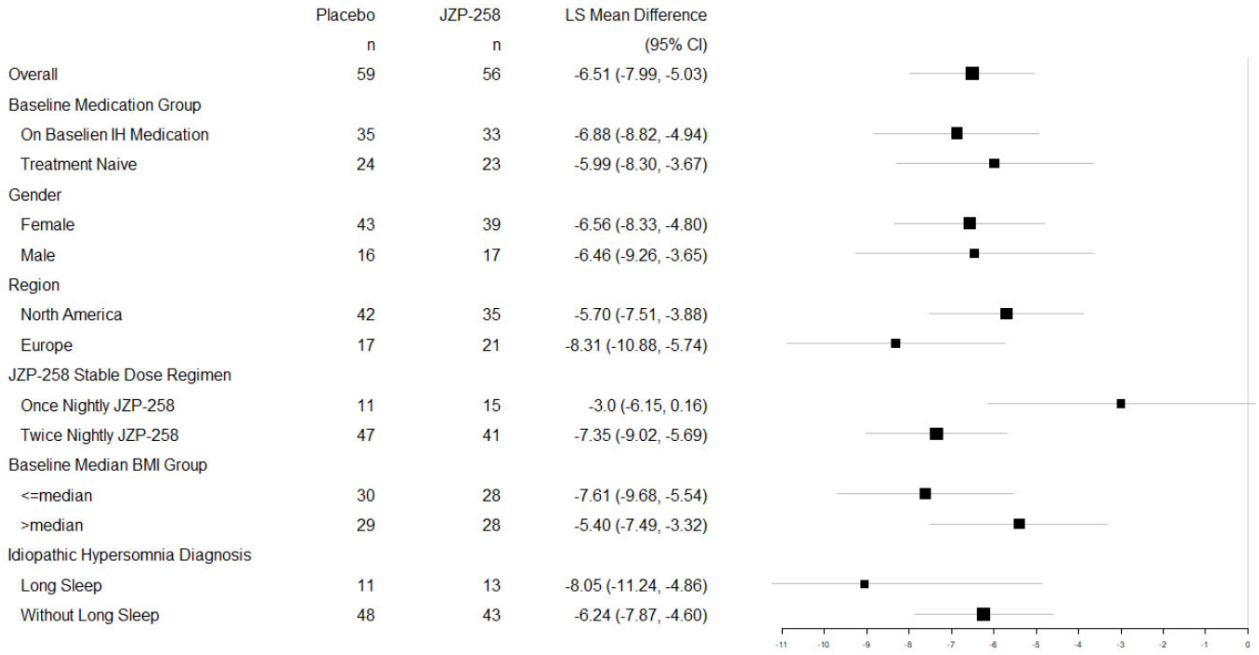
Table 7. Subgroup Analysis: Change in ESS from the end of SDP to the end of DBRWP by Randomized Treatment Group (mITT Analysis set)

Subgroup		Treatment Arm	Sample Size	Baseline Mean at the end of SDP (SD)	LS Mean Difference from Baseline (SE)	LS Mean Difference from Placebo (95% CI)
Baseline Medication Group	On Baseline IH Medication	JZP-258	33	6.9 (4.53)	0.58 (0.69)	-6.88 (-8.82, -4.94)
		Placebo	35	5.8 (3.76)	7.46 (0.68)	--
	Treatment Naïve	JZP-258	23	5.5 (3.99)	1.16 (0.83)	-5.99 (-8.30, -3.67)
		Placebo	24	5.9 (3.59)	7.14 (0.81)	--
Gender	Female	JZP-258	39	6.0 (4.34)	0.58 (0.66)	-6.56 (-8.33, -4.80)
		Placebo	43	5.9 (3.78)	7.14 (0.62)	--
	Male	JZP-258	17	7.1 (4.32)	1.37 (0.98)	-6.46 (-9.26, -3.65)
		Placebo	16	5.8 (3.41)	7.83 (1.01)	--
Region	North America	JZP-258	35	7.3 (4.24)	1.09 (0.70)	-5.70 (-7.51, -3.88)
		Placebo	42	6.2 (3.53)	6.78 (0.63)	--
	Europe	JZP-258	21	4.6 (4.02)	0.37 (0.88)	-8.31 (-10.88, -5.74)
		Placebo	17	5.1 (3.96)	8.68 (0.97)	--
JZP-258 stable dose regimen	Once Nightly	JZP-258	15	8.0 (4.78)	1.80 (1.04)	-3.0 (-6.15, 0.16)
		Placebo	11	4.4 (1.86)	4.80 (1.20)	--
	Twice Nightly	JZP-258	41	5.7 (4.03)	0.45 (0.63)	-7.35 (-9.02, -5.69)
		Placebo	47	6.3 (3.86)	7.80 (0.58)	--
Baseline Median BMI	≤ median	JZP-258	28	6.0 (3.78)	0.77 (0.76)	-7.61 (-9.68, -5.54)
		Placebo	30	5.2 (3.47)	8.38 (0.75)	--
	> median	JZP-258	28	6.6 (4.86)	0.91 (0.75)	-5.40 (-7.49, -3.32)
		Placebo	29	6.5 (3.79)	6.32 (0.74)	--
Idiopathic Hypersomnia Diagnosis	Long sleep	JZP-258	13	5.2 (4.17)	1.74 (1.09)	-8.05 (-11.24, -4.86)
		Placebo	11	5.3 (3.0)	9.79 (1.19)	--
	Without Long Sleep	JZP-258	43	6.6 (4.37)	0.51 (0.61)	-6.24 (-7.87, -4.60)
		Placebo	48	6.0 (3.81)	6.74 (0.58)	--

Abbreviations: ESS=Epworth Sleepiness Scale; SDP=Stable Dose Period; DBRWP=Double-blind Randomized Withdrawal Period; LS=lease square; CI=confidence interval; max=maximum; min=minimum; mITT=modified intent-to-treat; SD=standard deviation; SE=standard error.

Source: Reviewer using data provided by sponsor (adqsess.xpt)

Figure 5. Forest Plot of Subgroup Analysis: Change in ESS from the end of SDP to the end of DBRWP by Randomized Treatment Group (mITT Analysis set)



Abbreviations: ESS=Epworth Sleepiness Scale; LS=lease square; CI=confidence interval; SDP= Stable Dose Period; DBRWP=Double-Blind Randomized Withdrawal Period; mITT=modified intent-to-treat.
Source: Reviewer using data provided by sponsor (adqsess.xpt)

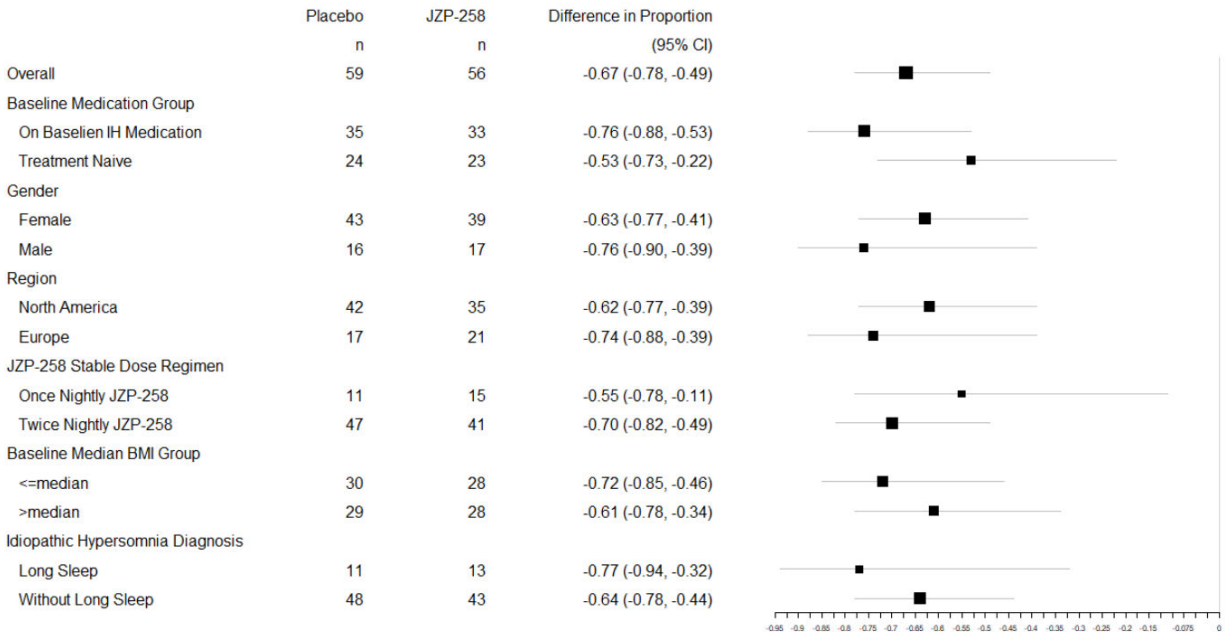
Table 8. Subgroup Analysis: PGIc at the end of DBRWP by Randomized Treatment Group (mITT Analysis set)

Subgroup		Treatment Arm	Sample Size	Difference In Proportion (95% CI)
Baseline Medication Group	On Baseline IH Medication	JZP-258	33	-0.76 (-0.88, -0.53)
		Placebo	35	--
	Treatment Naïve	JZP-258	23	-0.53 (-0.73, -0.22)
		Placebo	24	--
Gender	Female	JZP-258	39	-0.63 (-0.77, -0.41)
		Placebo	43	--
	Male	JZP-258	17	-0.76 (-0.90, -0.39)
		Placebo	16	--
Region	North America	JZP-258	35	-0.62 (-0.77, -0.39)
		Placebo	42	--
	Europe	JZP-258	21	-0.74 (-0.88, -0.39)
		Placebo	17	--
JZP-258 stable dose regimen	Once Nightly	JZP-258	15	-0.55 (-0.78, -0.11)
		Placebo	11	--
	Twice Nightly	JZP-258	41	-0.70 (-0.82, -0.49)
		Placebo	47	--

Subgroup		Treatment Arm	Sample Size	Difference In Proportion (95% CI)
Baseline Median BMI	≤ median	JZP-258	28	-0.72 (-0.85, -0.46)
		Placebo	30	--
	> median	JZP-258	28	-0.61 (-0.78, -0.34)
		Placebo	29	--
Idiopathic Hypersomnia Diagnosis	Long sleep	JZP-258	13	-0.77 (-0.94, -0.32)
		Placebo	11	--
	Without Long Sleep	JZP-258	43	-0.64 (-0.78, -0.44)
		Placebo	48	--

Abbreviations: CI=confidence interval; CMH=Cochran-Mantel-Haenszel; SDP=Stable Dose Period; DBRWP=Double-blind Randomized Withdrawal Period; mITT=modified intent-to-treat; PGIc=Patient Global Impression of Change.
Continuity corrected Wilson's 95% CI as modified by Newcombe were presented for the difference in proportion.
The p-value for comparing the proportion worsened on the PGIc between treatment groups is from CMH test stratified by baseline medication group.
Source: Reviewer using data provided by sponsor (adqgi.xpt)

Figure 6. Forest Plot of Subgroup Analysis: PGIc at the end of DBRWP by Randomized Treatment Group (mITT Analysis set)



Abbreviations: mITT=modified intent-to-treat; PGIc=Patient Global Impression of Change; DBRWP=Double-Blind Randomized Withdrawal Period; CI=confidence interval.
Source: Reviewer using data provided by sponsor (adqgi.xpt)

Table 9. Subgroup Analysis: Change in IHSS from the end of SDP to the end of DBRWP by Randomized Treatment Group (mITT Analysis set)

Subgroup		Treatment Arm	Sample Size	Baseline Mean at the end of SDP (SD)	Estimated Median Difference (95% CI)
Baseline Medication Group	On Baseline IH Medication	JZP-258	33	16.2 (9.13)	-12.0 (-15.0, -8.0)
		Placebo	35	15.3 (8.18)	--
	Treatment Naïve	JZP-258	23	14.4 (9.40)	-12.0 (-18.0, -6.0)
		Placebo	24	15.1 (7.32)	--
Gender	Female	JZP-258	39	14.3 (8.44)	-12.0 (-15.0, -8.0)
		Placebo	43	15.6 (7.95)	--
	Male	JZP-258	17	18.2 (10.51)	-12.0 (-19.0, -6.0)
		Placebo	16	14.3 (7.44)	--
Region	North America	JZP-258	35	15.9 (8.54)	-11.0 (-15.0, -7.0)
		Placebo	42	14.5 (7.46)	--
	Europe	JZP-258	21	14.8 (10.39)	-14.0 (-19.0, -6.0)
		Placebo	17	17.1 (8.45)	--
JZP-258 stable dose regimen	Once Nightly	JZP-258	15	16.7 (9.99)	-9.0 (-16.0, -3.0)
		Placebo	11	13.1 (3.27)	--
	Twice Nightly	JZP-258	41	15.0 (8.98)	-12.0 (-15.0, -8.0)
		Placebo	47	15.9 (8.42)	--
Baseline Median BMI	≤ median	JZP-258	28	15.5 (9.60)	-14.0 (-17.0, -10.0)
		Placebo	30	14.7 (8.28)	--
	> median	JZP-258	28	15.4 (8.95)	-9.0 (-14.0, -5.0)
		Placebo	29	15.8 (7.33)	--
Idiopathic Hypersomnia Diagnosis	Long sleep	JZP-258	13	15.2 (10.42)	-15.0 (-20.0, -9.0)
		Placebo	11	18.3 (8.47)	--
	Without Long Sleep	JZP-258	43	15.5 (8.93)	-11.0 (-14.0, -7.0)
		Placebo	48	14.5 (7.53)	--

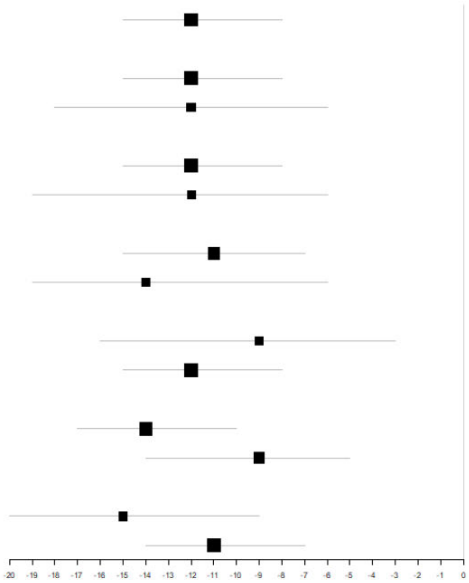
Abbreviations: SDP=Stable Dose Period; DBRWP=Double-blind Randomized Withdrawal Period; IHSS=Idiopathic Hypersomnia Severity Scale; CI=confidence interval; max=maximum; min=minimum; mITT=modified intent-to-treat; OL=Open label; Q1=quarter 1; Q3=quarter 3; SD=standard deviation; SDP=Stable Dose Period.

The estimated median difference between two treatment groups and 95% asymptotic CI are from Hodges-Lehmann estimate. The p-value has been obtained from a rank based on analysis of covariance model including the rank change in IHSS from the end of the OL SDP to the end of the DBRWP as the response variable; Covariates in the model included: baseline medication group, treatment group and ranked IHSS total score at the end of the OL SDP.

Source: Reviewer using data provided by sponsor (adqsihss.xpt)

Figure 7. Forest Plot of Subgroup Analysis: Change in IHSS from the end of SDP to the end of DBRWP by Randomized Treatment Group (mITT Analysis set)

	Placebo	JZP-258	Estimated Median Diff
	n	n	(95% CI)
Overall	59	56	-12.0 (-15.0, -8.0)
Baseline Medication Group			
On Baselien IH Medication	35	33	-12.0 (-15.0, -8.0)
Treatment Naive	24	23	-12.0 (-18.0, -6.0)
Gender			
Female	43	39	-12.0 (-15.0, -8.0)
Male	16	17	-12.0 (-19.0, -6.0)
Region			
North America	42	35	-11.0 (-15.0, -7.0)
Europe	17	21	-14.0 (-19.0, -6.0)
JZP-258 Stable Dose Regimen			
Once Nightly JZP-258	11	15	-9.0 (-16.0, -3.0)
Twice Nightly JZP-258	47	41	-12.0 (-15.0, -8.0)
Baseline Median BMI Group			
<=median	30	28	-14.0 (-17.0, -10.0)
>median	29	28	-9.0 (-14.0, -5.0)
Idiopathic Hypersomnia Diagnosis			
Long Sleep	11	13	-15.0 (-20.0, -9.0)
Without Long Sleep	48	43	-11.0 (-14.0, -7.0)



Abbreviations: SDP=Stable Dose Period ; DBRWP=Double-blind Randomized Withdrawal Period; IHSS=Idiopathic Hypersomnia Severity Scale; mITT=modified intent-to-treat; CI=confidence interval; Diff=Difference; OL=Open-Label.
The estimated median difference between two treatment groups and 95% asymptotic CI are from Hodges-Lehmann estimate. The p-value has been obtained from a rank based on analysis of covariance model including the rank change in IHSS from the end of the OL SDP to the end of the DBRWP as the response variable; Covariates in the model included: baseline medication group, treatment group and ranked IHSS total score at the end of the OL SDP.
Source: Reviewer using data provided by sponsor (adqsihss.xpt)

Baseline Medication Group, Gender, Region, JZP-258 Stable Dose Regimen, Baseline Median BMI Group, Idiopathic Hypersomnia Diagnosis

All subgroup analysis results presented in Table 7, Table 8, and Table 9 for the primary and key secondary efficacy endpoints showed consistent patterns with primary efficacy analysis results in the mITT population set – no evidently noticeable subgroup effect of JZP-258 compared to the placebo on the change in ESS and IHSS from the end of the SDP to the end of the DBRWP and PGIc at the end of DBRWP.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No statistical issues affected to the primary and key secondary efficacy endpoints.

5.2 Collective Evidence

Study JZP080-301 showed a statistically significant difference between JZP-258 and placebo in primary and key secondary efficacy endpoints (change in ESS and IHSS from the end of stable dose period to the end of double-blind randomized withdrawal period and PGIc at the end of double-blind randomized withdrawal period).

5.3 Conclusions and Recommendations

There are findings to support a significant treatment effect of JZP-258 compared to placebo in subjects aged 19-75 years having a primary diagnosis of IH according to the ICSD-2 or ICSD-3 criteria, measured by Epworth Sleeping Scale, Patient Global Impression of change and Idiopathic Hypersomnia Severity Scale.

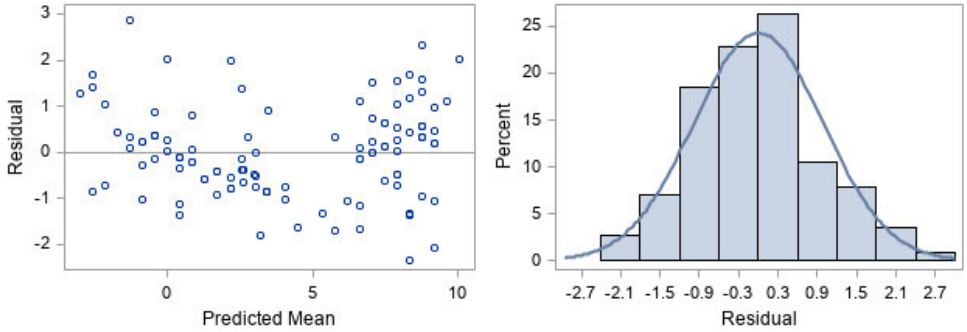
6 Appendix : Model Diagnostics

1. Model Diagnostics of Primary Efficacy Analysis on ESS (ANCOVA)

1.1 Constant error variance

An ANCOVA model is assumed to be linear with respect to the predicted value with constant variance. Pearson's residual plots are shown in Supplementary Figure 1, indicating no evidence of violating this assumption.

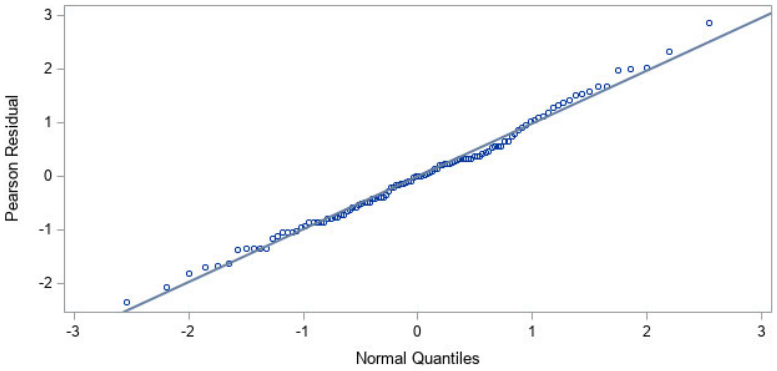
Supplementary Figure 1. Pearson's Residual plots



1.2 Normality of residuals

A Q-Q (quantile-quantile) plot shows that there is no significant deviation from linearity of the observations indicating no evidence of violating the normality assumption. Supplementary Table 1 also supports the normality assumption.

Supplementary Figure 2. Q-Q plot of Pearson's residual



2. Model Diagnostics of Key Secondary Efficacy Analysis on PGIc (Cochran-Mantel-Haenszel test)

Cochran-Mantel-Haenszel test estimates the common odds ratio summarizing the pooled effect across the different repeats of the experiment, assuming the odds ratio is the same in the different repeats. Based on Breslow-Day test (Supplementary Table 2), there does not appear to be a strong evidence for heterogeneity in the odds ratios for baseline medication groups.

Supplementary Table 2. Breslow-Day Test for Homogeneity of Odds Ratios

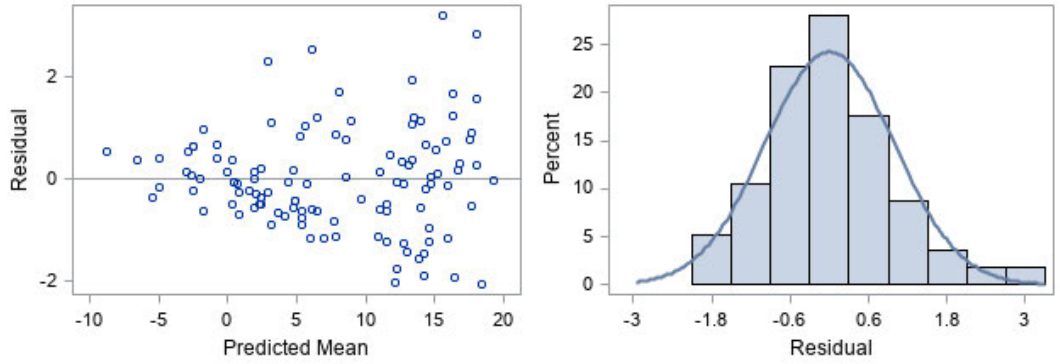
Breslow-Day Test for Homogeneity of Odds Ratios	
Chi-Square	3.1859
DF	1
Pr > ChiSq	0.0743

3. Model Diagnostics of Key Secondary Efficacy Analysis on IHSS (ANCOVA)

3.1 Constant error variance

Pearson's residual plots are shown in Supplementary Figure 1. It shows that the residual variance increases as the fitted values (predicted mean) increases, indicating a possibility of violating the assumption of constant error variance.

