CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21196/S-030

Trade Name:	Xyrem
Generic or Proper Name:	Sodium Oxybate
Sponsor:	Jazz Pharmaceuticals
Approval Date:	October 26, 2018
Indication:	For the treatment of cataplexy or excessive daytime sleepiness to pediatric patients 7 years of age and older with narcolepsy.

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 21196/S-030

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
REMS	**X**
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	**X**
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21196/S-030

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021196/S-030

SUPPLEMENT APPROVAL

Jazz Pharmaceuticals
Attention: Wheatley Spence, MS
Associate Director, Regulatory Affairs
1818 Market Street, Suite 2350
Philadelphia, PA 19103

Dear Ms. Spence:

Please refer to your Supplemental New Drug Application (sNDA) dated April 27, 2018, received April 27, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xyrem® (sodium oxybate) oral solution, 500 mg/mL.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated May 18, 2018.

This Prior Approval supplemental new drug application proposes to expand the use of Xyrem for the treatment of cataplexy or excessive daytime sleepiness to pediatric patients 7 years of age and older with narcolepsy, and proposes modifications to the approved Xyrem risk evaluation and mitigation strategy (REMS).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your April 27, 2018, submission includes final printed labeling (FPL) for your Prescribing Information, Instructions for Use, and Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this FPL is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. 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 titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

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, 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 most recent modification was approved on July 15, 2015. The REMS consists of a Medication Guide, 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 primarily of modifications to the REMS document and appended materials to align with labeling changes related to the new pediatric indication.

In accordance with section 505-1 of the FDCA, we have determined that the following additional REMS modifications are necessary to minimize burden on the healthcare delivery system of complying with the REMS:

Medication Guide: We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication

Guide as an element of the approved REMS to ensure that the benefits of Xyrem outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on April 27, 2018, amended and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on February 27, 2015.

The revised XYREM REMS Assessment Plan will include, but is not limited to, the following information:

For the 6-month assessment after approval of the finalized REMS and all subsequent REMS assessments submitted thereafter:

1.a. Program statistics (totals for the current REMS assessment reporting period and cumulative totals from approval of the finalized REMS, if feasible)

Jazz Pharmaceuticals will report to FDA the following:

- **Patients:**
  - Number of patients enrolled
  - Number of patients enrolled who received at least one shipment of XYREM
  - Number of duplicate patients detected by the Certified Pharmacy
  - Number of patients associated with more than one prescriber during their therapy
  - Number of patients who were disenrolled from the program and reasons for disenrollment
  - Number of patients who have discontinued XYREM after receiving at least one shipment of XYREM
    - Proportion of discontinued patients who were associated with a report of a serious adverse event, including death
  - Age and gender of enrolled patients.
- **Prescribers:**
  - Number of prescribers certified
  - Number of certified prescribers who have written at least one prescription for XYREM
  - Number of certified prescribers by specialty
  - Number of certified prescribers who were disenrolled during the reporting period and reasons for disenrollment

- Number of disenrolled prescribers who were associated with a XYREM prescription and number of disenrolled prescribers associated with a XYREM shipment
- Number of patients by current enrolled prescriber.

- **Certified Pharmacy**
  - If the Certified Pharmacy was decertified during the reporting period and reasons for decertification.

1.b. Dispensing and compliance data (totals for the current REMS assessment reporting period and cumulative totals from approval of the finalized REMS)

Jazz Pharmaceuticals will monitor and track shipping and handling of XYREM and report to FDA the following:

- Total number of prescriptions
- Total number of bottles and shipments sent
- Total number of first-time fills and refills
- Number of shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and RMRs completed
- Number of patients prescribed a daily dose greater than 9 g
- Number of prescriptions filled from a prescriber who was not enrolled
- Number of prescriptions for more than a 30 days' supply (first fill) or more than a 90 days' supply (refills) and reasons
- Number of RMRs submitted to the sponsor
  - Number of patients with an RMR
  - Number of patients with multiple RMRs
  - Number of alerts generated from RMRs
  - Number of RMRs generated from early refill requests
  - Number of RMRs generated for other reasons (list reasons)
  - Number of prescriber-related RMRs
- Number of patients with overlapping prescriptions (more than one active prescription)
- Number of duplicate patients who were shipped XYREM under more than one name or identifier
- Number of patients who were shipped XYREM after being disenrolled
- Number of patients who requested an early refill and reason for the request
  - Number of requests approved
  - Number of requests denied by the prescriber

  - Number of requests denied by the Certified Pharmacy
  - Number of patients with multiple requests for early refills
- Number of initial shipments sent to patients without completion of the XYREM REMS Program Patient Counseling Checklist
- Summary table from XYREM REMS Program Patient Counseling Checklists of the number of patients taking the following concomitant medications and who subsequently received at least one shipment of XYREM:
  - Sedative hypnotics
  - Alcohol
  - Other potentially interacting agents:
    - Sedating antidepressants, antipsychotics, or anti-epileptics
    - General anesthetic
    - Muscle relaxants
    - Opioid analgesics
    - Divalproex sodium or other valproate drug (e.g., valproic acid)
    - Illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB])
- Summary table from XYREM REMS Program Patient Counseling Checklists of the number of patients who have been diagnosed with the following conditions and who subsequently received at least one shipment of XYREM:
  - Sleep apnea
  - Asthma, COPD, or other conditions affecting the respiratory system
- Number of notifications by pharmacists to prescribers for the following situations and the outcome of the notification (dispensed XYREM, counseled patient, and summary of other actions):
  - Use with contraindicated medications (concomitant sedative hypnotics)
  - Use with other concomitant CNS-depressant medications (sedating antidepressants or antipsychotics, sedating anti-epileptics, general anesthetics, muscle relaxants, opioid analgesics, or illicit CNS depressants)
  - Patient report of alcohol use
  - Patient report of diagnosis of sleep apnea
  - Patient report of diagnosis of asthma, COPD, or other conditions affecting breathing
  - Suspected abuse, misuse, or diversion
  - Alerts regarding potential abuse, misuse, or diversion on the patient profiles
  - Prescription error
  - Early refill requests

1.c. Pharmacovigilance/surveillance (totals for the current REMS assessment reporting period and cumulative totals from start of program, if feasible)

Jazz Pharmaceuticals will provide to FDA the following:

- Summary tables of the number of reports of serious adverse events to include all outcomes of death, emergency department visits (when admitted to hospital), or hospitalizations resulting from or associated with the following:
  - Use with concurrent sedative hypnotics and alcohol
  - Intentional misuse
  - Abuse
  - Overdose
  - Medication error
- Cases of Sexual Abuse.

The summary tables will include the following data fields (CIOMS II line listings): date, report ID, report type, notifier, age, gender, start and stop date, dose, frequency, onset date, system organ class, outcome, and causality.

1.d. Program infrastructure and performance surveillance (information for the current REMS assessment reporting period)

Jazz Pharmaceuticals will provide to FDA the following:

- Call center report with number of calls received
- Summary of frequently asked questions
- Summary of any REMS-related problems identified
- Summary of program or system problems and a description of any corrective actions taken

1.e. A report on periodic assessments of the dispensing of the Medication Guide in accordance with 21 CFR 208.24

Jazz Pharmaceuticals will report to FDA on the dispensing of the Medication Guide as part of the REMS assessments.

1.f. With respect to REMS goals, an assessment of the extent to which the Elements to Assure Safe Use are meeting the goals or whether the goals or such elements should be modified

Jazz Pharmaceuticals will institute a system of oversight and review to evaluate whether the REMS is meeting its goals. If Jazz Pharmaceuticals determines, based on the results of the assessments, surveillance, and knowledge assessments, that modifications to the XYREM REMS program are needed (or that an element is no longer needed) to continue to ensure that the benefits of XYREM outweigh the risks and that the REMS is not unduly burdensome to

patient access or the healthcare system the company will submit a prior approval supplement to FDA proposing a revised REMS prior to implementing any changes to the approved REMS.

For the 12-month assessment after approval of the finalized REMS and all subsequent REMS assessments submitted thereafter:

1.g. Assessment of patients'and prescribers' understanding of the following:

- The risk of significant CNS and respiratory depression associated with XYREM even at recommended doses
- The contraindicated uses of XYREM
- The potential for abuse, misuse, and overdose associated with XYREM
- The safe use, handling, and storage of XYREM
- The XYREM REMS Program requirements.

Patient and prescriber knowledge assessments are described in Sections 5.j and 5.k and provided in Appendix 2 of the REMS supporting document.

1.h. Certified Pharmacy knowledge assessments

- Assessment of the understanding of all Certified Pharmacy staff involved in the XYREM REMS Program of the following:
  - The approved indications for XYREM
  - The abuse potential of XYREM
  - The contraindication of use of XYREM with sedative hypnotics and alcohol
  - The risk of significant CNS and respiratory depression associated with XYREM even at recommended doses
  - The XYREM REMS Program requirements
  - The types of information in the Central Database
  - Monitoring patients for signs of inappropriate prescribing, abuse, misuse, and diversion
  - The requirement to report all potential adverse events
- Assessment of pharmacists' understanding of the following:
  - Requirements for limiting the first prescription to a one-month supply and subsequent prescriptions to no more than a three-month supply
  - Prescriber notification requirements
  - Requirements for validating the prescriber's and patient's enrollment
  - The ability to disenroll a prescriber or patient for noncompliance with the XYREM REMS Program
  - Requirements for validating a XYREM prescription
  - Requirement for completing the XYREM REMS Program Patient Counseling Checklist

- Actions taken if the patient is using a contraindicated medication or other potentially interacting agent
- Patient counseling information
- Requirements to consult with the prescriber when clarification is needed for a prescription and/or for an early refill request
- Requirements for completing XYREM REMS Program RMRs
- Requirements for shipment of XYREM to the patient

The XYREM REMS Program Certified Pharmacy Knowledge Assessments are described in Section 5.l and provided in Appendix 1 of the REMS supporting document.

1.i. A summary report of audits of the Certified Pharmacy conducted during the assessment period

Jazz Pharmaceuticals will provide a summary of the audits of the Certified Pharmacy that were conducted during the assessment period, including the topics covered during the audit and the number of significant observations.

1.j. Patient knowledge survey

A representative sample of patients will be surveyed using a structured questionnaire annually following the first formal XYREM REMS Program assessment. The objective is to assess their knowledge of the key risk information and REMS requirements, including the serious risks associated with XYREM. The knowledge survey will be conducted according to industry standards and will assess patients and caregivers of pediatric patients who have received XYREM for at least one month.

The protocol includes details on the sample size and associated confidence intervals for various response rates: selection criteria for defining the sample, the expected number of patients or caregivers to be surveyed, recruitment strategies, how and when the surveys will be administered, an explanation of controls used to minimize bias, an explanation of the controls used to compensate for the limitations associated with the methodology, the survey instruments (questionnaires and/or moderator's guide), and any available background information on testing of survey questions and correlation to the information of the Medication Guide, the XYREM REMS Program Patient Quick Start Guide, and the XYREM REMS Program Brochure for Pediatric Patient and Their Caregivers.

Survey data collection will be completed approximately 10 months after implementation of the REMS, thus enabling XYREM knowledge assessments to be submitted to the FDA at the 12-month REMS assessment, at all subsequent REMS assessments, and as needed following substantive changes to the REMS-related educational materials. The protocol for the patient survey is provided in Appendix 2 of the REMS supporting document.

Data from the patient survey will be reported as descriptive statistics for the survey administration, study population, and survey questions. Results will include numbers of patients, patient contacts by the Certified Pharmacy, patient demographics, and response data showing level of patient understanding of the risks associated with XYREM use.

1.k. Prescriber knowledge survey

A representative sample of prescribers will be surveyed annually following the first formal XYREM REMS Program assessment. The objective is to assess their knowledge of the XYREM REMS key risk information and program requirements. The goal of this survey initiative will be to determine whether the XYREM REMS Elements to Assure Safe Use are effective in educating prescribers about the key risk information and the procedures to be followed in the XYREM REMS. The survey will be conducted according to industry standards and will assess prescribers who have prescribed XYREM.

The protocol includes details on the sample size and the associated confidence intervals for response rates, selection criteria for defining the sample, the expected number of prescribers to be surveyed, recruitment strategies, how and when the surveys will be administered, an explanation of the controls used to minimize bias, an explanation of the controls used to compensate for the limitations associated with the methodology, the survey instruments (questionnaires and/or moderator's guide), and any available background information on testing of survey questions and correlation to the messages of the prescribing information and XYREM REMS Program Prescriber Brochure.

Survey data collection will be completed approximately 10 months following implementation of the REMS, thus enabling XYREM knowledge assessments to be submitted to the FDA at the 12-month REMS assessment, at all subsequent assessments, and as needed following substantive changes to the REMS-related educational materials. The protocol for the prescriber survey is provided in Appendix 2 of the REMS supporting document. Results will include numbers of prescribers, prescriber contacts by the Certified Pharmacy, prescriber demographics, and response data showing level of prescriber understanding of safe use of XYREM, including approved indications; contraindications; risk of severe CNS/respiratory depression; abuse, misuse, and diversion; and death.

1.l. Certified Pharmacy training knowledge assessments

All Certified Pharmacy staff involved in the XYREM REMS Program will be required to complete Module A of the XYREM REMS Program Certified Pharmacy Training at least annually. In addition, all pharmacists involved in dispensing XYREM under the XYREM REMS Program will be required to complete Module B of the XYREM REMS Program Certified Pharmacy Training at least annually. A knowledge assessment must be successfully completed for each module as part of the training requirement. Successful completion of the knowledge assessments requires an 80% accuracy level. The Module A and Module B Knowledge Assessments are provided in Appendix 1 of the REMS supporting document.

The following metrics will assess the post-training knowledge assessment:

A. Number of completed post-training knowledge assessments including method of completion and number of attempts to complete by module
B. Summary of the most frequently missed post-training knowledge assessment questions by module
C. A summary of potential comprehension or perception issues identified with the post-training knowledge assessment by module

1.m. Surveillance and monitoring

Jazz Pharmaceuticals will periodically monitor available safety databases, such as those established by), the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS), the National Forensic Laboratory Information System, the National Drug Threat Assessment, and the for any information regarding abuse, misuse, or diversion of sodium oxybate. Any relevant information will be included in the REMS assessments.

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 1 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 21196 REMS ASSESSMENT METHODOLOGY

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 21196 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 21196/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 21196/S-000 PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 21196/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 21196/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 21196

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. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information 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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, call Vandna Kishore, Regulatory Project Manager, at Vandna.Kishore@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- REMS

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/

NICHOLAS A KOZAUER on behalf of ERIC P BASTINGS
10/26/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21196/S-030

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21196/S-030

PRIORITY REVIEW DESIGNATION
FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Jazz Pharmaceuticals
Attention: Wheatley Spence, MS
Associate Director, Regulatory Affairs
1818 Market Street, Suite 2350
Philadelphia, PA 19103

Dear Ms. Spence:

Please refer to your supplemental New Drug Application (sNDA) dated and received April 27, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xyrem ® (sodium oxybate) oral solution, 500 mg/mL.

We also refer to your amendments dated May 18, 2018.

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 October 27, 2018.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. 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 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 October 4, 2018.

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* and *PLLR Requirements for Prescribing Information* 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.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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 proposed package insert (PI), Medication Guide, and patient PI (as applicable). 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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. 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.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, contact Vandna Kishore, Regulatory Project Manager, at Vandna.Kishore@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS
06/14/2018
Signed for Dr. Dunn.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21196/S-030

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XYREM® (sodium oxybate) 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
- **Xyrem is a CNS depressant, and respiratory depression can occur with Xyrem use (5.1, 5.4)**

Abuse and Misuse
- **Xyrem is the sodium salt of 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)**

Xyrem is available only through a restricted program called the Xyrem REMS Program (5.3)

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

Indications and Usage (1)	MM/YYYY
Dosage and Administration (2.1, 2.2, 2.4)	MM/YYYY
Warnings and Precautions (5.1, 5.4, 5.5, 5.6, 5.7)	MM/YYYY

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

Xyrem 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)

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

Dosage for Adult Patients
- Initiate dosage at 4.5 g per night orally divided into two doses (2.1).
- Titrate to effect in increments of 1.5 g per night at weekly intervals (0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) (2.1).
- Recommended dosage range: 6 g to 9 g per night orally (2.1).

Total Nightly Dose	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

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

Important Administration Information for All Patients
- Take each dose while in bed and lie down after dosing (2.3).
- Allow 2 hours after eating before dosing (2.3).
- Prepare both doses prior to bedtime; dilute each dose with approximately ¼ cup of water in pharmacy-provided containers (2.3).
- Patients with Hepatic Impairment: starting dose is one-half of the original dosage per night, administered orally divided into two doses (2.4).
- Concomitant use with Divalproex Sodium: an initial reduction in Xyrem dose of at least 20% is recommended (2.5, 7.2).

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

Oral solution, 0.5 g per mL (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 Xyrem 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 Xyrem 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).
- High sodium content in Xyrem: Monitor patients with heart failure, hypertension, or impaired renal function (5.8).

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

Most common adverse reactions in adults (≥5% and at least twice the incidence with placebo) were nausea, dizziness, vomiting, somnolence, enuresis, and tremor (6.1).

Most common adverse reactions in pediatric patients (≥5%) were enuresis, nausea, headache, vomiting, weight decreased, decreased appetite, and dizziness (6.2).

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.

----------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 Xyrem (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and ABUSE AND MISUSE
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Adult Dosing Information
2.2 Pediatric Dosing Information
2.3 Important Administration Instructions for All Patients
2.4 Dosage Modification in Patients with Hepatic Impairment
2.5 Dosage Adjustment with Co-administration of Divalproex Sodium
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Central Nervous System Depression
5.2 Abuse and Misuse
5.3 Xyrem REMS Program
5.4 Respiratory Depression and Sleep-Disordered Breathing
5.5 Depression and Suicidality
5.6 Other Behavioral or Psychiatric Adverse Reactions
5.7 Parasomnias
5.8 Use in Patients Sensitive to High Sodium Intake
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Alcohol, Sedative Hypnotics, and CNS Depressants
7.2 Divalproex Sodium
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
10.1 Human Experience
10.2 Signs and Symptoms
10.3 Recommended Treatment of Overdose
10.4 Poison Control Center
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Cataplexy in Adult Narcolepsy
14.2 Excessive Daytime Sleepiness in Adult Narcolepsy
14.3 Cataplexy and Excessive Daytime Sleepiness in Pediatric Narcolepsy
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage
16.3 Handling and Disposal
17 PATIENT COUNSELING INFORMATION

*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**
  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 *[see Warnings and Precautions (5.1)]*. Many patients who received Xyrem during clinical trials in narcolepsy were receiving central nervous system stimulants *[see Clinical Trials (14)]*.
- **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 *[see Warnings and Precautions (5.2)]*.

  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 Xyrem REMS Program *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosing Information

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 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dosage range of 6 g to 9 g per night orally. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

Table 1: Recommended Adult Xyrem Dose Regimen (g = grams)

If A Patient's Total Nightly Dose 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

2.2 Pediatric Dosing Information

Xyrem is administered orally twice nightly. 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.

Table 2: Recommended Pediatric Xyrem Dosage for Patients 7 Years of Age and Older*

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

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

**If Xyrem is used in patients 7 years of age and older who weigh less than 20 kg, a lower starting dosage, lower maximum weekly dosage increases, and lower total maximum nightly dosage should be considered.
Note: Unequal dosages may be required for some patients to achieve optimal treatment.

2.3 Important Administration Instructions for All Patients

Take the first dose of Xyrem at least 2 hours after eating *[see Clinical Pharmacology (12.3)]*.

Prepare both doses of Xyrem prior to bedtime. Prior to ingestion, each dose of Xyrem should be diluted with approximately ¼ cup (approximately 60 mL) of water in the empty pharmacy containers provided. Patients should take both doses of Xyrem while in bed and lie down immediately after dosing as Xyrem may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking Xyrem, 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. Patients should remain in bed following ingestion of the first and second doses, and should not take the second dose until 2.5 to 4 hours after the first dose. Patients may need to set an alarm to awaken for the second dose. Rarely, patients may take up to 2 hours to fall asleep.

If the second dose is missed, that dose should be skipped and XYREM should not be taken again until the next night. Both Xyrem doses should never be taken at one time.

2.4 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)]*.

2.5 Dose Adjustment with Co-administration of Divalproex Sodium

Pharmacokinetic and pharmacodynamic interactions have been observed when Xyrem is co-administered with divalproex sodium. For patients already stabilized on Xyrem, it is recommended that addition of divalproex sodium should be accompanied by an initial reduction in the nightly dose of Xyrem by at least 20%. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting Xyrem dose when introducing Xyrem. Prescribers should monitor patient response and adjust dose accordingly *[see Drug Interactions (7.2)* and *Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Xyrem is a clear to slightly opalescent oral solution, in a concentration of 0.5 g per mL (0.5 g/mL of sodium oxybate equivalent to 0.413 g/mL of oxybate).

4 CONTRAINDICATIONS

- Xyrem is contraindicated in patients being treated with sedative hypnotic agents *[see Warnings and Precautions (5.1)]*.
- Patients should not drink alcohol when using Xyrem *[see Warnings and Precautions (5.1)]*.
- Xyrem is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency *[see Clinical Pharmacology (12.3)]*. This is a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Depression

Xyrem is a central nervous system (CNS) depressant. In adult clinical trials at recommended doses, obtundation and clinically significant respiratory depression occurred in patients treated with Xyrem. Alcohol and sedative hypnotics are contraindicated in patients who are using Xyrem. The concurrent use of 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 Xyrem is required, dose reduction or discontinuation of one or more CNS depressants (including Xyrem) should be considered. In addition, if short-term use of an opioid (e.g. post- or perioperative) is required, interruption of treatment with Xyrem should be considered.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that Xyrem 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 Xyrem. Patients should be queried about CNS depression-related events upon initiation of Xyrem therapy and periodically thereafter.

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

5.2 Abuse and Misuse

Xyrem is a Schedule III controlled substance. The active ingredient of Xyrem, sodium oxybate or gamma-hydroxybutyrate (GHB), is 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 Xyrem, 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, 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) *[see Drug Abuse and Dependence (9.2)]*.

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

5.3 Xyrem REMS Program

Xyrem is available only through a restricted distribution program called the Xyrem REMS Program 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 Xyrem REMS Program include the following:

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

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

5.4 Respiratory Depression and Sleep-Disordered Breathing

Xyrem may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported *[see Overdosage (10)]*.

In an adult study assessing the respiratory-depressant effects of Xyrem at doses up to 9 g per night in 21 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 an adult study assessing the effects of Xyrem 9 g per night in 50 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 desaturation events have been observed with Xyrem administration in adult and pediatric patients.

In adult clinical trials in 128 patients with narcolepsy, two subjects 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 and in postmenopausal women not on hormone replacement therapy as well as among patients with narcolepsy.

5.5 Depression and Suicidality

In adult clinical trials in 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 controlled adult trial, with patients randomized to fixed doses of 3 g, 6 g, or 9 g per night Xyrem or placebo, there was a single event of depression at the 3 g per night dose. In another adult controlled trial, with patients titrated from an initial 4.5 g per night starting dose, the incidences of depression were 1 (1.7%), 1 (1.5%), 2 (3.2%), and 2 (3.6%) for the placebo, 4.5 g, 6 g, and 9 g per night doses, respectively.

In the pediatric clinical trial in patients with narcolepsy (n=104), one patient experienced suicidal ideation while taking Xyrem.

The emergence of depression in patients treated with Xyrem 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 Xyrem.

5.6 Other Behavioral or Psychiatric Adverse Reactions

During adult clinical trials in patients with narcolepsy, 3% of 781 patients treated with Xyrem experienced confusion, with incidence generally increasing with dose.

Less than 1% of patients discontinued the drug because of confusion. Confusion was reported at all recommended doses from 6 g to 9 g per night. In a controlled trial in adults where patients were randomized to fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose-response relationship for confusion was demonstrated, with 17% of patients at 9 g per night experiencing confusion. In all cases in that controlled trial, the confusion resolved soon after termination of treatment. In Trial 3 where sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in one patient at the 9 g per night dose. In the

majority of cases in all adult clinical trials in patients with narcolepsy, confusion resolved either soon after termination of dosing or with continued treatment.