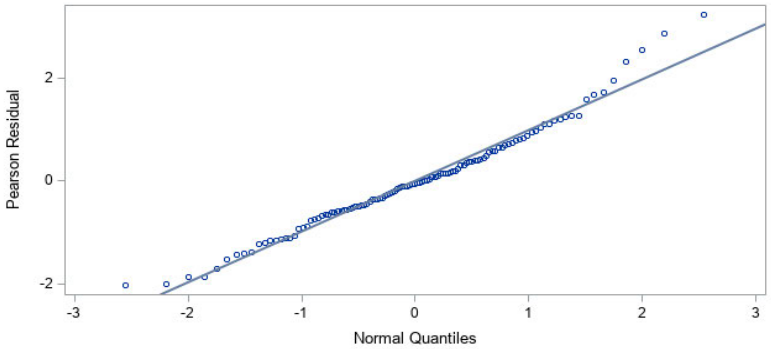
Supplementary Figure 3. Pearson's Residual plots



3.2 Normality of residuals

A Q-Q (quantile-quantile) plot shows deviations from linearity of the observations in upper tail, indicating there may be a violation of normality assumption (Supplementary Figure 4) and Shapiro-Wilk test result supports it (Supplementary Table 3). Hence, a non-parametric ANCOVA with the covariate and response variables replaced by their ranks was used for the primary efficacy analysis as prespecified in the SAP.

Supplementary Figure 4. Q-Q plot of Pearson's residual



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/s/

MINJEONG PARK
07/02/2021 11:15:25 AM

KUN JIN
07/02/2021 12:47:25 PM
I concur with the review.

HSIEN MING J HUNG
07/02/2021 05:29:14 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology

Integrated Clinical Pharmacology Review

NDA Number	212690 Efficacy Supplement 6 (SDN 108)
Link to EDR	\\CDSESUB1\evsprod\NDA212690\0105
Submission Date	02/12/2021
Submission Type	Efficacy Supplement – Priority review
Brand Name	XYWAV™
Generic Name	JZP-258
Dosage Form and Strength	Solution (0.5 g/ml), for oral administration
Proposed Indication	Treatment of Idiopathic Hypersomnia in adults
Proposed Dose/Regimen	XYWAV can be administered as a twice nightly or once nightly regimen. Twice nightly regimen: • Initiate dosage at ≤ 4.5 g per night divided into two doses (e.g., 2.25 g each). • Titrate to effect in increments of ≤ 1.5 g (in divided doses) per night at weekly intervals. • Recommended maximum total nightly dose of 9 g (in divided doses) Once nightly regimen: • Initiate dosage at ≤ 3 g per night • Titrate to effect in increments of ≤ 1.5 g per night at weekly intervals • Recommended maximum total nightly dose of 6 g
Applicant	Jazz Pharmaceuticals Ireland Limited.
Associated IND	49641
OCP Review Team	Gopichand Gottipati Ph.D., Mike Bewernitz, Ph.D., Atul Bhattaram, Ph.D., Bilal AbuAsal, Ph.D.

Table of Contents

Executive Summary

Jazz Pharmaceuticals Ireland Limited submitted this efficacy supplement (#6) of New Drug Application (NDA 212690) seeking approval for XYWAV™ (JZP-258 – used interchangeably with XYWAV in this review) for the treatment of Idiopathic Hypersomnia (IH) in adults. There are no current FDA-approved therapies for treatment of IH. JZP-258 is a 0.5 g/mL aqueous solution of mixture of calcium, potassium, magnesium, and sodium salts of oxybate; equivalent to 0.413 g/mL oxybate. JZP-258 was approved by the US FDA for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy on 07/21/2020.

The proposed adult Xywav dosing recommendations for treatment of IH is either *twice nightly regimen* – initiate at ≤ 4.5 g/night orally in two divided doses (e.g., 2.25 g each), titrate to effect in increments of ≤ 1.5 g (in divided doses) per night at weekly intervals to a maximum total nightly dose of 9 g (divided doses), or *once nightly regimen* – initiate at ≤ 3 g per night, titrate to effect in increments of ≤ 1.5 g per night at weekly intervals to a maximum total nightly dose of 6 g.

The application package included one phase 3 double-blind, placebo-controlled, randomized withdrawal study (JZP080-301) with an open-label safety extension period in adult patients with IH. The primary efficacy endpoint – least squares mean change in Epworth Sleepiness Scale (ESS) from the stable-dose period to the end of a 2-week double-blind randomized withdrawal period in JZP-258 arm was reported to be statistically significant than that in placebo group. In addition, the applicant conducted population PK and exposure-response analyses and included them in this submission. This NDA relies on the approved product XYWAV (also from the same applicant) for dosing recommendations for intrinsic and extrinsic factors. The applicant also used the population PK and exposure-response analyses from IH population to compare with narcolepsy population and justify revision of current XYWAV instructions in USPI for narcolepsy population to take without regards to food-intake.

The primary focus of this review is to evaluate the adequacy of the instructions for patients transitioning between once nightly and twice nightly regimens and vice-versa and evaluate the dosing recommendations for JZP-258 with regards to food-intake in IH and narcolepsy patient populations.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) recommends the approval of JZP-258 for the treatment of IH in adults. The OCP review team disagrees with the applicant's recommendation (b) (4) The review team recommends consistent dosing instructions – to administer Xywav at least 2 hours after meals for both IH and narcolepsy indications to avoid potential dosing errors due to differential dosing recommendations.

Key review issues with specific recommendations and comments are summarized below.

Review Issues	Recommendations and Comments
Evidence of effectiveness:	Effectiveness is supported by results from a double-blind, placebo-controlled, randomized-withdrawal, multicenter, phase 3 study (JZP080-301) in adult patients with IH provided the primary evidence of effectiveness. In this study patients were titrated to an optimal dose of JZP-258 based on tolerability/efficacy over a 10-14-week open-label period and continued this stable dose for 2 weeks. Subsequently, they were randomized to either continue the stable dose or to placebo over a 2 week double-blind withdrawal period. Please refer to the clinical and biometrics reviews for more information.
General dosing instructions:	The dosage and regimen of Xywav should be individualized based on clinical presentation The recommended nightly dosage in adult patients with IH

Dosing regimen	Starting Nightly Dose	Take 2.5 to 4 Hours Later:	Maximum Total Nightly Dose
Twice Nightly*†	≤ 4.5 g per night divided into two doses (e.g., 2.25 g each)	≤ 1.5 g per night per week (divided)	9 g (divided)
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			

Review Issues	Recommendations and Comments
Dosing in patient subgroups (intrinsic and extrinsic factors)	The dosing in patient subgroups based on intrinsic and extrinsic factors are identical to the recommendations provided in USPI for Xywav. Please refer to the USPI of Xywav for details.
Bridge between the "to-be-marketed" and clinical trial formulations	The commercial and clinical trial formulations are the same and therefore, no PK bridging studies were required.

1.2 Post-marketing Requirements

None.

2 Summary of Clinical Pharmacology Assessment

2.1 The Pharmacology and Clinical Pharmacokinetics

The information listed below is exclusively based on the clinical pharmacology information provided in the USPI for Xywav.

Mechanism of Action:

Oxybate is a CNS depressant. JZP-258 is a mixture of calcium oxybate, potassium oxybate, magnesium oxybate, and sodium oxybate (gamma hydroxybutyrate). Gamma-Hydroxy Butyrate (GHB)[1] is an endogenous compound and metabolite of the neurotransmitter GABA.

Absorption

- Following oral administration of JZP-258 in healthy adults in fasted state, the average Tmax for GHB was about 1.3 hours.
- Following oral administration of JZP-258, the plasma levels of GHB increased more than dose-proportionally, with Cmax increasing approximately 2-fold and AUC increasing 2.9-fold as the dose was doubled from 2.25 g to 4.5 g.
- Administration with food decreases exposures of GHB. Concomitant administration of JZP-258 with a standardized high fat meal resulted in a mean reduction in Cmax and AUC_{0-inf} of GHB by 33% and 16% respectively, while mean Tmax was unaffected.

[1] GHB and oxybate have been used interchangeably in this review

Distribution

GHB is a hydrophilic compound with an apparent volume of distribution averaging 190 mL/kg to 384 mL/kg. At GHB concentrations ranging from 3 mcg/mL to 300 mcg/mL, less than 1% is bound to plasma proteins.

Metabolism and Excretion

Animal studies indicate that metabolism is the major elimination pathway for GHB, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. No active metabolites have been identified.

The clearance of GHB is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible. GHB has a mean terminal elimination half-life of 0.66 hours.

(b) (4)

[redacted]

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The dosing recommendations for JZP-258 in adult IH patients are consistent with instructions provided to patients enrolled in the phase 3 study as noted in section 1.1.

2.2.2 Therapeutic individualization

No clinical studies were conducted by the applicant to inform therapeutic individualization for Xywav.

2.2.3 Outstanding Issues

None.

2.2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology review team accepts the labeling concepts proposed by the applicant, (b) (4) The review team recommends that the first dose of JZP-258 should be administered at least 2 hours after meals, consistent with existing USPI for Xywav, for both IH and narcolepsy indications. Please refer section 3.3.4 for additional details. Additionally, the review team recommends (b) (4) . Please refer to section 3.3.2 for additional details.

3 Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

Idiopathic hypersomnia is a rare disorder of central nervous system hypersomnolence. The primary manifestation is severe excessive daytime sleepiness (EDS). There are no current FDA-approved therapies for treatment of IH. JZP-258 is a mixed salt formulation consisting of calcium, potassium, magnesium, and sodium salts of oxybate; equivalent to 0.413 g/mL oxybate. JZP-258 was approved by US FDA on 07/21/2020 for treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy.

In a type-C meeting in July 2018, the agency held discussions with the applicant on the trial design and acceptability of a single adequate and well-controlled pivotal clinical study of Xywav for approval in IH indication (contingent on JZP-258 approval for narcolepsy indication [still under development at the time] by the time of submission for IH indication). Additionally, OCP review team recommended that PK sample collection in the proposed pivotal study JZP080-301 may help establish exposure-response relationships for Xywav in IH and facilitate the selection of an optimal dose of Xywav. In response, the applicant agreed to collect PK samples in a sub-study (N=28 IH patients).

In June 2019, Xywav supplement 6 received orphan drug designation, and in September 2020 received fast-track designation for treatment of IH in adults. In December 2020, at the pre-NDA meeting the applicant shared their proposed plan to conduct specific analyses to support dosing without regards to food-intake labeling update for narcolepsy indication. In addition to noting that the adequacy of applicant's proposed plan will be matter of review dependent on several factors, the agency pointed out that the frequency of cataplexy attacks was an outcome measure evaluated in phase 3 study 15-006 conducted in narcolepsy patients, but not an outcome measure in study JZP080-301 in IH patients.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Please refer to the general clinical pharmacology information included in the USPI for XYWAV®[2] for additional details on distribution, metabolism and excretion of GHB.

3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The evidence of effectiveness of JZP-258 for the treatment of Idiopathic Hypersomnia (IH) was demonstrated in one phase 3 clinical study (JZP080-301) in adult patients.

Study JZP080-301 was a double-blind, placebo-controlled, randomized-withdrawal, multicenter study (NCT03533114) in adult patients with IH. It consists of 2 parts – part 1 consisted of a 10-14 week open-label treatment titration and optimization period followed by a 2 week stable dose period (SDP) and finally a 2 week double-blind randomized-withdrawal period (DB RWP); followed by part 2, an optional 24-week open-label extension period. The study enrolled 154 subjects, 18 – 75 years, and a primary diagnosis of IH according to the International Classification of Sleep Disorders (ICSD)-2 or ICSD-3 criteria. Of the 123 subjects who entered the open-label treatment titration and optimization period, 116 were randomized 1:1, either to continue treatment with JZP-258 (N=57) or to placebo (N=59) in the 2 week DB RWP.

Participants who were taking a stable dose of Xyrem at study entry were switched gram for gram from Xyrem to the same dosing regimen of Xywav. Participants who were not taking Xyrem at study entry initiated JZP-258 either as a once or twice nightly dosing regimen at the discretion of the investigator. Twice-nightly doses of JZP-258 were administered in majority of patients (JZP-258 arm: 41/57, 72%; placebo (47/59, 80%)], while the rest received were once nightly doses [JZP-258 (16/57); placebo (11/59)], except for one subject in placebo arm who received thrice-nightly regimen.

The primary efficacy endpoint was the change in Epworth Sleepiness Scale (ESS) score as a measure of reduction in EDS in IH from the end of the SDP to the end of the DB RWP. The key secondary endpoints were Patient Global Impression of Change (PGIc): proportion of participants reporting worsening of symptoms at the DB RWP, and Idiopathic Hypersomnia Severity Scale (IHSS): Change in total score from end of SDP to the end of DB RWP. The results for study JZP080-301 met the pre-specified statistical criteria for both primary (summarized in Table 1 below) and

[2] USPI for Xywav accessed at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021196s035,212690s001s002lbl.pdf

secondary endpoints. Please refer to statistical review by Drs. Minjeong Park and Kun Jin and clinical review by Dr. Ranjit Mani for additional details.

Table 1 Primary Efficacy Endpoint Results, Change in ESS (mITT analysis set)

	Randomized Treatment Group	
	JZP-258 (N=56)	Placebo (N = 59)
End of Stable Dose Period (SDP)		
Mean (SD)	6.3 (4.33)	5.8 (3.66)
End of Double-Blind Randomized Withdrawal Period (DB RWP)		
Mean (SD)	7.0 (5.03)	13.3 (4.06)
Change from end of SDP to the end of DB RWP		
Least Squares Mean* (SE)	0.8 (0.54)	7.3 (0.53)
LS Means Diff (SE)	- 6.51 (0.747)	
p-value	< 0.0001	

SD = standard deviation, Source: Adapted based on JZP080-301 CSR Table 14 on pages 52, 53; Least Square Means and Standard Errors (SE) were obtained based on ANCOVA model.

3.3.2 Is the proposed dosing regimen appropriate for the general population for which the indication is being sought?

The proposed dosage recommendations for initiation, titration and maximum recommended daily dosages are acceptable in adult IH population. As noted in section 3.3.1, majority of patients were on twice nightly regimen. The maximum total daily dosage taken by patients in once nightly regimen in the phase 3 trial was 6 g and 4 subjects received this maximum nightly dose of 6 g.

The adult regimen is identical to those evaluated in their pivotal phase 3 study where they demonstrated efficacy/safety by meeting the pre-specified statistical criteria for both primary and secondary efficacy endpoints. The review team recommends administering the first dose of JZP-258 at least 2 hours after meals in IH population to maintain consistent dosing instructions with current approved USPI for narcolepsy indication. Please refer to Section 3.3.4 for more information.

The applicant proposed including specific instructions for patients transitioning between once nightly and twice nightly regimens and vice-versa. They are:

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In summary, the review team recommends (b) (4)

No new major safety concerns were observed in study JZP080-301 relative to those reported in the package insert of Xywav®. Overall, in the safety database, the most commonly reported AEs of study JZP080-301 included insomnia, dry mouth, fatigue, somnolence and tremor. Please refer to the clinical safety review by Dr. Ranjit Mani and for further details. In conclusion, we recommend the approval of the dosage regimens for JZP-258 in adult IH patients.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic/extrinsic factors?

The applicant did not conduct any studies in this current program to evaluate the impact of intrinsic/extrinsic factors. Please refer to the recommendations included in the USPI for XYWAV for additional details.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-Drug Interactions

Yes. The current approved USPI of Xywav[3] recommends taking Xywav at least 2 hours after eating. That recommendation was based on agency's review of the results of a food-effect study (JZP258-101, in healthy volunteers) and independent exposure-efficacy analyses conducted as part of assessing appropriateness of Xywav dosing recommendations for cataplexy and excessive daytime sleepiness associated with narcolepsy indication (NDA 212690). Briefly, the review team noted that there could be a potential for loss of efficacy in cataplexy frequency by 30-40% and in ESS scores by 10-20% when Xywav was taken with food. Please refer to Dr. Gottipati's Clinical Pharmacology Review (DARRTS dated 07/21/2020) for additional details.

The applicant did not conduct a dedicated food-effect study as part of their IH development program. In the pivotal study JZP080-301, adult IH participants were instructed to take Xywav without regards to food-intake and there were no restrictions on food intake timing relative to dosing timing (and the time of dosing relative to food-intake was not collected in all patients). At a subset of sites, adult IH patients were given the opportunity to participate in a PK sub-study and N=28 subjects enrolled. In this PK sub-study, the participants were instructed to abide by a similar routine (i.e., just as they did at home regarding timing of eating and timing of dosing) during the night the PK data was collected. Additionally, the time interval between dosing and food-intake was collected for all participants in this sub-study.

In the current supplemental NDA (sNDA #6) application for IH indication, the applicant proposed that Xywav can be taken without regard to food-intake. Furthermore, the applicant proposed revising Xywav dosing instructions to be taken without regards to food-intake for previously approved indication, i.e., cataplexy and excessive daytime sleepiness associated with narcolepsy.

Applicant's basis for dosing instructions without regards to food-intake in IH population:

1. As noted above, in the phase 3 trial JZP080-301, adult IH patients were instructed to take Xywav without regards to food-intake and there were no restrictions on food intake timing relative to dosing timing.
2. The applicant noted that the previously developed population PK model (based PK data from 13-010 and JZP258-101 studies conducted under NDA 212690) was updated with PK data in N=28 IH participants from sub-study in JZP080-301, and it adequately characterized the observed PK data. This updated popPK model showed that disease state (IH patients vs. health volunteers) does not affect oxybate PK. (b) (4)

[3] USPI for Xywav accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021196s035,212690s001s002lbl.pdf

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3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support approval of the to-be-marketed formulation?

Yes, the dosage form and strength of the commercial to-be-marketed formulation (oral solution) is the same as the formulation used by the applicant in their pivotal phase 3 study (JZP080-301).

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4.2 Pharmacometrics Assessment: Population PK Analyses

4.2.1 Applicant's Population PK analysis:

Applicant developed a population PK model to characterize Xywav (also known as JZP-258) PK in IH patients, assess the relationship of PK with demographics and other covariates, and conduct PK simulations of twice night dosing.

Summary of PK Data:

There were 3725 PK samples from n=134 subjects in three studies utilized for PPK analyses. A brief description of these studies is given in the table below.

Table 2: Summary of the characteristics of the studies used for PopPK analyses

	Study design and patient population (PK evaluable population)	Dosing regimen	Blood sample collection
JZP080-301	Double-Blind, Placebo-Controlled, Randomized Withdrawal trial in n=144 IH subjects age 18-75 years. PK collected in n=30 subjects.	Once nightly: JZP-258 at ≤ 3 g/night; max 6 g/night Twice nightly: JZP-258 at ≤ 4.5g/night; max 9 g/night Thrice nightly: Not a starting regimen. Available if needed for efficacy and tolerability	Twice nightly dosing: 0 (predose), 0.5, 0.75, 1, and 1.5 h after each dose. Once nightly dosing: 0 (predose), 0.5, 0.75, 1, 1.5, 2, 4, and 8 h after each dose.
13-010	Open-label, randomized, crossover study for relative BA/BE, food-effect study in n=60 healthy adult subjects	Trt A: 4.5 g JZP-258 (fasting) Trt B: 4.5 g JZP-258 (fed) Trt H: 2.25 g JZP-258 (fasting)	10, 20, 30, 45, 60, and 75 minutes postdose, and at 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, and 8 hours postdose following each treatment.
JZP258-101	Open-label, randomized, crossover study for relative BA/BE, food-effect study in n=48 health subjects age 18 to 45 years.	Trt A: 4.5 g JZP-258 (fasting) Trt C: 4.5 g JZP-258 (fed) Trt F: 4.5 g JZP-258 (fasting)	Predose, 10, 20, 30, 45, 60, and 75 minutes postdose, and at 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, and 8 hours postdose following each treatment.

Source: sequence 0105, module 5335, study-report-jazp-pmx-jzp258-2049-pker.pdf, page 13 of 134

Population PK Model

The structural model consists of two-compartments with first-order absorption with time lag and non-linear elimination (described with a Michaelis-Menten model). The PK parameters are first order oral absorption rate constant (Ka), absorption time lag, apparent maximum elimination rate (Vmax/F), concentration at which half of maximum elimination rate is achieved (Km), apparent volume of the central compartment (Vc/F), apparent intercompartmental clearance (Q/F), and apparent volume of the peripheral compartment (Vp/F).

Allometric Scaling: Vmax/F, Vc/F were scaled according to body weight normalized to 73 kg.

Inter-individual Variability: exponential

Residual Variability: additive error model

Covariates: Food effect on Ka and lag. Dose effect on Ka.

The final PPK model script and output are named pkscr3.txt and pkscr4.txt, respectively. The parameter estimates for the final PPK model are presented in the table below.

Table 3: Parameter estimates of the final PopPK model (run64)

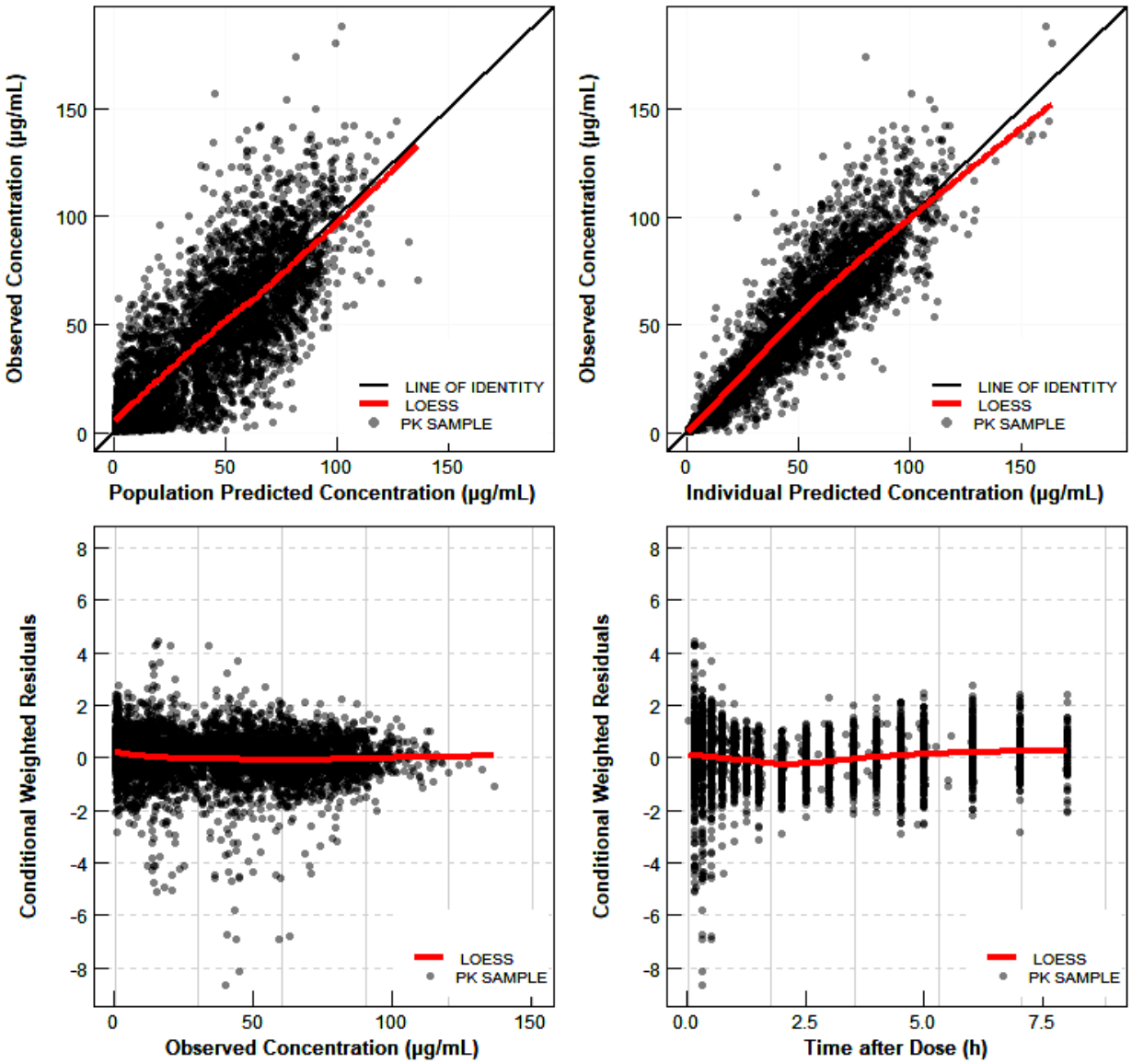
Parameter	Value	RSE	BSV (RSE)	Shrinkage
Objective Function Value	**-3041.411**	-		
Ka (h^{-1})	**1.556** × 0.700 if high fat meal × 1.169 if fasted × $(Dose/4.5)^{0.501}$	**35.30%** 46.20% 109% 28.60%	**53.5% (9.5%)**	**8.15%**
Lag (h)	**0.225** × 0.481 if fasted	**13.20%** 15%	**33.6% (15.8%)**	**18.9%**
V_{max}/F (L/h)	**1224.15** × $(Body\ Weight/73)^{0.572}$	**1.10%** 23.40%	**52.7% (16.0%)**	**5.38%**
K_m (µg/mL)	**17.46**	**4.20%**	**57.9% (21.3%)**	**11.2%**
Vc/F (L)	**29.67** × $(Body\ Weight/73)^{0.705}$	**1.20%** 14.20%		
Q/F (L/h)	**3.353**	**9.30%**		
Vp/F (L/h)	**16.61**	**36.30%**		
Proportional Error (%)	**35.20**	**5.00%**		

BSV = between-subject variability; V_{max}/F = apparent maximum velocity; K_m = Michaelis-Menten constant, Q/F = apparent distributional clearance between the central compartment and the peripheral compartment; Ka = absorption rate constant; Lag = absorption lag time; RSE = relative standard error; Vc/F = apparent volume of the central compartment; Vp/F = apparent volume of the peripheral compartment; WT = body weight.