Anxiety occurred in 5.8% of the 874 patients receiving Xyrem in adult clinical trials in another population.

Other neuropsychiatric reactions reported in adult clinical trials in patients with narcolepsy and the post-marketing setting included hallucinations, paranoia, psychosis, aggression, and agitation.

In the pediatric clinical trial 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 adult and pediatric patients taking Xyrem should be carefully monitored.

5.7 Parasomnias

Sleepwalking, defined as confused behavior occurring at night and at times associated with wandering, was reported in 6% of 781 patients with narcolepsy treated with Xyrem in adult controlled and long-term open-label studies, with <1% of patients discontinuing due to sleepwalking. Rates of sleepwalking were similar for patients taking placebo and patients taking Xyrem in controlled trials. It is unclear if some or all of the reported sleepwalking episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Five instances of significant injury or potential injury were associated with sleepwalking during a clinical trial of Xyrem in patients with narcolepsy.

Parasomnias, including sleepwalking, also have been reported in the pediatric clinical trial and in postmarketing experience with Xyrem. Therefore, episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

5.8 Use in Patients Sensitive to High Sodium Intake

Xyrem has a high salt content. In patients sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment), consider the amount of daily sodium intake in each dose of Xyrem. Table 3 provides the approximate sodium content per Xyrem dose.

Table 3

Approximate Sodium Content per Total Nightly Dose of Xyrem (g = grams)

Xyrem Dose	Sodium Content/Total Nightly Exposure
3 g per night	550 mg
4.5 g per night	820 mg
6 g per night	1100 mg
7.5 g per night	1400 mg
9 g per night	1640 mg

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)]*
- Use in Patients Sensitive to High Sodium Intake *[see Warnings and Precautions (5.8)]*

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

Xyrem was studied in three placebo-controlled clinical trials (Trials N1, N3, and N4, described in Sections 14.1 and 14.2) in 611 patients with narcolepsy (398 subjects treated with Xyrem, and 213 with placebo). A total of 781 patients with narcolepsy were treated with Xyrem in controlled and uncontrolled clinical trials.

Section 6.1 and Table 4 present adverse reactions from three pooled, controlled trials (N1, N3, N4) in patients with narcolepsy.

Adverse Reactions Leading to Treatment Discontinuation:

Of the 398 patients with narcolepsy treated with Xyrem, 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.

Commonly Observed Adverse Reactions in Controlled Clinical Trials:

The most common adverse reactions (incidence ≥5% and twice the rate seen with placebo) in patients treated with Xyrem were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.

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

Table 4 lists adverse reactions that occurred at a frequency of 2% or more in any treatment group for three controlled trials and were more frequent in any Xyrem treatment group than with placebo. Adverse reactions are summarized by dose at onset. Nearly all patients in these studies initiated treatment at 4.5 g per night. In patients who remained on treatment, adverse reactions tended to occur early and to diminish over time.

Table 4
Adverse Reactions Occurring in ≥2% of Adult Patients and More Frequently with Xyrem than Placebo in Three Controlled Trials (N1, N3, N4) by Body System and Dose at Onset

System Organ Class/Adverse Reaction	Placebo (n=213) %	Xyrem 4.5g (n=185) %	Xyrem 6g (n=258) %	Xyrem 9g (n=178) %
ANY ADVERSE REACTION	62	45	55	70
GASTROINTESTINAL DISORDERS				
Nausea	3	8	13	20
Vomiting	1	2	4	11
Diarrhea	2	4	3	4
Abdominal pain upper	2	3	1	2
Dry mouth	2	1	2	1
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS				
Pain	1	1	<1	3
Feeling drunk	1	0	<1	3
Edema peripheral	1	3	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Pain in extremity	1	3	1	1
Cataplexy	1	1	1	2
Muscle spasms	2	2	<1	2
NERVOUS SYSTEM DISORDERS				
Dizziness	4	9	11	15
Somnolence	4	1	3	8
Tremor	0	0	2	5
Paresthesia	1	2	1	3
Disturbance in attention	0	1	0	4
Sleep paralysis	1	0	1	3
PSYCHIATRIC DISORDERS				
Disorientation	1	1	2	3
Anxiety	1	1	1	2
Irritability	1	0	<1	3
Sleep walking	0	0	0	3
RENAL AND URINARY DISORDERS				
Enuresis	1	3	3	7
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Hyperhidrosis	0	1	1	3

Dose-Response Information

In clinical trials in narcolepsy, a dose-response relationship was observed for nausea, vomiting, paresthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking, and enuresis. The incidence of all these reactions was notably higher at 9 g per night.

In controlled trials in narcolepsy, discontinuations of treatment due to adverse reactions were greater at higher doses of Xyrem.

Pediatric Patients (7 Years of Age and Older)

In the pediatric clinical trial (Trial N5), 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 up to 377 days (median exposure 332 days).

Adverse Reactions Leading to Treatment Discontinuation

In the pediatric clinical trial, 5 of 104 patients reported adverse reactions that led to withdrawal from the study (hallucination, tactile; suicidal ideation; weight decreased; sleep apnea syndrome; and affect lability).

Adverse Reactions in the Pediatric Clinical Trial

The most common adverse reactions (>5%) were enuresis (18%), nausea (17%), headache (16%), vomiting (16%), weight decreased (12%), decreased appetite (8%), and dizziness (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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Xyrem. 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, decreased appetite, fall, fluid retention, hangover, headache, hypersensitivity, hypertension, memory impairment, nocturia, panic attack, vision blurred, and weight decreased.

7 DRUG INTERACTIONS

7.1 Alcohol, Sedative Hypnotics, and CNS Depressants

Xyrem should not be used in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of Xyrem *[see Warnings and Precautions (5.1)]*.

7.2 Divalproex Sodium

Concomitant use of Xyrem with divalproex sodium resulted in a 25% mean increase in systemic exposure to Xyrem (AUC ratio range of 0.8 to 1.7) and in a greater impairment on some tests of attention and working memory. An initial Xyrem dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking Xyrem *[see Dosage and Administration (2.5)* and *Clinical Pharmacology (12.3)]*. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of Xyrem 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 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 *[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

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

Oral administration of sodium oxybate (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 Xyrem and any potential adverse effects on the breastfed infant from Xyrem or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of Xyrem in the treatment of cataplexy or excessive daytime sleepiness in pediatric patients (7 years of age and older) with narcolepsy have been established in a double-blind, placebo-controlled, randomized-withdrawal study *[see Adverse Reactions (6.1) and Clinical Studies (14.3)]*.

In the pediatric clinical trial with Xyrem 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 *[see Warnings and Precautions (5.4, 5.5, 5.6, 5.7) and Adverse Reactions (6.1)]*.

Safety and effectiveness of Xyrem in pediatric patients below the age of 7 years 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 Xyrem in patients with narcolepsy did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects. In controlled trials 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 (20.5% v. 18.9%). Frequency of headaches was markedly increased in the elderly (38.5% v. 18.9%). 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 Xyrem, the starting dose should be reduced in patients with liver impairment *[see Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

9.2 Abuse

Xyrem (sodium oxybate), the sodium salt of GHB, 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.

The rapid onset of sedation, coupled with the amnestic features of Xyrem, 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 Xyrem according to state and federal regulations. It is safe to dispose of Xyrem down the sanitary sewer.

9.3 Dependence

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. The discontinuation effects of Xyrem have not been systematically evaluated in controlled clinical trials. 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.

Tolerance

Tolerance to Xyrem 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 Xyrem 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 Xyrem in the treatment of alcohol withdrawal have not been established.

10 OVERDOSAGE

10.1 Human Experience

Information regarding overdose with Xyrem 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 two cases of overdose with Xyrem 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.

10.2 Signs and Symptoms

Information about signs and symptoms associated with overdosage with Xyrem 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

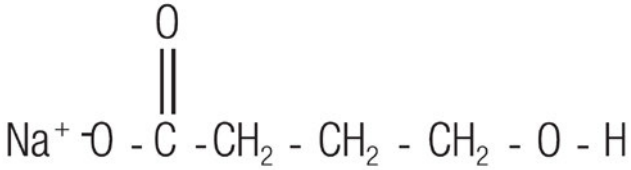
General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation 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 Xyrem 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 sodium 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

Sodium oxybate, a CNS depressant, is the active ingredient in Xyrem. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $C_4H_7NaO_3$, and the molecular weight is 126.09 g/mole. The chemical structure is:



Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. Each mL of Xyrem contains 0.5 g of sodium oxybate (equivalent to 0.413 g/mL of oxybate) in USP Purified Water, neutralized to pH 7.5 with malic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Xyrem is a CNS depressant. The mechanism of action of Xyrem in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous compound and metabolite of the neurotransmitter GABA. It is hypothesized that the therapeutic effects of Xyrem on cataplexy and excessive daytime sleepiness are mediated through $GABA_B$ actions 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 of Xyrem.

Absorption

Following oral administration of Xyrem, GHB is absorbed rapidly across the clinical dose range, with an absolute bioavailability of about 88%. The average peak plasma concentrations (C_{max}) following administration of each of the two 2.25 g doses given under fasting conditions 4 hours apart were similar. The average time to peak plasma concentration (T_{max}) ranged from 0.5 to 1.25 hours. Following oral administration of Xyrem, the plasma levels of GHB increased more than dose-proportionally, with blood levels increasing 3.7-fold as total daily dose is doubled from 4.5 g to 9 g. Single doses greater than 4.5 g have not been studied.

Effect of Food

Administration of Xyrem immediately after a high-fat meal resulted in delayed absorption (average T_{max} increased from 0.75 hr to 2 hr) and a reduction in C_{max} of GHB by a mean of 59% and of systemic exposure (AUC) by 37%.

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.

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 an elimination half-life of 0.5 to 1 hour.

Specific Populations

Geriatric Patients

There is limited experience with Xyrem 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 (age 48 to 64 years) and older (age 65 to 75 years) adults.

Pediatric Patients

The pharmacokinetics of sodium oxybate were evaluated in pediatric patients from 7 to 17 years of age (n=29). The pharmacokinetic characteristics of sodium oxybate were shown to be similar in adults and pediatric patients. Body weight was found to be the major intrinsic factor affecting oxybate pharmacokinetics.

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 Xyrem 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 Xyrem should be reduced in patients with liver impairment *[see Dosage and Administration (2.4)* 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 Xyrem and divalproex sodium, diclofenac, and ibuprofen:

- Divalproex sodium: Co-administration of Xyrem (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%, 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 (2.5)]*.
- Diclofenac: Co-administration of Xyrem (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 Xyrem (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 Xyrem 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 Xyrem 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 sodium oxybate *in vivo,* showed no clear evidence of carcinogenic activity. The plasma AUCs of sodium 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 (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

The efficacy of Xyrem for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy has been established in the following adequate and well-controlled trials:

- Cataplexy in adult narcolepsy in Trials N1 and N2 *[see Clinical Studies (14.1)]*
- Excessive Daytime Sleepiness (EDS) in adult narcolepsy in Trials N3 and N4 *[see Clinical Studies (14.2)]*
- Cataplexy and EDS in pediatric narcolepsy in Trial N5 *[see Clinical Studies (14.3)]*

14.1 Cataplexy in Adult Narcolepsy

The effectiveness of Xyrem in the treatment of cataplexy was established in two randomized, double-blind, placebo-controlled, multicenter, parallel-group trials (Trials N1 and N2) in patients with narcolepsy (see Table 5). In Trials N1 and N2, 85% and 80% of patients, respectively, were also being treated with CNS stimulants. The high percentages of concomitant stimulant use make it impossible to assess the efficacy and safety of Xyrem independent of stimulant use. In each trial, the treatment period was 4 weeks and the total nightly Xyrem doses ranged from 3 g to 9 g, with the total nightly dose administered as two equal doses. The first dose each night was taken at bedtime and the second dose was taken 2.5 to 4 hours later. There were no restrictions on the time between food consumption and dosing.

Trial N1 enrolled 136 narcoleptic patients with moderate to severe cataplexy (median of 21 cataplexy attacks per week) at baseline. Prior to randomization, medications with possible effects on cataplexy were withdrawn, but stimulants were continued at stable doses. Patients were randomized to receive placebo, Xyrem 3 g per night, Xyrem 6 g per night, or Xyrem 9 g per night.

Trial N2 was a randomized-withdrawal trial with 55 narcoleptic patients who had been taking open-label Xyrem for 7 to 44 months prior to study entry. To be included, patients were required to have a history of at least 5 cataplexy attacks per week prior to any treatment for cataplexy. Patients were randomized to continued treatment with Xyrem at their stable dose (ranging from 3 g to 9 g per night) or to placebo for 2 weeks. Trial N2 was designed specifically to evaluate the continued efficacy of sodium oxybate after long-term use.

The primary efficacy measure in Trials N1 and N2 was the frequency of cataplexy attacks.

Table 5
Median Number of Cataplexy Attacks in Trials N1 and N2

Trial/Dosage Group	Baseline	Median Change from Baseline	Comparison to Placebo (p-value)
Trial N1 (Prospective, Randomized, Parallel Group Trial)			
		(median attacks/week)	
Placebo (n=33)	20.5	-4	–
Xyrem 6 g per night (n=31)	23.0	-10	0.0451
Xyrem 9 g per night (n=33)	23.5	-16	0.0016
Trial N2 (Randomized-Withdrawal Trial)			
		(median attacks/2 weeks)	
Placebo (n=29)	4.0	21	–
Xyrem (n=26)	1.9	0	<0.001

In Trial N1, both the 6 g and 9 g per night Xyrem doses resulted in statistically significant reductions in the frequency of cataplexy attacks. The 3 g per night dose had little effect. In Trial N2, patients randomized to placebo after discontinuing long-term open-label Xyrem therapy experienced a significant increase in cataplexy attacks ($p<0.001$), providing evidence of long-term efficacy of Xyrem. In Trial N2, the response was numerically similar for patients treated with doses of 6 g to 9 g per night, but there was no effect seen in patients treated with doses less than 6 g per night, suggesting little effect at these doses.

14.2 Excessive Daytime Sleepiness in Adult Narcolepsy

The effectiveness of Xyrem in the treatment of excessive daytime sleepiness in patients with narcolepsy was established in two randomized, double-blind, placebo-controlled trials (Trials N3 and N4) (see Tables 6 to 8). Seventy-eight percent of patients in Trial N3 were also being treated with CNS stimulants.

Trial N3 was a multicenter randomized, double-blind, placebo-controlled, parallel-group trial that evaluated 228 patients with moderate to severe symptoms at entry into the study including a median Epworth Sleepiness Scale (see below) score of 18, and a Maintenance of Wakefulness Test (see below) score of 8.3 minutes. Patients were randomized to one of 4 treatment groups: placebo, Xyrem 4.5 g per night, Xyrem 6 g per night, or Xyrem 9 g per night. The period of double-blind treatment in this trial was 8 weeks. Antidepressants were withdrawn prior to randomization; stimulants were continued at stable doses.

The primary efficacy measures in Trial N3 were the Epworth Sleepiness Scale and the Clinical Global Impression of Change. The Epworth Sleepiness Scale is intended to evaluate the extent of sleepiness in everyday situations by asking the patient a series of questions. In these questions, patients were asked to rate their chances of dozing during each of 8 activities on a scale from 0-3 (0=never; 1=slight; 2=moderate; 3=high). Higher total scores indicate a greater tendency to sleepiness. The Clinical Global Impression of Change is evaluated on a 7-point scale, centered at *No Change*, and ranging from *Very Much Worse* to *Very Much Improved*. In Trial N3, patients were rated by evaluators who based their assessments on the severity of narcolepsy at baseline.

In Trial N3, statistically significant improvements were seen on the Epworth Sleepiness Scale score at Week 8 and on the Clinical Global Impression of Change score at Week 8 with the 6 g and 9 g per night doses of Xyrem compared to the placebo group.

Table 6
Change from Baseline in Daytime Sleepiness Score (Epworth Sleepiness Scale) at Week 8 in Trial N3 (Range 0-24)

Treatment Group	Baseline	Week 8	Median Change from Baseline at Week 8	p-value
Placebo (n=59)	17.5	17.0	-0.5	-
Xyrem 6 g per night (n=58)	19.0	16.0	-2.0	<0.001
Xyrem 9 g per night (n=47)	19.0	12.0	-5.0	<0.001

Table 7
Proportion of Patients with a Very Much or Much Improved Clinical Global Impression of Change in Daytime and Nighttime Symptoms in Trial N3

Treatment Group	Percentages of Responders (Very Much Improved or Much Improved)	Change from Baseline Significance Compared to Placebo (p-value)
Placebo (59)	22%	-
Xyrem 6 g per night (n=58)	52%	<0.001
Xyrem 9 g per night (n=47)	64%	<0.001

Trial N4 was a multicenter randomized, double-blind, placebo-controlled, parallel-group trial that evaluated 222 patients with moderate to severe symptoms at entry into the study including a median Epworth Sleepiness Scale score of 15, and a Maintenance of Wakefulness Test (see below) score of 10.3 minutes. At entry, patients had to be taking modafinil at stable doses of 200 mg, 400 mg, or 600 mg daily for at least 1 month prior to randomization. The patients enrolled in the study were randomized to one of 4 treatment groups: placebo, Xyrem, modafinil, or Xyrem plus modafinil. Xyrem was administered in a dose of 6 g per night for 4 weeks, followed by 9 g per night for 4 weeks. Modafinil was continued in the modafinil alone and the Xyrem plus modafinil treatment groups at the patient's prior dose. Trial N4 was not designed to compare the effects of Xyrem to modafinil because patients receiving modafinil were not titrated to a maximal dose. Patients randomized to placebo or to Xyrem treatment were withdrawn from their stable dose of modafinil. Patients taking antidepressants could continue these medications at stable doses.

The primary efficacy measure in Trial N4 was the Maintenance of Wakefulness Test. The Maintenance of Wakefulness Test measures latency to sleep onset (in minutes) averaged over 4 sessions at 2-hour intervals following nocturnal polysomnography. For each test session, the subject was asked to remain awake without using extraordinary measures. Each test session is terminated after 20 minutes if no sleep occurs, or after 10 minutes, if sleep occurs. The overall score is the mean sleep latency for the 4 sessions.

In Trial N4, a statistically significant improvement in the change in the Maintenance of Wakefulness Test score from baseline at Week 8 was seen in the Xyrem and Xyrem plus modafinil groups compared to the placebo group.

This trial was not designed to compare the effects of Xyrem to modafinil, because patients receiving modafinil were not titrated to a maximally effective dose.

Table 8
Change in Baseline in the Maintenance of Wakefulness Test Score (in minutes) at Week 8 in Trial N4

Treatment Group	Baseline	Week 8	Mean Change from Baseline at Week 8	p-value
Placebo (modafinil withdrawn) (n=55)	9.7	6.9	-2.7	-
Xyrem (modafinil withdrawn) (n=50)	11.3	12.0	0.6	<0.001
Xyrem plus modafinil (n=54)	10.4	13.2	2.7	<0.001

14.3 Cataplexy and Excessive Daytime Sleepiness in Pediatric Narcolepsy

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 (Trial N5) (NCT02221869). The study enrolled 106 pediatric patients (median age: 12 years; range: 7 to 16 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 on a stable dose of Xyrem or were Xyrem-naïve. CNS stimulants were allowed at entry, and approximately 50% of patients used 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 dose of Xyrem had been achieved, these patients entered the 2-week stable-dose period; patients on a stable dose of Xyrem at study entry remained on this dose for 3 weeks, prior to randomization. Efficacy was established at doses 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 *[see Clinical Studies (14.2) for description of scale]*. 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 adult clinical trials described above *[see Clinical Studies (14.2) for description and scoring]*. 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 9 and 10).

Pediatric patients on stable doses of Xyrem who were withdrawn from Xyrem treatment and 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 9).

Table 9
Number of Weekly Cataplexy Attacks and Epworth Sleepiness Scale (Child and Adolescent) Score (Trial N5)

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 10).

Table 10
Clinical Global Impression of Change (CGIc) for Cataplexy Severity and Narcolepsy Overall (Trial N5)

	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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Xyrem is a clear to slightly opalescent oral solution. Each prescription includes one bottle of Xyrem 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 Xyrem shipment.

Each amber bottle contains Xyrem oral solution at a concentration of 0.5 g per mL (0.5 g/mL of sodium oxybate equivalent to 0.413 g/mL of oxybate) and has a child-resistant cap.

One 180 mL bottle NDC 68727-100-01

16.2 Storage

Keep out of reach of children.

Xyrem should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 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

Xyrem is a Schedule III drug under the Controlled Substances Act. Xyrem should be handled according to state and federal regulations. It is safe to dispose of Xyrem 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 Xyrem can cause central nervous system depression, including respiratory depression, hypotension, profound sedation, syncope, and death. Instruct patients to not engage in activities requiring mental alertness or motor coordination, including operating hazardous machinery, for at least 6 hours after taking Xyrem. 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 Xyrem is gamma-hydroxybutyrate (GHB), which is associated with serious adverse reactions with illicit use and abuse *[see Warnings and Precautions (5.2)]*.

Xyrem REMS Program

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

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

Xyrem 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 Xyrem.

Sedation

Inform patients and/or caregivers that the patient is likely to fall asleep quickly after taking Xyrem (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. Instruct patients and/or caregivers that the patient should remain in bed following ingestion of the first and second doses. Instruct patients and/or caregivers that the patient should not take their second dose until 2.5 to 4 hours after the first dose.

Food Effects on Xyrem

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

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 Xyrem 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 Xyrem 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)]*.

Sodium Intake

Instruct patients and/or caregivers that Xyrem contains a significant amount of sodium and patients who are sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment) should limit their sodium intake *[see Warnings and Precautions (5.8)]*.

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Protected by U.S. Patent Nos. 6,472,431; 6,780,889; 7,262,219; 7,851,506; 8,263,650; 8,324,275; 8,461,203; 8,772,306; 8,859,619; 8,952,062; 9,050,302; 9,486,426; and 9,539,330

MEDICATION GUIDE
XYREM® (ZĪE-rem)
(sodium oxybate)
oral solution, CIII

Read this Medication Guide carefully before you start or your child starts taking XYREM 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 XYREM?

- XYREM is a central nervous system (CNS) depressant. Taking XYREM 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)
  - dizziness (syncope)
  - death
- XYREM is a federal controlled substance (CIII). The active ingredient of XYREM is a form of gamma-hydroxybutyrate (GHB) that is also a federal controlled substance (C-I). 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 or your child has any of these serious side effects. Ask your doctor if you are not sure if you are taking a medicine listed above.

- Anyone who takes XYREM 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 XYREM. Those activities should not be done until you know how XYREM affects you or your child.
- Keep XYREM in a safe place to prevent abuse and misuse. Selling or giving away XYREM 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 XYREM is available only by prescription and filled through the central pharmacy in the XYREM REMS Program. Before you receive or your child receives XYREM, your doctor or pharmacist will make sure that you understand how to take XYREM safely and effectively. If you have any questions about XYREM, ask your doctor or call the XYREM REMS Program at 1-866-997-3688.

What is XYREM?

XYREM 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)
- excessive daytime sleepiness (EDS)

It is not known if XYREM is safe and effective in children less than 7 years of age.

Do not take XYREM 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 XYREM, tell your doctor about all medical conditions, including if you or your child:

- have short periods of not breathing while sleeping (sleep apnea)
- snores, has trouble breathing, or has lung problems. You or your child may have a higher chance of having serious breathing problems when taking XYREM.
- 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	○ seeing or hearing things that are not real (hallucinations)
○ feeling more suspicious (paranoia)	○ being out of touch with reality (psychosis)
○ acting aggressive	○ agitation

- have liver problems
- are on a salt-restricted diet. XYREM contains a lot of sodium (salt) and may not be right for you or your child.
- have high blood pressure

- have heart failure
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if XYREM can harm unborn babies.
- are breastfeeding or plan to breastfeed. XYREM passes into breast milk. You and your doctor should decide if you or your child will take XYREM 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 sleep (sedatives). Know the medicines you take or your child takes. Keep a list of them to show your doctor and pharmacist when you or your child gets a new medicine.

How should I take or give XYREM?

- Read the **Instructions for Use** at the end of this Medication Guide for detailed instructions on how to take XYREM.
- Take or give XYREM exactly as your doctor tells you to take or give it.
- XYREM can cause physical dependence and craving for the medicine when it is not taken as directed.
- Never change the XYREM dose without talking to your doctor.
- XYREM can cause sleep very quickly without feeling drowsy. Some patients 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 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.
- XYREM is taken at night divided into 2 doses.
    - Adults: Take the first XYREM dose at bedtime while you are in bed and lie down immediately. Take the second XYREM dose 2 ½ to 4 hours after the first XYREM dose. You may want to set an alarm clock to make sure you wake up to take the second XYREM dose. You should remain in bed after taking the first and second doses of XYREM.
    - Child: Give the first XYREM 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 XYREM dose 2 ½ to 4 hours after the first XYREM dose. You may want to set an alarm clock to make sure you wake up to give the second XYREM dose. Your child should remain in bed after taking the first and second doses of XYREM.
- If you miss or your child misses the second XYREM dose, skip that dose and do not take or give XYREM again until the next night. Never take or give 2 XYREM doses at 1 time.
- Wait at least 2 hours after eating before taking XYREM.
- You or your child should see your doctor every 3 months for a check-up while taking XYREM. Your doctor should check to see if XYREM is helping to lessen your or your child's symptoms and if you feel or your child feels any side effects while taking XYREM.
- If you take or your child takes too much XYREM, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of XYREM?

XYREM can cause serious side effects, including:

- See **"What is the most important information I should know about XYREM?"**
- **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 use XYREM.
- **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

  Call your doctor right away if you have or your child has symptoms of mental health problems.
- **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 XYREM include:

- nausea
- sleepiness
- dizziness
- vomiting
- bedwetting
- tremor (in adults)

In pediatric patients, headache, decreased appetite, and weight decrease were also common.

Side effects may increase when taking higher doses of XYREM.

These are not all the possible side effects of XYREM. **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 XYREM?

- Store XYREM in the original bottle or in pharmacy containers with child-resistant caps provided by the pharmacy.
- Get emergency medical help right away if a child who has not been prescribed Xyrem drinks Xyrem. Store XYREM between 68°F to 77°F (20°C to 25°C).
- XYREM solution prepared after dilution should be taken within 24 hours.
- When you have finished using a XYREM bottle:
  - empty any unused XYREM down the sink drain
  - cross out the label on the XYREM bottle with a marker
  - place the empty XYREM bottle in the trash

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

General information about the safe and effective use XYREM.

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

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

What are the ingredients in XYREM?

Active ingredients: sodium oxybate

Inactive ingredients: purified water and malic acid

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For more information, go to www.XYREMREMS.com or call the XYREM REMS Program at 1-866-997-3688.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Issued: 10/2018

Instructions for Use
XYREM® (ZĪE-rem)
(sodium oxybate)
oral solution, CIII

Read this Instructions for Use carefully before you (or your child) start taking XYREM 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.

Note:

- **You will need to split your (or your child's) prescribed XYREM dose into 2 separate pharmacy containers for mixing.**
- **You will need to mix XYREM with water before you take or give your child the dose.**
- **Safely store the prepared XYREM doses and take within 24 hours. If the prepared dose was not taken within this time, throw the mixture away.**
- **Both XYREM doses should be taken while in bed.**
- **The pharmacy containers may be rinsed out with water and emptied into the sink drain.**

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

- Bottle of XYREM medicine
- Dosing syringe for measuring and dispensing the XYREM dose
- Measuring cup that is able to measure about ¼ cup of water (not provided with the XYREM shipment)
- 2 **empty** pharmacy containers with child-resistant caps for mixing, storing, and taking the XYREM doses
- Alarm clock (which may be included in the first shipment).

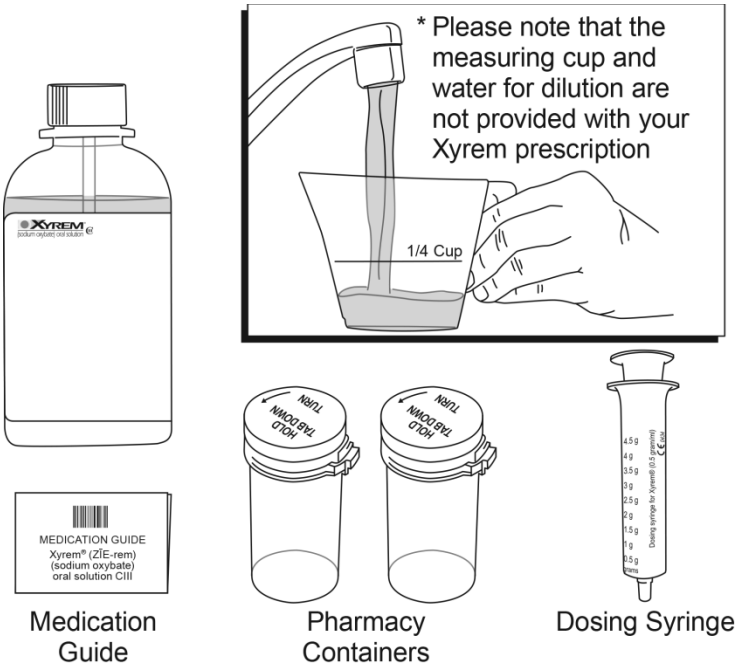

Figure A

Step 1: Setup

- Take the XYREM 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 XYREM prescription.
- Fill a measuring cup (not provided) with about ¼ cup of water available for diluting your 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.

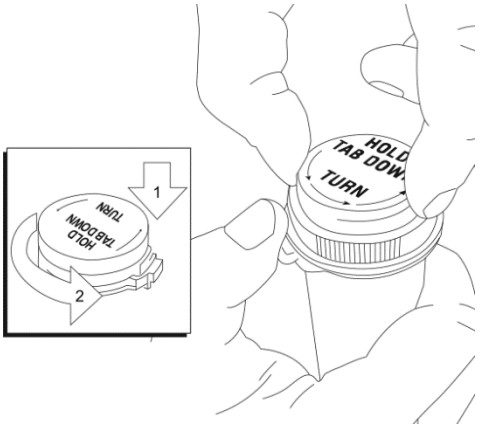

Figure B

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

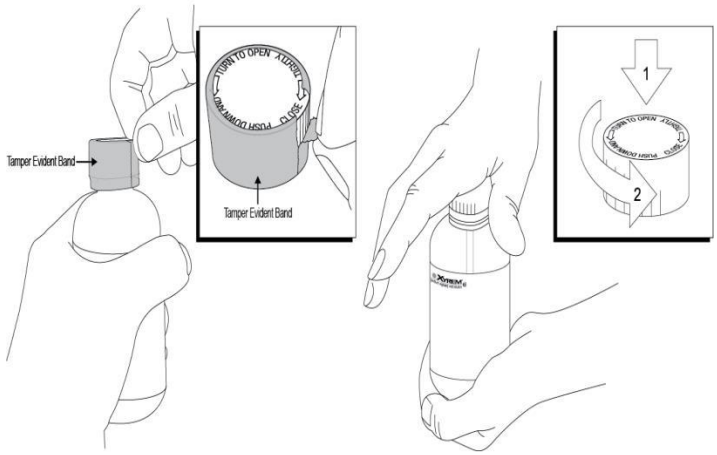

Figure C

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

Place the XYREM 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 hand. See Figure D.

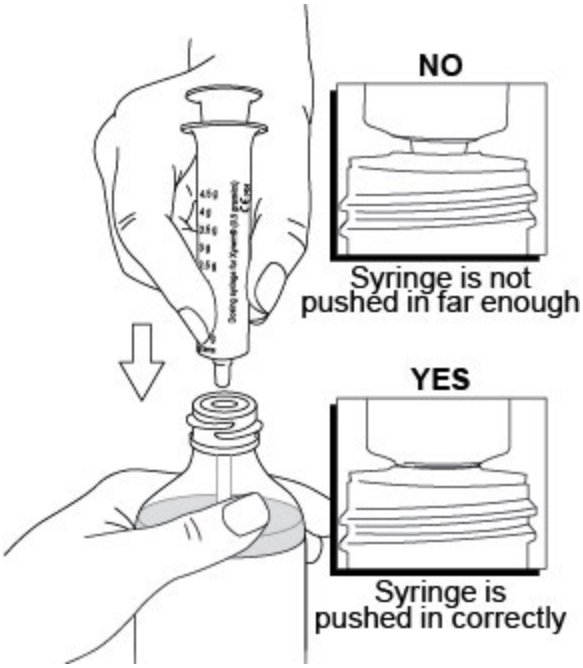

Figure D

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 you or your child's dose. See Figure E.

Figure E

Note: **The XYREM medicine will not flow into the syringe unless you keep the bottle upright.**

Figure F shows an example of drawing up a XYREM dose of 2.25g. Figure G shows an example if an air space forms when drawing up the dose.

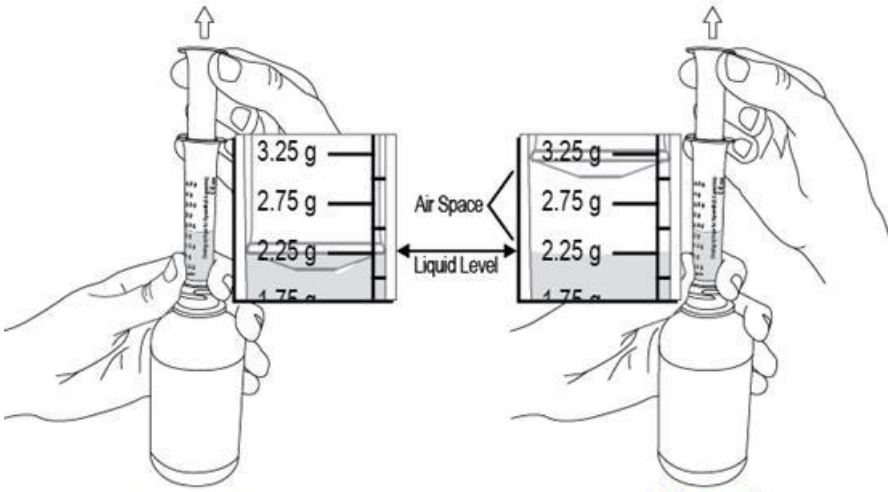

Figure F

Figure G

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 above.

- After you draw up the first divided XYREM dose, remove the syringe from the opening of the XYREM 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.

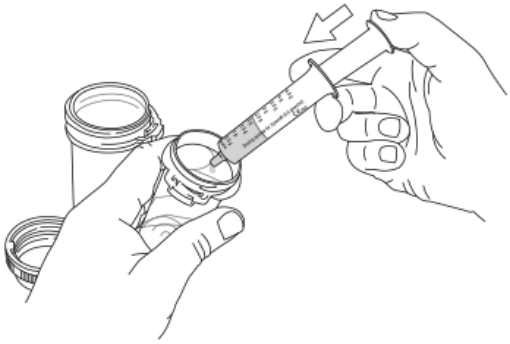

Figure H

- 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 XYREM.**
- **All shipped bottles of XYREM contain the concentrated medicine. Water for mixing the medicine is not provided in the shipment.**
- Place the child-resistant cap provided on 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 XYREM 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 XYREM doses

- 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 the syringe out with water and squirt the liquid into the sink drain.

Step 5. Take or give the first XYREM dose

- At bedtime, and before you take (or give) the first XYREM dose, put the second XYREM dose in a safe place. Caregivers should ensure all XYREM 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 XYREM 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 XYREM 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 patients 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 XYREM dose

- When you wake up 2½ to 4 hours later for your (or your child's) second dose of XYREM, 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 XYREM dose, turn off the alarm and take (or give your child) the second XYREM dose.
- Drink (or have your child drink) all of the second XYREM 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.

How should I store XYREM?

- Store XYREM in the original bottle or in pharmacy containers with child-resistant caps provided by the pharmacy.
- Store XYREM between 68°F to 77°F (20°C to 25°C).
- XYREM solution prepared after dilution should be taken within 24 hours.
- When you have finished using a XYREM bottle:
  - empty any unused XYREM down the sink drain
  - cross out the label on the XYREM bottle with a marker
  - place the empty XYREM bottle in the trash
- **Keep XYREM and all medicines out of the reach of children and pets.**

Distributed By:
Jazz Pharmaceuticals, Inc.
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These Instructions for Use have been approved by the U.S. Food and Drug Administration.
Revised: 10/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21196/S-030

REMS

Division of Risk Management
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type	NDA
Application Number	21196/S-030
PDUFA Goal Date	October 27, 2018
OSE RCM #	2018-1257
Reviewer(s)	Yasmeen Abou-Sayed, Pharm.D., Ana Tavakoli, M.A.
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins, Pharm.D.
Review Completion Date	October 26, 2018
Subject	Evaluation of REMS Modification
Established Name	Sodium Oxybate
Trade Name	Xyrem
Applicant:	Jazz Pharmaceuticals
Formulation	500 mg/ml oral solution
Dosing Regimen	Pediatric Dosing:

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	4.5g

Adult Dosing: 4.5 grams (g) per night 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 to the effective dose range of 6 g to 9 g per night orally.

Indication	Treatment of cataplexy and excessive daytime sleepiness in narcolepsy in patients 7 years and older

Table of Contents

Executive Summary 3

1 Introduction 3

2 Background 3

2.1 REGULATORY HISTORY 3

3 Benefit Assessment 4

4 Results of Review of Applicant Proposed REMS Modification 4

4.1 GENERAL COMMENTS 4

4.2 REMS DOCUMENT 5

4.3 REMS MATERIALS 5

4.3.1 Prescriber Enrollment Form 5

4.3.2 Prescriber Brochure 5

4.3.3 Prescription Form 5

4.3.4 Patient Quick Start Guide 6

4.3.5 Brochure for Pediatric Patients and their Caregivers 6

4.3.6 Certified Pharmacy Training Program 6

4.3.7 Pharmacy Knowledge Assessment – Module A 6

4.3.8 Patient Counseling Checklist 6

4.3.9 REMS Website Screenshots 6

4.4 REMS SUPPORTING DOCUMENT 6

5 Conclusion and Recommendations 7

6 Appendix 7

6.1 REFERENCES 7

6.2 APPENDED MATERIALS 7

Executive Summary

This is a review of Jazz Pharmaceuticals' proposed Risk Evaluation and Mitigation Strategy (REMS) modification for Xyrem (sodium oxybate), NDA 21196/S-030, submitted on April 27, 2018 and amended on September 27, 2018 and October 26, 2018. The REMS for Xyrem was originally approved on February 27, 2015 to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Xyrem. The currently approved REMS consists of a Medication Guide, elements to assure safe use (ETASU) including prescriber certification (A), pharmacy certification (B), and safe-use conditions (D), an implementation system, and a timetable for submission of assessments. The Applicant submitted the REMS modification as part of a supplemental application to support the expansion of the US indication to include the pediatric use of Xyrem for the treatment of cataplexy in narcolepsy and the treatment of excessive daytime sleepiness in narcolepsy. The Applicant's proposed modification includes updating the REMS document, appended materials, and REMS supporting document to align with labeling changes related to the new pediatric indication provided for in the efficacy supplement, and adding a new educational material for pediatric patients and their caregivers. (b) (4)

The appended materials were updated appropriately based on Agency recommendations sent on October 12, 18, 23, 25, and 26, 2018.

DRISK finds the Applicant's proposed REMS document, all appended materials, and REMS supporting document as submitted on October 26, 2018 to be acceptable. DRISK recommends approval of the REMS appended to this review.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed modification to the risk evaluation and mitigation strategy (REMS) for Xyrem (sodium oxybate), NDA 21196/S-030, submitted by Jazz Pharmaceuticals (Jazz) on April 27, 2018, and amended on September 27, 2018 and October 26, 2018. The Applicant submitted the REMS modification as part of a supplemental application for a new proposed indication for the treatment of cataplexy and excessive daytime sleepiness (EDS) in narcolepsy in pediatric patients. The supplemental application is under review in the Division of Neurology Products (DNP).

2 Background

2.1 Regulatory History

The following is a summary of the regulatory history for NDA 21196/S-030 relevant to this review:

- **April 27, 2018**: Jazz submitted supplemental NDA 21196/S-030 to support the expansion of the US adult labeling to include the pediatric use of Xyrem for the treatment of cataplexy in narcolepsy and the treatment of EDS in narcolepsy.[1] The submission included a proposed REMS modification to update the REMS with changes related to the new indication.

- **August 31, 2018:** The Agency provided via email a draft an Agency proposed updated REMS document that aligns with the *Format and Content of a REMS Document Draft Guidance for Industry*.[2]
- **September 13, 2018**: The Agency provided comments to the Applicant on their proposed REMS modification. The comments included a draft updated REMS document, (b) (4) acceptance of the proposed *Brochure for Pediatric Patients and their Caregivers*, (b) (4), and acceptance of other changes to incorporate the pediatric indication.
- **September 27, 2018**: The Applicant submitted a REMS amendment to NDA 21196/S-030.[3] The amendment included a redlined draft of the Agency's proposed redlined document, a rationale explaining the Applicant's proposed deviations from the Agency proposal, appended materials, and the REMS supporting document.
- **October 12, 2018**: The Agency sent communication via an information request (IR) to the Applicant in response to the Applicant's rationale sent on September 27, 2018, regarding modifications to the Agency's draft REMS Document.[4]
- **October 15, 2018**: The Applicant requested feedback via email on their revisions to the Agency's draft REMS document.[5]
- **October 18, 2018**: The Agency provided comments in an IR to the Applicant on their proposed modifications to the REMS materials sent on September 27, 2018; in addition, clarification on the Agency's format and content of the draft updated REMS document was provided.[6]
- **October 22, 2018:** The Applicant sent via email a redlined draft of the REMS document.[7]
- **October 23, 2018**: The Agency sent via email a redlined draft of the REMS document on October 22, 2018.[8]
- **October 25, 2018:** The Applicant sent via email a redlined REMS document, a rationale for not accepting Agency edits to the draft REMS document, appended REMS materials, and a REMS supporting document.[9]
- **October 25, 2018**: The Agency sent via email a redlined REMS document based upon the currently approved format and comments on the appended materials.[10]
- **October 25, 2018**: The Applicant sent via email a redlined draft of the updated REMS document provided to them by the Agency.[11]
- **October 26, 2018:** The Applicant submitted a REMS amendment to NDA 21196/S-030 that incorporated all Agency recommendations.[12]

3 Benefit Assessment

The Clinical Reviewer recommends approval of Xyrem in patients 7 years of age and older on the basis of efficacy and safety information currently available.[13]

4 Results of Review of Applicant Proposed REMS Modification

4.1 General comments

The Applicant addressed and incorporated the Agency's comments on the proposed modified REMS.

Reviewer Comment: DRISK finds the updates throughtout the Xyrem REMS materials to align with finalized labeling to be acceptable.

4.2 REMS DOCUMENT

From September 13, 2018 through October 26, 2018, the Agency and the Applicant discussed the format and content of the REMS document. The Agency provided the Applicant with a draft REMS document to conform with the formatting outlined in the October 2017 *Draft Guidance for Industry, Format and Content of a REMS Document* on August 31, 2018. (b) (4)

Reviewer Comment: DRISK finds the REMS document submitted on October 26, 2018, to be acceptable.

4.3 REMS MATERIALS

4.3.1 Prescriber Enrollment Form

The Applicant removed language printed at the bottom of the form with indicated that the Prescriber could report adverse events to the Applicant directly or FDA as requested in the October 25, 2018 DRISK comments.

Reviewer Comment: DRISK finds the Prescriber Enrollment Form *acceptable.*

4.3.2 Prescriber Brochure

The Applicant updated this material to align with finalized labeling. This included:

- Pages 2, 6: indication language
- Pages 11, 14, 17: administration instructions
- Page 13: use in special populations
- Page 16: pediatric dosing table on page 16

Reviewer Comment: DRISK finds the Prescriber Brochure *acceptable.*

4.3.3 Prescription Form

The Applicant removed the text prior to the Prescriber Signature at the bottom of page 1 (b) (4) in reference to the Patient Quick Start Guide or the Brochure for Pediatric Patients and their Caregivers, as requested in the October 25, 2018 DRISK comments. (b) (4)

Reviewer Comment: DRISK finds the Prescription Form *acceptable.*

4.3.4 Patient Quick Start Guide

The Applicant updated the dosing language on page 12 to align with finalized labeling.

Reviewer Comment: DRISK finds the Patient Quick Start Guide *acceptable.*

4.3.5 Brochure for Pediatric Patients and their Caregivers

The Applicant updated the dosing language on page 12 to align with finalized labeling. Additionally, the Applicant incorporated the Agency's recommendation to more clearly state that the purpose of the REMS is to educate the stakeholder on the risks of treatment, on pages 3, 6, and 27. They also incorporated a modification to a statement on page 14, which equated Xyrem with other medications that cause sleepiness.

Reviewer Comment: DRISK finds the Brochure for Pediatric Patients and their Caregivers *acceptable.*

4.3.6 Certified Pharmacy Training Program

The Applicant updated this material to align with finalized labeling. The updates included the indication language on pages 2 and 5, and the boxed warning on page 6.

Reviewer Comment: All proposed modifications to the Certified Pharmacy Training Program *are acceptable.*

4.3.7 Pharmacy Knowledge Assessment – Module A

The Applicant updated the indication language in Question 1 to align with finalized labeling.

Reviewer Comment: DRISK finds the Pharmacy Knowledge Assessment – Module A *acceptable.*

4.3.8 Patient Counseling Checklist

The Applicant updated the administration instructions on page 2 to align with finalized labeling.

Reviewer Comment: DRISK finds the Patient Counseling Checklist *acceptable.*

4.3.9 REMS Website Screenshots

(b) (4)

No additional changes were proposed to the REMS Website.

Reviewer Comment: DRISK finds the REMS Website Screenshots *acceptable.*

4.4 REMS Supporting Document

(b) (4)

The Applicant incorporated all Agency recommendations for the Assessment Plan, which included additional metrics associated with the Certified Pharmacy post-training knowledge assessment:

Reviewer Comment: DRISK finds the REMS Supporting Document *acceptable.*

5 Conclusion and Recommendations

DRISK finds the proposed REMS for Xyrem, as submitted on October 26, 2018, acceptable.

DRISK recommends approval of the REMS appended to this review.

6 Appendix

6.1 References

[1] Jazz. Supplemental New Drug Application for Xyrem, NDA 21196 S-030, April 27, 2018.

[2] Parncutt, S.Email correspondence with Jazz Pharmaceuticals, Inc. RE: REMS Modification for Xyrem, NDA 21196/S-030, August 31, 2018.

[3] Jazz. REMS Amendment for Xyrem, NDA 21196/S-030, September 27, 2018.

[4] Kishore, V. Email correspondence with Jazz Pharmaceuticals, Inc. RE: REMS Modification for Xyrem, NDA 21196/S-030, October 12, 2018.

[5] Jazz, E-mail correspondence with Agency RE: REMS Modification for Xyrem, NDA 21196/S-030, October 15, 2018.

[6] Abou-Sayed, Y. Division of Risk Management. Evaluation of REMS Modification for Xyrem, NDA 21196/S-030, October 16, 2018.

[7] Jazz, E-mail correspondence with Agency RE: REMS Modification for Xyrem, NDA 21196/S-030, October 22, 2018.

[8] Kishore, V. Email correspondence with Jazz Pharmaceuticals, Inc. RE: REMS Modification for Xyrem, NDA 21196/S-030, October 23, 2018.

[9] Jazz, E-mail correspondence with Agency RE: REMS Modification for Xyrem, NDA 21196/S-030, October 25, 2018.

[10] Kishore, V. Email correspondence with Jazz Pharmaceuticals, Inc. RE: REMS Modification for Xyrem, NDA 21196/S-030, October 25, 2018.

[11] Jazz, E-mail correspondence with Agency RE: REMS Modification for Xyrem, NDA 21196/S-030, October 25, 2018.

[12] Jazz. REMS Amendment for Xyrem, NDA 21196/ S-030, October 26, 2018.

[13] Mani, R. Division of Neurology Products. Clinical Review for Xyrem NDA 21196/S-030, October 26, 2018.