Source: sequence 0105, module 5335, study-report-jazp-pmx-jzp258-2049-pker.pdf, page 93 of 134

The diagnostic plots for the final PPK model are presented below.

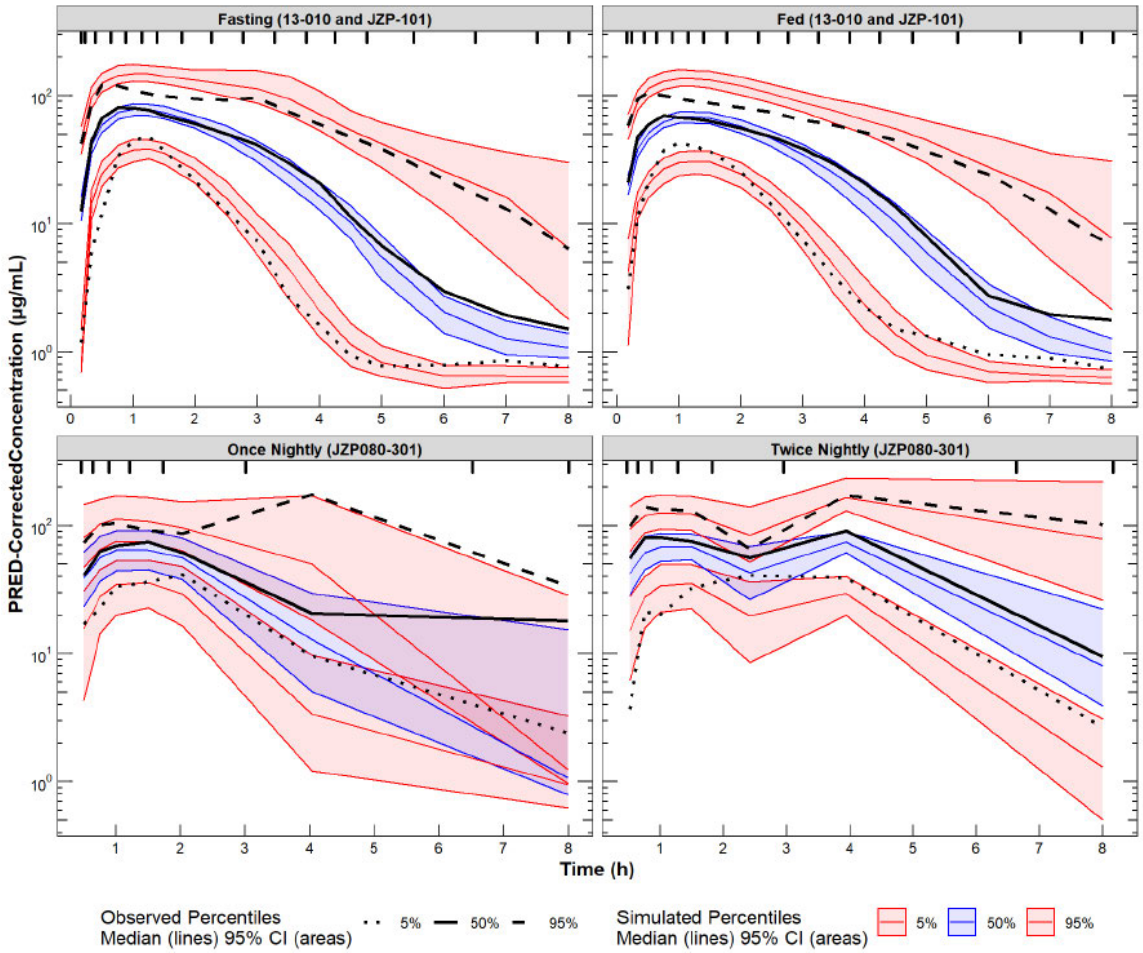
Figure 1 Diagnostic Plots for the final PPK model (run64)



Source: sequence 0105, module 5335, study-report-jazp-pmx-jzp258-2049-pker.pdf, page 31 of 134

The visual predictive check for the final PPK model (run64) are presented below.

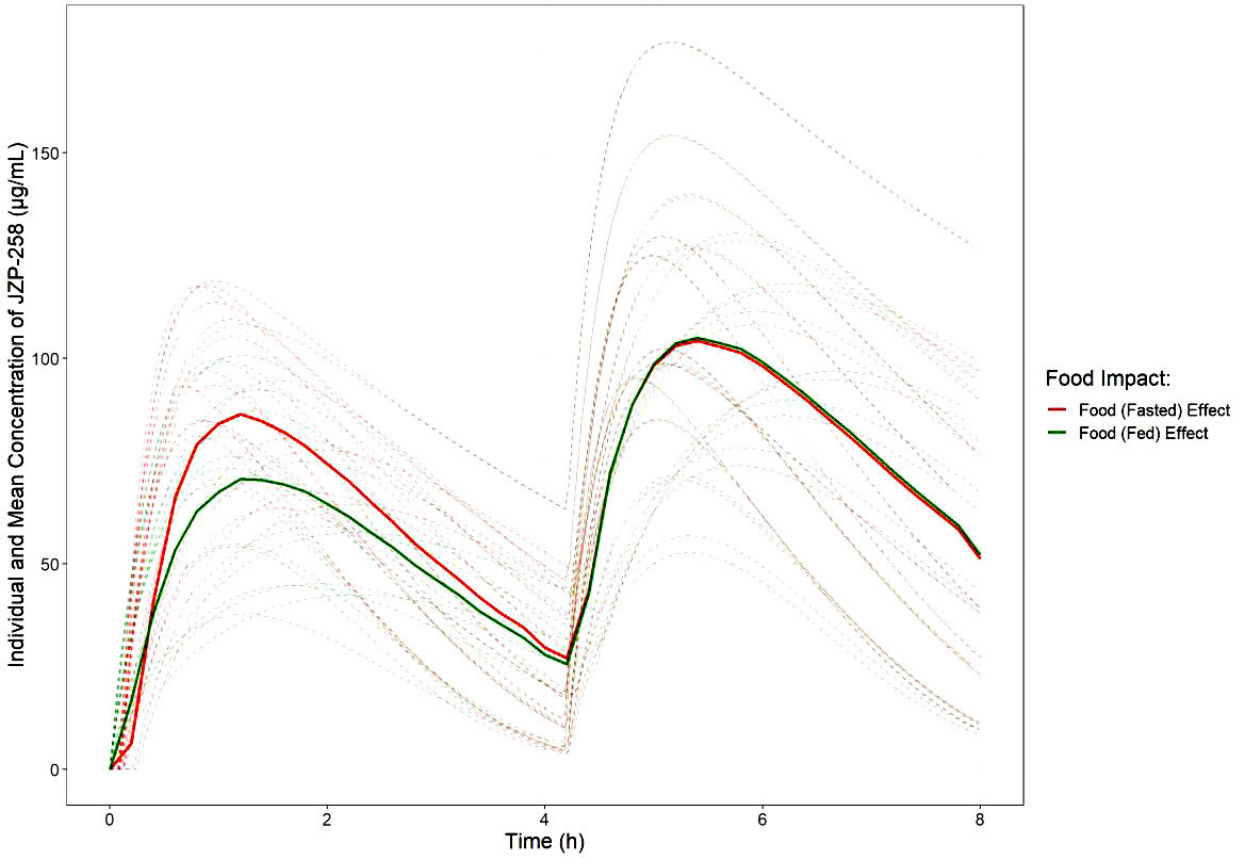
Figure 2 Visual predictive check of the final popPK model



Source: sequence 0105, module 5335, study-report-jazp-pmx-jzp258-2049-pker.pdf, page 32 of 134

The Applicant simulated the mean PK profile as well as individual PK profiles for twice nightly doses of JZP-258 (4.5 g x 2) under fed as well as fasting conditions (see figure below).

Figure 3 Simulated PK Profile for Twice Night Dosing in a Fasted versus Fed state



Solid red line = mean profile of JZP-258 under fasted conditions;
dotted red line = individual profile of JZP-258 under fasted conditions;
Solid green line = mean profile of JZP-258 under fed conditions;
dotted green line = individual profile of JZP-258 under fed conditions.

Source: sequence 0105, module 5335, study-report-jazp-pmx-jzp258-2049-pker.pdf, page 36 of 134

[*Reviewer comment: Based on the diagnostic plots, there is no apparent signs of systematic bias with respect to the magnitude of concentration nor the time after administration. Based on the VPC, in healthy volunteers (studies 13-010 and JZP-101), the PPK model characterizes the central tendency and variability well for both fasted and fed conditions. The VPC for patients in study 301 indicates that the model performs best in the vicinity of Tmax. The central tendency is well-described for patients at all times whereas as time approaches 8-hours post-dose, predictions of the extreme concentration values (lowest and highest) are less accurate (possibly due to less frequent PK sampling at these later times [i.e. samples at 0.5, 0.75, 1, 1.5, 2, 4, and 8 hours in Study 301], and a subset of observed concentrations approaching the LLOQ of 0.75 µg/mL). Overall, the PPK model is acceptable.*]

4.2.2 Applicant's Exposure-Response Analyses

The Applicant conducted exposure-response analyses for efficacy and for safety. These analyses are contained in the same report, study-report-jazp-pmx-jzp258-2049-pker.pdf, submitted to module 5335 in sequence 0105.

4.2.2.1 Exposure-Response for Efficacy

Exposure-response analyses for the Epworth Sleepiness Scale (ESS) efficacy endpoint utilized data from Trial 301 in IH patients and Trial 15-006 in narcolepsy patients. Exposure-response analyses for the Idiopathic Hypersomnia Severity Scale (IHSS) efficacy endpoint utilized data from Trial 301 in IH patients.

The Applicant determined that the "very shallow" relationship between exposure and ΔESS for IH patients and is comparable to that of narcolepsy patients. The Applicant determined that the exposure-response relationship for ΔIHSS was not statistically significant.

[*Reviewer comment: The exposure-response analyses were not reviewed for the following reasons:*

1. *Regarding the narcolepsy indication (and Trial 15-006 in narcolepsy patients), this submission does not contain any new information. As such, there is no need to further review the exposure-response information regarding Trial 15-006 in narcolepsy patients (which was reviewed previously by OCP).*
2. *Based on discussion with the medical officer, "the excessive daytime sleepiness of idiopathic hypersomnia may be distinct in both its clinical features and pathophysiology from narcolepsy". As such, the review team is unable to rule out the possibility that the mechanism of action by which Xywav affects ESS in IH may differ from the mechanism of action by which Xywav affects ESS in cataplexy. Thus, the Applicant's comparison of ESS - E-R between the narcolepsy indication and IH indication is not appropriate.*

   The Applicant viewed such an E-R similarity to support dosing changing the narcolepsy dosing to occur without regard to food (as was the case in the IH Study 301). However, at the time this review was archived, the review team and Applicant have since agreed that dosing to narcolepsy will not change and the IH indication will inherit the recommendation to take the first nightly dose of at least 2 hours after eating.

]

4.2.2.2 Exposure-Response for Safety

The Applicant assessed the relationship between exposure and safety in n=56 subjects randomized to JZP-258 and completed the double-blind randomized withdrawal period in Trial 301. There were n=13 subjects that experienced any TEAE out of these 56 subjects. The TEAEs reported in study 301 are summarized in the table below.

Table 4: TEAEs Reported in ≥ 2 % of subjects in Study 301

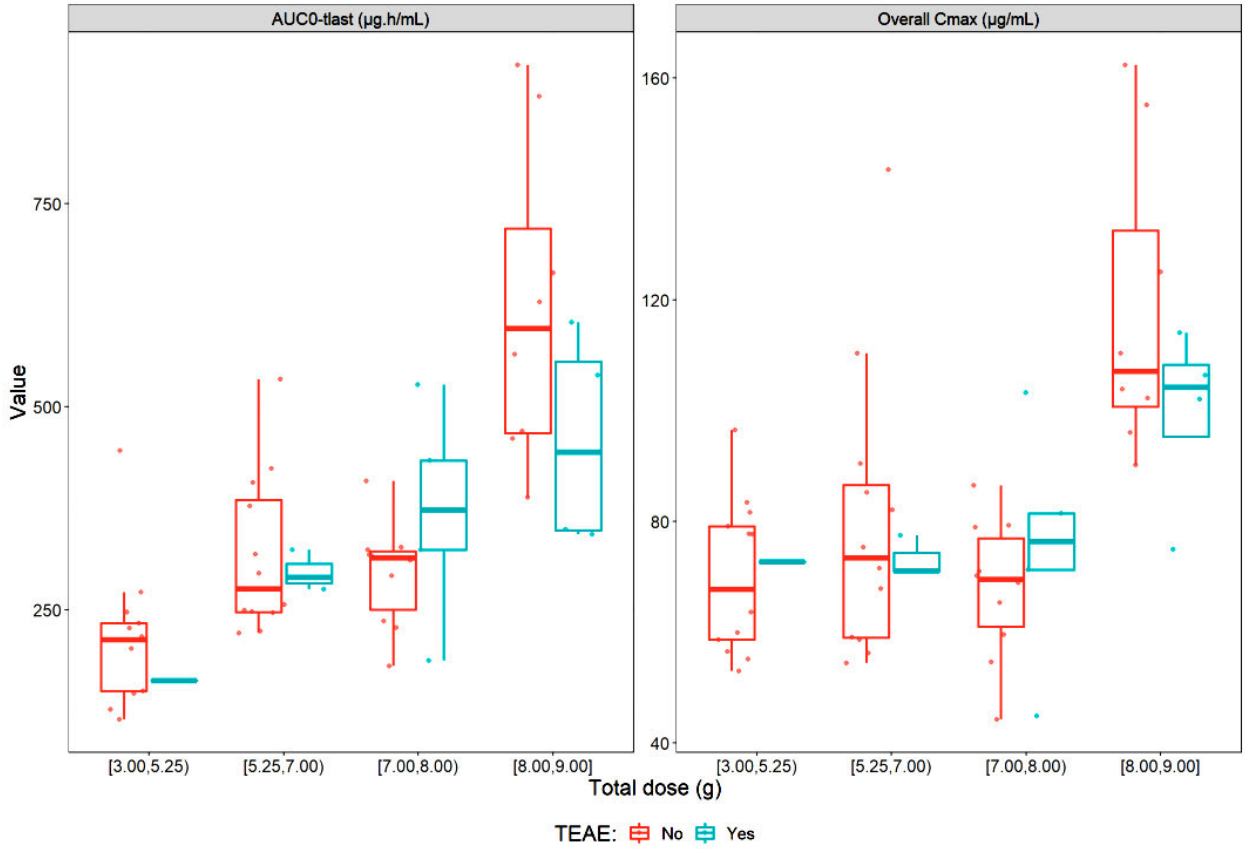
System Organ Class Preferred Term, n (%)	Randomized Treatment Group for DBRW Phase	
	JZP-258 (N=57)	Placebo (N=59)
Any TEAE	**14 (24.6)**	**17 (28.8)**
Gastrointestinal Disorders	**5 (8.8)**	**3 (5.1)**
Vomiting	2 (3.5)	2 (3.4)
Diarrhoea	1 (1.8)	2 (3.4)
Psychiatric Disorders	**2 (3.5)**	**9 (15.3)**
Insomnia	0	6 (10.2)

Source: Tables 9.3.1.2.4 and 9.3.1.3.2 ofClinical Study Report (JZP080-301)

Source: sequence 0105, module 5335, study-report-jazp-pmx-jzp258-2049-pker.pdf, page 48 of 134

The Applicant performed a graphical analysis comparing the simulated PK in subjects that experienced a TEAE versus subjects that did not experience a TEAE (see figure below).

Figure 4: Comparison of Simulated PK For Subjects With a TEAE vs Without a TEAE



Note: Subjects are grouped into quartiles of total daily dose on x-axis. Y-axis represents the value of the PK parameters (Cmax or AUC).

Source: sequence 0105, module 5335, study-report-jazp-pmx-jzp258-2049-pker.pdf, page 49 of 134

Applicant concludes that across the range of exposures observed in Study 301, a significant relationship between exposures and TEAE is not expected.

[*Reviewers comments: Overall, the Applicant's graphical analyses do not suggest a relationship between the TEAE incidence and PK across the range of exposures explored.*]

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GOPICHAND GOTTIPATI
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MICHAEL A BEWERNITZ
08/11/2021 11:53:23 PM
Pharmacometric review was in concurrence with Dr. Atul Bhattaram

BILAL S ABU ASAL
08/12/2021 08:27:23 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s006

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 20, 2021
To:	Teresa Wheelous Regulatory Project Manager **Division of Neurology I (DN1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Aline Moukhtara, RN, MPH Team Leader **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	XYWAV (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate)
Dosage Form and Route:	oral solution, CIII
Application Type/Number:	NDA 212690
Supplement Number:	006
Applicant:	Jazz Pharmaceuticals, Inc.

1 INTRODUCTION

On February 12, 2021, Jazz Pharmaceuticals, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy for approved New Drug Application (NDA) #212690/S-006 XYWAV (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate). This sNDA provides an efficacy supplement, prior-approval, that aims to expand the indication of XYWAV for the treatment of adult patients with idiopathic hypersomnia (IH), and a REMS supplement, prior approval, that proposes modifications to the current XYWAV and XYREM REMS in light of this new indication for use. Jazz Pharmaceuticals, Inc. remains the Authorized US Agent for this sNDA.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology I (DN1) on March 26, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for XYWAV (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate) oral solution, CIII.

2 MATERIAL REVIEWED

- Draft XYWAV (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate) MG and IFU received on February 12, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 12, 2021, and July 7, 2021, respectively.
- Draft XYWAV (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate) Prescribing Information (PI) received on February 12, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 12, 2021, and July 7, 2021, respectively.
- Approved XYWAV (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate) labeling dated February 11, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

3 Pages Draft Labeling have been withheld in full as b4 (CCI/TS) immediately following this page

MEDICATION GUIDE
XYWAV™ (ZYE wave)
(calcium, magnesium, potassium, and sodium oxybates)
oral solution, CIII

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

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

- XYWAV is a central nervous system (CNS) depressant. Taking XYWAV with other CNS depressants, such as medicines used to make you or your child fall asleep, including opioid analgesics, benzodiazepines, sedating antidepressants, antipsychotics, sedating anti-epileptic medicines, general anesthetics, muscle relaxants, alcohol, or street drugs, may cause serious medical problems, including:
  - trouble breathing (respiratory depression)
  - low blood pressure (hypotension)
  - changes in alertness (drowsiness)
  - fainting (syncope)
  - death

  Ask your doctor if you are not sure if you are, or your child is, taking a medicine listed above.
- XYWAV is a federal controlled substance (CIII). The active ingredient of XYWAV is a form of gamma-hydroxybutyrate (GHB) that is also a federal controlled substance (CI). Abuse of illegal GHB, either alone or with other CNS depressants, may cause serious medical problems, including:
  - seizure
  - trouble breathing (respiratory depression)
  - changes in alertness (drowsiness)
  - coma
  - death

  Call your doctor right away if you have or your child has any of these serious side effects.
- Anyone who takes XYWAV should not do anything that requires them to be fully awake or is dangerous, including driving a car, using heavy machinery, or flying an airplane, for at least 6 hours after taking XYWAV. Those activities should not be done until you know how XYWAV affects you or your child.
- Keep XYWAV in a safe place to prevent abuse and misuse. Selling or giving away XYWAV may harm others and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
- Because of the risk of CNS depression, abuse, and misuse, XYWAV is available only by prescription, and filled through the central pharmacy in the XYWAV and XYREM REMS. You or your child must be enrolled in the XYWAV and XYREM REMS to receive XYWAV. For information on how to receive XYWAV, visit www.XYWAVXYREMREMS.com. Before you receive or your child receives XYWAV, your doctor or pharmacist will make sure that you understand how to take XYWAV safely and effectively. If you have any questions about XYWAV, ask your doctor or call the XYWAV and XYREM REMS at 1-866-997-3688.

What is XYWAV?

XYWAV is a prescription medicine used to treat the following symptoms:

- in people 7 years of age or older with narcolepsy:
  - sudden onset of weak or paralyzed muscles (cataplexy), or
  - excessive daytime sleepiness (EDS)
- in adults with idiopathic hypersomnia (IH):

(b) (4)

It is not known if XYWAV is safe and effective in children less than 7 years of age with narcolepsy.
It is not known if XYWAV is safe and effective in children with IH.

Do not take XYWAV if you or your child:

- takes other sleep medicines or sedatives (medicines that cause sleepiness).
- drinks alcohol.
- has a rare problem called succinic semialdehyde dehydrogenase deficiency.

Before taking XYWAV, tell your doctor about all of your medical conditions, including if you or your child:

- have a history of drug abuse.
- have short periods of not breathing while sleeping (sleep apnea).
- has trouble breathing or has lung problems. You or your child may have a higher chance of having serious breathing problems when taking XYWAV.

- have or had depression or has tried to harm yourself or themselves. You or your child should be watched carefully for new symptoms of depression.
- has or had behavior or other psychiatric problems such as:
  - anxiety
  - feeling more suspicious (paranoia)
  - acting aggressive
  - seeing or hearing things that are not real (hallucinations)
  - being out of touch with reality (psychosis)
  - agitation
- have liver problems.
- are pregnant or plan to become pregnant. It is not known if XYWAV can harm your unborn baby.
- are breastfeeding or plan to breastfeed. XYWAV passes into breast milk. You and your doctor should decide if you or your child will take XYWAV or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your doctor if you take or your child takes other medicines to help you or your child sleep (sedatives). Know the medicines you take or your child takes. Keep a list of them to show your doctor and pharmacist when you get or your child gets a new medicine.

How should I take or give XYWAV?

- Read the **Instructions for Use** at the end of this Medication Guide for detailed instructions on how to take XYWAV.
- Take or give XYWAV exactly as your doctor tells you to take or give it. Your doctor may change the dose or dosing routine if needed.
- XYWAV can cause physical dependence and craving for the medicine when it is not taken as directed.
- Never change the dose without talking to your doctor.
- XYWAV can cause sleep very quickly without feeling drowsy. Some people fall asleep within 5 minutes and most fall asleep within 15 minutes. The time it takes to fall asleep might be different from night to night.
- Falling asleep quickly, including while standing or while getting up from the bed, has led to falls with injuries that have required some people to be hospitalized.
- XYWAV can be taken 1 time or 2 times a night as prescribed by your doctor.
- **If you or your child have been prescribed XYWAV 2 times a night**: divide the total nightly dose into 2 doses to be taken at bedtime.
  - **Adults:** Take the first XYWAV dose at bedtime while you are in bed and lie down immediately. Take the second XYWAV dose 2½ to 4 hours after the first XYWAV dose. You may want to set an alarm clock to make sure you wake up to take the second XYWAV dose. You should remain in bed after taking the first and second doses of XYWAV.
  - **Children:** Give the first XYWAV dose at bedtime or after an initial period of sleep, while your child is in bed and have them lie down immediately. Give the second XYWAV dose 2½ to 4 hours after the first XYWAV dose. You may want to set an alarm clock to make sure you wake up to give the second XYWAV dose. Your child should remain in bed after taking the first and second doses of XYWAV.
  - If you miss or your child misses the second XYWAV dose, skip that dose and do not take or give XYWAV again until the next night. Never take or give 2 XYWAV doses at 1 time.
- **If you have been prescribed XYWAV 1 time a night:** Take your XYWAV dose at bedtime while you are in bed and lie down immediately. You should remain in bed after taking XYWAV.
- If you take or your child takes too much XYWAV, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of XYWAV?

XYWAV may cause serious side effects, including:

- See **"What is the most important information I should know about XYWAV?"**
- **breathing problems, including:**
  - slower breathing.
  - trouble breathing.
  - short periods of not breathing while sleeping (sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they take XYWAV.
- **mental health problems, including:**
  - confusion
  - seeing or hearing things that are not real (hallucinations)
  - unusual or disturbing thoughts (abnormal thinking)
  - feeling anxious or upset
  - depression
  - thoughts of killing yourself or trying to kill yourself
  - increased tiredness
  - feelings of guilt or worthlessness
  - difficulty concentrating

Call your doctor right away if you have or your child has symptoms of mental health problems, or a change in weight or appetite.

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

The most common side effects of XYWAV in adults with narcolepsy or IH include:

- nausea
- headache
- dizziness
- anxiety
- insomnia
- decreased appetite
- excessive sweating (hyperhidrosis)
- vomiting
- diarrhea
- dry mouth
- parasomnia (a sleep disorder that can include abnormal dreams, abnormal rapid eye movement (REM) sleep, sleep paralysis, sleep talking, sleep terror, sleep-related eating disorder, sleepwalking and other abnormal sleep-related events)
- somnolence
- fatigue
- tremor

The most common side effects of XYWAV (which also contains oxybate like XYWAV) in children include:

- nausea
- bedwetting
- vomiting
- headache
- weight decrease
- decreased appetite
- dizziness
- sleep walking

These are not all the possible side effects of XYWAV. **For more information, ask your doctor or pharmacist.**
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XYWAV?

- Store XYWAV in the original bottle prior to mixing with water. After mixing with water, store XYWAV in the pharmacy containers with child-resistant caps provided by the pharmacy.
- Store XYWAV at room temperature between 68°F to 77°F (20°C to 25°C).
- XYWAV solution prepared after mixing with water should be taken within 24 hours.
- When you have finished using a XYWAV bottle:
  - empty any unused XYWAV down the sink drain.
  - cross out the label on the XYWAV bottle with a marker.
  - place the empty XYWAV bottle in the trash.
- XYWAV comes in a child-resistant package.

Keep XYWAV and all medicines out of the reach of children and pets.

General information about the safe and effective use of XYWAV.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XYWAV for a condition for which it was not prescribed. Do not give XYWAV to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about XYWAV that is written for health professionals.

What are the ingredients in XYWAV?

Active ingredient: calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate (gamma-hydroxybutyrate (GHB).

Inactive ingredients: purified water and sucralose.

Distributed By:
Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304
For more information, go to www.XYWAVXYREMREMS.com or call the XYWAV and XYREM REMS at 1-866-997-3688.
This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: ##/202#

8 Pages Draft Labeling have been withheld in full as b4 (CCI/TS) Immediately following this page

INSTRUCTIONS FOR USE
XYWAV™ (ZYE wave)
(calcium, magnesium, potassium, and sodium oxybates)
oral solution, CIII

This Instructions for Use contains information on how to take XYWAV. Read this Instructions for Use carefully before you (or your child) start taking XYWAV and each time you (or your child) get a refill. There may be new information. This information does not take the place of talking to your doctor about your (or your child's) medical condition or treatment.

Important Information:

- **Your doctor will provide instructions to take XYWAV 2 times a nightor1 time a night.**
  - **For 2 times a night, you will need to split your (or your child's) prescribed XYWAV dose into 2 separate pharmacy containers for mixing.**
  - **For 1 time a night, you will use the dosing syringe to draw up your prescribed XYWAV dose and empty the dose into 1 pharmacy container for mixing. You will only need 1 pharmacy container to prepare your dose.**
- **You (or your child) should take XYWAV while in bed. Lie down immediately after taking XYWAV and remain in bed afterwards.**
- **You will need to mix XYWAV with water before you take or give your child the dose.**
- **Safely store the prepared XYWAV doses and take within 24 hours after mixing. If the prepared dose was not taken within this time, throw the mixture away. See "Throwing away (disposing of) XYWAV" section below for instructions about how to safely throw away XYWAV.**
- **The pharmacy container(s) may be rinsed out with water and emptied into the sink drain.**

Supplies you will need for mixing and taking (or giving your child) XYWAV. See Figure A:

- Bottle of XYWAV medicine
- Dosing syringe for measuring and dispensing the XYWAV dose
- Measuring cup that is able to measure about ¼ cup of water (not provided with the XYWAV shipment)
- 1 or 2 **empty** pharmacy containers with child-resistant caps for mixing, storing, and taking the XYWAV doses
- Alarm clock (not pictured, which may be included in the first shipment)
- Medication Guide

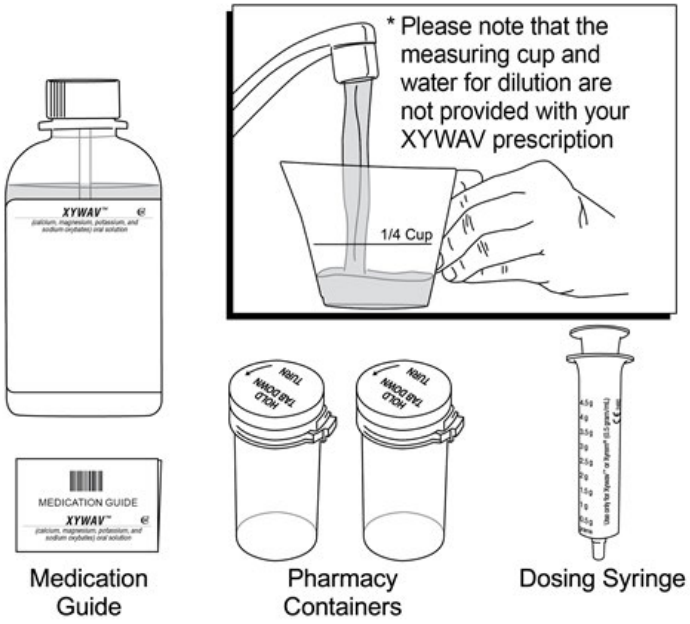


Figure A

Note: If you or your child are prescribed XYWAV 2 times a night, see the instructions for 2 times a night dosing. If you are prescribed XYWAV 1 time a night, see the instructions for 1 time a night dosing.

2 times a night dosing

Step 1: Setup

- Take the XYWAV bottle, syringe, and pharmacy containers out of the shipping box.
- Take the syringe out of the plastic wrapper. Use only the syringe provided with the XYWAV prescription.
- Fill a measuring cup (not provided) with about ¼ cup of water available for mixing your (or your child's) dose.

- **Make sure the pharmacy containers are empty.**
- Open both pharmacy containers by holding the tab under the cap and turning counterclockwise (to the left). See Figure B.

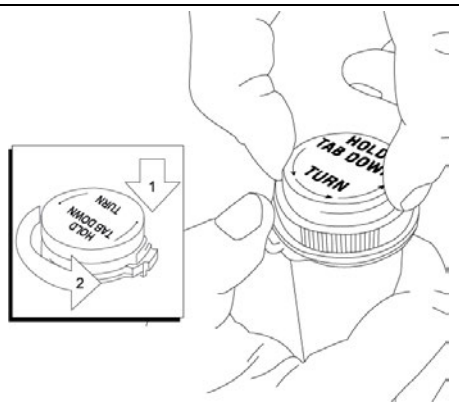


Figure B

- Remove the tamper evident band by pulling at the perforations and then remove the child-resistant bottle cap from the XYWAV bottle by pushing down while turning the cap counterclockwise. See Figure C.

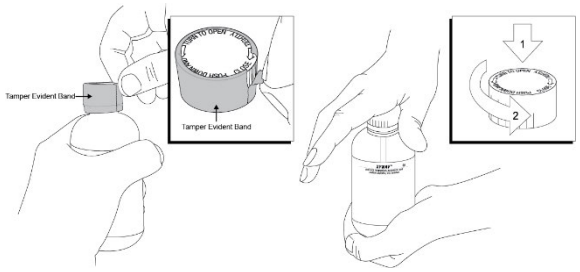


Figure C

Step 2. Prepare the first XYWAV dose (prepare before bedtime).

Place the XYWAV bottle on a hard, flat surface and grip the bottle with one hand. Firmly press the syringe into the center opening of the bottle with the other hand. See Figure D.

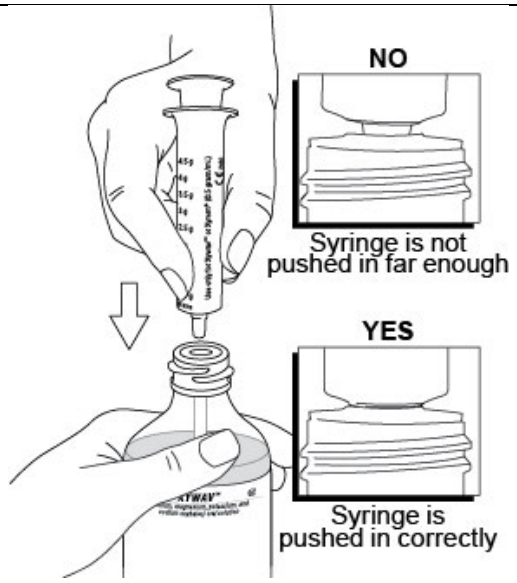
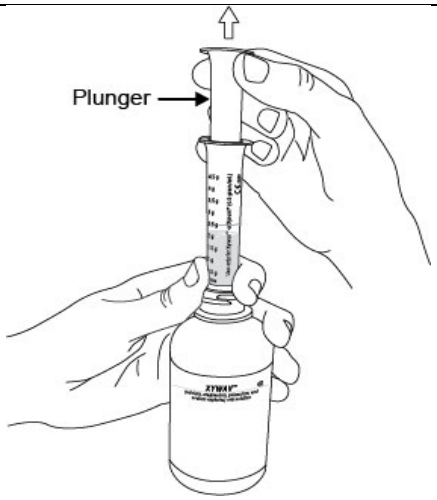
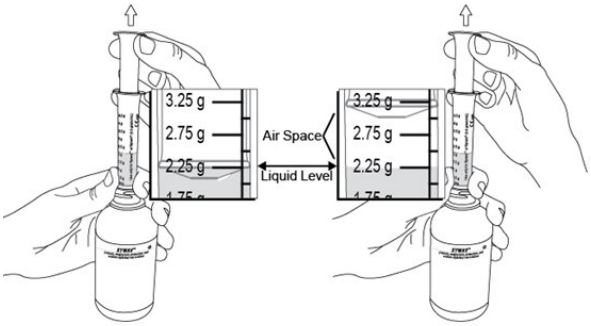
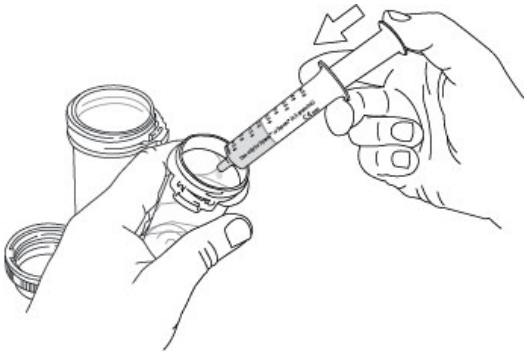


Figure D

Pull back on the plunger until the medicine flows into the syringe and the liquid level is lined up with the marking on the syringe that matches your or your child's dose. See Figure E.	 **Figure E** **Note: The XYWAV medicine will not flow into the syringe unless you keep the bottle upright.**
Figure F shows an example of drawing up a 2.25 g dose of XYWAV. Figure G shows an example if an air space forms when drawing up the medicine. **Note:** If an air space forms between the plunger and the liquid when drawing up the medicine, line up the liquid level with the marking on the syringe that matches your (or your child's) dose. See Figure G.	 **Figure F** **Figure G**
• After you draw up the first divided dose, remove the syringe from the opening of the XYWAV bottle. • Empty all of the medicine from the syringe into one of the provided **empty** pharmacy containers by pushing down on the plunger until it stops. See Figure H.	 **Figure H**

- Using a measuring cup, pour about ¼ cup of water into the pharmacy container. **Be careful to add only water to the pharmacy container and not more XYWAV.**
- **All shipped bottles of XYWAV contain the concentrated medicine. Water for mixing the medicine is not provided in the shipment.**
- Place the child-resistant cap provided with the filled pharmacy container on the pharmacy container and turn the cap clockwise (to the right) until it clicks and locks into its child-resistant position. See Figure I.

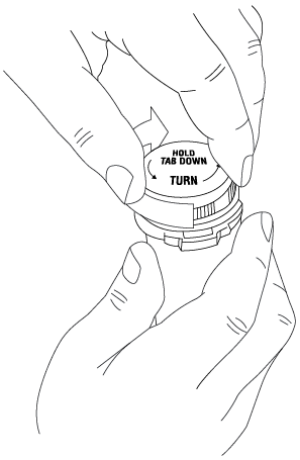


Figure I

Step 3. Prepare the second XYWAV dose (prepare before bedtime)

- Repeat Step 2 drawing up the amount of medicine prescribed for your (or your child's) second dose:
  - emptying the syringe into the second pharmacy container
  - adding about ¼ cup of water and
  - closing the pharmacy container

Step 4. Store the prepared XYWAV doses

- Put the cap back on the XYWAV bottle and store the XYWAV bottle and both prepared doses in a safe and secure place. Store in a locked place if needed.
- Keep the XYWAV bottle and both prepared XYWAV doses out of the reach of children and pets.
- Rinse the syringe out with water and squirt the liquid into the sink drain by pushing down on the plunger until it stops.

Step 5. Take or give the first XYWAV dose

- At bedtime, and before you take (or give) the first XYWAV dose, put the second XYWAV dose in a safe place. Caregivers should make sure all XYWAV doses are kept in a safe place until given. You may want to set an alarm clock for 2½ to 4 hours later to make sure you wake up to take (or give) the second dose.
- When it is time to take (or give) the first XYWAV dose, remove the cap from the pharmacy container by pressing down on the child-resistant locking tab and turning the cap counterclockwise.
- Drink (or have your child drink) all of the first XYWAV dose while sitting in bed. Put the cap back on the first pharmacy container and immediately lie down to sleep (or have your child lie down to sleep).
- You (or your child) should fall asleep soon. Some people fall asleep within 5 minutes and most fall asleep within 15 minutes. Some patients take less time to fall asleep, and some take more time. The time it takes you (or your child) to fall asleep might be different from night to night.

Step 6. Take or give the second XYWAV dose

- When you wake up 2½ to 4 hours later for your (or your child's) second dose of XYWAV, take the cap off the second pharmacy container.
- If you (or your child) wake up before the alarm and it has been at least 2½ hours since the first XYWAV dose, turn off the alarm and take (or give your child) the second XYWAV dose.
- Drink (or have your child drink) all of the second XYWAV dose while sitting in bed. Put the cap back on the second pharmacy container and immediately lie down (or have your child lie down) to continue sleeping.

1 time a night dosing

Step 1: Setup

- Take the XYWAV bottle, syringe, and 1 pharmacy container out of the shipping box.
- Take the syringe out of the plastic wrapper. Use only the syringe provided with the XYWAV prescription.
- Fill a measuring cup (not provided) with about ¼ cup of water available for mixing with your dose.

- **Make sure the pharmacy container is empty.**
- Open the pharmacy container by holding the tab under the cap and turning counterclockwise (to the left). See Figure B.

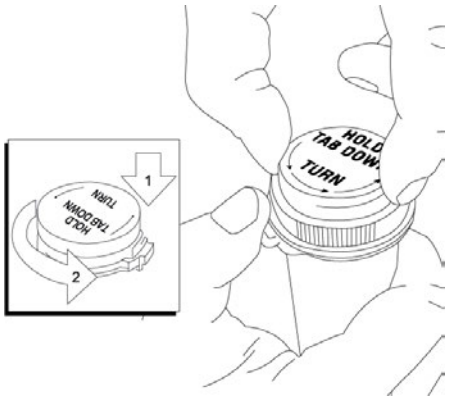


Figure B

- Remove the tamper evident band by pulling at the perforations and then remove the child-resistant bottle cap from the XYWAV bottle by pushing down while turning the cap counterclockwise. See Figure C.

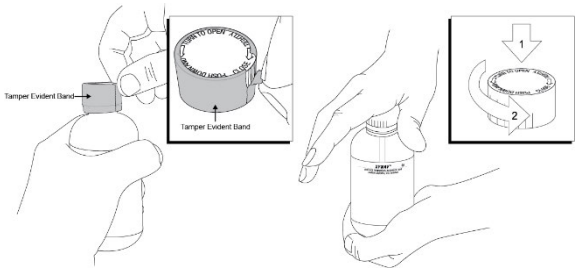


Figure C

Step 2. Prepare the XYWAV dose (prepare before bedtime).

Place the XYWAV bottle on a hard, flat surface and grip the bottle with one hand. Firmly press the syringe into the center opening of the bottle with the other hand. See Figure D.

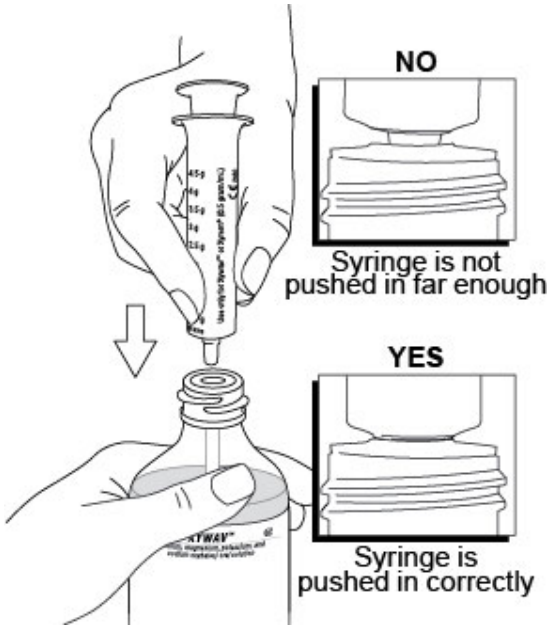


Figure D

Pull back on the plunger until the medicine flows into the syringe and the liquid level is lined up with the marking on the syringe that matches your dose. You may need to draw up the medicine a second time to make up your total prescribed dose.

See Figure E.

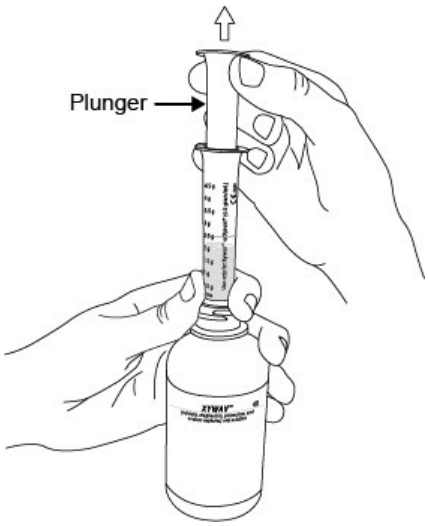


Figure E

Note: The XYWAV medicine will not flow into the syringe unless you keep the bottle upright.

Figure F shows an example of drawing up 2.25 g of XYWAV. Figure G shows an example if an air space forms when drawing up the medicine.

Note: If an air space forms between the plunger and the liquid when drawing up the medicine, line up the liquid level with the marking on the syringe that matches your dose. See Figure G.

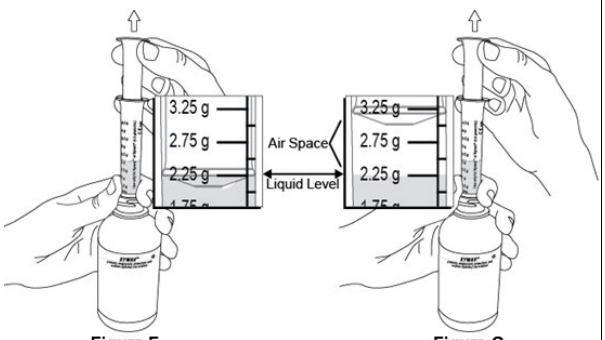


Figure F **Figure G**

- After you draw up the medicine, remove the syringe from the opening of the XYWAV bottle.
- Empty all of the medicine from the syringe into a single provided **empty** pharmacy container by pushing down on the plunger until it stops. See Figure H.
- For doses requiring 2 draws from the XYWAV bottle, empty the second draw into the same pharmacy container.

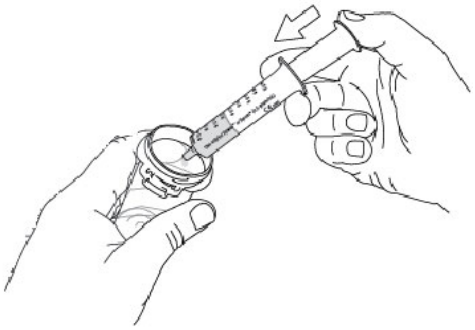


Figure H

- After you finish adding your XYWAV dose to the pharmacy container, use a measuring cup to pour about ¼ cup of water into the pharmacy container. **Be careful to add only water to the pharmacy container and not more XYWAV.**
- **All shipped bottles of XYWAV contain the concentrated medicine. Water for mixing the medicine is not provided in the shipment.**
- Place the child-resistant cap provided with the filled pharmacy container on the pharmacy container and turn the cap clockwise (to the right) until it clicks and locks into its child-resistant position. See Figure I.