6.2 Appended Materials

Xyrem REMS Document

Prescriber Enrollment Form

Prescriber Brochure

Patient Enrollment Form

Prescription Form

Patient Quick Start Guide

Brochure for Pediatric Patients and their Caregivers

Certified Pharmacy Training Program

Pharmacy Knowledge Assessment – Module A

Pharmacy Knowledge Assessment – Module B

Patient Counseling Checklist

Risk Management Report

REMS Website Screenshots

Initial REMS approval: 02/27/2015
Most Recent Modification: October 2018

NDA 21-196 XYREM® (SODIUM OXYBATE) ORAL SOLUTION

Jazz Pharmaceuticals, Inc.
3180 Porter Drive
Palo Alto, CA 94304
Phone: 650-496-3777
E-mail: regulatory@jazzpharma.com

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL:

The goal of the XYREM REMS is to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of XYREM by:

A. Informing prescribers, pharmacists, and patients of:
   1. The risk of significant CNS and respiratory depression associated with XYREM
   2. The contraindication of use of XYREM with sedative hypnotics and alcohol
   3. The potential for abuse, misuse, and overdose associated with XYREM
   4. The safe use, handling, and storage of XYREM

B. Ensuring that pharmacy controls exist prior to filling prescriptions for XYREM that:
   1. Screen for concomitant use of sedative hypnotics and other potentially interacting agents
   2. Monitor for inappropriate prescribing, misuse, abuse, and diversion of XYREM
   3. Notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion.

II. REMS ELEMENTS:

A. Elements to Assure Safe Use

1. Healthcare Providers who prescribe XYREM are specially certified.

a. Jazz Pharmaceuticals will ensure that healthcare providers who prescribe XYREM are specially certified in the XYREM REMS Program. To become certified to prescribe XYREM, each prescriber must complete and submit to the XYREM REMS

Program the XYREM REMS Program Prescriber Enrollment Form, which includes the prescriber agreeing to:

i. Review the Prescribing Information (PI) and the XYREM REMS Program Prescriber Brochure.

ii. Screen each patient for whom XYREM is prescribed for:

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

iii. Counsel each patient prior to initiating therapy regarding the serious risks and safe use, handling, and storage of XYREM.

iv. Enroll each patient in the XYREM REMS Program by completing and submitting the XYREM REMS Program Patient Enrollment Form to the XYREM REMS Program.

v. Evaluate each patient within the first 3 months of starting XYREM therapy, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while on XYREM therapy.

a. Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
b. Serious adverse events
c. 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.

vi. 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.

b. The prescriber will complete the XYREM REMS Program Prescription Form for each initial prescription and for patients who are reinitiating XYREM after a lapse in therapy of 6 months or longer and submit the form to the XYREM REMS Program. By completing and signing this form, the prescriber acknowledges:

i. Having an understanding of

a. The approved indications of XYREM

b. The serious risks associated with XYREM

c. The Prescribing Information (PI) and the XYREM REMS Program Prescriber Brochure.

ii. Having screened the patient for the following:

a. History of alcohol or substance abuse

b. History of sleep-related breathing disorders

c. History of compromised respiratory function

d. Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents

e. History of depression or suicidality.

iii. Having counseled the patient on:

a. The serious risks associated with XYREM

b. Contraindications (alcohol and sedative hypnotics) and implications of concomitant use of XYREM with other potentially interacting agents

c. Preparation and dosing instructions for XYREM

d. Risk of abuse and misuse associated with XYREM

e. Risk of operating hazardous machinery, including automobiles or airplanes, for the first 6 hours after taking a dose of XYREM

f. Safe use, handling, and storage of XYREM.

iv. That XYREM is medically appropriate for the patient.

v. Having listed all known prescription and nonprescription medications and doses on the XYREM REMS Program Prescription Form.

c. Jazz Pharmaceuticals will:

i. Ensure that the XYREM REMS Program Prescriber Enrollment Form can be completed via facsimile, mail, E-mail, or other means; that the XYREM REMS Program Patient Enrollment Form can be completed via facsimile,

mail, or other means; and that the XYREM REMS Program Prescription Form can be completed via facsimile or mail.

ii. Ensure that materials appended to the XYREM REMS document will be made available through the XYREM REMS Program website (www.XYREMREMS.com) or by calling the XYREM REMS Program at 1-866-997-3688.

iii. Ensure that a prescriber is enrolled in the XYREM REMS Program only after verification that the XYREM REMS Program Prescriber Enrollment Form is complete and all enrollment requirements are met.

iv. Ensure that prescribers are notified when they are successfully enrolled in the XYREM REMS Program and are eligible to prescribe XYREM.

v. Maintain a secure and validated XYREM REMS Program Central Database containing information related to prescriber and patient enrollment, prescriptions, and concomitant medications (see Section II.C.1.c.).

vi. Ensure that enrolled prescribers continue to meet the requirements of the XYREM REMS Program and can disenroll non-compliant prescribers if the requirements are not met.

d. The following are part of the XYREM REMS Program and are appended:

i. XYREM REMS Program Prescriber Enrollment Form

ii. XYREM REMS Program Prescriber Brochure

iii. XYREM REMS Program Patient Enrollment Form

iv. XYREM REMS Program Prescription Form

v. XYREM REMS Program Patient Quick Start Guide

vi. XYREM REMS Program Brochure for Pediatric Patients and their Caregivers

vii. XYREM REMS Program website (www.XYREMREMS.com).

2. XYREM will be dispensed only by the central pharmacy that is specially certified.

a. Jazz Pharmaceuticals will certify a central pharmacy that is contracted with Jazz Pharmaceuticals to distribute and dispense XYREM (the XYREM REMS Program Certified Pharmacy). XYREM will not be stocked in retail pharmacy outlets. To become certified in the XYREM REMS Program, the pharmacy must agree to:

i. Dispense XYREM only to patients enrolled in the XYREM REMS Program pursuant to a valid prescription written by a prescriber enrolled in the XYREM REMS Program (see Section II.B.1.b).

ii. Ensure that all pharmacy staff involved in the XYREM REMS Program complete the XYREM REMS Program Pharmacy Training Program and Pharmacy Knowledge Assessment Module A.

iii. Ensure that all XYREM REMS Program pharmacists also complete the pharmacist training in the XYREM REMS Program Pharmacy Training Program, Pharmacy Knowledge Assessment Module A, and Pharmacy Knowledge Assessment Module B.

iv. Utilize the secure and validated XYREM REMS Program Central Database.

v. Provide 24-7 toll-free access to a XYREM REMS Program pharmacist.

vi. Ship XYREM directly to each patient or a patient-authorized adult designee, and track and verify receipt of each shipment of XYREM.

vii. Limit the first shipment to a one-month supply of XYREM, and subsequent shipments to no more than a three-month supply of XYREM.

viii. Document and report all potential adverse events reported by all sources, including any CNS depression, respiratory depression, loss of consciousness, coma, and death, and any cases of suspected abuse, misuse, or diversion to Jazz Pharmaceuticals.

b. Prior to dispensing XYREM, the XYREM REMS Program Certified Pharmacy ensures that a XYREM REMS Program pharmacist will:

i. Ensure the completion of the XYREM REMS Program Patient Counseling Checklist and its requirements and the documentation of information received in the XYREM REMS Program Central Database.

ii. Validate each XYREM REMS Program Prescription, by:

a. Verifying in the XYREM REMS Program Central Database that both the prescriber and patient are enrolled in the XYREM REMS Program and that the patient has no other active XYREM prescription

b. Confirming all 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.

iii. Review the patient information contained in the XYREM REMS Program Central Database, including:

a. 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 with XYREM.

b. Alerts and XYREM REMS Program Risk Management Reports (RMRs) regarding potential abuse, misuse, or diversion.

c. The XYREM REMS Program Certified Pharmacy will ship XYREM directly to each patient using an overnight service. In addition, the XYREM REMS Program Certified Pharmacy will verify that:

i. The shipment will be sent to a patient's confirmed shipping address.

ii. The patient or patient-authorized adult designee will be available to receive the shipment.

iii. The first shipment will include a copy of the Patient Quick Start Guide (for adult patients) or the Brochure for Pediatric Patients and Their Caregivers (for pediatric patients).

iv. Receipt of each shipment is confirmed and shipment and receipt dates are entered into the XYREM REMS Program Central Database.

d. The XYREM REMS Program Certified Pharmacy will monitor and report to Jazz Pharmaceuticals all instances of patient or prescriber behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion of XYREM.

i. The XYREM REMS Program Certified Pharmacy will document these events, including all requests for early refills, in the XYREM REMS Program Central Database by completing an RMR.

ii. Prior to granting an early refill request or if abuse, misuse, or diversion is suspected, the pharmacist will review the patient's RMR history and any alerts, and ensure the request or concern has been discussed with the prescriber prior to shipping XYREM.

iii. All reports of lost, stolen, destroyed, or spilled drug will be documented in the XYREM REMS Program Central Database by completing an RMR.

iv. Repeated reports of lost, stolen, destroyed, or spilled drug may be documented as an alert to the patient profile stored in the XYREM REMS Program Central Database.

v. The XYREM REMS Program Certified Pharmacy and/or prescriber may disenroll a patient from the XYREM REMS Program after review of incidents suggestive of abuse, misuse, or diversion.

e. The following materials are part of the REMS and are appended:

i. XYREM REMS Program Certified Pharmacy Training Program

ii. XYREM REMS Pharmacy Knowledge Assessment Module A

iii. XYREM REMS Pharmacy Knowledge Assessment Module B

iv. XYREM REMS Program Patient Counseling Checklist

v. XYREM REMS Program Risk Management Report Form

3. **XYREM will be dispensed and shipped only to patients who are enrolled in the XYREM REMS Program with documentation of safe use conditions.**

a. Jazz Pharmaceuticals will ensure that XYREM is dispensed only by the XYREM REMS Program Certified Pharmacy, by direct shipment, to patients enrolled in the XYREM REMS Program.

b. Jazz Pharmaceuticals will ensure that patients are enrolled in the XYREM REMS Program only if a prescriber enrolled in the XYREM REMS Program completes the XYREM REMS Patient Enrollment Form and submits the form to the XYREM REMS Program.

c. Jazz Pharmaceuticals will ensure that XYREM is dispensed and shipped to patients only after the patient has signed the prescriber-completed XYREM REMS Program Patient Enrollment Form and acknowledged that:

i. He/she has been counseled on the serious risks and safe use of XYREM

ii. He/she has asked the prescriber any questions about XYREM

d. Following enrollment, the patient remains in the XYREM REMS Program unless Jazz Pharmaceuticals, the XYREM REMS Program Certified Pharmacy, and/or prescriber determines the patient should be disenrolled. Reasons for disenrollment

include: multiple suspicious early refill requests or other information that indicates possible abuse, misuse, or diversion.

e. A disenrolled patient may be re-enrolled in the XYREM REMS Program. In order to re-enroll a patient who had been previously disenrolled for suspicions of abuse, misuse, or diversion, the XYREM REMS Program Certified Pharmacy must consult with the prescriber seeking to re-enroll the patient and communicate all relevant patient history to the prescriber, and both the pharmacist and the requesting prescriber must agree to re-enroll the patient.

f. A patient may change prescribers provided that the new prescriber is also enrolled in the XYREM REMS Program and that the new prescription does not overlap with another active prescription for XYREM.

g. If a pediatric patient's caregiver changes, the new caregiver must be counseled by the Certified Pharmacy on the serious risks and safe use of XYREM and acknowledge that he/she has asked any questions about XYREM before XYREM is dispensed and shipped.

B. Implementation System

1. The Implementation System for the XYREM REMS includes the following:

a. Jazz Pharmaceuticals will ensure that XYREM is dispensed only by the XYREM REMS Program Certified Pharmacy.

b. XYREM will be shipped only to patients enrolled in the XYREM REMS Program or the enrolled patient-authorized adult designee, pursuant to a valid prescription written by a prescriber enrolled in the XYREM REMS Program that does not overlap with another active prescription for XYREM.

c. Jazz Pharmaceuticals will ensure that a secure and validated XYREM REMS Program Central Database is maintained. The XYREM REMS Program Central Database will contain patient and prescriber enrollment status, all completed data forms, prescription and shipment data, as well as information related to dosing, concomitant medications, and behavior that raises suspicion of abuse, misuse, or diversion, including complete RMR histories.

d. Jazz Pharmaceuticals will monitor the XYREM REMS Program Certified Pharmacy for timely reporting to Jazz Pharmaceuticals of any behavior by patients or prescribers enrolled in the XYREM REMS Program that raises suspicion of abuse, misuse, or diversion.

e. Jazz Pharmaceuticals will monitor the XYREM REMS Program Central Database to ensure compliance with the XYREM REMS Program and to evaluate the implementation of the elements under Section II.B. Jazz Pharmaceuticals will ensure that appropriate corrective actions are implemented to address compliance concerns.

f. Jazz Pharmaceuticals will audit the XYREM REMS Program Certified Pharmacy after approval of the XYREM REMS to ensure that it implements the XYREM REMS Program as directed. Thereafter, Jazz Pharmaceuticals will audit the XYREM REMS Program Certified Pharmacy at least annually, identify all issues of noncompliance, and institute appropriate corrective actions, potentially including pharmacy decertification.

g. Jazz Pharmaceuticals will monitor the XYREM REMS Program Certified Pharmacy for timely reporting to Jazz Pharmaceuticals of all potential adverse events.

h. Jazz Pharmaceuticals will monitor and evaluate the implementation of the Elements to Assure Safe Use and take reasonable steps to work to improve implementation of these elements.

D. Timetable for Submission of Assessments

Jazz Pharmaceuticals will submit the REMS assessments every 6 months from the date of the REMS approval (02/2015) for the first year, and then 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 annual assessment will conclude no earlier than 60 days before the submission date for that assessment. The XYREM submissions will be submitted so that they are received by FDA on or before the due date.

XYREM REMS PROGRAM PRESCRIBER ENROLLMENT FORM

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

Complete and submit form online at www.XYREMREMS.com, OR scan and e-mail to XYREMPrescribers@express-scripts.com, OR fax to XYREM REMS Program at 1-866-470-1744 (toll free), OR mail to XYREM REMS Program, PO Box 66589, St. Louis, MO 63166-6589.
For more information, please call the XYREM REMS Program at 1-866-997-3688 (toll free).

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 XYREM.

☐ 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 have read the Prescribing Information (PI) and the XYREM REMS Program Prescriber Brochure and understand that:

- XYREM is a Schedule III 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
- 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

☐ I agree to:

- Enroll each patient in the XYREM REMS Program
- 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 XYREM
- Evaluate patients within the first 3 months of starting XYREM. It is recommended that patients be re-evaluated every 3 months thereafter while taking 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 XYREMREMS.com.

Step 3: Prescriber signature is required below for enrollment in the XYREM REMS Program.

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 XYREM REMS Program. I agree that I may be contacted in the future by mail, e-mail, fax, and/or telephone concerning XYREM, the XYREM REMS Program, and other XYREM programs and services.

***Prescriber Signature:** _____ ***Date:** _____

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

XYREM REMS

XYREM® (sodium oxybate) oral solution

Reference ID: 4341335

XYREM REMS

PRESCRIBER BROCHURE

Includes important prescribing information
for adult and pediatric patients

XYREM® (sodium oxybate) oral solution

Reference ID: 4341335

XYREM REMS

Dear Prescriber,

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

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

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

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

Please review the Prescribing Information for XYREM.

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

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

If you require any additional assistance or information, please call the XYREM REMS Program at **1-866-XYREM88® (1-866-997-3688)** or visit **www.XYREMREMS.com.**

Sincerely,

Jazz Pharmaceuticals

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- XYREM is contraindicated in patients being treated with sedative hypnotics.
- Patients should not drink alcohol when using XYREM.
- XYREM is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency.

WARNINGS AND PRECAUTIONS

CNS Depression

- XYREM is a CNS depressant. Concurrent use of XYREM with other CNS depressants, including but not limited to opioid analgesics; benzodiazepines; sedating antidepressants, antipsychotics, or anti-epileptics; general anesthetics; muscle relaxants; and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.
  - If use of these CNS depressants in combination with XYREM is required, dose reduction or discontinuation of one or more CNS depressants (including XYREM) should be considered.
  - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with XYREM should be considered.
- Patients who have sleep apnea or compromised respiratory function may be at a higher risk of developing respiratory depression, loss of consciousness, coma, and death with XYREM use.

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

Abuse and Misuse

- XYREM is a Schedule III controlled substance.
- The active ingredient of XYREM, sodium oxybate, is the sodium salt of gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse events, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. Illicit GHB has also been associated with drug-facilitated sexual assault.
- The rapid onset of sedation, coupled with the amnestic features of XYREM, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).
- You should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of XYREM (e.g., increase in size or frequency of dosing; reports of lost, stolen, or spilled medication; drug-seeking behavior; feigned cataplexy).

XYREM REMS Program

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

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

XYREM® (sodium oxybate) oral solution

Depression, Suicidality, and Other Behavioral/Neuropsychiatric Adverse Events

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

Use in Patients Sensitive to High Sodium Intake

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

Most Common Adverse Events

- In three controlled clinical trials with adult patients, the most common adverse reactions (incidence ≥5% and twice the rate seen with placebo) in XYREM-treated patients were nausea (20%), dizziness (15%), vomiting (11%), somnolence (8%), enuresis (7%), and tremor (5%).
- Of the 398 XYREM-treated adult patients with narcolepsy, 10.3% of patients discontinued because of adverse reactions compared with 2.8% of patients receiving placebo. The most common adverse reaction leading to discontinuation was nausea (2.8%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.
- The overall adverse reaction profile of Xyrem in pediatric patients (7 years of age and older) is similar to that in adult patients. In a study of 104 pediatric narcolepsy patients treated with XYREM, the majority of events were mild or moderate in severity. The most common adverse reactions (>5%) were enuresis (18%), nausea (17%), headache (16%), vomiting (16%), weight decreased (12%), decreased appetite (8%), and dizziness (6%).

Please see Prescribing Information for XYREM.

TABLE OF CONTENTS

PRESCRIBING XYREM—A BRIEF GUIDE 6

RESPONSIBILITIES OF THE XYREM REMS PROGRAM CERTIFIED PHARMACY 10

GUIDELINES FOR DOSING AND TITRATING XYREM 11

ADDITIONAL INFORMATION ABOUT XYREM 12

USE IN SPECIFIC POPULATIONS 13

PATIENT COUNSELING INFORMATION 14

PEDIATRIC PATIENT SUPPLEMENT 16

Prescribing Information is also included

XYREM REMS

Prescribing XYREM—A Brief Guide

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

PRESCRIBERS OF XYREM

PRESCRIBER ENROLLMENT

Prescribing XYREM requires a one-time enrollment.

- **If you are prescribing XYREM for the first time**, complete the **XYREM REMS Program Prescriber Enrollment Form**, found either accompanying this XYREM REMS Program Prescriber Brochure or online at www.XYREMREMS.com. Please:
  - Submit the form online at www.XYREMREMS.com *or*
  - Scan and send via e-mail to XYREMPrescribers@express-scripts.com *or*
  - Mail to **XYREM REMS Program, PO Box 66589, St. Louis, MO 63166-6589** *or*
  - Fax to **1-866-470-1744** (toll free).
- On the **XYREM REMS Program Prescriber Enrollment Form**, please confirm that:
  - You understand that Xyrem is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy
  - You have read and understand the Prescribing Information and this XYREM REMS Program Prescriber Brochure

SCREEN

- You agree to screen each patient for:
  - History of alcohol or substance abuse
  - History of sleep-related breathing disorders
  - History of compromised respiratory function
  - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
  - History of depression or suicidality

COUNSEL

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

ENROLL

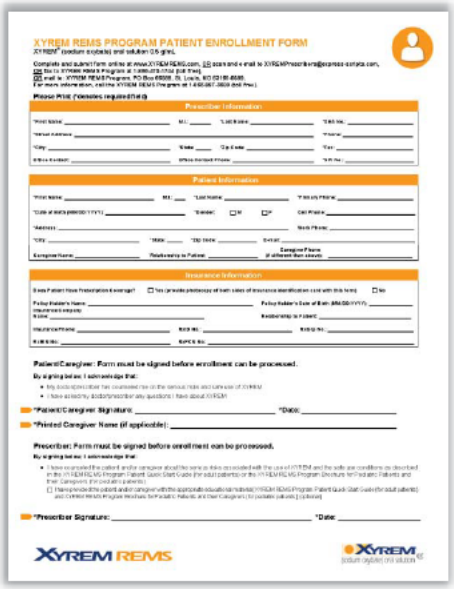
- You will enroll each patient in the XYREM REMS Program by completing the one-time XYREM REMS Program Patient Enrollment Form and submitting the form to the XYREM REMS Program. A pediatric patient must have a caregiver
- You will evaluate each patient within the first 3 months of starting XYREM, including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

REPORT

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

PATIENT ENROLLMENT

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


XYREM REMS PROGRAM PATIENT ENROLLMENT FORM

Prescriber Information

Patient Information

Insurance Information

Patient/Caregiver: Form must be signed before enrollment can be processed.

*Patient/Caregiver Signature: *Date:

*Printed Caregiver Name (if applicable):

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

*Prescriber Signature: *Date:

XYREM REMS

XYREM (sodium oxybate) oral solution

PRESCRIBING REQUIREMENTS

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

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

PATIENT EVALUATION

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

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

REFILL PRESCRIPTIONS

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

XYREM REMS

Responsibilities of the XYREM REMS Program Certified Pharmacy

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

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

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

Please be sure to review the Prescribing Information prior to prescribing XYREM for your patients.

Guidelines for Dosing and Titrating XYREM

DOSING XYREM

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

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

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

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

RECOMMENDED ADULT XYREM DOSE REGIMEN				
	1st Dose	2nd Dose	Total Nightly Dose	
Recommended starting dose	2.25 g	2.25 g	4.5 g	
	3 g	3 g	6 g	Effective Dosing Range
	3.75 g	3.75 g	7.5 g	
Maximum dose	4.5 g	4.5 g	9 g	

IMPORTANT ADMINISTRATION INSTRUCTIONS

- Inform patients that all bottles contain concentrated medication ONLY and that water for dilution is not contained in the box. Advise patients to keep XYREM in the provided bottle(s)
- Patients should prepare both nighttime doses at bedtime
  - Instruct patients to make sure that pharmacy vials are empty prior to preparing each dose
  - Each dose of XYREM should be diluted with about ¼ cup of water
  - Patients should be instructed to store XYREM bottles and prepared nightly doses in a secure place out of the reach of children and pets
- Doses should be taken at least 2 hours after eating
- Both doses should be taken while in bed and the patient should lie down immediately after dosing
- The first dose should be taken at bedtime and the second dose 2.5 to 4 hours later

XYREM® (sodium oxybate) oral solution

XYREM REMS

Additional Information About XYREM

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

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

WHEN PRESCRIBING A CONTROLLED SUBSTANCE:

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

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

DEPENDENCE AND TOLERANCE

Dependence

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

Tolerance

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

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

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

Use in Specific Populations

PREGNANCY

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

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

LABOR AND DELIVERY

XYREM has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate, newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid and 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 Xyrem and any potential adverse effects on the breastfed infant from Xyrem or from the underlying maternal condition.

PEDIATRIC USE

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

GERIATRIC USE

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

RACE AND GENDER EFFECTS

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

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

XYREM® (sodium oxybate) oral solution

XYREM REMS

Patient Counseling Information

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

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

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

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

ALCOHOL OR SEDATIVE HYPNOTICS

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

SEDATION

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

FOOD EFFECTS ON XYREM

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

RESPIRATORY DEPRESSION

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

PARTICIPATING IN HAZARDOUS ACTIVITIES

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

SUICIDALITY

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

SLEEPWALKING

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

SODIUM INTAKE

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

SAFE HANDLING, STORAGE, AND DISPOSAL

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

Pediatric Patient Supplement

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

PRESCRIBING XYREM FOR PEDIATRIC PATIENTS

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

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

RESPONSIBILITIES OF THE XYREM REMS PROGRAM CERTIFIED PHARMACY FOR PEDIATRIC PATIENTS

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

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

Each pediatric patient receiving XYREM must have a caregiver

GUIDELINES FOR DOSING AND TITRATING XYREM FOR PEDIATRIC PATIENTS

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

Recommended Pediatric Xyrem Dosage for Patients 7 Years of Age and Older*

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

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

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

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

IMPORTANT ADMINISTRATION INSTRUCTIONS FOR PEDIATRIC PATIENTS

- Inform caregivers that they should ensure that all XYREM doses are kept in a safe place until given
- Inform caregivers and patients that all bottles contain concentrated medication ONLY and that water for dilution is not contained in the box. Advise caregivers to keep XYREM in the provided bottle(s)
- Inform caregivers and patients that it is important to follow a consistent nightly routine for taking XYREM
  - Caregivers should prepare both nighttime doses at bedtime

- Instruct caregivers to make sure that pharmacy containers are empty prior to preparing each dose
- Each dose of XYREM should be diluted with about ¼ cup of water
- Caregivers should be instructed to store XYREM bottles and prepared nightly doses in a secure place out of the reach of children and pets

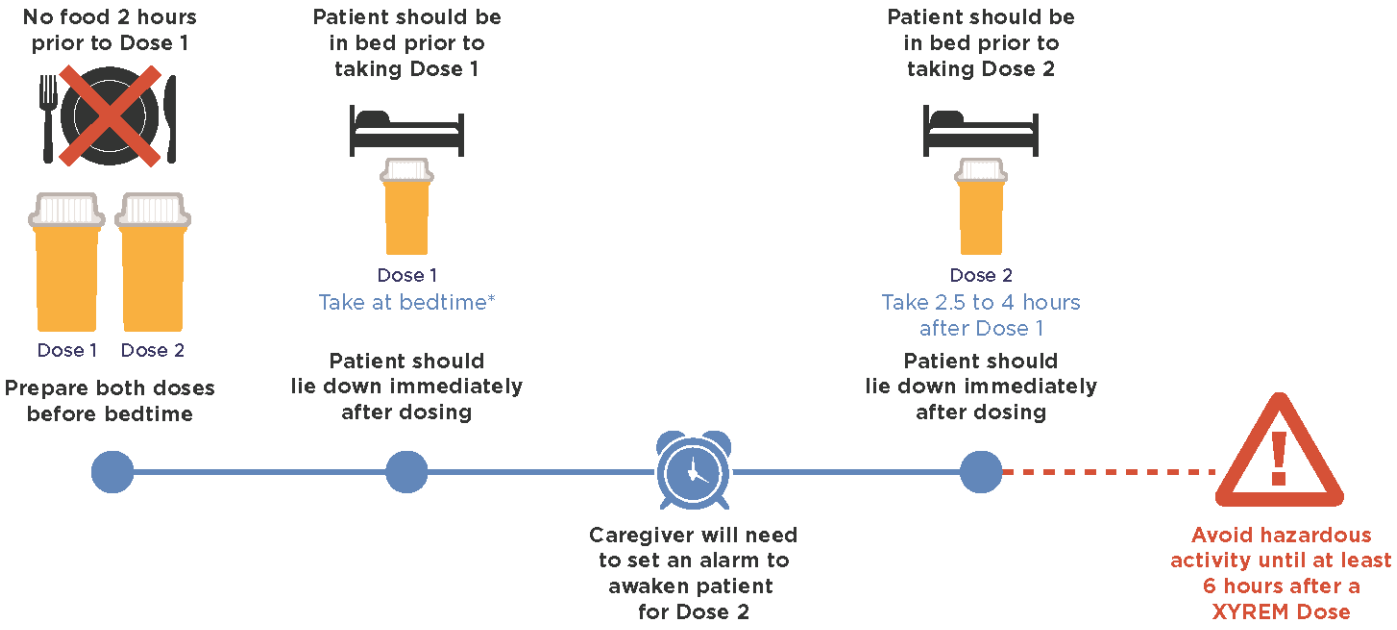
– Doses should be taken at least 2 hours after eating

– Both doses should be taken while in bed and the patient should lie down immediately after dosing

- Encourage the child to urinate prior to taking the first nightly dose of XYREM

– Caution against hazardous activities requiring complete mental alertness or motor coordination (e.g., driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYREM does not affect the patient adversely

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



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

CONSIDERATIONS FOR INCLUDING PEDIATRIC PATIENTS IN THEIR OWN CARE

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


FPO
PI

Jazz Pharmaceuticals®

XYREM® (sodium oxybate) oral solution

REVXXXX

XYREM REMS PROGRAM PATIENT ENROLLMENT FORM

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

Complete and submit form online at www.XYREMREMS.com, OR scan and e-mail to XYREMPrescribers@express-scripts.com, OR fax to XYREM REMS Program at 1-866-470-1744 (toll free), OR mail to: XYREM REMS Program, PO Box 66589, St. Louis, MO 63166-6589. For more information, call the XYREM REMS Program at 1-866-997-3688 (toll free).

Please Print (*denotes required field)

Prescriber Information

*First Name: _____ M.I.: _____ *Last Name: _____ *DEA No.: _____

*Street Address: _____ *Phone: _____

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

Office Contact: _____ Office Contact Phone: _____ *NPI No.: _____

Patient Information

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

*Date of Birth (MM/DD/YYYY): _____ *Gender: ☐ 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 XYREM
- I have asked my doctor/prescriber any questions I have about XYREM

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

***Printed Caregiver Name (if applicable): _____**

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

By signing below, I acknowledge that:

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

***Prescriber Signature: _____ *Date: _____**

XYREM REMS

XYREM® (sodium oxybate) oral solution

Reference ID: 4341335

XYREM REMS PROGRAM PRESCRIPTION FORM

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

Form available online at www.XYREMREMS.com, must be printed, signed, and either:
Fax to XYREM REMS Program: 1-866-470-1744 (toll free)
OR mail to XYREM REMS Program, PO Box 66589, St. Louis, MO 63166-6589.
For more information, call the XYREM REMS Program at 1-866-997-3688 (toll free).

Please Print (*denotes required field; †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

***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: Take first dose p.o., diluted in ¼ cup of water, at bed ime. 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 full 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 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.
****For patients who weigh less than 20 kg, lower starting dosage, maximum weekly dosage increases and total maximum nightly dosage should be considered.**
Note: Unequal dosages may be required for some patients to achieve optimal treatment.

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 XYREM REMS Program will send him or her a copy of the XYREM Medication Guide with each prescription fill and the appropriate educational material (XYREM REMS Program Patient Quick Start Guide for adult patients and XYREM REMS Program Brochure for Pediatric Patients and their Caregivers for pediatric patients) with the first prescription fill.

***Prescriber Signature:** _____ ***Date:** _____

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

XYREM REMS

XYREM (sodium oxybate) oral solution

Reference ID: 4341335

XYREM REMS PROGRAM PRESCRIPTION FORM

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

Prescriber: Signature verification is required on the **FRONT** page of this XYREM REMS Program 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 XYREM REMS Program

I have read and understand the Prescribing Information and XYREM REMS Program 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 REMS

PATIENT QUICK START GUIDE

Important information about the safe use and handling of XYREM

Reference ID: 4341335

XYREM (sodium oxybate) oral solution

XYREM REMS

Dear Patient,

Welcome to the XYREM REMS Program. 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 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) for XYREM. The purpose of the XYREM REMS Program is to make sure the benefits of XYREM outweigh the risks. All patients must be enrolled in the XYREM REMS Program 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 XYREM REMS Program to tell you how the XYREM REMS Program helps you get started with taking XYREM and to answer any questions you may have about XYREM.

Any questions? Please call the XYREM® REMS Program at 1-866-997-3688.
Please see the Medication Guide for more detailed information 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 REMS Program 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 XYREM REMS Program toll free at 1-866-XYREM88® (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 XYREM REMS Program services helpful.

Sincerely,

Jazz Pharmaceuticals

XYREM® (sodium oxybate) oral solution

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 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 XYREM® REMS Program 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 XYREM REMS PROGRAM?

Because of the serious risks associated with XYREM, the FDA has required a special program called REMS for XYREM. Enrollment in the XYREM REMS Program 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.

XYREM REMS

Table of Contents

ENROLLING IN THE XYREM REMS PROGRAM 8
- What am I required to do in this program? 8
- Do I have to enroll in this program? 8

FILLING YOUR XYREM PRESCRIPTION 9
- How is my prescription filled? 9
- What does the Certified Pharmacy do? 9
- What will I get with my XYREM prescription? 10
- How do I get my XYREM refills? 10
- Can my local pharmacy provide XYREM? 10

HOW DO I TAKE MY XYREM? 11
- How do I prepare my doses? 11
- How do I take my doses? 13
- What should I do if I miss a XYREM dose? 13
- How soon will I see a change in my symptoms? 14
- What are the side effects of XYREM? 14
- Are there any precautions I should take while on XYREM? 15
- How often should my healthcare provider check my progress with XYREM? 16

Reference ID: 4341335

STORAGE AND SAFETY TIPS AT HOME 17
How do I store XYREM? 17
How do I properly dispose of XYREM? 17
What if I have concerns about having XYREM in my home? 18

INSURANCE COVERAGE 19
Will insurance pay for my XYREM? 19
What is the pharmacy's role with my insurance? 19

GETTING MORE INFORMATION 20
Where can I get more information about XYREM? 20

XYREM REMS

Enrolling in the XYREM REMS Program

WHAT AM I REQUIRED TO DO IN THIS PROGRAM?

As a patient, your responsibility is to discuss the safe use of XYREM with your healthcare provider and to read this XYREM REMS Program 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 XYREM REMS Program. 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 XYREM REMS Program 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 XYREM REMS Program 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.

XYREM REMS

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 XYREM-specific 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 XYREM REMS Program 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.

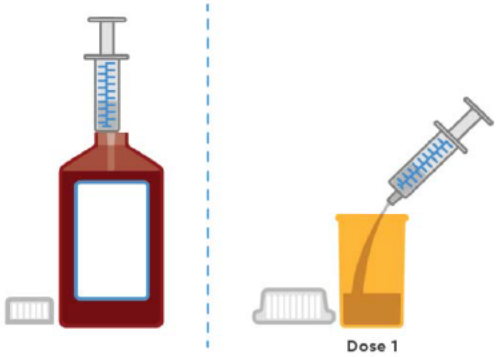
XYREM REMS

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 medication flows into the syringe and the liquid level is aligned with the corresponding tick mark for 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 one of the provided **empty** pharmacy containers by pushing down on the plunger until it stops.



Any questions? Please call the XYREM® REMS Prog

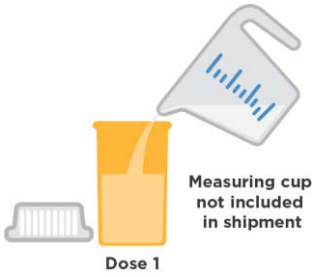
Please see the Medication Guide for more detailed info

XYREM® (sodium oxybate) oral solution

Reference ID: 4341335

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?

You should allow **at least** 2 hours after a meal before taking your first dose of 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. As with any medicine that causes sleepiness, 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

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 XYREM REMS Program.

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.

XYREM REMS

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.

Reference ID: 4341335

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.

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 REMS

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

Reference ID: 4341335

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 REMS

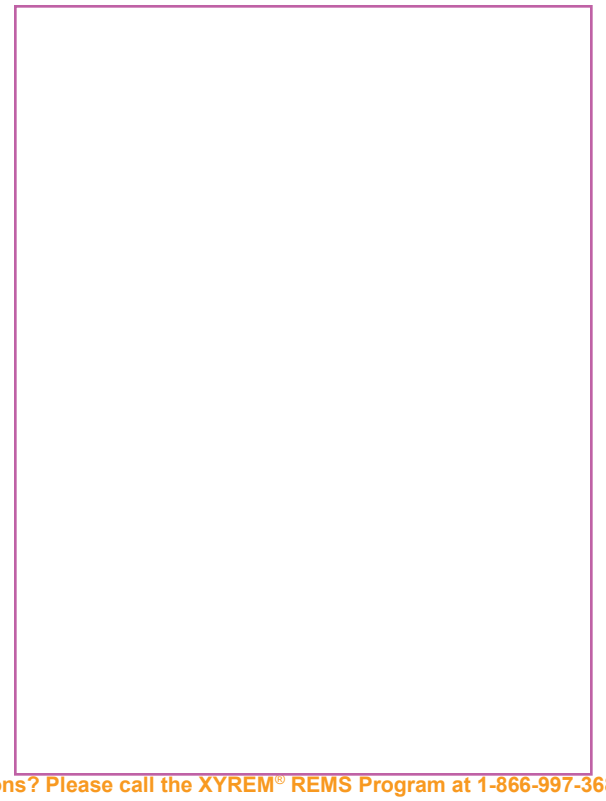
Getting More Information

WHERE CAN I GET MORE INFORMATION ABOUT XYREM?

For more information about XYREM, contact the XYREM REMS Program:

- **Phone**: 1-866-XYREM88® (1-866-997-3688)
- **Fax**: 1-866-470-1744 (toll free)
- **Outside the US**: +314-475-6000, ext 361 587
- **Website**: www.XYREMREMS.com

Notes



Any questions? Please call the XYREM® REMS Program at 1-866-997-3688.

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

Reference ID: 4341335

KEEP THIS BOOKLET AS A HELPFUL REMINDER

If you have questions or need information, contact the XYREM® REMS Program.

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

Jazz Pharmaceuticals®

XYREM® (sodium oxybate) oral solution

REVXXXX

Reference ID: 4341335

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

XYREM REMS

BROCHURE FOR PEDIATRIC PATIENTS AND THEIR CAREGIVERS

Important information about the safe use and handling of XYREM

Reference ID: 4341335

XYREM (sodium oxybate) oral solution

XYREM REMS

Dear Caregiver,

Welcome to the XYREM REMS Program. 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 XYREM REMS Program.

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 the XYREM REMS Program is to make sure the benefits of XYREM outweigh the risks. All patients must be enrolled in the XYREM REMS Program 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 of the XYREM REMS Program to counsel you on the serious risks and safe use of Xyrem, to tell you how the XYREM REMS Program helps you get your child started with taking XYREM, 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 REMS Program 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

XYREM REMS

If you have any additional questions about XYREM, please call your child's healthcare provider, or you can contact the XYREM REMS Program toll free at 1-866-XYREM88® (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 XYREM REMS Program 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 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 2 ½ 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 XYREM REMS PROGRAM?

Because of the serious risks associated with XYREM, the FDA has required a special program called REMS for XYREM. Enrollment in the XYREM REMS Program 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 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 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.

XYREM REMS

Table of Contents

PREPARATION AND ADMINISTRATION OF XYREM 11

What will I get with my child's XYREM prescription? 11

How do I prepare my child's doses? 12

How do I give my child's doses? 14

What do I do if my child misses a dose? 15

How soon will we see a change in symptoms? 16

What are the side effects of XYREM? 16

Are there any precautions that should be taken while my child is on XYREM? 17

HOW OFTEN SHOULD MY CHILD'S HEALTHCARE PROVIDER CHECK ON MY CHILD'S PROGRESS ON XYREM? 18

STORAGE AND SAFETY TIPS AT HOME 19

How do I store XYREM? 19

How do I properly dispose of XYREM? 19

What if I have concerns about having XYREM in my home? 19

IMPORTANT INFORMATION YOUR CHILD MUST KNOW ABOUT TAKING XYREM 20
What should my child know about taking XYREM? 20

INCLUDING YOUR CHILD IN HIS OR HER CARE 24
How can I prepare my child to be able to carry out one or more safe use activities? 24

ENROLLING YOUR CHILD IN THE XYREM REMS PROGRAM 25
Does my child have to enroll in this program? 25
What am I required to do in this program? 25
How is my child's prescription filled? 27
What else does the Certified Pharmacy do? 27
How do I get XYREM refills for my child? 28
Can my local pharmacy provide XYREM for my child? 28

INSURANCE COVERAGE 29

Will insurance pay for my child's XYREM? 29

What is the pharmacy's role with my child's insurance? 29

CONTACT INFORMATION 30

Whom should I contact with concerns or for more information about XYREM? 30

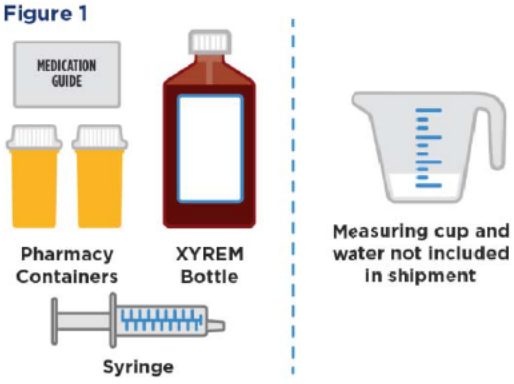
Preparation and Administration of XYREM

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 XYREM-specific 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

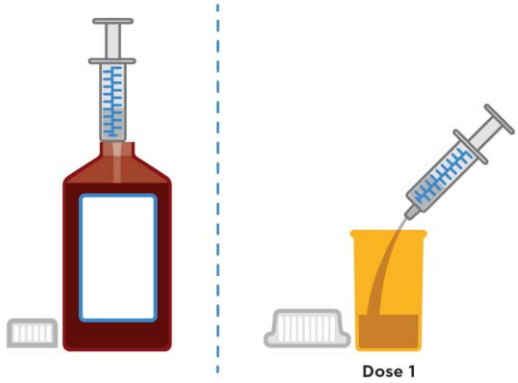


XYREM® (sodium oxybate) oral solution

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 one of the provided **empty** pharmacy containers by pushing down on the plunger until it stops (Figure 2).

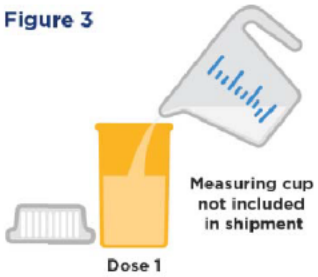
Figure 2



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.

Figure 3



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.

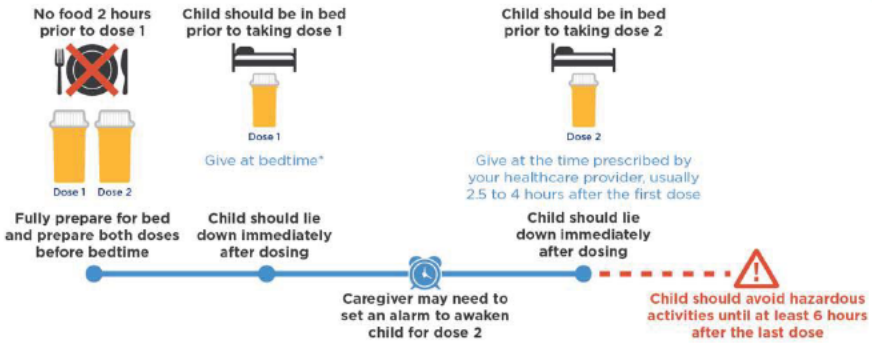
Rinse out the syringe and pharmacy containers with water after each use. Please refer to the Instructions for Use within the Medication Guide for additional details.

HOW DO I GIVE MY CHILD'S DOSES?

You should allow **at least** 2 hours after your child eats a meal before giving the first dose of 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 2 ½ 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.

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 once
- 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

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XYREM REMS

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.

The most common side effects with XYREM in pediatric patients are bedwetting, nausea, headache, throwing up, and weight loss. 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 XYREM REMS Program.

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.

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

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.

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XYREM REMS

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.

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.

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.

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

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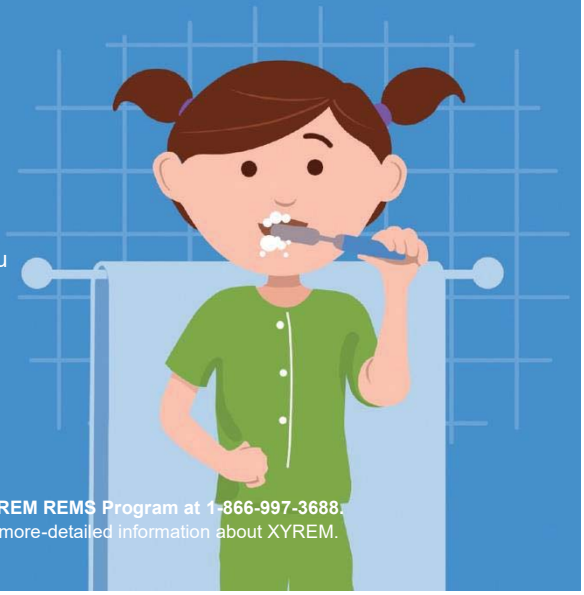
XYREM REMS

Important Information Your Child Must Know About Taking XYREM

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

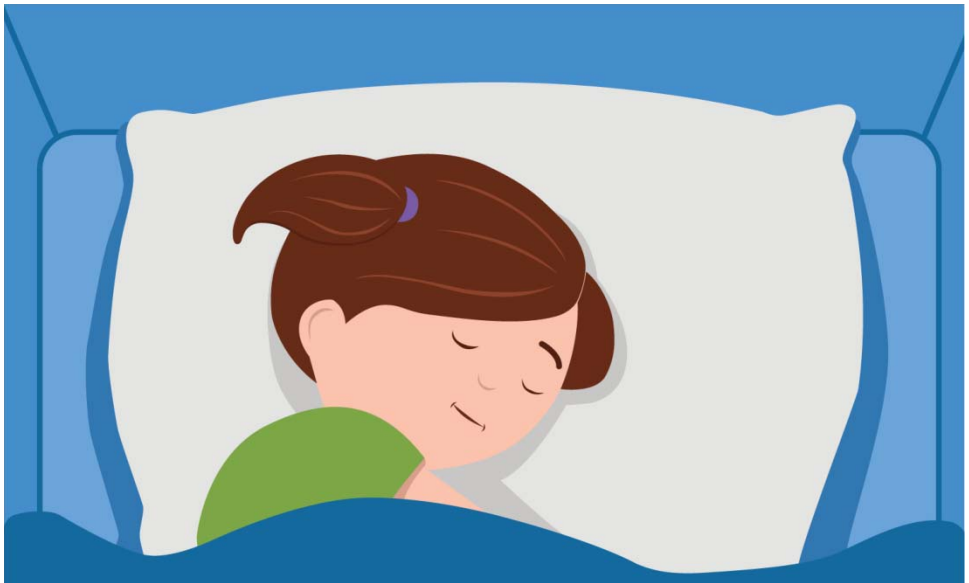
WHAT SHOULD MY CHILD KNOW ABOUT TAKING XYREM?



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 XYREM REMS Program at 1-866-997-3688.
Please see the Medication Guide for more-detailed information about XYREM.



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

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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 XYREM REMS Program at 1-866-997-3688.

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

Reference ID: 4341335

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 one 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

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XYREM REMS

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.

XYREM REMS

Enrolling Your Child in the XYREM REMS Program

DOES MY CHILD HAVE TO ENROLL IN THIS PROGRAM?

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 XYREM REMS Program. 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 AM I REQUIRED TO DO IN THIS PROGRAM?

As a caregiver of a pediatric patient who is in the XYREM REMS Program, 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

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- 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 XYREM REMS Program toll free at 1-866-XYREM88® (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 XYREM REMS Program 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.

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.

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XYREM REMS

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 XYREM REMS Program central 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.

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XYREM REMS

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-XYREM88® (1-866-997-3688)
- **Fax:** 1-866-470-1744 (toll free)
- **Outside the US:** +314-475-6000, ext. 361 587
- **Website:** www.XYREMREMS.com

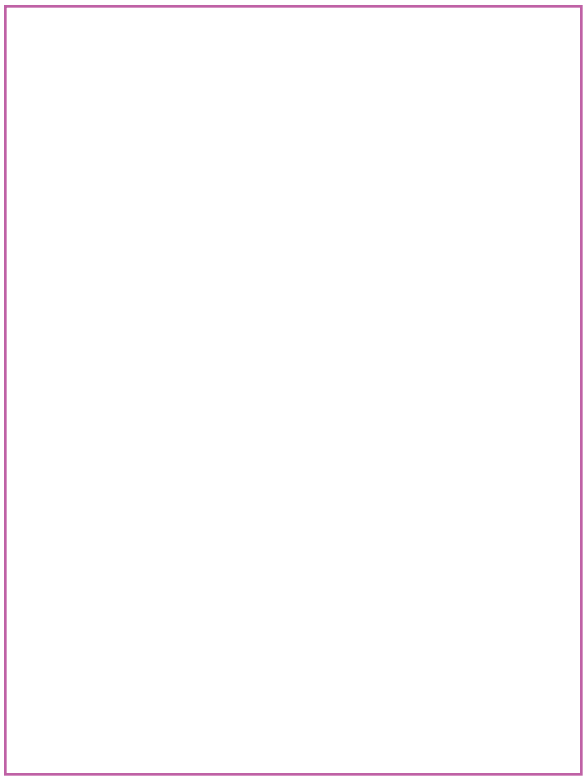
TO REPORT ALL SIDE EFFECTS, YOU CAN CONTACT:

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

FOR EMERGENCIES:

- Call 911

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



Reference ID: 4341335

KEEP THIS BOOKLET AS A HELPFUL REMINDER

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

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

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REVXXXX

Reference ID: 4341335

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

XYREM REMS Program

Certified Pharmacy Training
Modules A and B

All XYREM REMS Program 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 XYREM REMS Program Certified Pharmacy Staff,

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

THE XYREM REMS PROGRAM

The FDA has determined that a REMS is necessary to ensure that the benefits of 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 XYREM by:

1. Informing prescribers, pharmacists, and patients of:
   - The risk of significant central nervous system (CNS) and respiratory depression associated with XYREM
   - The contraindication of use of XYREM with sedative hypnotics and alcohol
   - The potential for abuse, misuse, and overdose associated with XYREM
   - The safe use, handling, and storage of XYREM
2. Ensuring that pharmacy controls exist prior to filling prescriptions for XYREM that:
   - Screen for concomitant use of sedative hypnotics and other potentially interacting agents
   - Monitor for inappropriate prescribing, misuse, abuse, and diversion of 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 XYREM REMS Program that includes important information about XYREM and the responsibilities of the Certified Pharmacy staff involved in the dispensing of XYREM.