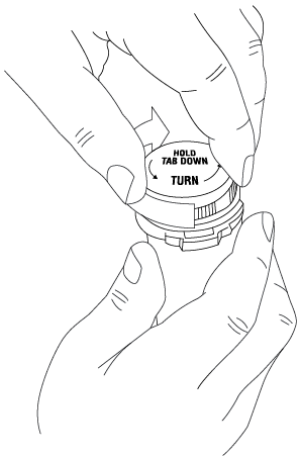


Figure I

Step 3. Store the prepared XYWAV dose

- Put the cap back on the XYWAV bottle and store the XYWAV bottle and the prepared dose in a safe and secure place. Store in a locked place if needed.
- Keep the XYWAV bottle and the prepared XYWAV dose out of the reach of children and pets.
- Rinse the syringe out with water and squirt the liquid into the sink drain by pushing down on the plunger until it stops.

Step 4. Take the XYWAV dose

- Make sure the XYWAV dose is kept in a safe place until taken.
- When it is time to take the XYWAV dose, remove the cap from the pharmacy container by pressing down on the child-resistant locking tab and turning the cap counterclockwise.
- Drink all of the XYWAV dose while sitting in bed. Put the cap back on the pharmacy container and immediately lie down to sleep.
- You should fall asleep soon. Some people fall asleep within 5 minutes and most fall asleep within 15 minutes. Some patients take less time to fall asleep, and some take more time. The time it takes you to fall asleep might be different from night to night.

How should I store XYWAV?

- Store XYWAV in the original bottle prior to mixing with water. After mixing, store XYWAV in the pharmacy containers provided by the pharmacy. The caps on the original bottle and pharmacy containers are child-resistant.
- Store XYWAV at room temperature between 68°F to 77°F (20°C to 25°C).
- XYWAV solution prepared after mixing with water should be taken within 24 hours or emptied down the sink drain.

Throwing away (disposing of) XYWAV

- When you have finished using a XYWAV bottle:
  - empty any unused XYWAV down the sink drain
  - cross out the label on the XYWAV bottle with a marker (not provided with the XYWAV shipment)
  - place the empty XYWAV bottle in the trash
- **Keep XYWAV and all medicines out of the reach of children and pets.**

Distributed By:
Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: ##/202#

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARIA T NGUYEN
07/20/2021 07:57:26 AM
DMPP-OPDP review of calcium oxybate, potassium oxybate, magnesium (XYWAV) NDA 212690 S006 MG and IFU

ALINE M MOUKHTARA
07/20/2021 05:08:20 PM

NYEDRA W BOOKER
07/20/2021 07:11:11 PM

LASHAWN M GRIFFITHS
07/20/2021 11:28:40 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 14, 2021

To: Ranjit Mani, Clinical Reviewer
Division of Neurology Products 1 (DN1)

Teresa Wheelous, Regulatory Project Manager, DN1

Tracy Peters, Associate Director for Labeling, DN1

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII

NDA: 212690 s6

In response to the DN1 consult request dated March 26, 2021, OPDP has reviewed the proposed product labeling (PI) and Medication Guide and Instructions for Use (IFU) for XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII (Xywav). This supplement (s6) pertains to the indication for idiopathic hypersomnia in adults.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN1 on July 7, 2021 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

31 Pages Draft Labeling have been withheld in full as b4 (CCI/TS) immediately following this page

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/s/

DHARA SHAH
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 13, 2021
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 212690/S-006
Product Name and Strength:	Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Jazz Pharmaceuticals Ireland Limited
FDA Received Date:	December 18, 2020 and February 12, 2021
OSE RCM #:	2021-336
DMEPA Safety Evaluator:	Justine Kalonia, PharmD
DMEPA (Acting) Team Leader:	Celeste Karpow, PharmD, MPH

1 REASON FOR REVIEW

Jazz Pharmaceuticals Ireland Limited submitted a Prior Approval Efficacy supplement (S-006) for Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution to expand the indication of Xywav to include the treatment of adult patients with Idiopathic Hypersomnia (IH). Subsequently, the Division of Neurology 1 (DN 1) requested that we review the proposed revisions to the Xywav prescribing information (PI), medication guide (MG), and instructions for use (IFU), for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E -N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 below includes the identified medication error issues with the submitted revisions the prescribing information (PI), medication guide (MG), and instructions for use (IFU) our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	With the addition of the proposed "once nightly" regimen, the term "per night orally" could be improved for clarity.	We are concerned "per night orally" dosing regimens may be misinterpreted when used in reference to both twice nightly and once nightly dosing regimens, such that users may mistake "per night	Consider revising the language, "per night orally" (b) (4)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		orally" to mean one dose instead of two doses or vice versa.	(b) (4) "as one dose" (for the once nightly regimen).
Highlights of Prescribing Information			
1.	There is no statement to alert the healthcare provider that additional dosing information is in the Full Prescribing Information (FPI).	We are concerned that the specifics of the dosing regimens may not be captured in the Highlights of Prescribing Information (HPI).	Consider adding a statement under Dosage and Administration heading in Highlights of PI to alert the healthcare provider that additional important information is in the FPI. For example, "See Full Prescribing Information for completing dosing instructions."
2.	We note the Sponsor has deleted the table demonstrating equal nightly doses from the HPI and added language from the bottom of that table about unequal doses as a bullet point in the HPI.	This may lead to misinterpretation.	Consider adding a bullet point to alert providers that equal divided doses are still acceptable for this product or revise the current bullet point. For example, consider revising "Some patients may achieve better responses with unequal doses at bedtime and 2.5 to 4 hours later" (b) (4)
3.	For "Dosage for Adult Patients with Idiopathic Hypersomnia", we note the 3rd bullet does not include a unit of measure after "6".	It is unclear what "6" is, and as presented it may be misinterpreted as "6 total nightly doses".	Add the unit of measure, g, after the number "6" to prevent medication errors.
4.	(b) (4)		
Full Prescribing Information – Section 2 Dosage and Administration			
1.	(b) (4)		

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) [redacted]	(b) (4) [redacted]	(b) (4) [redacted]
Full Prescribing Information – Section 17 Patient Counseling			
1.	The following statement under the section titled *Administration Instructions* does not apply to all patients: "Inform patients that their nightly dose may require multiple draws. Instruct patients on how to perform the draws from the bottle."	Informing all patients that their nightly dose may require multiple draws could lead to confusion for patients whose dose does not require multiple draws. Providers will inform patients whose dose requires multiple draws when prescribing the product.	Consider revising the sentence "Inform patients that their nightly dose may require multiple draws. Instruct patients on how to perform the draws from the bottle." (b) (4) [redacted]
Medication Guide			
1.	The following statement could be revised for clarity: "If you or your child have been prescribed XYWAV	The statement is redundant and potentially misleading.	Revise the statement, "If you or your child have been prescribed XYWAV 2 times a night: (b) (4) [redacted] "If you (or your

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	2 times a night: (b) (4) [redacted]		child) are prescribed XYWAV 2 times a night, divide the total nightly dose into 2 doses to be taken at bedtime and 2½ to 4 hours later."
Instructions for Use			
1.	The proposed new section of the IFU, *ONCE NIGHTLY DOSING*, contains instructions specifically for the proposed indication of idiopathic hypersomnia in adult patients, (b) (4) [redacted]	Caregivers of pediatric patients taking Xywav for narcolepsy may confuse these instructions as an option for once nightly dosing, which is not the intended use for that age group and indication.	We recommend you specify the proposed indication and patient population of *idiopathic hypersomnia in adult patients* in the header for the *ONCE NIGHTLY DOSING* IFU. (b) (4) [redacted]

4 CONCLUSION

Our evaluation of the proposed Xywav prescribing information (PI), medication guide (MG), and instructions for use (IFU) identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Xywav that Jazz Pharmaceuticals Ireland Limited submitted on February 12, 2021.

Table 3. Relevant Product Information for Xywav

Initial Approval Date	July 21, 2020
Active Ingredient	calcium, magnesium, potassium, and sodium oxybates
Indication	• Cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy (**approved** July 21, 2020) • Idiopathic Hypersomnia (IH) in adults (**proposed** indication under review)
Route of Administration	oral
Dosage Form	solution
Strength	0.5 g/mL total salts (equivalent to 0.413 g/mL of oxybate)
Dose and Frequency	**Adult Patients with Narcolepsy:** • Initiate dose at 4.5 g per night, (b) (4) • Titrate to effect in increments of up to 1.5 g per night per week. • Recommended dosage range is 6 g to 9 g per night • (b) (4) **Pediatric Patients with Narcolepsy (7 years of age and older):** • Recommended starting dose, titration regimen, and maximum total nightly dose are based on body weight.

Table 2: Recommended (b) (4) XYWAV 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 nightly dose of XYWAV may be given at bedtime or after an initial period of sleep.

** If XYWAV 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 nightly doses at bedtime and 2.5 to 4 hours later.

(b) (4)

	(b) (4)
How Supplied	Amber bottle containing 180 mL of solution
Storage	Stored between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) (see USP Controlled Room Temperature).
Container Closure	Amber bottle with child-resistant caps

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 13, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 212690. Our search identified 3 previous reviews,[a,b,c] and we considered our previous recommendations to see if they are applicable for this current review.

Table 4. Summary of Previous DMEPA Reviews for Xywav

OSE RCM #	Review Date	Summary of Recommendations
2020-132	June 11, 2020	We reviewed the proposed labels and labeling and provided recommendations to the Division and Applicant.
2020-132-1	June 17, 2020	We reviewed the revised container label and provided recommendations to the Applicant.
2020-132-2	June 24, 2020	We found the Applicant had implemented all of our recommendations for the container label and we had no additional recommendations at the time.

[a] Kalonia, J. Label and Labeling Review for Xywav (NDA 212690). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 11. RCM No.: 2020-132.

[b] Kalonia, J. Label and Labeling Review Memo for Xywav (NDA 212690). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 17. RCM No.: 2020-132-1.

[c] Kalonia, J. Label and Labeling Review Memo for Xywav (NDA 212690). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 24. RCM No.: 2020-132-2.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Xywav labels and labeling submitted by Jazz Pharmaceuticals Ireland Limited received on February 12, 2021.

- Prescribing Information, Instructions for Use, and Medication Guide (image not shown), available from: \\CDSESUB1\evsprod\nda212690\0105\m1\us\annotated-draft-labeling-text---word.docx

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JUSTINE H KALONIA
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s006

RISK ASSESSMENT AND RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	212690; 021196
Supplement Number, Date Received	Supplement 006 received February 12, 2021 (sequence 0105, NDA 212690); amended June 21, June 25, July 21, August 2, August 5 and August 10, 2021 Supplement 036 received February 12, 2021 (sequence 0566, NDA 021196); amended June 21, June 25, July 21, August 2, August 5 and August 10, 2021
Action Date	August 12, 2021
OSE RCM #	2021-313
Reviewer Name(s)	Donella Fitzgerald, PharmD Anahita Tavakoli, MA
Team Leader	Jacqueline Sheppard, PharmD
Deputy Division Director	Doris Auth, PharmD
Review Completion Date	August 11, 2021
Subject	Review of proposed REMS Modification
Established Name	Calcium, magnesium, potassium and sodium oxybates (Xywav); Sodium oxybate (Xyrem)
Trade Name	Xywav; Xyrem
Name of Applicant	Jazz Pharmaceuticals, Inc.
Therapeutic Class	Central nervous system depressants
Formulation(s)	0.5 g/mL oral solutions

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EXECUTIVE SUMMARY

This is a review of the proposed modifications to the Risk Evaluation and Mitigation Strategy (REMS) for Xywav and Xyrem (calcium, magnesium, potassium and sodium oxybates; sodium oxybate), (NDA 212690/S-006; NDA 021196/S-036), submitted by Jazz Pharmaceuticals, Inc. (Jazz) on February 12, 2021 and amended June 21, June 25, July 21, August 2, August 5 and August 10, 2021.

The REMS for Xyrem was originally approved on February 27, 2015 and the REMS for Xywav was approved on July 21, 2020. The two drugs are subject to the same REMS, known as the Xywav and Xyrem REMS, that mitigates the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Xywav and Xyrem. The most recent REMS modification was approved on February 11, 2021. The REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Jazz submitted the REMS modification as part of a Xywav efficacy supplement for a new idiopathic hypersomnia (IH) indication. Jazz's proposed modifications to the REMS consists of:

- Changes to the REMS materials to align with the proposed indication of Idiopathic Hypersomnia
- Changes to the REMS assessment timetable
- Change of the reporting interval for the Knowledge, Attitude, and Behavior Surveys from annually to every other year

In addition, the following modifications were communicated during the course of the review:

- Changes to the *Patient Counseling Checklist* to capture additional information regarding concomitant medication and alcohol use

The Division of Risk Management finds the proposed modifications to the Xywav and Xyrem REMS to be acceptable and recommends approval of the REMS Modification. There are changes to the Timetable for Submission of Assessments of the REMS and the Assessment Plan. The modification does not impact the REMS goals, elements, or ETASU.

1 Introduction

This review evaluates the proposed modification to the REMS for Xywav and Xyrem (calcium, magnesium, potassium and sodium oxybates; sodium oxybate), (NDA 212690/S-006; NDA 021196/S-036), submitted by Jazz Pharmaceuticals, Inc. (Jazz) on February 12, 2021[1] and amended June 21, June 25, July 21, August 2, August 5 and August 10, 2021.

Jazz submitted the REMS modification as part of a Xywav efficacy supplement for a new idiopathic hypersomnia (IH) indication. The modification proposes changes to the materials and supporting document to incorporate the new indication in the REMS, as well as a revised timetable for submission of assessments in the REMS document.

2 Background

2.1 PRODUCT INFORMATION

For updated assessment of the Product Information, refer to the June 15, 2021 interim review[2].

2.2 REGULATORY HISTORY

- **07/17/02:** Xyrem, NDA 021196, approved with a Risk Minimization Action Plan.
- **02/27/15:** Xyrem REMS approved.
- **07/21/20:** Xywav, NDA 212690, approved with a REMS and joined the existing Xyrem REMS to form the Xywav and Xyrem REMS.
- **02/12/21:** Xywav and Xyrem REMS modification submitted as part of the Xywav Prior Approval Efficacy Supplement (Xywav NDA 212690/S-006; Xyrem NDA 021196/S-036).
- **6/15/21:** Interim Comments (IC) on the REMS materials issued. Agency recommendations were communicated regarding the collection of indication on the prescription forms, absence of a Spanish certificate of translation for the REMS website and additional editorial changes on several of the REMS materials.
- **06/21/21:** Jazz submitted a REMS amendment that consisted of changes to the Timetable for Submission of Assessments (REMS document) and reporting interval for the Knowledge, Attitude and Behavior Surveys (Supporting document).
- **6/23/21:** Information Request (IR) issued regarding Agency proposed changes to the Patient Counseling Checklist concerning concomitant medication use.
- **6/25/21:** Jazz submitted a REMS amendment in response to the IC sent June 15, 2021.
- **7/9/21:** Jazz submitted a response to the IR issued on June 23, 2021. Their response consisted of clarifying questions regarding the IR (the questions were also emailed to the FDA on July 6th, 2021). They did not submit the *Patient Counseling Checklist*.
- **7/14/21:** The Agency issued a General Advice letter to respond to Jazz's clarifying questions submitted on July 9, 2021.
- **7/21/21:** Jazz submitted a REMS amendment in response to the IR issued on June 23, 2021.
- **7/28/21:** IC on the REMS materials issued. Agency recommendations were communicated regarding necessary changes to the Timetable for Assessments in the REMS document, further changes to the *Patient Counseling Checklist* and revisions to other materials based on updated draft labeling.
- **8/2/21:** Jazz submitted a REMS amendment in response to the IR issued on July 28, 2021.
- **8/5/21:** IC on the REMS materials issued. Agency recommendations were communicated regarding the *Patient Counseling Checklist*, *Prescriber Brochure* and *Prescription Forms*.
- **8/5/21:** Jazz submitted a labeling/REMS amendment. The REMS materials were revised to align with draft labeling changes. Jazz also proposed additional changes to the concomitant medication language in the *Patient Counseling Checklist*.
- **8/9/21:** IR issued that recommended revisions to Jazz's proposed changes to the concomitant medication language in the *Patient Counseling Checklist*.
- **8/10/21:** Jazz submitted a REMS amendment in response to the IC issued August 5, 2021 and the IR issued August 9, 2021.

3 Therapeutic Context and Treatment Options

For updated assessment of the Therapeutic Context and Treatment Options, refer to the June 15, 2021 interim review.[3]

4 Benefit Assessment

The pivotal trial (JZP080-301/Study 2, NCT03533114) supporting the efficacy of Xywav for the treatment of idiopathic hypersomnia (IH) in adults as a once or twice nightly regimen was a double-blind, placebo-controlled, randomized-withdrawal study. It consisted of a minimum 10-week open label treatment titration and optimization period (with up to 4 additional weeks) to allow for an optimally effective and tolerable dose and regimen, followed by a 2-week stable dose period (SDP), a 2-week double-blind, randomized withdrawal period (DB RWP), and a 24 week open label safety extension period. One hundred fifteen patients were randomized 1:1 to continue treatment with Xywav or to placebo (56 Xywav, 59 placebo) in the 2-week DB RWP.

The primary efficacy endpoint for Study 2 was the change in Epworth Sleepiness Scale[a] (ESS) score, as a measure of reduction in excessive daytime sleepiness from the end of the SDP to the end of the DB RWP. The Applicant reported that the study results demonstrated that patients taking stable doses of Xywav who were withdrawn from Xywav treatment and randomized to placebo during DB RWP experienced significant (p-value<0.0001) worsening in ESS score compared with patients randomized to continue treatment with Xywav across all dosing regimens[4], as shown in the below table:

MEDIAN CHANGE IN EPWORTH SLEEPINESS SCALE (ESS) for Study 2

ESS Score		
	Placebo (N=59)	**XYWAV (N=56)**
Baseline End of 2-Week SDP		
Median	5.0	6.5
End of 2-Week DB RWP		
Median	14.0	7.0
Median Change from End of 2-Week SDP to End of 2-Week DB RWP		
Median	8.0	0.0
p-value	<0.0001	

SDP=Stable Dose Period
DB RWP=Double-blind Randomized-withdrawal Period

[a] Epworth Sleepiness Scale is an 8-item self-reported questionnaire by which patients rate their perceived likelihood of falling asleep during usual daily life activities. Each of the 8 items on the ESS is rated from 0 (would never doze) to 3 (high chance of dozing), with a maximum score of 24.

The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness for the treatment of idiopathic hypersomnia in adults.[5]

5 Risk Assessment and Safe-Use Conditions

Xywav is under review for a new indication for IH in adults. The safety population for the IH study program consists of 154 adults with a mean Xywav exposure of 204 days. Exposure included titration, the randomized withdrawal period, and an open-label extension. 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%) and parasomnia (5%).[6]

5.1 SERIOUS ADVERSE REACTIONS

There were no fatal treatment emergent adverse events. Four participants reported 9 serious adverse events (SAEs). One participant each experienced SAEs of non-cardiac chest pain, rhabdomyolysis, and syncope; 1 participant with congenital kidney disease experienced 5 SAEs of nephrolithiasis and an SAE of pyelonephrolithiasis. All SAEs were assessed by the Investigator as not related to study drug.

5.2 CENTRAL NERVOUS SYSTEM DEPRESSION

The Xywav label includes a boxed warning for central nervous system (CNS) depression. Because Xywav is a CNS depressant, respiratory depression can occur with use. In the clinical trial data for the IH indication, there was one report of respiratory depression (1 Xywav, 0 naïve[b]), three reports of impaired attention or cognition (1 Xywav, 2 naïve), ten reports of depressed consciousness [somnolence/syncope/sedation] (3 Xywav, 7 naïve) and four reports of confusion (3 Xywav, 1 naïve). The approved label includes a warning to monitor for impaired motor/cognitive function, and to use caution when considering the concurrent use of Xywav with other CNS depressants.

5.3 ABUSE AND MISUSE

The Xywav label includes a boxed warning and REMS for abuse and misuse. The active moiety of Xywav is gamma-hydroxybutyrate (GHB); the abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma and death.[7] Participants in the clinical trial for the IH efficacy supplement were monitored for signs of abuse of study drug via routine medical monitoring and compliance audits for protocol deviations and lost, stolen, missing or unaccounted-for medicine. Jazz investigated 14 reports for abuse potential, but the adjudication process did not identify any participants with evidence of abuse or misuse.[8]

Mitigation of the risk of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion is the goal of the Xywav and Xyrem REMS. Approval of the IH indication would require changes to the REMS to incorporate the new indication in the materials. These changes would not affect how the REMS operates, patient access to the drug, or the burden on the health care delivery system.

[b] Naïve – study participants not currently taking Xyrem or a stimulant or alerting agent

6 Expected Postmarket Use

Xywav is only available through the Xywav and Xyrem REMS Program that is designed to mitigate the risk of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion. Due to these serious risks, the REMS requires a number of safe use conditions for the stakeholders, including program enrollment, education, counseling and restricted distribution. Patients prescribed Xywav for the IH indication will be subject to the REMS requirements.

7 Review of Proposed REMS Modifications

7.1 REMS GOAL

The Applicant did not propose changes to the REMS Goal.

7.2 REMS DOCUMENT

The Applicant did not propose further changes to the REMS Document with the amendment submitted August 10, 2021.

Reviewer Comment: The REMS document is acceptable.

7.3 REMS REQUIREMENTS

7.3.1 Addition or Removal of ETASU

The Applicant did not propose addition or removal of ETASU.

7.3.2 REMS Participant Requirements and Materials

7.3.2.1 Healthcare Provider

7.3.2.1.1 Prescriber Brochure – the Applicant addressed the Agency recommendations that were communicated in the IC issued August 5, 2021. No further changes were proposed.

7.3.2.1.2 Xywav Prescription Form - the Applicant addressed the Agency recommendations that were communicated in the IC issued August 5, 2021. No further changes were proposed.

7.3.2.1.3 Xyrem Prescription Form - the Applicant addressed the Agency recommendations that were communicated in the IC issued August 5, 2021. No further changes were proposed.

Reviewer Comment: The Prescriber Brochure, Xywav Prescription Form and Xyrem Prescription Form are acceptable.

7.3.2.2 Patients

The Applicant did not propose changes to the patient requirements or materials with the amendment submitted August 10, 2021.

Reviewer Comment: The patient materials are acceptable.

7.3.2.3 Pharmacies that dispense

7.3.2.3.1 Patient Counseling Checklist - the Applicant addressed the Agency recommendations that were communicated in the IC issued August 5, 2021 and the IR issued August 9, 2021. No further changes were proposed.

Reviewer Comment: The Patient Counseling Checklist is acceptable.

7.3.3 REMS Applicant Requirements and Materials

7.3.3.1 Operations

7.3.3.1.1 REMS Website - The Applicant did not propose additional changes to the REMS Website with the amendment submitted August 10, 2021.

Reviewer Comment: The REMS website is acceptable.

7.4 REMS ASSESSMENT TIMETABLE

The Applicant did not propose additional changes to the timetable for submission of assessments of the REMS.

Reviewer Comment: The REMS assessment timetable is acceptable.

8 Supporting Document

The REMS Supporting Document was changed to include the background of the REMS Modification currently under review. Additional changes were made to align with draft labeling for the IH indication. During the course of the review, Jazz also proposed to revise the text regarding the reporting interval for the Knowledge, Attitude, and Behavior Surveys. The reporting interval was changed from annually to every other year.