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

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

Sincerely,

Jazz Pharmaceuticals

Table of Contents

MODULE A: XYREM REMS PROGRAM 5

IMPORTANT SAFETY INFORMATION 5

- INDICATIONS AND USAGE 5
- HOW SUPPLIED 5
- CONTROLLED SUBSTANCE SCHEDULING 5
- BOXED WARNING 6
- CONTRAINDICATIONS 6
- WARNINGS AND PRECAUTIONS 6

XYREM REMS PROGRAM REQUIREMENTS 7

OVERVIEW OF CERTIFIED PHARMACY RESPONSIBILITIES 7

- DATABASE 7
- ENROLLMENT PROCESSING AND MAINTENANCE 8
- PRESCRIPTION PROCESSING 8
- SHIPPING 9
- MONITORING FOR INAPPROPRIATE PRESCRIBING, ABUSE, MISUSE, AND DIVERSION 9
- ADVERSE EVENT REPORTING 10
- ONGOING PATIENT AND CAREGIVER EDUCATION 10

MODULE B: XYREM REMS PROGRAM TRAINING FOR PHARMACISTS 12

XYREM REMS PROGRAM REQUIREMENTS 12

CERTIFIED PHARMACY RESPONSIBILITIES 13

- PATIENT COUNSELING AND SCREENING 14
- CLINICAL USAGE CLARIFICATIONS 15
- PRESCRIPTION REFILLS 15
- MONITORING AND ASSESSING FOR SIGNS OF ABUSE, MISUSE, AND DIVERSION 16
- SHIPPING PROCEDURES 16
- INVENTORY CONTROL 17

XYREM REMS Program

Certified Pharmacy Training Module A

Training for Pharmacy Staff Involved in the XYREM REMS Program

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

Module A: XYREM REMS Program

IMPORTANT SAFETY INFORMATION

Indications and Usage

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

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

How Supplied

XYREM is shipped from the XYREM REMS Program Certified Pharmacy directly to patients. Each shipment to a patient will contain:

- The prescribed amount of medication, contained in one or more bottles of XYREM
- A press-in-bottle adaptor (PIBA) pre-inserted into the bottle
- A XYREM-specific 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 (XYREM dose mixed with water)
- A XYREM Medication Guide

Controlled Substance Scheduling

The active ingredient in XYREM is sodium 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 XYREM, and used as prescribed for therapeutic purposes are Schedule III drugs
- The active ingredient of XYREM is classified as a Schedule I controlled substance when used for any other reason or by anyone other than for whom it was prescribed. Federal law prohibits the transfer of XYREM to any persons other than the patient for whom it was prescribed.

Boxed Warning

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 Xyrem REMS Program.

Contraindications

- XYREM is contraindicated in:
  - Patients who take sedative hypnotic agents
  - Patients who drink alcohol while using 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

- XYREM is a CNS depressant.
- Concurrent use of 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 XYREM is required, dose reduction or discontinuation of one or more CNS depressants (including XYREM) should be considered.
  - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with XYREM should be considered.
- Patients who have sleep apnea or compromised respiratory function may be at a higher risk of developing respiratory depression, loss of consciousness, coma, and death with XYREM use.
- Healthcare providers should caution patients/caregivers against hazardous activities requiring complete mental alertness or motor coordination (e.g., driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYREM does not affect the patient adversely.

Abuse, Misuse, and Diversion

- The active ingredient of XYREM, sodium oxybate or GHB, is 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 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 XYREM.

XYREM REMS Program Requirements

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

Required Components of this program include:

- Use of the central Certified Pharmacy.
- Healthcare Providers who prescribe XYREM must have completed the XYREM REMS Program Prescriber Enrollment Form and must comply with the requirements of the XYREM REMS Program.
- To receive XYREM, patients must be enrolled in the XYREM REMS Program and adult patients or caregivers (for pediatric patients) must be counseled on the serious risks and safe use of XYREM. Patients are enrolled by prescribers who must fill out and submit the XYREM REMS Program Patient Enrollment Form. Prescribers must also complete and submit the XYREM REMS Program Prescription Form for all new XYREM prescriptions and for XYREM prescriptions for patients restarting XYREM treatment after not receiving XYREM for 6 months or more.
- Further information is available at www.XYREMREMS.com.

Overview of Certified Pharmacy Responsibilities

DATABASE

The Certified Pharmacy will utilize the secure and validated XYREM REMS Program 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 XYREM REMS Program 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 Patient Enrollment Form is received, the Central Database must be searched to determine if the patient is already enrolled in the XYREM REMS Program.
  - 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 XYREM REMS Program 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 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 XYREM REMS Program, and that he or she is eligible to prescribe 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 XYREM REMS Program 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 XYREM REMS Program.
- Enrollment status is maintained in the XYREM REMS Program 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 XYREM REMS Program.
  - Following enrollment the patient remains in the XYREM REMS Program 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 XYREM REMS Program, 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 XYREM REMS Program Prescription Form, the prescription information will be entered into the Central Database.
- The Certified Pharmacy will validate all prescriptions prior to dispensing XYREM. This includes verifying that:
  - The prescription form is complete and signed by the prescriber.

- The prescriber is enrolled in the XYREM REMS Program and has active DEA, state license, and NPI numbers.
- The patient is enrolled in the XYREM REMS Program and has no other active XYREM prescriptions.
  - If the Certified Pharmacy receives overlapping prescriptions for XYREM for a patient, the Certified Pharmacy will notify and consult each prescriber.
    - Prescriptions are considered overlapping when more than one prescription for 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 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 XYREM fill 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.

- Prior to dispensing 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 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 XYREM REMS Program Patient Quick Start Guide (for adult patients) or XYREM REMS Program Brochure for Pediatric Patients and Their Caregivers (for pediatric patients).
  - A pharmacist must counsel the patient or caregiver (for pediatric patients) by completing the XYREM REMS Program Patient Counseling Checklist prior to the initial dispensing of XYREM.

SHIPPING

All 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 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 XYREM.
- Inform a XYREM REMS Program 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 XYREM REMS Program have access to ongoing education during XYREM treatment:

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

XYREM REMS Program

Certified Pharmacy Training Module B

XYREM REMS Program Training for Pharmacists Involved in the Dispensing of XYREM

All XYREM REMS Program 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 XYREM, training must be completed annually.

Module B: XYREM REMS Program Training for Pharmacists

All pharmacists involved in dispensing XYREM must complete the following additional training at least annually. The XYREM REMS Program 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 XYREM REMS Program. 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 XYREM REMS Program Patient Counseling Checklist
- Detailed monitoring including completion of an 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.

XYREM REMS Program Requirements

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

Required components of this program include:

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

CERTIFIED PHARMACY RESPONSIBILITIES

The central Certified Pharmacy will:

- Limit the first prescription fill to a one-month supply of XYREM and limit subsequent prescription fills to no more than a 3-month supply
- Report potential adverse events to the XYREM REMS Program
- 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:
    - 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
    - Quantity of 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 XYREM is 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 XYREM.

PATIENT COUNSELING AND SCREENING

- Prior to dispensing Xyrem, the XYREM REMS Program Certified Pharmacy ensures the completion of the XYREM REMS Program Patient Counseling Checklist and its requirements and the documentation of the information received in the XYREM REMS Program Central Database.
  - For new patients (first shipment of XYREM) , and for patients who are restarting XYREM treatment after not receiving XYREM for 6 months or longer, the XYREM REMS Program 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 XYREM and that he or she has asked any questions he or she has about XYREM; the XYREM REMS Program 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 XYREM REMS Program 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 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 XYREM REMS Program 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 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 XYREM REMS Program 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 XYREM REMS Program pharmacist via the 24/7 toll-free telephone help line.

CLINICAL USAGE CLARIFICATIONS

The pharmacist must:

- Review the information on each XYREM REMS Program 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 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 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 XYREM REMS Program 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 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 XYREM REMS Program 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 XYREM to the patient only if approved by the prescriber
- Send new shipments to replace 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 XYREM REMS Program RMR.

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

- Risk management events must be documented in the Central Database by completing a XYREM REMS Program 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 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 XYREM REMS Program after review and discussion of incidents suggestive of abuse and misuse.
  - All RMRs must be reported to Jazz Pharmaceuticals.

SHIPPING PROCEDURES

- XYREM must be shipped via an overnight service with receipt signature required.
  - XYREM is 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 XYREM shipment includes:
  - The prescribed amount of medication, contained in one or more bottles of XYREM
  - A press-in-bottle adaptor (PIBA) that is pre-inserted into the bottle
  - A XYREM-specific 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 (XYREM dose mixed with water)
  - A 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 XYREM inventory 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

XYREM REMS Program Overview

1. 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. GHB, the active ingredient in XYREM, is a controlled substance 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. XYREM is contraindicated in patients:

A. Who take sedative hypnotics

B. Who drink alcohol while using 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. XYREM is a CNS depressant. 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 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 XYREM does not affect the patient adversely

(Answer: C)

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

   (Answer: E)

6. In processing enrollment information, the XYREM REMS Program 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 XYREM REMS Program and can prescribe 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 XYREM REMS Program

   (Answer: D)

7. Which of the following is NOT true of caregivers of pediatric patients within the XYREM REMS Program?
   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 XYREM

   (Answer: B)

8. Which of the following is NOT entered in the Central Database in the XYREM REMS Program?
   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 XYREM, the Certified Pharmacy will verify that:
   - The XYREM REMS Program 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 XYREM REMS Program and has active DEA, state license, and NPI numbers;
   - The patient is enrolled in the XYREM REMS Program and has no other active XYREM prescriptions; and
   - 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. 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 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 XYREM
   C. Inform a XYREM REMS Program 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)

11. 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 XYREM REMS Program

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 XYREM REMS Program Patient Counseling Checklist with new patients (or their caregiver for pediatric patients) and patients (or their caregiver for pediatric patients) who have not received XYREM for 6 months or longer
    B. Detailed monitoring, including completion of a 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 XYREM REMS Program will:
    A. Limit the first prescription to a one-month supply and subsequent prescriptions 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 Central Database will contain the following information that must be available for ongoing review to ensure XYREM (sodium oxybate) oral solution, 0.5 g/mL, is 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 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. Prior to shipment of XYREM, the XYREM REMS Program Patient Counseling Checklist must be completed as follows:
   - For initial prescriptions and for patients restarting XYREM after not receiving 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 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.
   - For new caregivers of already enrolled pediatric patients, complete the entire checklist

   A. True
   B. False

   (Answer: A)

5. If patient use of a contraindicated medication is confirmed and the prescriber has not indicated prior knowledge, the pharmacist will contact and consult the prescriber prior to shipping XYREM.
   A. True
   B. False

   (Answer: A)

6. 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)

7. Which of the following is NOT true for the prescription refill process?
   A. Up to 5 refills are allowed on a 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)

8. 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)

9. 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)

10. In monitoring and assessing for signs of abuse, misuse, or diversion, a pharmacist must document risk management events in the XYREM REMS Program Central Database by completing a XYREM REMS RMR. 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)

11. 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)

XYREM REMS Program Patient Counseling Checklist

(Prior to dispensing XYREM, the XYREM REMS Program Certified Pharmacy ensures the completion of the checklist and its requirements and documents the information received in the XYREM REMS Program 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

(Complete this section for new patients [first shipment of XYREM], existing patients who are restarting XYREM treatment after not receiving XYREM 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 XYREM treatment after not receiving XYREM for 6 months or longer)

☐ Ask if the prescriber reviewed the appropriate XYREM REMS Program material with the patient/caregiver (Patient Quick Start Guide for adult patients, Program Brochure for Pediatric Patients and Their Caregivers for pediatric patients) and explain that this material will be included with the first shipment and that all drug shipments to the patient will include the XYREM Medication Guide

_____ **(Pharmacist Name)** _____/_____/_____ **(Date/Time)**

☐ Verify that the patient/caregiver has been counseled on **Therapy Expectations** below

- During clinical trials with XYREM, many patients with narcolepsy saw some improvement with excessive daytime sleepiness and/or cataplexy in the first weeks after beginning XYREM therapy. However, the response to XYREM 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 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

- 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 XYREM into one 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 XYREM into the second pharmacy container, adding about 1/4 cup of water, and closing the pharmacy container. The water does not come with XYREM. The patient/caregiver can use either tap or bottled water. The solution should remain clear, and it will taste salty. 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 XYREM doses are kept in a safe place until given.
- The patient/caregiver should call the XYREM REMS Program with any questions regarding how 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 Medication Guide for additional information on preparation of XYREM doses.
- When the patient is ready to go to sleep, the first dose of XYREM should be taken while sitting in bed and the patient should lie down immediately after dosing.
  - The first dose of XYREM 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 XYREM should be taken 2.5 to 4 hours after the first dose of XYREM is taken.
  - If a dose is missed, the patient should NEVER take two doses of XYREM at once.
- The diluted medication MUST be used within 24 hours of preparation. Discard any unused medication down the sink or toilet drain.
- When 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 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 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 XYREM drinks XYREM.
- XYREM should be stored at room temperature.

_____ **(Pharmacist Name)** _____/_____/_____ **(Date/Time)**

☐ Verify that the patient/caregiver has been counseled on **Precautions Needed for XYREM Use**

- XYREM is classified as a controlled substance medication. 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.
- The active ingredient in XYREM is sodium 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 XYREM included: nausea, dizziness, vomiting, somnolence, enuresis, and tremor. In clinical trials in pediatric patients, the most commonly observed side effects associated with the use of XYREM included: enuresis, nausea, headache, vomiting, weight decreased, decreased appetite, and dizziness. Some side effects may be more likely to be observed with higher doses of XYREM.
- 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 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 XYREM does not affect them adversely.
- When taking 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 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 XYREM can affect an unborn baby.
- Patient is breastfeeding. XYREM passes into breast milk. The patient/caregiver should talk to the prescriber to decide if the patient will take 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 XYREM.
- Patient has mental health problems.
- Patient walks during sleep.
- Patient is on a salt-restricted diet, has high blood pressure, heart failure, or kidney problems. XYREM contains sodium (salt) 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 XYREM.

Step 3: Screening

(Complete this section for new patients, existing patients who are restarting XYREM treatment after not receiving XYREM 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., diazepam, phenobarbital, or zolpidem)?

   ☐ 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); 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 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 XYREM treatment after not receiving XYREM 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
- ☐ 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

If any medication types or medical conditions listed above 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: _____/_____/_____

Prescriber consult outcome: _____

_____ (**Pharmacist Name**) _____/_____/_____ (**Date/Time**)

Step 5: Completion Summary

(Complete this section for new patients, existing patients who are restarting XYREM treatment after no receiving XYREM 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 (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)**

XYREM REMS Program 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 XYREM REMS Program 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 XYREM REMS Program Prescriber Enrollment Form, Prescription Form, or Patient Enrollment 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 XYREM REMS Program 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.

XYREM REMS Program 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) _____

XYREM REMS

XYREM (sodium oxybate) oral solution

Reference ID: 4341335

Welcome to the XYREM® REMS Program

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 program ensures that XYREM® (sodium oxybate) is dispensed only from the Certified Pharmacy.

What is XYREM®?

XYREM® 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.

Important Safety Information

Prescribing Information

Enroll in the XYREM® REMS Program

Prescriber

XYREM® (sodium oxybate) oral solution, 0.5 g/mL is available only through a restricted distribution program called the XYREM® REMS Program. Use this website to enroll yourself, enroll your patients, and prescribe XYREM.

Enroll as Prescriber

Patient or Caregiver

Learn more about the XYREM REMS Program, a special program required by the Food and Drug Administration (FDA) to make sure the benefits of XYREM outweigh the risks. All patients must be enrolled in the XYREM REMS Program to receive XYREM.

Enroll as Patient or Caregiver

Program Overview

The XYREM REMS Program is designed to ensure that prescribers and patients are educated on and understand the risks and safe use conditions of XYREM and agree to follow the requirements of the XYREM REMS Program.

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

- All prescribers must enroll in the XYREM REMS Program and comply with requirements for prescribing XYREM
- All patients must be enrolled in the XYREM REMS Program to receive XYREM
- All patients are required to be counseled on the serious risks and safe use of XYREM
- XYREM will be dispensed only by the central pharmacy that is specially certified

Please call the XYREM REMS Program at **1-866-XYREM88 (1-866-997-3688)** for needed assistance

Goal of the XYREM REMS

The goal of the XYREM REMS is to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of XYREM by:

Informing prescribers, pharmacists, patients, and caregivers of:

- The risk of significant CNS and respiratory depression associated with XYREM
- The contraindication of use of XYREM with sedative hypnotics and alcohol
- The potential for abuse, misuse, and overdose associated with XYREM
- The safe use, handling, and storage of XYREM

Ensuring that pharmacy controls exist prior to filling prescriptions for XYREM that:

- Screen for concomitant use of sedative hypnotics and other potentially interacting agents
- Monitor for inappropriate prescribing, misuse, abuse, and diversion of XYREM
- Notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion

Prescriber Read & Enroll

Before enrolling in the XYREM REMS, ensure you're familiar by reading the XYREM® (sodium oxybate) Prescribing Information and the Prescriber Brochure. Then, complete the one-time Prescriber Enrollment Form below.

Access Prescribing Information ›
Access Prescriber Brochure ›
Roles & Responsibilities

What You Should Know

To become certified, each prescriber must complete a XYREM REMS Program Prescriber Enrollment Form once and submit it to the XYREM REMS Program via fax, email, or mail.

In addition to enrolling, use the links below to access important information concerning what you need to know as a prescriber of XYREM.

Important Update for Prescribers ›

Enroll as Prescriber

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.

Two Ways To Enroll

Online

Complete enrollment online by filling out the form below.

Submit Form Online

Begin Enrollment
Simply enter your name and e-mail to begin your online enrollment.
* = Required Fields

First Name*
Last Name*
E-mail Address*
Confirm E-mail Address*

Continue Online Enrollment

DocuSign® makes enrollment easy. By using DocuSign, the XYREM REMS can ensure that your personal information can stay safe, secure, and protected.

Print

Download Prescriber Enrollment Form ›

Submit Printed Form

Scan and e-mail to:
XYREMPrescribers@express-scripts.com ›

OR

Fax to:
XYREM® REMS Program
1-866-470-1744 (toll free)

OR

Mail to:
XYREM REMS Program
PO Box 66589
St. Louis, MO 63166-6589

Prescriber Read & Enroll

Before enrolling in the XYREM REMS, ensure you're familiar by reading the XYREM® (sodium oxybate) Prescribing Information and the Prescriber Brochure. Then, complete the one-time Prescriber Enrollment Form below.

Access Prescribing Information ›
Access Prescriber Brochure ›
Roles & Responsibilities

Prescriber Roles & Responsibilities

Prescribers enrolled in the XYREM REMS Program agree to perform the following:

1. Review the Prescribing Information (PI) and the XYREM REMS Program 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 XYREM on the serious risks and safe use and handling of XYREM using the XYREM REMS Program Quick Start Guide.
4. Enroll each patient in the XYREM REMS Program by completing the XYREM REMS Program Patient Enrollment Form and submitting the form to the XYREM REMS Program.
5. Evaluate each patient within the first 3 months of starting XYREM therapy, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while taking XYREM:
   - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
   - Serious adverse events
   - Signs of abuse and misuse, including:
     i. an increase in dose or frequency of dosing
     ii. reports of lost, stolen, or spilled medication
     iii. 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 XYREM REMS Program Prescription Form and submit it to the XYREM REMS Program. By completing and signing this form, the prescriber acknowledges:

1. Having an understanding of:
   - The approved indications for XYREM:
     i. Treatment of cataplexy in narcolepsy
     ii. Treatment of excessive daytime sleepiness in narcolepsy
   - The serious risks associated with XYREM
   - The Prescribing Information and XYREM REMS Program Prescriber Brochure
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 XYREM
   - Contraindications (alcohol and sedative hypnotics) and implications of concomitant use of XYREM with other potentially interacting agents
   - Preparation and dosing instructions for XYREM
   - Risk of abuse and misuse associated with XYREM
   - Risk of operating hazardous machinery including automobiles or airplanes for the first 6 hours after taking a dose of XYREM
   - Safe use, handling, and storage of XYREM
4. That XYREM is medically appropriate for the patient
5. Having listed all known prescription and nonprescription medications and doses on the XYREM REMS Program Prescription Form

First Name*

Last Name*

E-mail Address*

Confirm E-mail Address*

Continue Online Enrollment

DocuSign® makes enrollment easy. By using DocuSign, the XYREM REMS can ensure that your personal information can stay safe, secure, and protected.

Print

Download Prescriber Enrollment Form ›

Submit Printed Form

Scan and e-mail to:
XYREMPrescribers@express-scripts.com ›

OR

Fax to:
XYREM® REMS Program
1-866-470-1744 (toll free)

OR

Mail to:
XYREM REMS Program
PO Box 66589
St. Louis, MO 63166-6589

Counsel & Enroll Patients

Before enrolling, patients can use the Quick Start Guide and Brochure for Pediatric Patients and Their Caregivers below to find out more concerning the use of XYREM.

A Guide for Adult Patients

Click below to read the Patient Quick Start Guide for counseling adult patients.

Access Patient Quick Start Guide

For Caregivers of Pediatric Patients

Use the Brochure for Pediatric Patients and their Caregivers to gain counsel for designated caregivers of pediatric patients.

Access Brochure for Pediatric Patients and Their Caregivers

Enroll Patients

Choose one of the two methods described below. Complete your application and submit it to the Certified Pharmacy for processing.

Two Ways To Enroll Patients

Online

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.

Submit Form Online

Begin Enrollment

Simply enter your name and e-mail to begin your online enrollment.

* = Required Fields

First Name*

Last Name*

E-mail Address*

Confirm E-mail Address*

Continue Online Enrollment

DocuSign® makes enrollment easy. By using DocuSign, the XYREM REMS Program can ensure that your personal information can stay safe, secure, and protected.

Print

If you downloaded the patient enrollment form, 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.

Download Patient Enrollment Form ›

Submit Printed Form

Scan and e-mail to:
XYREMPrescribers@express-scripts.com ›

or

Fax to:
XYREM® REMS Program
1-866-470-1744 (toll free)

or

Mail to:
XYREM REMS Program
PO Box 66589
St. Louis, MO 63166-6589

Prescribe XYREM®
(sodium oxybate)

Utilize the resources below to understand the benefits and risks of XYREM and prescribe XYREM to patients. For more information, please call the XYREM REMS Program toll free at 1-866-XYREM88 (1-866-997-3688).

Begin Prescription Form Online ›

Prescribing XYREM

To prescribe XYREM, both prescriber and patient must be enrolled in the XYREM REMS Program.

Enroll as Prescriber ›

Enroll Patients ›

Complete the Prescription Form

All prescription forms must be **submitted** via fax or mail only.
Choose one of the two methods described below to prescribe XYREM.

Ways To Complete the Prescription Form

Start the prescription process by filling in the online form. The form will be checked by the Certified Pharmacy for completeness. You will be notified once your enrollment is complete.