Reviewer Comment: The REMS Supporting Document is acceptable.

9 REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be addressed in the REMS Modification Approval letter. During the course of the REMS modification review, the Assessment Plan was revised to align with the additional indication, revisions to the Patient Counseling Checklist, and changes to the timetable when Knowledge, Attitude, and Behavior Surveys are to be performed.

The revised REMS Assessment Plan must include, but is not limited to, the following:

Program Implementation and Operations

1. REMS Enrollment Statistics (per reporting period and cumulatively)
   a. Patients:
      i. Number and percentage of newly enrolled patients stratified by age, geographic region (defined by US Census), indication, and gender
      ii. Number and percentage of active patients enrolled (patients who received at least one shipment of XYWAV or XYREM during the reporting period) stratified by age, geographic region (defined by US Census), and gender
      iii. Number and percentage of patients who have discontinued XYWAV or XYREM after receiving at least one shipment of XYWAV or XYREM. Include demographics of discontinued patients and reasons for discontinuation.
      iv. Number and percentage of patients who transitioned from XYREM to XYWAV
      v. Number and percentage of patients who transitioned from XYWAV to XYREM.
   b. Healthcare Providers:
      i. Number and percentage of newly certified healthcare providers stratified by professional designation (i.e. MD, DO, PA, NP), medical specialty, and geographic region (defined by US Census)
      ii. Number and percentage of active certified healthcare providers (healthcare providers who have written at least one prescription for XYWAV or XYREM during the reporting period) stratified by professional designation (i.e. MD, DO, PA, NP), medical specialty, and geographic region (defined by US Census)
      iii. Number of patients by current enrolled prescriber.
   c. Certified Pharmacy
      i. If the Certified Pharmacy was decertified during the reporting period and reasons for decertification.
2. Utilization Data (per reporting period and cumulatively)
   a. Number and percentage of XYREM prescriptions (new and refills) dispensed
   b. Number and percentage of XYWAV prescriptions (new and refills) dispensed
   c. Number and percentage of XYREM bottles and shipments sent
   d. Number and percentage of XYWAV bottles and shipments sent.

3. REMS Program Operation and Performance Data (per reporting period and cumulatively)
    a. REMS Program Central Database Report
        i. Number and percentage of contacts by stakeholder type (e.g. patients, healthcare providers, pharmacy, other)
        ii. Summary of reasons for contacts (e.g., enrollment questions) by reporter (authorized representative, patient, healthcare provider, other)
        iii. Call center report with number of calls received and a summary of reasons for calls by stakeholder type
        iv. Summary of frequently asked questions by stakeholder type and topic
        v. Summary of any REMS-related problems identified and a description of any corrective actions taken
        vi. If the summary reason for the calls indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues
        vii. Summary of program or system problems and a description of any corrective actions taken.

4. REMS Program Compliance (per reporting period and cumulatively)
    a. Audits: Summary of audit activities including but not limited to:
        i. A copy of the audit plan for each audited stakeholder.
        ii. The number of audits expected, and the number of audits performed
        iii. The number and type of deficiencies noted
        iv. For those with deficiencies noted, report the status of corrective and preventative action (CAPA) proposed to address the deficiencies. The status to include completion status.
        v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
        vi. Provide details on deviations for the CAPA proposed, including timelines, and mitigating steps to address the deviations
        vii. Confirm documentation of completion of training for relevant staff
        viii. Review of accumulative findings to identify any trends of potential repeat issues, and steps to be taken to address these findings
        ix. A summary report of the processes and procedures that are implemented to be in compliance with the REMS requirements.
    b. A summary report of noncompliance, associated corrective and preventive actions (CAPA) plans, and the status of CAPA plans including but not limited to:
        i. A copy of the Noncompliance Plan which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
        ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:

1) The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
2) The source of the noncompliance data
3) The results of root cause analysis
4) What action(s) were taken in response.

c. Healthcare Providers
   i. Number and percentage of certified prescribers who were disenrolled during the reporting period and reasons for disenrollment. Include if any prescribers were re-certified.
   ii. Number of disenrolled prescribers who were associated with a XYWAV and XYREM prescription and number of disenrolled prescribers associated with a XYWAV and XYREM shipment
   iii. Number and percentage of XYWAV prescriptions filled from a prescriber who was not enrolled.
   iv. Number and percentage of XYREM prescriptions filled from a prescriber who was not enrolled.

d. Certified Pharmacy
   i. Number and percentage of XYWAV prescriptions dispensed for more than a 30 days' supply (first fill) or more than a 90 days' supply (refills) and reasons
   ii. Number and percentage of XYREM prescriptions dispensed for more than a 30 days' supply (first fill) or more than a 90 days' supply (refills) and reasons
   iii. Number and percentage of XYWAV shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and Risk Management Reports (RMRs) completed
   iv. Number and percentage of XYREM shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and Risk Management Reports (RMRs) completed
   v. Number and percentage of initial XYWAV shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist.
   vi. Number and percentage of initial XYREM shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist.

e. Patients
   i. Number and percentage of patients who were disenrolled from the program and reasons for disenrollment
   ii. Number and percentage of patients associated with more than one prescriber during their therapy
   iii. Number and percentage of patients prescribed a daily dose of XYWAV of >9 g
   iv. Number and percentage of patients prescribed a daily dose of XYREM of >9 g

v. Number and percentage of patients with overlapping prescriptions (more than one active prescription shipped)
vi. Number and percentage of patients with concurrent XYWAV and XYREM prescriptions
vii. Number of duplicate patients detected by the Certified Pharmacy
viii. Number and percentage of duplicate patients who were shipped XYWAV or XYREM under more than one name or identifier
ix. Number and percentage of patients who were shipped XYWAV or XYREM after being disenrolled
x. Number and percentage of patients who requested an early refill of XYWAV and reason for the request
   1) Number and percentage of requests approved
   2) Number and percentage of requests denied by the prescriber
   3) Number and percentage of requests denied by the Certified Pharmacy
   4) Number and percentage of patients with multiple requests for early refills.
xi. Number and percentage of patients who requested an early refill of XYREM and reason for request
   1) Number and percentage of requests approved
   2) Number and percentage of requests denied by the prescriber
   3) Number and percentage of requests denied by the Certified Pharmacy
   4) Number and percentage of patients with multiple requests for early refills.

Safe Use Behaviors

5. Pharmacy Notifications (per reporting period and cumulatively, for both XYWAV and XYREM)
   a. A summary of the notifications by pharmacies to prescribers for both XYWAV and XYREM. For each of the following situations, include the number and percentage of notifications, number of unique patients, the outcome of the pharmacy notification (e.g. counseled patient, discussed with prescriber and prescriber's designee) and outcome of XYWAV and XYREM prescription disposition (e.g. prescriber approved shipment, prescriber requested shipment hold, prescriber denied shipment, pharmacy approved shipment):
      i. Use with sedative-hypnotics indicated for sleep (e.g., eszopiclone, zaleplon, zolpidem, temazepam, suvorexant, quazepam, estazolam, flurazepam, triazolam, tasimelteon, ramelteon). Indicate specific actions taken by the prescriber and the prescriber rationale for continuing treatment in response to the notification including the following:
         - Treatment with Xywav/Xyrem will discontinue
         - Sedative hypnotic will be discontinued
         - Dosage of sedative hypnotic has been/will be reduced
         - Information unavailable
         - No action (continue sedative hypnotic with Xywav or Xyrem)
         - Prescriber's rationale for continued use of sedative hypnotic with Xywav or Xyrem

- Sedative hypnotic will not be taken at the same time as Xywav/Xyrem
- Sedative hypnotic will be taken at the same time as Xywav/Xyrem
- Sedative hypnotic will be taken as a sleep aid
- Sedative hypnotic will be taken for different indication per medical need
- Xywav/Xyrem dose regimen changed
- No rationale provided

ii. Benzodiazepines (e.g., diazepam, alprazolam or any not listed in metric 5.a.i.). Indicate specific actions taken by the prescriber and the prescriber rationale for continuing treatment in response to the notification including the following:
   - Treatment with Xywav/Xyrem will discontinue
   - Benzodiazepine will be discontinued
   - Dosage of benzodiazepine has been/will be reduced
   - Information unavailable
   - No action (continue benzodiazepine with Xywav or Xyrem)
   - Prescriber's rationale for continued use of benzodiazepine with Xywav or Xyrem
     - Benzodiazepine will not be taken at the same time as Xywav/Xyrem
     - Benzodiazepine will be taken at the same time as Xywav/Xyrem
     - Benzodiazepine will be taken as a sleep aid
     - Benzodiazepine will be taken for different indication per medical need
     - Xywav/Xyrem dose regimen changed
     - No rationale provided

iii. Use with other concomitant CNS-depressant medications (sedating antidepressants or antipsychotics, sedating anti-epileptics, sedating antihistamines, general anesthetics, muscle relaxants, opioid analgesics, or illicit CNS depressants)
iv. Patient report of alcohol use
v. Patient report of diagnosis of sleep apnea
vi. Patient report of diagnosis of asthma, COPD, or other conditions affecting breathing
vii. Suspected abuse, misuse, or diversion
viii. Alerts regarding potential abuse, misuse, or diversion on the patient profiles
ix. Prescription error
x. Early refill requests

6. Risk Management Reports (RMRs) (per reporting period and cumulatively, for both XYWAV and XYREM)
    a. Number and percentage of RMRs submitted
    b. Number and percentage of unique patients with a RMR
    c. Number and percentage of unique patients with multiple RMRs
    d. Number and percentage of alerts generated from RMRs
    e. Number and percentage of RMRs generated from early refill requests
    f. Number and percentage of RMRs generated for other reasons (list reasons)
    g. Number and percentage of prescriber-related RMRs
    h. Number and percentage of RMRs that included an adverse event.

7. REMS Program Patient Counseling Checklist (per reporting period and cumulatively, for both XYWAV and XYREM)
    a. Summary table for both XYWAV and XYREM from REMS Program Patient Counseling Checklists of the number and percentage of patients taking the following concomitant medications and who subsequently received at least one shipment of drug:
        i. Sedative hypnotics indicated for sleep (e.g., eszopiclone, zaleplon, zolpidem, temazepam, suvorexant, quazepam, estazolam, flurazepam, triazolam, tasimelteon, ramelteon)
        ii. Alcohol
        iii. Other potentially interacting agents:
            - Benzodiazepines (e.g., diazepam, alprazolam or any not listed in metric 7.a.i.)
            - Sedating antidepressants or antipsychotics, sedating anti epileptics, and sedating antihistamines
            - General anesthetics
            - Muscle relaxants
            - Opioid analgesics
            - Divalproex sodium or other valproate drug (e.g.,valproic acid)
            - Illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB]).
    b. Summary tables for both XYWAV and XYREM from REMS Program Patient Counseling Checklists of the number and percentage of patients who have been diagnosed with the following conditions and who subsequently received at least one shipment of drug:
    c. Sleep apnea
    d. Asthma, COPD, or other conditions affecting the respiratory system.

Health Outcomes and/or Surrogates of Health Outcomes

8. Pharmacovigilance/surveillance (per reporting period)
    a. Separate summary tables for XYWAV and XYREM of the number of reports of serious adverse events. The summary tables will include the following data fields (CIOMS II line listings): date, report ID, report type, notifier, age, gender, indication, start and stop date, dose, frequency, onset date, system organ class,

outcome, and causality. All tables should include an overall narrative summary of the adverse events and data fields reported.

i. All cases of death
   1) Number, percentage, and type of RMRs, notifications, and alerts associated with any reported deaths.

ii. All outcomes of death, emergency department visits (when admitted to hospital), or hospitalizations resulting from or associated with the following:
   1) Use with concurrent sedative hypnotics and alcohol. Provide a breakdown of concomitant sedative hypnotics usage (ex. zolpidem=6%, eszopiclone=3%)
   2) Intentional misuse
   3) Abuse
   4) Overdose
   5) Medication error

iii. Cases of sexual abuse

iv. Proportion of discontinued patients who were associated with a report of a serious adverse event, including death.

Knowledge

9. Knowledge, Attitude, and Behavior (KAB) Surveys of Patients, Caregivers, and Healthcare Providers (to be submitted every other year beginning with the April 2023 assessment)
   a. Assessment of patients'/caregivers' and healthcare providers' understanding of the following:
      i. The risk of significant CNS and respiratory depression associated with XYWAV and XYREM even at recommended doses
      ii. The contraindicated uses of XYWAV and XYREM
      iii. The potential for abuse, misuse, and overdose associated with XYWAV and XYREM
      iv. The safe use, handling, and storage of XYWAV and XYREM
      v. The XYWAV and XYREM REMS Program requirements.

10. Knowledge, Attitude, and Behavior (KAB) Surveys of Pharmacists (to be submitted every other year beginning with the April 2023 assessment)
   a. Assessment of pharmacists' understanding of the following:
      i. The risk of significant CNS and respiratory depression associated with XYWAV and XYREM even at recommended doses
      ii. The contraindicated uses of XYWAV and XYREM
      iii. The potential for abuse, misuse, and overdose associated with XYWAV and XYREM
      iv. The safe use, handling, and storage of XYWAV and XYREM
      v. The XYWAV and XYREM REMS Program requirements.

11. Certified Pharmacy knowledge assessments (per reporting period and cumulatively)

a. Number of pharmacy staff who completed post-training knowledge assessments including method of completion and the number of attempts needed to complete.
    i. Provide a breakdown of scores within Module A and B
b. Summary of the most frequently missed post-training knowledge assessment questions
c. Summary of potential comprehension or perception issues identified with the post-training knowledge assessment by module
d. Number of pharmacy staff who did not pass the knowledge assessments.

12. The requirements for assessments of an approved REMS under section 505-1 (g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

10 Discussion

Jazz Pharmaceuticals, Inc. submitted a Xywav and Xyrem REMS modification and amendments as part of a Xywav efficacy supplement (NDA 212690/S-006) for a new idiopathic hypersomnia indication. The modification proposes changes to the materials and supporting document to incorporate the new indication in the REMS. Jazz also proposed changes to the Assessment Plan (AP) and Timetable for Assessments. The AP was revised to capture the indication for use and the Timetable was revised to reflect that the 8th REMS assessment is due on April 26, 2022 and annually thereafter. In addition to the applicant proposed changes with this modification, the Agency also recommended changes to the *Patient Counseling Checklist* to capture additional information regarding concomitant medication and alcohol use. On August 10, 2021 Jazz submitted an updated REMS proposal that reflected the comments and information requests issued by the Agency during the course of the review.

11 Conclusions and Recommendations

DRM finds the proposed REMS modification for Xywav (NDA 212690/S-06) and Xyrem (NDA 021196/S-036) as submitted on August 10, 2021 acceptable. The REMS materials were amended to be consistent with the revised REMS document. DRM recommends approval of the REMS Modification for Xywav and Xyrem, received on February 12, 2021 and last amended on August 10, 2021 and appended to this review.

The timetable for submission of assessments of the REMS has been revised. Jazz Pharmaceuticals must submit a REMS Assessment on April 26, 2022, and annually thereafter.

The REMS Assessment Plan, as summarized in the REMS Supporting Document, has been revised to be consistent with the REMS Modification for Xywav and Xyrem and will be included in the REMS Modification Approval letter.

12 References

[1] Jazz Pharmaceuticals, Inc. Risk Evaluation and Mitigation Strategy for Xywav and Xyrem, February 11, 2021.

[2] Fitzgerald, D. REMS review for Xywav (calcium, magnesium, potassium and sodium oxybates), NDA 212690, June 15, 2021.

[3] Fitzgerald, D. REMS review for Xywav (calcium, magnesium, potassium and sodium oxybates), NDA 212690, June 15, 2021.

[4] Jazz Pharmaceuticals, Inc. Summary of Clinical Efficacy for Xywav (NDA 212690/S-06), August 8, 2021.

[5] Mani, R.B. Personal Communication, August 4, 2021.

[6] Jazz Pharmaceuticals, Inc. Summary of Clinical Safety for Xywav (NDA 212690/S-06), August 9, 2021.

[7] Jazz Pharmaceuticals, Inc. Prescribing Information for Xywav (NDA 212690/S-06), August 10, 2021.

[8] Jazz Pharmaceuticals, Inc. Summary of Clinical Safety for Xywav (NDA 212690/S-06), August 10, 2021.

13 Appendix

REMS Document

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DONELLA A FITZGERALD
08/11/2021 05:06:46 PM

ANAHITA TAVAKOLI
08/11/2021 05:13:28 PM

JACQUELINE E SHEPPARD
08/11/2021 05:43:45 PM

DORIS A AUTH
08/12/2021 06:12:24 AM

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	212690; 021196
Supplement Number, Date Received	Supplement 006 received February 12, 2021 (sequence 0105, NDA 212690); amended June 21, June 25, July 21 and August 2, 2021. Supplement 036 received February 12, 2021 (sequence 0566, NDA 021196); amended June 21, June 25, July 21 and August 2, 2021.
Action Date	August 12, 2021
OSE RCM #	2021-313
Reviewer Name(s)	Donella Fitzgerald, PharmD Anahita Tavakoli, MA
Team Leader	Jacqueline Sheppard, PharmD
Deputy Division Director	Doris Auth, PharmD
Review Completion Date	August 5, 2021
Subject	Review of proposed REMS Modification
Established Name	Calcium, magnesium, potassium and sodium oxybates (Xywav); Sodium oxybate (Xyrem)
Trade Name	Xywav; Xyrem
Name of Applicant	Jazz Pharmaceuticals, Inc.
Therapeutic Class	Central nervous system depressants
Formulation(s)	0.5 g/mL oral solutions

Table of Contents

EXECUTIVE SUMMARY

This is a review of the proposed modifications to the Risk Evaluation and Mitigation Strategy (REMS) for Xywav and Xyrem (calcium, magnesium, potassium and sodium oxybates; sodium oxybate), (NDA 212690/S-006; NDA 021196/S-036), submitted by Jazz Pharmaceuticals, Inc. (Jazz) on February 12, 2021 and amended June 21, June 25, July 21 and August 2, 2021.

The REMS for Xyrem was originally approved on February 27, 2015 and the REMS for Xywav was approved on July 21, 2020. The two drugs are subject to the same REMS, known as the Xywav and Xyrem REMS, that mitigates the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Xywav and Xyrem. The most recent REMS modification was approved on February 11, 2021. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Jazz's proposed modifications to the REMS consists of:

- Changes to the REMS materials to align with the proposed indication of Idiopathic Hypersomnia
- Changes to the REMS assessment timetable
- Change of the reporting interval for the Knowledge, Attitude, and Behavior Surveys from annually to every other year

In addition, the following modifications were communicated during the course of the review:

- Changes to the *Patient Counseling Checklist* to capture additional information regarding concomitant medication and alcohol use

DRM does not find the proposed REMS modification for the Xywav and Xyrem REMS as submitted on February 12, 2021 and amended June 21, June 25, July 21, and August 2, 2021, to be acceptable, as described in Sections 4-7 of this review. The Comments to the Applicant in Section 10 should be sent in an Information Request to Jazz. The Applicant should be instructed to submit a REMS amendment addressing these comments within 3 business days.

1 Introduction

This review evaluates the proposed modification to the REMS for Xywav and Xyrem (calcium, magnesium, potassium and sodium oxybates; sodium oxybate), (NDA 212690/S-006; NDA 021196/S-036), submitted by Jazz Pharmaceuticals, Inc. (Jazz) on February 12, 2021[1] and amended June 21, June 25, July 21 and August 2, 2021.

Jazz submitted the REMS modification as part of a Xywav efficacy supplement for a new idiopathic hypersomnia (IH) indication. The modification proposes changes to the materials and supporting document to incorporate the new indication in the REMS, as well as a revised timetable for submission of assessments in the REMS document. On August 2, 2021, Jazz submitted a REMS amendment which is the focus of this review.

2 Background

a. PRODUCT INFORMATION

For updated assessment of the Product Information, refer to the June 15, 2021 interim review[2].

b. REGULATORY HISTORY

The following is a summary of the regulatory history relevant to this review:

- **07/17/02:** Xyrem, NDA 021196, approved with a Risk Minimization Action Plan.
- **02/27/15:** Xyrem REMS approved.
- **07/21/20:** Xywav, NDA 212690, approved with a REMS and joined the existing Xyrem REMS to form the Xywav and Xyrem REMS.
- **02/12/21:** Xywav and Xyrem REMS modification submitted as part of the Xywav Prior Approval Efficacy Supplement (Xywav NDA 212690/S-006; Xyrem NDA 021196/S-036).
- **6/15/21:** Interim Comments (IC) on the REMS materials issued. Agency recommendations were communicated regarding the collection of indication on the prescription forms, absence of a Spanish certificate of translation for the REMS website and additional editorial changes on several of the REMS materials.
- **06/21/21:** Jazz submitted a REMS amendment that consisted of changes to the Timetable for Submission of Assessments (REMS document) and reporting interval for the Knowledge, Attitude and Behavior Surveys (Supporting document).
- **6/23/21:** Information Request (IR) issued regarding Agency proposed changes to the Patient Counseling Checklist concerning concomitant medication use.
- **6/25/21:** Jazz submitted a REMS amendment in response to the Interim Comments sent June 15, 2021.
- **7/9/21:** Jazz submitted a response to the IR issued on June 23, 2021. Their response consisted of clarifying questions regarding the IR (the questions were also emailed to the FDA on July 6th, 2021). They did not submit the Patient Counseling Checklist.
- **7/14/21:** The Agency issued a General Advice letter to respond to Jazz's clarifying questions submitted on July 9, 2021.
- **7/21/21:** Jazz submitted a REMS amendment in response to the IR issued on June 23, 2021.
- **7/28/21:** Interim Comments on the REMS materials issued. Agency recommendations were communicated regarding necessary changes to the Timetable for Assessments in the REMS document, further changes to the Patient Counseling Checklist and revisions to other materials based on updated draft labeling.
- **8/2/21:** Jazz submitted a REMS amendment in response to the IR issued on July 28, 2021.

3 Therapeutic Context and Treatment Options

For updated assessment of the Therapeutic Context and Treatment Options, refer to the June 15, 2021 interim review[3].

4 Review of Proposed REMS Modifications

a. REMS Goals

The Applicant did not propose changes to the goals.

b. REMS Document

The Applicant accepted the Agency's recommended changes that were communicated in the Interim Comments issued July 28, 2021. No further edits were proposed.

Reviewer Comment: No comment at this time.

c. REMS Requirements

i. REMS Participant Requirements and Materials

1. Healthcare Provider

a. *Prescriber Brochure*
   i. Editorial changes were proposed to align with draft labeling

b. *Prescriber Enrollment Form*
   i. Editorial changes were proposed to align with draft labeling

c. *Xywav Prescription Form*
   i. The applicant made edits to the dosing language to align with draft label changes.
   ii. (b) (4) [redacted]

d. *Xyrem Prescription Form*
   i. The applicant did not propose changes to the form, (b) (4) [redacted]

Reviewer Comments: The Prescriber Brochure, Xywav Prescription Form and Xyrem Prescription Form require additional changes. The Prescriber Brochure must be revised to address language that is promotional in tone as discussed in section 7 of this review (Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials). The Xywav Prescription Form requires changes to incorporate language regarding once nightly dosing as included in the draft labeling. Additionally, for both the Xywav and Xyrem Prescription Forms,

Jazz must provide clarification regarding their comment in the Total Quantity section that states "Process improvement change". For a detailed depiction of proposed changes, see attached redlined documents.

2. Patients

a. *Xywav Patient Quick Start Guide*
   i. Editorial changes were proposed to align with draft labeling

b. *Xyrem Patient Quick Start Guide*
   i. Editorial changes were proposed to align with draft labeling

c. *Xywav Brochure for Pediatric Patients and their Caregivers*
   i. Editorial changes were proposed to align with draft labeling

d. *Xyrem Brochure for Pediatric Patients and their Caregivers*
   i. Editorial changes were proposed to align with draft labeling

e. *Patient Enrollment Form*
   i. Editorial changes were proposed to align with other REMS materials.

Reviewer Comment: No comments at this time.

3. Health care settings/prescribers/pharmacies that dispense

a. *Certified Pharmacy Training*
   i. Editorial changes were proposed to align with draft labeling

b. *Module A Knowledge Assessment - Pharmacy*
   i. Editorial changes were proposed to align with draft labeling

c. *Patient Counseling Checklist*
   i. Editorial changes were proposed to align with draft labeling
   ii. (b) (4)

(b) (4)

ii. REMS APPLICANT REQUIREMENTS AND MATERIALS

Operations

REMS Website – Editorial changes were proposed to align with draft labeling.

Reviewer Comments: No comments at this time.

d. REMS Assessment Timetable

The Applicant accepted the Agency's recommended changes that were communicated in the Interim Comments issued July 28, 2021. No further edits were proposed.

Reviewer Comments: No comments at this time.

5 Supporting Document

The REMS Supporting Document was changed to include the background of the REMS Modification currently under review. The Applicant proposed changes to align with the draft labeling and an edit to the Assessment Plan that is discussed below in Section 6 REMS Assessment Plan.

Reviewer Comment: No comments at this time.

6 REMS Assessment Plan

Jazz proposed one editorial change to the Assessment Plan (AP) included in the Interim Comments issued July 28, 2021 (b) (4) indicated below:

iii. (b) (4)

Reviewer Comment: We agree with the proposed change. Further changes may be required based on the on-going review of the Xywav efficacy supplement for a new idiopathic hypersomnia indication.

7 Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on May 18, 2021 to provide feedback on the content of the updated REMS materials. The OPDP review was completed by Lynn Panholzer on August 2, 2021.

The OPDP recommendations are summarized below:

OPDP considers the following statements promotional in tone and recommends revising them in the REMS piece:

- XYWAV and XYREM REMS Patient Counseling Checklist
  - **Benefit**
    - Page 2: "During a clinical trial with Xywav, (b) (4) patients with idiopathic hypersomnia experienced improvement in symptoms of idiopathic hypersomnia in the first few weeks of therapy. However, the response varies from patient to patient. It may also take time to find the right dose that works for the patient. The prescriber will determine the dose that is appropriate."
      - These claims are promotional in tone and focus on promoting the purported benefits of the treatment rather than on educating about the serious risks of treatment.

(b) (4)

<u>Reviewer comments:</u> We are in agreement with OPDP's recommendations and have updated the language to state "some" patients (b) (4)

(b) (4)

<u>Reviewer comments:</u> We are in agreement with OPDP's recommendations and have updated the language to include, "In some patients, improvement may occur".

- Pharmacy Knowledge Assessment: Module A
  - **General Comment**
    - Question 9: "In validating a prescription for XYWAV or, the Certified Pharmacy will verify that . . . ."
      - We believe the tradename "XYREM" was inadvertently omitted from this sentence, and that the sentence should read, "In

validating a prescription for XYWAV or **XYREM**, the Certified Pharmacy will verify that . . ." (bolded emphasis added).

Reviewer comments: We are in agreement with OPDP's recommendations and the most recently submitted REMS material is accurate and in-line with OPDP's recommendation.

- XYREM PRESCRIPTION FORM
  - **Indications/Use**
    - Page 1: "***Indication for Use** (required for initial prescription and any change in diagnosis) **Select one:** □ Narcolepsy with Cataplexy and/or EDS **OR** □ Other"

This presentation includes a check box for the approved use of Xyrem, plus a check box for an "Other" indication, which suggests an unapproved use. Given that the purpose of the REMS is to ensure that the benefit of use of Xyrem outweighs the risks, and that benefit and safety have not been demonstrated for an unapproved use, it isn't clear that including an "Other" indication category is appropriate on a REMS prescription form.

Reviewer comments: We are not in agreement with OPDP's recommendations as "other" was added as a checkbox, by DRM's Assessment Team, in collaboration with the Division of Neurology's recommendations to capture additional pertinent information from Jazz.

- XYWAV PRESCRIPTION FORM
  - **Indications/Use**
    - Page 1: "***Indication for Use** (required for initial prescription and any change in diagnosis) **Select one:** □ Narcolepsy with Cataplexy and/or EDS **OR** □ Idiopathic Hypersomnia **OR** □ Other"
      - This presentation includes check boxes for each of the two approved uses of Xywav, plus a check box for an "Other" indication, which suggests an unapproved use. Given that the purpose of the REMS is to ensure that the benefit of use of Xywav outweighs the risks, and that benefit and safety have not been demonstrated for an unapproved use, it isn't clear that including an "Other" category is appropriate on a REMS prescription form.

Reviewer comments: We are not in agreement with OPDP's recommendations as "other" was added as a checkbox, by DRM's Assessment Team, in collaboration with the Division of Neurology's recommendations to capture additional pertinent information from Jazz.

- Page 1: [redacted] (b) (4) who sleep more than 8 hours per night, the first dose of XYWAV may be given at bedtime or after an initial period of sleep."
  - [redacted] (b) (4)

(b) (4)

Reviewer comments: *We are in agreement with OPDP's recommendations and have updated the language to include "For pediatric patients who sleep more than 8 hours.".*

- Page 1: "**Dispensing Instructions**
  Directions: Take first dose p.o., diluted in ¼ cup of water, at bedtime. Take second dose p.o., diluted in ¼ cup of water 2.5 to 4 hours later.
  Note: Prepare both doses at the same time prior to bedtime. The XYWAV shipment does not include water for dilution."

  - Xywav can be given as a once-nightly dose for the IH indication. The "Dispensing Instructions" are not accurate for a patient being prescribed a once nightly dose. We recommend that there be a "Dispensing Instructions" option that is appropriate for a patient taking a once nightly dose.

    Similarly, the Titrated XYWAV Dosing and Fixed Xywav Dosing sections have spaces for both first and second doses. Although the prescriber could leave the second dose spaces blank if the patient is being prescribed a once-nightly dose, it isn't clear if these sections could be confusing to the prescribers. Should there be separate sections for once nightly dosing, or at least an instruction to, for example, leave the second dose sections blank if the patient is prescribed a once nightly dose?

Reviewer comments: *We are in agreement with OPDP's recommendations and have updated the form as recommended.*

8 Discussion

Jazz Pharmaceuticals submitted a Xywav and Xyrem REMS modification and amendments as part of a Xywav efficacy supplement (NDA 212690/S-006) for a new idiopathic hypersomnia indication. The modification proposes changes to the materials and supporting document to incorporate the new indication in the REMS. Additionally, the Applicant proposes to revise the Timetable for Assessments in the REMS document. In response to Agency comments issued on July 28, 2021, Jazz submitted a REMS amendment on August 2, 2021 which is the focus of this review. Further edits to the REMS modification proposal may be required as the Division of Neurology 1 proceeds with review of the proposed changes to the Xywav label.

9 Conclusions and Recommendations

DRM does not find the proposed REMS modification for the Xywav and Xyrem REMS as submitted on February 12, 2021 and amended June 21, June 25, July 21 and August 2, 2021, to be acceptable, as described in Section 10 of this review. Send the comments in Section 10 to Jazz Pharmaceuticals, Inc. in an Information Request and instruct the Applicant to submit a REMS amendment within 3 business days.

10 Comments to the Applicant

We have the following comments on the proposed REMS modification, submitted on February 12, 2021 and amended June 21, June 25, July 21 and August 2, 2021. Review of the REMS proposal is ongoing; these comments should not be considered final. Submit a REMS amendment within 3 business days that addresses these comments. Include the REMS document, all appended materials and the REMS supporting document, submitted as separate documents in the same submission; include a Word tracked changes version, a Word clean version, and a .pdf version of the REMS Document, all appended materials and supporting document. Include all formatting when submitting REMS materials including any logos, coloring, shading, or other design features.

The comments provided are based on the current proposed labeling. However, all materials must be revised to be consistent with the final FDA-approved labeling.

(b) (4)

Xywav Prescription Form

- Address Agency comments regarding the dosing language and provide clarification regarding your "Process improvement change" comment included in the redlined document you submitted on August 2, 2021. See attached redlined document for additional details.

Xyrem Prescription Form

- Provide clarification regarding your "Process improvement change" comment included in the redlined document you submitted on August 2, 2021. See attached redlined document for additional detail.

Patient Counseling Checklist

- Address the Agency comment regarding reinsertion of deleted text. See attached redlined document for additional detail.

11 References

[1] Jazz Pharmaceuticals, Inc. Risk Evaluation and Mitigation Strategy for Xywav and Xyrem, February 11, 2021

[2] Fitzgerald, D. REMS review for Xywav (calcium, magnesium, potassium and sodium oxybates), NDA 212690, June 15, 2021

[3] Fitzgerald, D. REMS review for Xywav (calcium, magnesium, potassium and sodium oxybates), NDA 212690, June 15, 2021

12 Appendix

(b) (4)

Xywav Prescription Form

Xyrem Prescription Form

Patient Counseling Checklist

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/s/

DONELLA A FITZGERALD
08/05/2021 01:38:29 PM

ANAHITA TAVAKOLI
08/05/2021 01:51:08 PM

JACQUELINE E SHEPPARD
08/05/2021 02:15:10 PM

DORIS A AUTH
08/05/2021 02:25:47 PM

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	212690; 021196
Supplement Number, Date Received	Supplement 006 received February 12, 2021 (sequence 0105, NDA 212690); amended June 21, June 25 and July 21, 2021. Supplement 036 received February 12, 2021 (sequence 0566, NDA 021196); amended June 21, June 25 and July 21, 2021.
Action Date	August 12, 2021
OSE RCM #	2021-313
Reviewer Name(s)	Donella Fitzgerald, PharmD Anahita Tavakoli, MA
Team Leader	Jacqueline Sheppard, PharmD
Deputy Division Director	Doris Auth, PharmD
Review Completion Date	July 28, 2021
Subject	Review of proposed REMS Modification
Established Name	Calcium, magnesium, potassium and sodium oxybates (Xywav); Sodium oxybate (Xyrem)
Trade Name	Xywav; Xyrem
Name of Applicant	Jazz Pharmaceuticals, Inc.
Therapeutic Class	Central nervous system depressants
Formulation(s)	0.5 g/mL oral solutions

Table of Contents

1 Introduction

This review evaluates the proposed modification to the REMS for Xywav and Xyrem (calcium, magnesium, potassium and sodium oxybates; sodium oxybate), (NDA 212690/S-006; NDA 021196/S-036), submitted by Jazz Pharmaceuticals, Inc. (Jazz) on February 12, 2021[1] and amended June 21, June 25 and July 21, 2021.

Jazz submitted the REMS modification as part of a Xywav efficacy supplement for a new idiopathic hypersomnia (IH) indication. The modification proposes changes to the materials and supporting document to incorporate the new indication in the REMS, as well as a revised timetable for submission of assessments in the REMS document.

2 Background

a. PRODUCT INFORMATION

For updated assessment of the Product Information, refer to the June 15, 2021 interim review[2].

b. REGULATORY HISTORY

The following is a summary of the regulatory history relevant to this review:

- **07/17/02:** Xyrem, NDA 021196, approved with a Risk Minimization Action Plan.
- **02/27/15:** Xyrem REMS approved.
- **07/21/20:** Xywav, NDA 212690, approved with a REMS and joined the existing Xyrem REMS to form the Xywav and Xyrem REMS.
- **02/12/21:** Xywav and Xyrem REMS modification submitted as part of the Xywav Prior Approval Efficacy Supplement (Xywav NDA 212690/S-006; Xyrem NDA 021196/S-036).
- **6/15/21:** Interim Comments (IC) on the REMS materials issued. Agency recommendations were communicated regarding the collection of indication on the prescription forms, absence of a Spanish certificate of translation for the REMS website and additional editorial changes on several of the REMS materials.
- **06/21/21:** Jazz submitted a REMS amendment that consisted of changes to the Timetable for Submission of Assessments (REMS document) and reporting interval for the Knowledge, Attitude and Behavior Surveys (Supporting document).
- **6/23/21:** Information Request (IR) issued regarding Agency proposed changes to the Patient Counseling Checklist concerning concomitant medication use.
- **6/25/21:** Jazz submitted a REMS amendment in response to the Interim Comments sent June 15, 2021.
- **7/9/21:** Jazz submitted a response to the IR issued on June 23, 2021. Their response consisted of clarifying questions regarding the IR (the questions were also emailed to the FDA on July 6th, 2021). They did not submit the Patient Counseling Checklist.
- **7/14/21:** The Agency issued a General Advice letter to respond to Jazz's clarifying questions submitted on July 9, 2021.

- **7/21/21:** Jazz submitted a REMS amendment in response to the IR issued on 6/23/21.

3 Therapeutic Context and Treatment Options

For updated assessment of the Therapeutic Context and Treatment Options, refer to the June 15, 2021 interim review[3].

4 Review of Proposed REMS Modifications

a. REMS Goals

The Applicant did not propose changes to the goals.

b. REMS Document

Changes to the timetable for submission of assessments of the REMS were proposed by the Applicant. See section *4.d. REMS Assessment Timetable* of this review for additional information.

Reviewer Comment: The REMS document also requires an editorial change. (b) (4) [redacted]

c. REMS Requirements

i. REMS Participant Requirements and Materials

1. Healthcare Provider

a. Xywav Prescription Form

i. The applicant agreed with the Agency's recommendation[3] (b) (4) [redacted] "Other" (b) (4) [redacted]

b. Xyrem Prescription Form

i. The applicant agreed with the Agency's recommendation[4] (b) (4) [redacted] "Other" (b) (4) [redacted]

(b) (4)

(b) (4)

2. **Patients**
   a. *Xywav Patient Quick Start Guide*
      i. (b) (4)
   b. *Xywav Brochure for Pediatric Patients and Their Caregivers*
      i. (b) (4)

Reviewer Comment: The language in these materials must be revised to align with draft labeling.

3. **Health care settings/prescribers/pharmacies that dispense**
   a. *Patient Counseling Checklist*
      i. Jazz included the list of sedative hypnotics and benzodiazepines that the Agency recommended in the June 23, 2021 IR, (b) (4)

Reviewer Comments: We agree with the use of check box options (b) (4) *use, however the Patient Counseling Checklist requires additional editorial changes. See attached redlined document.*

ii. REMS APPLICANT REQUIREMENTS AND MATERIALS

Operations

REMS Website – As directed in the Interim Comments sent June 26, 2021, Jazz provided a Certificate of Translation for the Spanish versions of the Patient materials. The certificate is for the approved version of the materials; it does not include changes proposed with this REMS modification. Jazz proposes to submit an updated certificate within two months of the action date for the efficacy supplement/REMS modification for Xywav S-006 and Xyrem S-036.

Reviewer Comments: We agree with this proposal.

d. REMS Assessment Timetable

The Applicant proposed changes to the REMS Assessment Timetable as indicated below (underline is used for added text, strikethrough is used for deleted text):

Jazz Pharmaceuticals must submit its 8th REMS Assessment on April 26, 2022 and annually thereafter (b) (4) 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.

Reviewer Comments: We agree with changing the assessment timetable, but recommend that the language in the approved REMS Document be revised as indicated below:

Jazz Pharmaceuticals must submit a REMS Assessments (b) (4) *on April 26, 2022, 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.*

5 Supporting Document

At this time, our comments on the supporting document are specific to the Assessment Plan and discussed in *Section 6 REMS Assessment Plan* of this review.

6 REMS Assessment Plan

The REMS Assessment Plan (AP) is summarized in the REMS Supporting Document and will be addressed in the REMS Modification approval letter. In the April 21, 2021 REMS amendment, Jazz proposed to change the reporting interval for the Knowledge Attitude and Behavior (KAB) stakeholder surveys from annually to every other year.

Reviewer Comment: We agree with changing the reporting interval for the KAB stakeholder surveys; however, we recommend edits to the language Jazz proposed. Other editorial changes are also necessary. Refer to the attached redlined AP for our proposed edits. Further changes may be required based on the on-going review of the Xywav efficacy supplement for a new idiopathic hypersomnia indication.

7 Discussion

Jazz Pharmaceuticals submitted a Xywav and Xyrem REMS modification and amendments as part of a Xywav efficacy supplement (NDA 212690/S-006) for a new idiopathic hypersomnia indication. The modification proposes changes to the materials and supporting document to incorporate the new indication in the REMS. Additionally, the Applicant proposes to revise the Timetable for Assessments in the REMS document. Further edits to the REMS modification proposal may be required as the Division of Neurology 1 proceeds with review of the proposed changes to the Xywav label.

8 Conclusions and Recommendations

DRM does not find the proposed REMS modification for the Xywav and Xyrem REMS as submitted on February 12, 2021 and amended June 21, June 25 and July 21, 2021, to be acceptable, as described in Section 11 of this review. Send the comments in Section 11 to Jazz Pharmaceuticals, Inc. in an Information Request and instruct the Applicant to submit a REMS amendment within 3 business days.

9 Comments to the Applicant

We have the following comments on the proposed REMS modification, submitted on February 12, 2021 and amended June 21, June 25 and July 21, 2021. Review of the REMS proposal is ongoing; these comments should not be considered final. Submit a REMS amendment within 3 business days that addresses these comments. Include the REMS document, all appended materials and the REMS supporting document, submitted as separate documents in the same submission; include a Word tracked changes version, a Word clean version, and a .pdf version of the REMS Document, all appended materials and supporting document. Include all formatting when submitting REMS materials including any logos, coloring, shading, or other design features.

The comments provided are based on the current proposed labeling. However, all materials must be revised to be consistent with the final FDA-approved labeling.

REMS document

- We agree with revising the Timetable for Submission of Assessments; however, we recommend changes to the language you proposed. See the attached redlined document for the revised language and additional editorial changes.

Xywav Prescription Form

- (b) (4)

Xyrem Prescription Form

- (b) (4)

(b) (4)

Xywav Patient Quick Start Guide

- (b) (4)

Xywav Brochure for Pediatric Patients and Their Caregivers

- (b) (4)

Patient Counseling Checklist

- (b) (4)

REMS Website

- Patient materials: Spanish version - we acknowledge receipt of your most recent (March 2021) Certificate of Translation and agree with your proposal to submit an updated certificate within two months of the action date for the Xywav efficacy supplement/Xywav and Xyrem REMS modification (Xywav NDA 212690/S-006; Xyrem NDA 021196/S-036).

REMS Assessment Plan

- We agree with changing the reporting interval for the Knowledge Attitude and Behavior stakeholder surveys; however, we recommend edits to the language you proposed. Refer to the attached redlined Assessment Plan for our proposed edits.

10 References

[1] Jazz Pharmaceuticals, Inc. Risk Evaluation and Mitigation Strategy for Xywav and Xyrem, February 11, 2021

[2] Fitzgerald, D. REMS review for Xywav (calcium, magnesium, potassium and sodium oxybates), NDA 212690, June 15, 2021

[3] Fitzgerald, D. REMS review for Xywav (calcium, magnesium, potassium and sodium oxybates), NDA 212690, June 15, 2021

11 Appendix

REMS document

Patient Counseling Checklist

Assessment Plan

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Xywav Xyrem Rems Assessment Plan

The Xywav Xyrem REMS assessment plan must include but is not limited to the following items.

The Assessment Plan revisions are included below. Additions are noted with underline and deletions are noted with ~~strikethrough~~.

Program Implementation and Operations

(b) (4)

1. REMS Enrollment Statistics (per reporting period and cumulatively)
   a. Patients:
      i. Number and percentage of newly enrolled patients stratified by age, geographic region (defined by US Census), indication, and gender
      ii. Number and percentage of active patients enrolled (patients who received at least one shipment of XYWAV or XYREM during the reporting period) stratified by age, geographic region (defined by US Census), and gender
      iii. Number and percentage of patients who have discontinued XYWAV or XYREM after receiving at least one shipment of XYWAV or XYREM. Include demographics of discontinued patients and reasons for discontinuation.
      iv. Number and percentage of patients who transitioned from XYREM to XYWAV
      v. Number and percentage of patients who transitioned from XYWAV to XYREM.
   b. Healthcare Providers:
      i. Number and percentage of newly certified healthcare providers stratified by professional designation (i.e. MD, DO, PA, NP), medical specialty, and geographic region (defined by US Census)
      ii. Number and percentage of active certified healthcare providers (healthcare providers who have written at least one prescription for XYWAV or XYREM during the reporting period) stratified by professional designation (i.e. MD, DO, PA, NP), medical specialty, and geographic region (defined by US Census)
      iii. Number of patients by current enrolled prescriber.
   c. Certified Pharmacy
      i. If the Certified Pharmacy was decertified during the reporting period and reasons for decertification.
2. Utilization Data (per reporting period and cumulatively)
   a. Number and percentage of XYREM prescriptions (new and refills) dispensed
   b. Number and percentage of XYWAV prescriptions (new and refills) dispensed

c. Number and percentage of XYREM bottles and shipments sent
d. Number and percentage of XYWAV bottles and shipments sent.

3. REMS Program Operation and Performance Data (per reporting period and cumulatively)
   a. REMS Program Central Database Report
      i. Number and percentage of contacts by stakeholder type (e.g. patients, healthcare providers, pharmacy, other)
      ii. Summary of reasons for contacts (e.g., enrollment questions) by reporter (authorized representative, patient, healthcare provider, other)
      iii. Call center report with number of calls received and a summary of reasons for calls by stakeholder type
      iv. Summary of frequently asked questions by stakeholder type and topic
      v. Summary of any REMS-related problems identified and a description of any corrective actions taken
      vi. If the summary reason for the calls indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues
      vii. Summary of program or system problems and a description of any corrective actions taken.