Complete Form Online

Begin Enrollment

Enter your name and e-mail to start the prescription process.
* = Required Fields

First Name*

Last Name*

E-mail Address*

Confirm E-mail Address*

Continue to Prescription Form

Please contact your Jazz Pharmaceuticals Specialty Sales Consultant or call the XYREM REMS Program at 1-866-997-3688 to obtain a XYREM REMS Program Prescription Form.

Submit Printed Form

Complete Offline:
Sign the completed prescription form

&

Fax to:
XYREM® REMS Program
1-866-470-1744 (toll free)

or

Mail to:
XYREM REMS Program
PO Box 66569
St. Louis, MO 63166-6569

Resources and Materials

Materials for Prescribers

XYREM® (sodium oxybate) Prescribing Information
Download >

XYREM® REMS Program Prescriber Enrollment Form
Download > Enroll Online >

XYREM® REMS Program Patient Enrollment Form
Download > Enroll Online >

XYREM® REMS Program Prescription Form
Download > Begin Online >

XYREM® REMS Program Prescriber Brochure
Download >

Materials for Adult Patients

XYREM® REMS Program Patient Quick Start Guide
Download >

XYREM® REMS Program Patient Enrollment Form
Download > Enroll Online >

Materials for Caregivers of Pediatric Patients

XYREM® REMS Program Brochure for Pediatric Patients & their Caregivers
Download >

XYREM® REMS Program Patient Enrollment Form
Download > Enroll Online >

XYREM® (sodium oxybate) oral solution

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/

YASMEEN I ABOU-SAYED
10/26/2018

DONELLA A FITZGERALD
10/26/2018

JAMIE C WILKINS PARKER
10/26/2018

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Division of Risk Management
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type	NDA
Application Number	21196/S-030
PDUFA Goal Date	October 27, 2018
OSE RCM #	2018-1257
Reviewer(s)	Yasmeen Abou-Sayed, Pharm.D., Ana Tavakoli, M.A.
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins, Pharm.D.
Review Completion Date	October 16, 2018
Subject	Evaluation of REMS Modification
Established Name	Sodium Oxybate
Trade Name	Xyrem
Applicant:	Jazz Pharmaceuticals
Formulation	500 mg/ml oral solution
Dosing Regimen	Pediatric Dosing (Proposed):

Patient Weight	Initial Dose		Titration Regimen	Maximum Recommended Dose	
	Take at Bedtime	Take 2.5 to 4 Hours Later	(to clinical effect)	Take at Bedtime	Take 2.5 to 4 Hours Later
(b) (4)					
20 kg to <30 kg	≤ 1 g	≤ 1 g	(b) (4)	≤ 3 g	≤ 3 g
30 kg to <45 kg	≤ 1.5 g	≤ 1.5 g		≤ 3.75 g	≤ 3.75 g
≥45 kg	≤ 2.25 g	≤ 2.25 g		≤ 4.5 g	≤ 4.5 g

Adult Dosing: 4.5 grams (g) per night 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 to the effective dose range of 6 g to 9 g per night orally.

Indication	(b) (4)

Table of Contents

Executive Summary 3

1 Introduction 3

2 Background 3

2.1 REGULATORY HISTORY 3

3 Results of Review of Applicant Proposed REMS Modification 4

3.1 GENERAL COMMENTS 4

3.2 REMS DOCUMENT 4

3.3 REMS MATERIALS 4

3.3.1 MEDICATION GUIDE 4

3.3.2 CERTIFIED PHARMACY TRAINING PROGRAM 4

3.3.3 PATIENT COUNSELING CHECKLIST 5

3.3.4 PATIENT QUICK START GUIDE 5

3.3.5 PRESCRIBER BROCHURE 5

3.3.6 BROCHURE FOR PEDIATRIC PATIENTS AND THEIR CAREGIVERS 6

3.3.7 REMS WEBSITE SCREENSHOTS 6

3.4 REMS SUPPORTING DOCUMENT AND ASSESSMENT PLAN 6

4 Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials 7

4.1 PRESCRIBER BROCHURE 7

4.2 BROCHURE FOR PEDIATRIC PATIENTS AND THEIR CAREGIVERS 8

5 Agency Proposed REMS Modifications 9

5.1 REMS DOCUMENT 9

6 Conclusion and Recommendations 9

7 Comments to the Applicant 10

8 Appendix 11

8.1 REFERENCES 11

8.2 APPENDED MATERIALS 11

Executive Summary

This is a review of Jazz Pharmaceuticals' proposed Risk Evaluation and Mitigation Strategy (REMS) modification for Xyrem (sodium oxybate), NDA 21196/S-030, submitted on April 27, 2018 and amended on September 27, 2018. The REMS for Xyrem was originally approved on February 27, 2015 to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Xyrem. The REMS consists of a (b) (4) elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The ETASU includes prescriber certification (A), pharmacy certification (B), and safe-use conditions (D). The Applicant submitted the REMS modification as part of a supplemental application to support the expansion of the US indication to include the pediatric use of Xyrem for the treatment of cataplexy in narcolepsy and the treatment of excessive daytime sleepiness in narcolepsy.

The appended materials were updated appropriately based on Agency recommendations from the previous comments sent on September 13, 2018, (b) (4) However, the Applicant proposes further modifications to the REMS Document. The Applicant also proposed changes to the Assessment Plan to include reports of Xyrem patients who are victims of sexual abuse and expansion of surveys to include assessment of pediatric patients and their caregivers.

Based on ongoing review of the REMS document, materials and supporting document, the proposed REMS modification for Xyrem requires further changes to be acceptable. Comments should be sent to Jazz in an Information Request and the Applicant should submit a REMS amendment to address those comments.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed modification to the risk evaluation and mitigation strategy (REMS) for Xyrem (sodium oxybate), NDA 21196/S-030, submitted by Jazz Pharmaceuticals (Jazz) on April 27, 2018, and amended on September 27, 2018. The Applicant submitted the REMS modification as part of a supplemental application for a new proposed indication for the treatment of cataplexy and excessive daytime sleepiness (EDS) in narcolepsy in pediatric patients. The supplemental application is under review in the Division of Neurology Products (DNP).

2 Background

2.1 Regulatory History

The following is a summary of the regulatory history for NDA 21196/S-030 relevant to this review:

- **September 13, 2018**: The Agency provided comments to the Applicant on their proposed REMS modification. The comments included an Agency proposed updated REMS document that aligns with the *Format and Content of a REMS Document Draft Guidance for Industry,* (b) (4) acceptance of the proposed *Brochure for Pediatric Patients and their Caregivers*, (b) (4) and acceptance of other changes to incorporate the pediatric indication.
- **September 27, 2018**: The Applicant submitted a REMS amendment to NDA 21196/S-030.[1]

3 Results of Review of Applicant Proposed REMS Modification

3.1 General comments

The Applicant addressed the Agency's comments on the REMS modification proposal, as detailed in the Information Request on September 13, 2018, with the exception of the Agency proposed REMS document. Reference to the (b) (4) as a REMS material was removed throughout the REMS. The Applicant also incorporated the Agency recommendation to update the pediatric indication language, to specify that Xyrem is indicated for patients 7 years and older. Jazz has indicated that they will update this throughout the REMS materials upon final approval of the labeling. Lastly, removal of the (b) (4) as a REMS material was also accepted.

Reviewer Comment: DRISK finds the changes to the Xyrem REMS materials acceptable. See section 6.2 below for comments regarding the REMS Document.

3.2 REMS Document

The Applicant submitted a draft REMS Document with proposed revisions that do not conform with the *Draft Guidance for Industry, Format and Content of a REMS Document*.

Reviewer Comment: Agency feedback on the draft REMS document will be provided in a later review.

3.3 REMS Materials

(b) (4)

3.3.2 Certified Pharmacy Training Program

The Applicant noted where language would be updated, regarding the pediatric indication, pending final approved language from the labeling (pages (b) (4) and 5). The following statement was added on page 8, under the heading "Enrollment Processing and and Maintenance" to respond to the Agency's request for clarification on the identification number for pediatric caregivers:

> "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."

The Agency's recommendation to start the statement on page 14 with "Instruct" rather than (b) (4) was accepted:

> (b) (4) Instruct the patient/caregiver to alert the pharmacy to any new medication the patient begins as soon as possible."

Reviewer Comment: The pediatric indication must be updated to align with the final labeling. The Agency agrees with all other proposed modifications to the Certified Pharmacy Training Program.

3.3.3 PATIENT COUNSELING CHECKLIST

The Applicant accepted the request to restore instructional text to the Patient Counseling Checklist and made an additional change to the text to ensure the language correlates with that of the *Certified Pharmacy Training Program*. This change was made on pages 1, (b) (4), 7 and 8:

> "Complete this section for new patients, existing patients who are restarting XYREM treatment after not receiving XYREM for 6 months or longer, and patients who report (b) (4) a new medication or new comorbid medical condition listed in Step 4 of this checklist."

Reviewer Comment: All proposed modifications to the Patient Counseling Checklist *are acceptable.*

3.3.4 PATIENT QUICK START GUIDE

(b) (4) The Agency recommendation to restore the list of serious side effects possible with Xyrem, on page 4 of this material, was accepted by the Applicant.

Reviewer Comment: All proposed modifications to the Patient Quick Start Guide *are acceptable.*

3.3.5 PRESCRIBER BROCHURE

The Applicant noted where language would be updated regarding the pediatric indication, pending final approved language from the labeling (pages 2, (b) (4), 6, (b) (4)). (b) (4)

(b) (4)

(b) (4)

Reviewer Comment: The pediatric labeling language on pages 2 and (b) (4) should be aligned with the final labeling, indicating the approved pediatric patient population. The pediatric dosing and titration table on page 18 must be aligned with the final labeling

Also, the Applicant's explanation that operationally, the tracking of patient refills would not be changed, is acceptable. Further review of this material has been provided by the Office of Prescription Drug Promotion (OPDP) in section 7.1 of this review.

3.3.6 BROCHURE FOR PEDIATRIC PATIENTS AND THEIR CAREGIVERS

The Applicant noted where language would be updated on page 2, regarding the pediatric indication, pending final approved language from the labeling. (b) (4)

Reviewer Comment: The pediatric labeling language must be aligned with the final labeling, to indicate the pediatric patient population will be ages 7 and up. Further review of this material has been provided by OPDP in section 7.2 of this review.

3.3.7 REMS WEBSITE SCREENSHOTS

The Applicant did not resubmit redlined *REMS Website Screenshots* addressing the Agency's comments described in the September 13, 2018 Information Request, however they did indicate that they will submit updated REMS Website screenshots incorporating edits in a final submission once all labeling changes are finalized.

Reviewer Comment: We have previously commented on the REMS Website (see August 28, 2018 DRISK review).

3.4 REMS SUPPORTING DOCUMENT AND ASSESSMENT PLAN

Supporting Document

General changes to the supporting document based on Agency feedback include:

(b) (4)

- Language was added to the supporting document to align with existing practices to validate a prescriber's National Provider Identifier (NPI)

(b) (4)

The Applicant updated adverse event data based on the proposed label for this supplement, on pages 5 through 8 of the supporting document. The Applicant also provided detail as to how a unique identification number would be assigned to a pediatric caregiver, and subsequently tracked in the Central Database, in response to an Agency request (page 11). Additionally, the Applicant clarified how the REMS operates with respect to tracking of patient refills and notifying a prescriber prior to a prescription running out of refills or expiring (page 11).

Reviewer Comment: The proposed modifications to the supporting document, (b) (4) *, which is outlined below, are acceptable.*

Assessment Plan

The Applicant proposes adding cases where a Xyrem patient is a victim of sexual abuse to the assessment plan metrics. Additionally, caregivers of pediatric patients will be added as a stakeholder group to be surveyed to collect data for annual assessments. The Applicant will submit the survey methodology protocol at least 90 days prior to administration of the survey. The timetable for submission of assessments is to remain annually as stated in the currently approved REMS.

Reviewer Comment: We have reviewed the proposed modifications to the assessment plan and agree with all proposed modifications. Additionally, the Applicant should add the following metrics to assess the post-training knowledge assessment:

1) Certified Pharmacy Post -Training Knowledge Assessments (KA)

(b) (4)

4 Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted by DRISK to provide feedback on the content of the updated *Prescriber Brochure*, and the *Brochure for Pediatric Patients and their Caregivers*. Their consult was received on September 26, 2018, and a summary of the recommendations is given below.

4.1 PRESCRIBER BROCHURE

A summary of OPDP's recommendations on the *Prescriber Brochure* is as follows:

1. With respect to REMS-specific risks, additional language that is in the Prescribing Information (PI) should be replicated within this REMS material. This includes detailed language specific to CNS depression (respiratory depression, emergence of depression, and suicidality) and illicit use and abuse of GHB.

   Reviewer Comment: DRISK is not in agreement with this recommendation; we have determined that this information is adequately addressed in the PI for healthcare providers (HCPs); they are encouraged to review the PI in addition to the Prescriber Brochure.

2. Removing risk language from the Prescriber Brochure, which is consistent with the PI. (b) (4)

   Reviewer Comment: DRISK is not in agreement with OPDP's comment. The language in the Prescriber Brochure intentionally mirrors that of the PI to ensure that the REMS language is consistent with labeling.

(b) (4)

4.2 BROCHURE FOR PEDIATRIC PATIENTS AND THEIR CAREGIVERS

A summary of OPDP's recommendations on the *Brochure for Pediatric Patients and Their* Caregivers is as follows:

1. With respect to REMS-specific risks, additional language that is in the Medication Guide (MG) should be replicated within this material. This includes detailed language specific to sleepwalking, CNS depression, sleep apnea, and falling asleep while in bed. Additionally, they recommend adding a more comprehensive list of common adverse events to the material.

Reviewer Comment: DRISK is not in agreement with this recommendation; we have determined that this information is adequately addressed in the MG for patients and their caregivers to review, and the Counseling section of the PI for healthcare providers (HCPs).

2. Omit non-REMS information; (b) (4)

Reviewer Comment: DRISK is not in agreement with OPDP's recommendation as we feel this information has been grandfathered in this program at this time, and as there is currently only one pharmacy, modifying the materials may disrupt operations.

3. Multiple recommendations to more clearly state that the purpose of the REMS is to educate the stakeholder on the risks of treatment. (b) (4)

    a. Page 3 – "…you will receive a call from the Certified Pharmacy of the XYREM REMS Program to (b) (4)

Reviewer Comment: DRISK agrees with OPDP's recommendation. The Applicant should modify this statement to read "…you will receive a call from the Certified Pharmacy of the

XYREM REMS Program to counsel you on the serious risks and safe use of XYREM, *to tell you how the XYREM REMS Program helps you get your child started with taking XYREM, and to answer any questions you or your child may have about XYREM."*

b. Page 6 – "This brochure (b) (4)

Reviewer Comment: DRISK agrees with OPDP's recommendation. The Applicant should modify this statement to read "This brochure provides information on the serious risks and safe use of Xyrem, and answers important questions about how to use XYREM properly, how to store it safely, and how to get your child's XYREM."

c. Page 27 – "You will then receive a call from the Certified Pharmacy (b) (4)

Reviewer Comment: DRISK agrees with OPDP's recommendation. The Applicant should modify this statement to read "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."

(b) (4)

Reviewer Comment: DRISK agrees with OPDP's recommendation. The phrase at the beginning of this statement minimizes the risks associated with Xyrem sedation. The Applicant should modify this statement to read "If your child continues evening activities after taking his or her dose…"

5 Agency Proposed REMS Modifications

5.1 REMS Document

The Applicant did not accept the Agency's draft REMS document that was updated to align with the draft guidance, *Format and Content of a REMS Document Guidance for Industry* published in October 2017.

Reviewer Comment: The Agency will provide comment on the REMS Document in a separate communication.

6 Conclusion and Recommendations

DRISK finds the proposed REMS modification for Xyrem, which includes changes to the REMS document, appended materials, and the supporting document, as submitted on September 27, 2018, not acceptable.

We recommend that the comments in Section 10 be sent to Jazz in an Information Request and that the Applicant is instructed to submit a REMS amendment within 3 business days that addresses these comments.

7 Comments to the Applicant

The following comments and attached REMS materials and supporting document are based on the Agency's ongoing review of the proposed Risk Evaluation and Mitigation Strategy (REMS) modification submitted as part of NDA 021196/S-030. Submit a REMS amendment within 3 business days that addresses these comments. Your amendment should include 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 all appended materials and supporting document.

1. **General Comments**

   We remind you that the labeling, REMS document, appended REMS materials, and REMS supporting document must all be aligned. The acceptability of the proposed changes will be dependent upon the final version of the FDA-approved labeling. We will provide comment on the REMS Document in a separate communication.

2. **REMS Materials**

   The following REMS Materials have been reviewed. In addition to the below comments, see the attached redlined documents:

   a. **General**
   Throughout the REMS materials, where the pediatric indication is referenced, include language specifying that Xyrem is indicated for patients 7 years and older.

   b. **Certified Pharmacy Training Program**
   The pediatric indication language should be updated when labeling is finalized. Please see attached document for recommendations. The Agency agrees with all other proposed modifications to this material.

   c. **Patient Counseling Checklist**
   All proposed modifications to this material are acceptable.

   d. **Patient Quick Start Guide**
   All proposed modifications to this material are acceptable

   e. **Prescriber Brochure**
   The pediatric labeling language on pages (b) (4) 4, and pediatric dosing and titration table on page 18, should be updated when labeling is finalized. We have made edits to reflect the most recent version of the label. Please see attached document for recommendations.

f. Brochure for Pediatric Patients and their Caregivers

We have made edits, see attached document for suggested changes. The pediatric indication language should be updated when labeling is finalized.

g. REMS Website Screenshots

Submit updated REMS Website Screenshots incorporating the Agency's feedback from September 13, 2018.

3. REMS supporting document

All proposed modifications to the supporting document are acceptable, including your proposed changes to the assessment plan. However, the following metrics should be added to assess the post-training knowledge assessment:

a. Certified Pharmacy Post -Training Knowledge Assessments (KA)
   i. Number of completed post-training knowledge assessments including method of completion and number of attempts to complete by module
   ii. Summary of the most frequently missed post-training knowledge assessment questions by module
   iii. A summary of potential comprehension or perception issues identified with the post-training knowledge assessment by module

Make updates to the patient survey protocol based on the new indication and materials and submit the protocol to the Agency 90 days before you begin the survey.

8 Appendix

8.1 References

[1] Jazz. REMS Amendment for Xyrem, NDA 21196 S-030, September 27, 2018.

8.2 Appended Materials

Certified Pharmacy Training Program

Prescriber Brochure

Brochure for Pediatric Patients and their Caregivers

72 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) Immediately Following this Page

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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/

YASMEEN I ABOU-SAYED
10/16/2018

DONELLA A FITZGERALD
10/16/2018

JAMIE C WILKINS PARKER
10/16/2018

Division of Risk Management
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type	NDA
Application Number	21196/S-030
OSE RCM #	2018-1257
Reviewer(s)	Yasmeen Abou-Sayed, Pharm.D. Ana Tavakoli, M.A.
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins, Pharm.D.
Review Completion Date	August 27, 2018
Subject	Evaluation of REMS Modification
Established Name	Sodium Oxybate
Trade Name	Xyrem
Applicant:	Jazz Pharmaceuticals
Formulation	500 mg/ml oral solution
Dosing Regimen	4.5 grams (g) per night 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 to the effective dose range of 6 g to 9 g per night orally.
Indication	Treatment of cataplexy and excessive daytime sleepiness in narcolepsy.

Table of Contents

Executive Summary 4

1 Introduction 4

2 Background 4

2.1 Product Information 4

2.2 Regulatory History 5

3 Therapeutic Context and Treatment Options 6

3.1 Description of the Medical Condition 6

3.2 Description of Current Treatment Options 6

4 Benefit Assessment 6

5 Risk Assessment and Safe-Use Conditions 7

5.1 Suicidal Ideation 8

5.2 Abuse or Misuse of Study Drug 9

6 Results of Review of Applicant Proposed REMS Modification 9

6.1 General comments 9

6.2 REMS Document 9

6.3 REMS Materials 10

6.3.1 Medication Guide 10

6.3.2 Certified Pharmacy Training Program 10

6.3.2.1 Pharmacy Knowledge Assessment A and B 10

6.3.3 Patient Counseling Checklist 11

6.3.4 Patient Enrollment Form 11

6.3.5 Patient Quick Start Guide 11

6.3.6 Prescriber Brochure 12

6.3.7 Prescriber Enrollment Form 14

6.3.8 Prescription Form 14

6.3.9 Risk Management Report Form 15

(b) (4)

6.3.11 Brochure for Pediatric Patients and Their Caregivers 15

6.3.12 Website Screenshots 15

(b) (4)

6.4 REMS Supporting Document and Assessment Plan 16
7 Agency Proposed REMS Modifications 17
7.1 REMS Document 17
(b) (4)
8 Conclusion and Recommendations 17
9 Comments to the Applicant 17
10 Appendix 20
10.1 References 20
10.2 Appended Materials 21

Executive Summary

This is a review of Jazz Pharmaceuticals' proposed Risk Evaluation and Mitigation Strategy (REMS) modification for Xyrem (sodium oxybate), NDA 21196/S-030, submitted on April 27, 2018. The REMS for Xyrem was originally approved on February 27, 2015 to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Xyrem. The REMS consists of a Medication Guide, elements to assure safe use (ETASU) A, B, and D, an implementation system, and a timetable for submission of assessments. The Applicant submitted the REMS modification as part of a supplemental application to support the expansion of the US indication to include the pediatric use of Xyrem for the treatment of cataplexy in narcolepsy and the treatment of excessive daytime sleepiness in narcolepsy.

The Applicant proposes modifications to the REMS document and appended materials to align with labeling changes related to the new pediatric indication. The proposal would add new materials to the existing REMS, including a *Brochure for Pediatric Patients and Their Caregivers*, (b) (4) The Applicant also proposed changes to the Assessment Plan to include reports of Xyrem patients who are victims of sexual abuse and expansion of surveys to include assessment of pediatric patients and their caregivers.

In addition to the Applicant's proposed changes, the Agency recommends that the REMS document be updated to conform to the Agency current thinking on Formatting of REMS documents as outlined in the *Format and Content of a REMS Document Guidance for Industry* published in October 2017. (b) (4)

Therefore, the proposed REMS modification for Xyrem is currently not acceptable. Comments should be sent to Jazz in an Information Request and that the Applicant submit a complete REMS amendment to address those comments.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed modification to the risk evaluation and mitigation strategy (REMS) for Xyrem (sodium oxybate), NDA 21196/S-030, submitted by Jazz Pharmaceuticals (Jazz) on April 27, 2018. The Applicant submitted the REMS modification as part of a supplemental application for a new proposed indication for the treatment of cataplexy and excessive daytime sleepiness (EDS) in narcolepsy in pediatric patients. The supplemental application is under review in the Division of Neurology Products (DNP).

2 Background

2.1 Product Information

Xyrem (sodium Oxybate), a Schedule III controlled substance, is the sodium salt of gamma-hydroxybutyrate (GHB). GHB is a potent central nervous system (CNS) depressant. Xyrem was approved under subpart H in 2002 for the treatment of cataplexy in narcolepsy and in 2005 for the treatment of EDS in narcolepsy. The recommended starting dose in adult patientsis 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 and should not ordinarily be administered.

The main safey concerns of Xyrem at the time of approval were clinically significant CNS and respiratory depression at recommended doses and abuse, misuse, and diversion[a]. Additional safey concerns identified postmarketing include medication errors and worsening of sodium Oxybate-induced respiratory depression with concomitant use of hypnotics, sedatives, sedating antidepressants and antipsychotics, opioids, general anesthetics, and muscle relaxants (Warnings & Precautions) and if used in the presence of comorbid conditions such as those with respiratory compromise (Warnings & Precautions).

Since its approval, Xyrem was available only through a restricted distribution program under 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 inorder 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) A, B, and D, an implementation system, and a timetable for submission of assessments. The goal of the Xyrem REMS is to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Xyrem.[b]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 21196/S-030 relevant to this review:

- **April 27, 2018**: Jazz submitted supplemental NDA 21196/S-030 to support the expansion of the US adult labeling to include the pediatric use of Xyrem for the treatment of cataplexy in narcolepsy and the treatment of EDS in narcolepsy.[1] The submission included a proposed REMS modification to align the REMS with labeling changes related to the new indication.