4. REMS Program Compliance (per reporting period and cumulatively)
   a. Audits: Summary of audit activities including but not limited to:
      i. A copy of the audit plan for each audited stakeholder.
      ii. The number of audits expected, and the number of audits performed
      iii. The number and type of deficiencies noted
      iv. For those with deficiencies noted, report the status of corrective and preventative action (CAPA) proposed to address the deficiencies. The status to include completion status.
      v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
      vi. Provide details on deviations for the CAPA proposed, including timelines, and mitigating steps to address the deviations
      vii. Confirm documentation of completion of training for relevant staff
      viii. Review of accumulative findings to identify any trends of potential repeat issues, and steps to be taken to address these findings
      ix. A summary report of the processes and procedures that are implemented to be in compliance with the REMS requirements.
   b. A summary report of noncompliance, associated corrective and preventive actions (CAPA) plans, and the status of CAPA plans including but not limited to:
      i. A copy of the Noncompliance Plan which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
      ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:

1) The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
2) The source of the noncompliance data
3) The results of root cause analysis
4) What action(s) were taken in response.

c. Healthcare Providers
   i. Number and percentage of certified prescribers who were disenrolled during the reporting period and reasons for disenrollment. Include if any prescribers were re-certified.
   ii. Number of disenrolled prescribers who were associated with a XYWAV and XYREM prescription and number of disenrolled prescribers associated with a XYWAV and XYREM shipment
   iii. Number and percentage of XYWAV prescriptions filled from a prescriber who was not enrolled.
   iv. Number and percentage of XYREM prescriptions filled from a prescriber who was not enrolled.

d. Certified Pharmacy
   i. Number and percentage of XYWAV prescriptions dispensed for more than a 30 days' supply (first fill) or more than a 90 days' supply (refills) and reasons
   ii. Number and percentage of XYREM prescriptions dispensed for more than a 30 days' supply (first fill) or more than a 90 days' supply (refills) and reasons
   iii. Number and percentage of XYWAV shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and Risk Management Reports (RMRs) completed
   iv. Number and percentage of XYREM shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and Risk Management Reports (RMRs) completed
   v. Number and percentage of initial XYWAV shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist.
   vi. Number and percentage of initial XYREM shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist.

e. Patients
   i. Number and percentage of patients who were disenrolled from the program and reasons for disenrollment
   ii. Number and percentage of patients associated with more than one prescriber during their therapy
   iii. Number and percentage of patients prescribed a daily dose of XYWAV of >9 g
   iv. Number and percentage of patients prescribed a daily dose of XYREM of >9 g
   v. Number and percentage of patients with overlapping prescriptions (more than one active prescription shipped)

vi. Number and percentage of patients with concurrent XYWAV and XYREM prescriptions
vii. Number of duplicate patients detected by the Certified Pharmacy
viii. Number and percentage of duplicate patients who were shipped XYWAV or XYREM under more than one name or identifier
ix. Number and percentage of patients who were shipped XYWAV or XYREM after being disenrolled
x. Number and percentage of patients who requested an early refill of XYWAV and reason for the request
    1) Number and percentage of requests approved
    2) Number and percentage of requests denied by the prescriber
    3) Number and percentage of requests denied by the Certified Pharmacy
    4) Number and percentage of patients with multiple requests for early refills.
xi. Number and percentage of patients who requested an early refill of XYREM and reason for request
    1) Number and percentage of requests approved
    2) Number and percentage of requests denied by the prescriber
    3) Number and percentage of requests denied by the Certified Pharmacy
    4) Number and percentage of patients with multiple requests for early refills.

Safe Use Behaviors

5. Pharmacy Notifications (per reporting period and cumulatively, for both XYWAV and XYREM)
   a. A summary of the notifications by pharmacies to prescribers for both XYWAV and XYREM. For each of the following situations, include the number and percentage of notifications, number of unique patients, the outcome of the pharmacy notification (e.g. counseled patient, discussed with prescriber and prescriber's designee) and outcome of XYWAV and XYREM prescription disposition (e.g. prescriber approved shipment, prescriber requested shipment hold, prescriber denied shipment, pharmacy approved shipment):
      i. Use with sedative-hypnotics indicated for sleep (b) (4) (e.g., eszopiclone, zaleplon, zolpidem, temazepam, suvorexant, quazepam, estazolam, flurazepam, triazolam, tasimelteon, ramelteon). Indicate specific actions taken by the prescriber and the prescriber rationale for continuing treatment in response to the notification including the following:
         - Treatment with Xywav/Xyrem will discontinue
         - Sedative hypnotic will be discontinued
         - Dosage of sedative hypnotic has been/will be reduced
         - Information unavailable
         - No action (continue sedative hypnotic with Xywav or Xyrem)
         - Prescriber's rationale for continued use of sedative hypnotic with Xywav or Xyrem
            - Sedative hypnotic will not be taken at the same time as Xywav/Xyrem

- Sedative hypnotic will be taken at the same time as Xywav/Xyrem
- Sedative hypnotic will be taken as a sleep aid
- Sedative hypnotic will be taken for different indication per medical need
- Xywav/Xyrem dose regimen changed
- No rationale provided

ii. Benzodiazepines (e.g., diazepam, alprazolam or any not listed in metric 5.a.i.). Indicate specific actions taken by the prescriber and the prescriber rationale for continuing treatment in response to the notification including the following:
- Treatment with Xywav/Xyrem will discontinue
- Benzodiazepine will be discontinued
- Dosage of benzodiazepine has been/will be reduced
- Information unavailable
- No action (continue benzodiazepine with Xywav or Xyrem)
- Prescriber's rationale for continued use of benzodiazepine with Xywav or Xyrem
  - Benzodiazepine will not be taken at the same time as Xywav/Xyrem
  - Benzodiazepine will be taken at the same time as Xywav/Xyrem
  - Benzodiazepine will be taken as a sleep aid
  - Benzodiazepine will be taken for different indication per medical need
  - Xywav/Xyrem dose regimen changed
  - No rationale provided

iii. Use with other concomitant CNS-depressant medications (opioid analgesics, (b) (4) sedating antidepressants or antipsychotics, sedating anti-epileptics, sedating antihistamines, general anesthetics, muscle relaxants, opioid analgesics, or illicit CNS depressants)
iv. Patient report of alcohol use
v. Patient report of diagnosis of sleep apnea
vi. Patient report of diagnosis of asthma, COPD, or other conditions affecting breathing
vii. Suspected abuse, misuse, or diversion
viii. Alerts regarding potential abuse, misuse, or diversion on the patient profiles
ix. Prescription error
x. Early refill requests

6. Risk Management Reports (RMRs) (per reporting period and cumulatively, for both XYWAV and XYREM)
   a. Number and percentage of RMRs submitted

b. Number and percentage of unique patients with a RMR
c. Number and percentage of unique patients with multiple RMRs
d. Number and percentage of alerts generated from RMRs
e. Number and percentage of RMRs generated from early refill requests
f. Number and percentage of RMRs generated for other reasons (list reasons)
g. Number and percentage of prescriber-related RMRs
h. Number and percentage of RMRs that included an adverse event.

7. REMS Program Patient Counseling Checklist (per reporting period and cumulatively, for both XYWAV and XYREM)
   a. Summary table for both XYWAV and XYREM from REMS Program Patient Counseling Checklists of the number and percentage of patients taking the following concomitant medications and who subsequently received at least one shipment of drug:
      i. Sedative hypnotics indicated for sleep [redacted] (b) (4) [redacted] (e.g., eszopiclone, zaleplon, zolpidem, temazepam, suvorexant, quazepam, estazolam, flurazepam, triazolam, tasimelteon, ramelteon)
      ii. Alcohol
      iii. Other potentially interacting agents:
         - Benzodiazepines (e.g., diazepam, alprazolam or any not listed in metric 7.a.i.)
         - Sedating antidepressants or antipsychotics, sedating anti epileptics, and sedating antihistamines
         - General anesthetics
         - Muscle relaxants
         - Opioid analgesics
         - Divalproex sodium or other valproate drug (e.g.,valproic acid)
         - Illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB]).
   b. Summary tables for both XYWAV and XYREM from REMS Program Patient Counseling Checklists of the number and percentage of patients who have been diagnosed with the following conditions and who subsequently received at least one shipment of drug:
   c. Sleep apnea
   d. Asthma, COPD, or other conditions affecting the respiratory system.

Health Outcomes and/or Surrogates of Health Outcomes

8. Pharmacovigilance/surveillance (per reporting period)
   a. Separate summary tables for XYWAV and XYREM of the number of reports of serious adverse events. The summary tables will include the following data fields (CIOMS II line listings): date, report ID, report type, notifier, age, gender, indication, start and stop date, dose, frequency, onset date, system organ class, outcome, and causality. All tables should include an overall narrative summary of the adverse events and data fields reported.
      i. All cases of death
         1) Number, percentage, and type of RMRs, notifications, and alerts associated with any reported deaths.

ii. All outcomes of death, emergency department visits (when admitted to hospital), or hospitalizations resulting from or associated with the following:
    1) Use with concurrent sedative hypnotics and alcohol. Provide a breakdown of concomitant sedative hypnotics usage (ex. zolpidem=6%, eszopiclone=3%)
    2) Intentional misuse
    3) Abuse
    4) Overdose
    5) Medication error
iii. Cases of sexual abuse
iv. Proportion of discontinued patients who were associated with a report of a serious adverse event, including death.

Knowledge

9. Knowledge, Attitude, and Behavior (KAB) Surveys of Patients, Caregivers, and Healthcare Providers (b) (4) (to be submitted every other year beginning with the April 2023 assessment)
    a. Assessment of patients'/caregivers' and healthcare providers' understanding of the following:
        i. The risk of significant CNS and respiratory depression associated with XYWAV and XYREM even at recommended doses
        ii. The contraindicated uses of XYWAV and XYREM
        iii. The potential for abuse, misuse, and overdose associated with XYWAV and XYREM
        iv. The safe use, handling, and storage of XYWAV and XYREM
        v. The XYWAV and XYREM REMS Program requirements.

10. Knowledge, Attitude, and Behavior (KAB) Surveys of Pharmacists (b) (4) (to be submitted (b) (4) every other year beginning with the April 2023 assessment)
    a. Assessment of pharmacists' understanding of the following:
        i. The risk of significant CNS and respiratory depression associated with XYWAV and XYREM even at recommended doses
        ii. The contraindicated uses of XYWAV and XYREM
        iii. The potential for abuse, misuse, and overdose associated with XYWAV and XYREM
        iv. The safe use, handling, and storage of XYWAV and XYREM
        v. The XYWAV and XYREM REMS Program requirements.
11. Certified Pharmacy knowledge assessments (per reporting period and cumulatively)
    a. Number of pharmacy staff who completed post-training knowledge assessments including method of completion and the number of attempts needed to complete.
        i. Provide a breakdown of scores within Module A and B
    b. Summary of the most frequently missed post-training knowledge assessment questions

c. Summary of potential comprehension or perception issues identified with the post-training knowledge assessment by module
d. Number of pharmacy staff who did not pass the knowledge assessments.

12. The requirements for assessments of an approved REMS under section 505-1 (g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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/s/

DONELLA A FITZGERALD
07/28/2021 02:44:36 PM

ANAHITA TAVAKOLI
07/28/2021 02:45:37 PM

JACQUELINE E SHEPPARD
07/28/2021 02:50:00 PM

DORIS A AUTH
07/28/2021 02:54:58 PM

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	212690; 021196
Supplement Number, Date Received	Supplement 006 received February 12, 2021 (sequence 0105, NDA 212690); Supplement 036 received February 12, 2021 (sequence 0566, NDA 021196)
Action Date	August 12, 2021
OSE RCM #	2021-313
Reviewer Name(s)	Donella Fitzgerald, PharmD Anahita Tavakoli, MA
Team Leader	Jacqueline Sheppard, PharmD
Deputy Division Director	Doris Auth, PharmD
Review Completion Date	June 15, 2021
Subject	Review of proposed REMS Modification
Established Name	Calcium, magnesium, potassium and sodium oxybates (Xywav); Sodium oxybate (Xyrem)
Trade Name	Xywav; Xyrem
Name of Applicant	Jazz Pharmaceuticals, Inc.
Therapeutic Class	Central nervous system depressants
Formulation(s)	0.5 g/mL oral solutions

Table of Contents

1 Introduction

This review evaluates the proposed modification to the REMS for Xywav and Xyrem (calcium, magnesium, potassium and sodium oxybates; sodium oxybate), (NDA 212690/S-006; NDA 021196/S-036), submitted by Jazz Pharmaceuticals, Inc. (Jazz) on February 12, 2021.

Jazz submitted the REMS modification as part of a Xywav efficacy supplement for a new idiopathic hypersomnia (IH) indication. The modification proposes changes to the materials and supporting document to incorporate the new indication in the REMS.

2 Background

a. PRODUCT INFORMATION[1]

Xywav and Xyrem are central nervous system depressants, approved for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. Xywav and Xyrem are available as 0.5g/ml oral solutions. The recommended starting dose in adult patients is 4.5 grams (g) per night administered orally in two equal divided doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later. The dose should be increased by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dose range of 6 to 9 g per night orally. Doses higher than 9 g per night have not been studied for either Xyrem or Xywav and should not ordinarily be administered. The dosing regimen for pediatric patients age 7 and up is in the table below:

Table 1 – Xywav and Xyrem Dosage for Pediatric 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	≤ 1 g	≤ 1 g	0.5 g	0.5 g	3 g	3 g
30 kg to < 45	≤ 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

Xyrem was approved in 2002 with a Risk Minimization Action Plan (RiskMAP) that required the following:

- Prescribers enrolled in the RiskMAP in order to prescribe Xyrem
- Patients enrolled in the RiskMAP in order to receive Xyrem
- A single, central, specialty pharmacy dispensed Xyrem only via direct shipment to an enrolled patient pursuant to a prescription written by an enrolled prescriber

Xyrem was identified as a product deemed to have in effect an approved REMS because there were elements to assure safe use in effect on the effective date of the Food and Drug Administration Amendments Act of 2007 (FDAAA). The REMS was approved on February 27, 2015 consisting of a

Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Xywav was approved on July 21, 2020 and joined the Xyrem REMS to form the Xywav and Xyrem REMS. 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: [1,2]

1. Informing prescribers, pharmacists, and patients of:
    - The risk of significant 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 there are signs of potential abuse, misuse, or diversion.

The ETASU in the Xywav and Xyrem REMS include:

- Healthcare providers who prescribe Xyrem must be certified by reviewing the training materials and enrolling in the REMS.
- The pharmacy that dispenses Xywav and Xyrem must be specially certified by reviewing the training materials. Pharmacists who dispense Xywav and Xyrem must counsel new patients and those restarting treatment after 6 months or longer. They also need to document patient and prescriber behavior that may be indicative of abuse, misuse, or diversion.
- Patients who receive Xywav and Xyrem must review the educational materials and be enrolled in the REMS by their provider.

b. REGULATORY HISTORY

The following is a summary of the regulatory history relevant to this review:

- **07/17/02:** Xyrem, NDA 021196, approved with a Risk Minimization Action Plan.
- **02/27/15:** Xyrem REMS approved.
- **07/21/20:** Xywav, NDA 212690, approved with a REMS and joined the existing Xyrem REMS to form the Xywav and Xyrem REMS.

[1] The goal of mitigating diversion in this REMS refers to preventing the sale or transfer of the drug outside the framework of the REMS in order to mitigate the risks of central nervous system depression, respiratory depression, abuse, and misuse.

[2] The goal of mitigating diversion in this REMS refers to preventing the sale or transfer of the drug outside the framework of the REMS in order to mitigate the risks of CNS depression, respiratory depression, abuse, and misuse.

- **02/12/21:** Xywav and Xyrem REMS modification submitted as part of the Xywav Prior Approval Efficacy Supplement (Xywav NDA 212690/S-006; Xyrem NDA 021196/S-036).

3 Therapeutic Context and Treatment Options

a. DESCRIPTION OF THE MEDICAL CONDITION

Idiopathic hypersomnia (IH) is a sleep disorder that is characterized by chronic excessive daytime sleepiness and difficulty waking up from nocturnal sleep or daytime naps. People with IH may fall asleep unintentionally or at inappropriate times, interfering with daily functioning. Common symptoms of this disease include memory, attention and concentration deficits, headaches, sleep drunkenness, sleep paralysis and hallucinations[2]. Symptoms may remain stable over time or fluctuate in severity. IH is a rare disease estimated to occur in approximately 20 to 50 cases per million[3]. The onset of disease typically occurs between 10 and 30 years of age. The underlying causes of IH are not known.

b. DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are no FDA-approved treatments for IH. Patients are often prescribed drugs that are approved to treat narcolepsy, however the use of these medications is often inadequate to improve symptoms[4]. Modafinil and armodafinil are commonly prescribed for IH patients. Caution is advised with the use of these wakefulness-promoting agents as they are associated with instances of serious rash, including Stevens-Johnson syndrome, as well as hypersensitivity/anaphylaxis and psychiatric symptoms. Traditional psychostimulants (amphetamines, methylphenidate and derivatives) are also used for patients with IH. These should also be prescribed with caution as they are known to cause hypertension, tachycardia, mood fluctuations, and dependency. Non-pharmacologic treatment approaches such as behavior modification are not generally effective for people with IH[5].

4 Review of Proposed REMS Modifications

a. REMS Goals

The Applicant did not propose changes to the goals.

b. REMS Document

The Applicant did not propose changes other than updating the document with the modification approval date.

c. REMS Requirements

i. REMS Participant Requirements and Materials

1. **Healthcare Provider** – changes were proposed to the below materials to incorporate the new IH indication:
    a. *Prescriber Enrollment Form*
    b. *Prescriber Brochure*
    c. *Xywav Prescription Form*
        i. (b) (4)
    d. *Xyrem Prescription Form*
        i. (b) (4)

(b) (4)

2. **Patients** - changes were proposed to the below materials to incorporate the new IH indication:
    a. *Patient Enrollment Form*
    b. *Xywav Patient Quick Start Guide*
    c. *Xyrem Patient Quick Start Guide*
    d. *Xywav Brochure for Pediatric Patients and Their Caregivers*
    e. *Xyrem Brochure for Pediatric Patients and Their Caregivers*

    Reviewer Comment: No comments at this time.

3. **Health care settings/prescribers/pharmacies that dispense** - changes were proposed to the below materials to incorporate the new IH indication:
    a. *Patient Counseling Checklist*
    b. *Pharmacy Training Modules*
    c. *Pharmacy Knowledge Assessment*

    Reviewer Comments: The Patient Counseling Checklist requires editorial changes. See attached redlined document. There are no comments on the Pharmacy Training Modules or Pharmacy Knowledge Assessment at this time.

ii. REMS APPLICANT REQUIREMENTS AND MATERIALS

Operations

REMS Website - changes were proposed to incorporate the new IH indication.

Reviewer Comments: We have no comments on the proposed changes at this time but note that the REMS website includes Spanish versions of the Patient Materials. Jazz should submit a Certificate of Translation assuring that the Spanish version of the REMS materials is identical in content to the English version and the translation is accurate.

d. REMS Assessment Timetable

The timetable for submission of assessments of the REMS remains the same as that approved on February 27, 2015.

5 Supporting Document

The REMS Supporting Document was changed to include the background of the REMS Modification currently under review. Additional editorial changes were proposed.

Reviewer Comment: No comments at this time.

6 REMS Assessment Plan

The REMS Assessment Plan (AP) is summarized in the REMS Supporting Document and will be addressed in the REMS Modification Approval letter. The proposed revisions to the REMS AP included in this update include changes to the Program Implementation and Operations metric 2.a.1. and Health Outcomes and/or Surrogates of Health Outcomes metric 9a. The word "indication" has been inserted in each of these two metrics to track the number of patients enrolled by indication and reports of serious adverse events by indication.

Reviewer Comment: We agree with the proposed changes to the AP, at this time. Further changes may be required based on the on-going review of the Xywav efficacy supplement for a new idiopathic hypersomnia indication.

7 Discussion

Jazz Pharmaceuticals submitted a Xywav and Xyrem REMS modification as part of a Xywav efficacy supplement (NDA 212690/S-006) for a new idiopathic hypersomnia indication. The modification proposes changes to the materials and supporting document to incorporate the new indication in the REMS. Further edits may be required as the Division of Neurology 1 proceeds with review of the proposed changes to the Xywav label.

8 Conclusions and Recommendations

DRM does not find the proposed REMS modification for the Xywav and Xyrem REMS as submitted on February 12, 2021 to be acceptable, as described in Section 11 of this review. Send the comments in Section 11 to Jazz Pharmaceuticals, Inc. in an Information Request and instruct the Applicant to submit a REMS amendment within 10 business days.

9 Comments to the Applicant

We have the following comments on the proposed REMS modification, submitted on February 12, 2021. Review of the REMS proposal is ongoing; these comments should not be considered final. Submit a REMS amendment within 10 business days that addresses these comments. Include the REMS document, all appended materials and the REMS supporting document, submitted as separate documents in the same submission; include a Word tracked changes version, a Word clean version, and a .pdf version of the REMS Document, all appended materials and supporting document. Include all formatting when submitting REMS materials including any logos, coloring, shading, or other design features.

The comments provided are based on the current proposed labeling. However, all materials must be revised to be consistent with the final FDA-approved labeling.

Prescriber Enrollment Form

- See editorial comments in the attached redlined document.

Prescriber Brochure

- See editorial comments in the attached redlined document

Xywav Prescription Form

- (b) (4)

Xyrem Prescription Form

- (b) (4)

Patient Counseling Checklist

- See editorial comment in the attached redlined document.

REMS Website

Patient materials (Spanish version) - we request that you submit a Certificate of Translation assuring that the Spanish version of the REMS materials is identical in content to the English version and the translation is accurate.

10 References

[1] Abou-Sayed, Y. REMS review for Xywav (calcium, magnesium, potassium and sodium oxybates), NDA 212690, January 19, 2021

[2] Chervin, RD, Idiopathic Hypersomnia. In: UpToDate, Scammell, TE (Ed), UpToDate, Waltham, MA, 2021. Retrieved May 27, 2021 from https://www.uptodate.com/contents/idiopathic-hypersomnia

[3] Chervin, RD, Idiopathic Hypersomnia. In: UpToDate, Scammell, TE (Ed), UpToDate, Waltham, MA, 2021. Retrieved May 28, 2021 from https://www.uptodate.com/contents/idiopathic-hypersomnia

[4] National Institutes of Health: Genetic and Rare Diseases Information Center. Idiopathic Hypersomnia. Retrieved May 28, 2021 from https://rarediseases.info.nih.gov/diseases/8737/idiopathic-hypersomnia

[5] National Institutes of Health: Genetic and Rare Diseases Information Center. Idiopathic Hypersomnia. Retrieved May 29, 2021 from https://rarediseases.info.nih.gov/diseases/8737/idiopathic-hypersomnia

[6] Jazz Pharmaceuticals, Inc. Risk Evaluation and Mitigation Strategy for Xywav and Xyrem, February 11, 2021.

11 Appendix

Prescriber Enrollment Form

Prescriber Brochure

Xywav Prescription Form

Xyrem Prescription Form

Patient Counseling Checklist

35 Pages draft labeling have been withheld in full as b4 (CCI/TS) immediately following this page

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/s/

DONELLA A FITZGERALD
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ANAHITA TAVAKOLI
06/15/2021 10:25:19 AM

JACQUELINE E SHEPPARD
06/15/2021 10:45:41 AM

DORIS A AUTH
06/15/2021 10:50:48 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s006

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

NDA 212690/S-006

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Jazz Pharmaceuticals Ireland Limited
Attention: Arthur Merlin d'Estreux, M.Sc.
Director, Global Regulatory Lead – Neurosciences
One Commerce Square
2005 Market Street
Philadelphia, PA 19103

Dear Mr. d'Estreux:

Please refer to your Supplemental New Drug Application (sNDA) dated February 12, 2021, received February 12, 2021, submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) oral solution.

We also refer to your amendment dated December 18, 2020.

The current sNDA seeks to expand the current indication for XYWAV™ to the treatment of adult patients with idiopathic hypersomnia.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is August 12, 2021.[1]

We are reviewing your application according to the processes described in the draft guidance for industry *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications*.[2] Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm
[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 19, 2021.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and PLLR Requirements for Prescribing Information[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products;
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential;
- Regulations and related guidance documents;
- A sample tool illustrating the format for Highlights and Contents;
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and;
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the

[3] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[4] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

proposed Prescribing Information (PI),and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

Do not submit launch materials until you have received our proposed revisions to the Prescribing Information (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see FDA.gov.[6] If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

[5] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

If you have any questions, contact Teresa Wheelous, Regulatory Project Manager, at teresa.wheelous@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Director (Acting)
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
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