[a] 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.

[b] 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.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Narcolepsy is a chronic neurological disorder characterized by EDS, cataplexy (attacks of loss of muscle tone precipitated by emotional gestures lasting for several minutes), sleep paralysis and hypnagogic hallucinations.[2] The prevalence of narcolepsy with cataplexy is between 25 and 50 per 100,000 people (incidence 0.74 per 100,000 patient years).[3] Narcolepsy patients, compared to the general US population, have a higher incidence of obstructive sleep apnea (50-68%)[4]; major depressive disorder (17%), social anxiety disorder (21%), and panic disorder (12%).[5] Pediatric narcolepsy is associated with several co-morbid conditions, including metabolic diseases (including diabetes), obesity, precocious puberty and psychiatric comorbidities.[6]

In pediatric patients diagnosed with narcolepsy, the onset of narcolepsy symptoms was noted in as many as 11.7% of children prior to age 5[7], and 59% of children prior to age 15.[8] The diagnosis of narcolepsy is often delayed as the disorder is rare with low general awareness relative to other chronic diseases. While the median age of diagnosis has been reported as 33 years, the corresponding median age of symptom onset was 16 years.[9]

3.2 Description of Current Treatment Options

Management of narcolepsy in children and adolescents includes pharmacological and nonpharmacological approaches. No approved treatments based on observations from randomized controlled trials for pediatric narcolepsy exist. Consequently, treatments used for adults are often used to treat children with narcolepsy, despite the fact that they are prescribed off-label.[10] Currently, Xyrem is the only approved drug for cataplexy. Other drugs used to treat EDS are CNS stimulants such as modafinil, methylphenidate (both FDA approved), and amphetamines (used off-label); while cataplexy is treated off-label with tricyclic antidepressants and selective serotonin reuptake inhibitors.

4 Benefit Assessment

The Xyrem pediatric clinical program consists of a single ongoing Phase 2/3 study (13-005, National Clinical Trial [NCT] 02221869) of Xyrem in the treatment of 106 pediatric subjects, ages 7 to 17 with narcolepsy with cataplexy. Study 13-005 is a double blind, placebo-controlled, randomized-withdrawal, multicenter study of efficacy and safety of Xyrem with an open-label pharmacokinetic (PK) evaluation and safety extension with up to 1 year of treatment exposure (Part 1). Subjects who completed Part 1 were allowed to transition into or re-enroll in the ongoing, open-label Part 2 of the study, in which only safety data were collected.

Patients in Study 13-005 were titrated up to a stable dose, maintained for a 2-3 week period followed by a 2-week double-blind treatment period. The primary efficacy endpoint was the change in the weekly number of cataplexy attacks from the last 2 weeks of the stable dose period, to the 2 weeks of the double-blind treatment period. Key secondary endpoints measured were the Clinical Global Impression of Change (CGI-C) for cataplexy severity and change in the Epworth Sleepiness Scale for Children and Adolescents (ESS [CHAD]) score from the end of the stable dose period to the end of double-blind treatment period.

Xyrem-naïve subjects were titrated on Xyrem over a period of up to 10 weeks. Xyrem doses during the titration period were administered in 2 equally divided doses at night-time 2.5 to 4 hours apart in Xyrem-naive subjects. In Xyrem-naive subjects, the dosing schedule was initiated and titrated as follows in Table 1:

Table 1 – Pediatric dosing of Xyrem in grams (g) based on patient weight in kilograms (kg)

Patient Weight	Initial Nightly Dose	Dose titration	Max Nightly Dose
< 30 kg	≤2g	≤ 1g/night/week	6g
≥ 30 kg to < 45 kg	≤3g	≤ 1g/night/week	7.5g
≥ 45 kg	≤ 4.5g	≤ 1.5g/night/week	9g

Study 13-005 met its primary and key secondary efficacy endpoints and demonstrated the superiority of Xyrem over placebo in the frequency and severity of cataplexy attacks, EDS, and overall narcolepsy severity. The efficacy results were as follows:

- Primary Endpoint
  - Pediatric subjects on stable doses of Xyrem who were withdrawn from Xyrem treatment and randomized to placebo during the double-blind treatment period experienced a significant increase in weekly cataplexy attacks compared with subjects who were randomized to continue treatment with Xyrem (median: 12.71 vs 0.27, respectively; $p < 0.0001$).
- Key Secondary Endpoints
  - Compared with subjects randomized to continue receiving Xyrem, subjects randomized to receive placebo during the double-blind treatment period experienced a statistically significant worsening in cataplexy severity, with mean change in CGIc scores for cataplexy severity in placebo at -1.5 vs. Xyrem at -0.4 ($p = 0.0006$).
  - Compared with subjects randomized to continue receiving Xyrem, subjects randomized to receive placebo during the double-blind treatment period experienced a statistically significant worsening of EDS, with median change in ESS (CHAD) scores of 3.0 in placebo vas 0.0 in Xyrem ($p = 0.0004$).

5 Risk Assessment and Safe-Use Conditions

The safety database for the pediatric indication consists of the same 106 patients from study 13-005. Of the 106 patients, 104 took study drug. Overall, the AEs reported in pediatric patients with narcolepsy were similar to those observed in adults. No new safety concerns have been identified in the pediatric population.

Across all treatment periods, 72.1% of subjects reported AEs in the safety population who took study drug (N = 104). Most AEs were mild or moderate in severity, and 50% of subjects experienced AEs considered by the investigator to be related to study drug. The most common events (occurring at > 5% frequency)

determined to be AE reactions were enuresis (18%), nausea (17%), headache (16%), vomiting (16%), weight decreased (12%), decreased appetite (8%), and dizziness (6%).

AEs of special interest, which were prespecified based on the known effects of Xyrem, occurred in 28.8% of subjects while receiving Xyrem across all treatment periods. Table 2 details the AEs of special interest, and number of subjects who experienced them. Five subjects experienced AEs leading to withdrawal from the study, which included events with tactile hallucination, suicidal ideation, decreased weight, sleep apnea, and affect lability.

Table 2 – Adverse events of special interest in pediatric patients taking Xyrem

AE of special interest	Number of subjects
Confusion	5
Acute psychosis	1 (withdrew from study)
Affect lability	1 (withdrew from study)
Somnolence	9
Respiratory depression	2 (central sleep apnea, 1 withdrew from study)
Depression/Suicidality	1 (withdrew from study)
Anxiety	6
Parasomnia	12
Abuse or misuse of study drug	2 (terminated early due to treatment noncompliance)
Weight loss	13 (1 withdrew from study)

The events of suicidal ideation and acute psychosis were categorized as serious adverse events (SAEs)[c] . No deaths were reported in the pediatric development program.

5.1 SUICIDAL IDEATION

The Columbia Suicide Severity Rating Scale (C-SSRS) was administered at each contact with subjects during the study, and measured suicidal ideation or behavior. Among subjects who took study drug, 2 subjects responded positively to the C-SSRS, indicating suicidal ideation or behavior was present in those subjects. In both subjects, the positive responses were associated with SAEs. Subject (b) (6) was a 13-year old white male who responded positively to questions on non-suicidal self-injurious behavior after an SAE of acute psychosis was reported. The event occurred during the dose titration period and led to study drug

[c] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

interruption; the subject later resumed treatment with Xyrem at a lower dose without recurrence of the event. Subject (b) (6) was a 14-year old white male who responded positively in response to questions on suicidal ideation in the C-SSRS at an early termination visit after the SAE of suicidal ideation was reported (the patient withdrew from the study due to the event). Current labeling for Xyrem includes monitoring for emerging or increased depression and suicidality in section 5, (Warnings and Precautions), of the prescribing information (PI).

5.2 Abuse or Misuse of Study Drug

No specific events categorized as Abuse or Misuse of Study Drug have been reported as of the data cutoff date of February 10, 2017in Study 13-005.

6 Results of Review of Applicant Proposed REMS Modification

6.1 General comments

Overall, the proposed modifications to the Xyrem REMS are intended to incorporate pediatric patients and their caregivers into the existing operation. The Applicant proposed numerous formatting and editorial changes, typographical corrections, and administrative changes throughout the REMS document, REMS materials, and REMS supporting document. Among those modifications are:

- Language inserted throughout the REMS materials to incorporate the pediatric indication, as well as to add the caregiver as a stakeholder wherever the 'patient' is mentioned, and allow for caregiver attestation
- Incorporation of caregiver-specific language in the *Patient Counseling Checklist* for the pharmacist to use when counseling caregivers on the risks and safe use of Xyrem
- Language updated throughout REMS materials to align with the currently approved Xyrem label with regards to participation in hazardous activities
- Updating the strength of Xyrem from '500 mg/ml' to '0.5 g/ml' consistently throughout materials to align with the labeling.

Reviewer Comment: DRISK agrees with the proposed editorial changes and inclusion of the caregiver as a stakeholder throughout the REMS materials.

6.2 REMS Document

In addition to the inclusion of the pediatric population and caregiver as a stakeholder in the REMS, the Applicant proposes:

- (b) (4)
- Including in the first shipment of Xyrem a copy of the *Patient Quick Start Guide* (for adult patients) or the *Brochure for Pediatric Patients and Their Caregivers* (for pediatric patients)

- When a pediatric patient's caregiver changes, counseling the new caregiver, by the Certified Pharmacy, on the serious risks and safe use of XYREM and acknowledging that he/she has asked any questions about XYREM before XYREM is dispensed and shipped

Reviewer Comment: The content of the proposed additions to the REMS document is reasonable, however, additional changes to the language in the REMS document are required. See section 8.1 for Agency proposed changes to the REMS document.

6.3 REMS MATERIALS

(b) (4)

6.3.2 CERTIFIED PHARMACY TRAINING PROGRAM

The Applicant proposes changes throughout this material to incorporate pediatric patients and their caregivers into the program. The certified pharmacy is directed to ensure each pediatric patient has a caregiver on file prior to dispensing each prescription (page 9 and 14). Also, the pharmacist is directed to (b) (4) . Further, the Applicant has clarified the process for prescription renewals and refills, as well as the existing requirement to complete the *Patient Counseling Checklist* if a new medication or comorbid condition has been identified (page 14). Additionally, the Applicant clarifies the process where the certified pharmacy completes the *Patient Counseling Checklist* for patients restarting treatment after a lapse in therapy exceeding 6 months (page 8 and 14). With regard to prescriber enrollment, the Applicant has added pharmacy validation of the prescriber's current NPI number (pages 8 and 9). Also, language has been added which allows for electronic prescribing of Xyrem refills and renewals, in alignment with current federal and state laws allowing controlled substances to be prescribed electronically (page 15).

Reviewer Comment: The statement on page 14 (b) (4) *DRISK proposes starting the sentence as "Instruct the patient/caregiver to alert…" (see attached redlined document for details). Detail on the assignment of a caregiver identification number should be provided under the enrollment and prescription processing sections on pages 8 and 9. All other proposed modifications to this material are acceptable.*

6.3.2.1 PHARMACY KNOWLEDGE ASSESSMENT A AND B

The Applicant proposes making *Pharmacy Knowledge Assessment A* and *B* REMS appended materials, as they are currently housed in the REMS supporting document.

Reviewer Comment: Inclusion of the knowledge assessments as REMS appended materials is acceptable.

6.3.3 PATIENT COUNSELING CHECKLIST

The following changes to the *Patient Counseling Checklist* (PCC) are being proposed to accommodate the pediatric patient into the pharmacy workflow:

- Requiring the *PCC* be completed when a "change of care responsibility" occurs (page 1)
- Adding a field to record caregiver name and ID number (page 1)
- Including counseling information specific to side effects in pediatric patients (page 3)
- Adding a field to document when a change of care for a pediatric patient is the reason for the *PCC*, and that the patient/caregiver has had the opportunity to ask any any questions about Xyrem (b) (4)
- (b) (4)

The Applicant has also provided detailed instructions on marking out confidential information on the prescription label prior to disposal (page 2). Further, the PCC has been updated to align with approved language from the label on the restriction of partaking in hazardous activities while taking Xyrem (page 3).

Reviewer Comment: (b) (4) *All additional modifications are acceptable.*

6.3.4 PATIENT ENROLLMENT FORM

Updates to this material include providing the option to the prescriber to complete the form online via the REMS website. Additionally, the Applicant proposes to rearrage the order of the collection of stakeholder information, by placing the prescriber information on top. Finally, the Applicant proposes including a field within the patient information box to include, for pediatric patients, the caregiver name, relationship to patient, and phone number.

Reviewer Comment: All proposed changes to the Patient Enrollment Form *are acceptable.*

6.3.5 PATIENT QUICK START GUIDE

On the cover of this material, the Applicant proposes removing the pictographs and text providing details on the contents of the *Patient Quick Start Guide*. Further proposed modifications are detailed by page number below:

- Page 2 – Inclusion of text to direct pediatric patients and caregivers to refer to the *Brochure for Pediatric Patients and Their Caregivers*, rather than the *Patient Quick Start Guide.*

- Page 3 – Addition of the underlined text to one of introductory paragraphs:
    - "Before you can receive your first shipment of XYREM, a pharmacist at the Certified Pharmacy will ask if your healthcare provider reviewed the XYREM REMS Program 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. (b) (4) -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."

- Page 4 – Changed safety messaging by adding underlined text and deleting strikethrough text:

    - "XYREM can cause serious side effects, including (b) (4) ~~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~~"

- Page 11 – Instructions on how to prepare doses on pages 11-14 were changed to align with current language in the Instructions for Use (IFU).

- (b) (4) – Language on the proper disposal of Xyrem and marking out of personal information on the prescription label has been updated by removing the strikethrough text and adding the underlined text:

    - (b) (4) To properly dispose of XYREM, pour any unused XYREM down the sink or toilet drain. Mark out (b) (4) all personal information on the prescription label, including the XYREM name, to make it unreadable (b) (4) before putting the empty bottle in the trash."

Reviewer Comment: The safety messaging on page 4 should be restored to the original text. Removal of the adverse events listed minimizes important risks patients should be educated about and should be reporting to their prescriber. (b) (4) *All other proposed modifications to the* Patient Quick Start Guide *are acceptable.*

6.3.6 PRESCRIBER BROCHURE

On the cover of this material, the Applicant proposes removing the pictographs. Additional proposed modifications are detailed by page number below:

- Page 2 – Addition of the *Brochure for Pediatric Patients and their Caregivers* to list of REMS materials
- Page 4 – Addition of pediatric adverse event data from clinical trials
- Page 5 – Table of Contents – addition of heading for pediatric patient supplement
- Page 6
    - Lists all methods by which a prescriber can enroll in the REMS, to increase stakeholder access, including a new option for online enrollment via the REMS website.
    - Added specific drug classes of concern (sedative hypnotics, other CNS depressants, or other potentially interacting agents) to the field for screening for concomitant medications
- Page 7 – Enrollment
    - Added requirement to counsel caregiver for pediatric patients
    - Removed instructions to complete the *Supplemental Patient Authorization Form* – a non-REMS material
- Page 8 – Prescribing Requirements
    - Modified language regarding use of the Prescription Form from:

      (b) (4)

      to:

      "Write prescriptions using the **XYREM REMS Program Prescription Form** (general prescription forms will not be accepted) for initial prescriptions and for patients who are reinitiating XYREM after a lapse in therapy of 6 months or longer. The prescription form may also be used for refills and renewals."

    - Addition of language to direct the prescriber to "indicate the presence of comorbid conditions" on the *Prescription Form*.
- Page 9 – Refills
    - Modified language regarding refill procedures from:

      (b) (4)

      to:

      "Prescription refills and renewals may be conveyed by phone, fax, mail, or electronically. The Certified Pharmacy with the XYREM REMS Program will send you a XYREM REMS Program Prescription Form upon your request. The prescription form is also available online at XYREMREMS.com. Prescription refills and renewals must be documented in the XYREM REMS Program Central Database"

- Added language to remind prescribers if they are accessing the *Prescription Form* online, it must be printed and signed prior to faxing/mailing it in
- Added language to allow electronic transmission of refill prescriptions

- Page 10 – Pharmacy responsibilities – Added language to describe pharmacy responsibilities for review of concomitant medications, and subsequent consultation with prescriber if needed
- Page 14 – Use in Specific Populations
  - Updated language on pregnancy, labor and delivery, and lactation based on information in sections 8.1 and 8.2 in the current label, and removed outdated information
  - Updated pediatric use section to include summary of pediatric efficacy and safety from section 8.4 in proposed label
- Page 18 - 20 – Addition (b) (4) to provide information specific to pediatric prescribing, education, and counseling, in addition to previously detailed operation of the Xyrem REMS. Provides detail on the of process of (b) (4) weight-based dosing regimen for pediatric patients, and specific instructions for pediatric administration of Xyrem
- (b) (4)

Reviewer Comment: (b) (4) *All other proposed changes are acceptable.*

6.3.7 PRESCRIBER ENROLLMENT FORM

This material has been updated to include a listing of all options available for completion and submission of the form, including the option for online enrollment via the REMS website.

Reviewer Comment: All proposed changes to the Prescriber Enrollment Form *acceptable.*

6.3.8 PRESCRIPTION FORM

The *Prescription Form* has been modified to add fields for the pediatric population, including patient weight, and including the caregiver in the prescriber verification field and attestations. Additionally, website information to access and print the *Prescription Form* online has been added, to increase stakeholder access.

Reviewer Comment: (b) (4) *However it is currently available on the publicly accessible REMS@FDA website, therefore*

adding accessibility to the form via the REMS website *is acceptable. All proposed changes to the* Prescription Form *are acceptable.*

6.3.9 RISK MANAGEMENT REPORT FORM

All proposed modifications to the *Risk Management Report (RMR) Form* are editorial, including using the RMR abbreviation in place of 'Risk Management Report' in several places.

Reviewer Comment: The proposed changes to the Risk Management Report Form *are acceptable.*

(b) (4)

6.3.11 BROCHURE FOR PEDIATRIC PATIENTS AND THEIR CAREGIVERS

The applicant proposes adding the *Brochure for Pediatric Patients and Their Caregiver* to meet the informational requirement for the new stakeholder group in the REMS. The brochure mirrors the content of the *Patient Quick Start Guide* for the first 19 pages, and explains the role of the caregiver in ensuring that safe use conditions are maintained when Xyrem has been prescribed to a pediatric patient. Pages 20-23 of the brochure provide information directed towards the pediatric patient, explaining proper use of Xyrem, as well as communicating risks in a method appropriate for a pediatric patient. The remainder of the brochure provides guidance to the caregiver on the safe use of Xyrem, including transitioning a pediatric patient to being able to carry out safe use of Xyrem independently, filling prescriptions, insurance coverage, contact information, (b) (4) The certified pharmacy will ensure that this brochure, instead of the *Patient Quick Start Guide*, is included in the first Xyrem shipment for all newly enrolled pediatric patients.

Reviewer Comment: The addition of the Brochure for Pediatric Patients and Their Caregiver *to the REMS Materials is acceptable. It provides education for the new stakeholder group and fulfills the informational portion of the REMS goal.* (b) (4)

6.3.12 WEBSITE SCREENSHOTS

Changes to the website are largely editorial in nature and include changing titles for navigation (from (b) (4) to "Resources and Materials", and (b) (4) to "Prescriber Enrollment"). The phone number to contact the REMS program has been added to the bottom of all webpages. Bulleted lists of hyperlinked REMS materials for prescribers and patients have been changed to buttons that can be clicked on to navigate to the corresponding material. The website also adds functionality that allows for the prescriber to enroll themselves or a patient online, instead of only navigating to a pdf which may be filled out, then subsequently faxed or mailed in. Additionally, when a stakeholder navigates to "Resources and Materials", two separate radio buttons are available to allow navigation to materials for adult patients or materials for caregivers of pediatric patients.

Reviewer Comment: The Applicant stated that the Prescription Form is currently accessible via the REMS@FDA website, and want to make it available on the Xyrem REMS Website. DRISK agrees with this availability. (b) (4) *All other proposed modifications to the* REMS Website *are acceptable.*

(b) (4)

6.4 REMS SUPPORTING DOCUMENT AND ASSESSMENT PLAN

Supporting Document

The Applicant has added language related to use in pediatric patients, including clinical trial information. Jazz has also added language regarding the proposal to allow the Xyrem REMS prescription form to be available via the REMS Program website. Additionally, the supporting document includes detail on the newly proposed REMS materials: the *Brochure for Pediatric Patients and Their Caregivers*, *Pharmacy Knowledge Assessment A/B*, (b) (4)

(b) (4)

(b) (4)

(b) (4)

7 Agency Proposed REMS Modifications

7.1 REMS DOCUMENT

The REMS document should be updated to conform to Agency current thinking as outlined via the REMS document template included in the *Format and Content of a REMS Document Guidance for Industry* released in October 2017 and available at https://www.fda.gov/downloads/Drugs/.../Guidances/UCM184128.pdf. DRISK has drafted a proposed REMS document using the new draft guidance. The REMS document is currently undergoing final internal clearance.

Reviewer Comment: The draft updated REMS document should be sent to the Applicant.

(b) (4)

8 Conclusion and Recommendations

DRISK finds the proposed REMS modification for Xyrem, which includes changes to the REMS document, appended materials, and the supporting document, as submitted on April 27, 2018, not acceptable. We recommend that the comments in Section 9 be sent to Jazz in an Information Request and that the Applicant is instructed to submit a complete REMS amendment within 10 business days that addresses these comments.

9 Comments to the Applicant

The following comments and attached draft REMS Document, REMS materials and supporting document are based on the Agency's ongoing review of the proposed Risk Evaluation and Mitigation Strategy (REMS) modification submitted as part of NDA 021196/S-030. Submit a REMS amendment within 10 business

days that addresses these comments. Your amendment should include a complete REMS proposal (REMS Document, all appended materials, and 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.

1. **General Comments**

(b) (4) This program has patient directed materials that are focused on the REMS associated risks, (b) (4)

2. **REMS Document**

We have attached a draft version of the updated REMS document to align with current Agency thinking on the formatting of REMS documents as outlined in the *Format and Content of a REMS Document Guidance for Industry*, released in October 2017. It is the Agency's intent that the newly formatted REMS document reflect your current operations of the REMS.

3. **REMS Materials**

The following REMS Materials have been reviewed. In addition to the below comments, see the attached redlined documents:

a. **Certified Pharmacy Training Program**

The statement on page 14 (b) (4) Start the sentence as "Instruct the patient/caregiver…" (b) (4) All other proposed modifications to this material are acceptable.

b. **Pharmacy Knowledge Assessment A and B**

Inclusion of these materials as appended REMS materials is acceptable.

(b) (4)

d. **Patient Enrollment Form**

All proposed changes to the Patient Enrollment Form are acceptable.

e. **Patient Quick Start Guide**

(b) (4)

All other proposed modifications to the Patient Quick Start Guide are acceptable.

f. Prescriber Brochure

(b) (4)

The full content of this Brochure is still under review; further comment will be provided at a later date..

g. Prescriber Enrollment Form

All proposed modifications to this form are acceptable.

h. Prescription Form

All proposed modifications to this form are acceptable.

i. Risk Management Report Form

All proposed modifications to this form are acceptable.

(b) (4)

k. Brochure for Pediatric Patients and their Caregivers

The addition of the *Brochure for Pediatric Patients and Their Caregivers* as an appended REMS Material is acceptable. (b) (4)

l. REMS Website Screenshots

DRISK finds it acceptable to add the Prescription Form to the materials accessible from the Xyrem REMS website. (b) (4) All other proposed modifications to the REMS Website are acceptable.

(b) (4)

4. REMS supporting document

The supporting document should remove all reference to the (b) (4) and the (b) (4) as an element of the REMS as DRISK does not agree with inclusion of the (b) (4) in the REMS, and the (b) (4) will be removed from the REMS and maintained as part of labeling. Additional information is required regarding your current procedures for refills of Xyrem. (b) (4) Additionally, the supporting document continues to undergo review; further comment will be provided at a later date.

10 Appendix

10.1 References

[1] Jazz. REMS Modification for Xyrem, NDA 21196 S-030, April 27, 2018.

[2] Yves Dauvilliers et al. Narcolepsy with cataplexy. Lancet 2007: 369: 499-511.

[3] Longstreth et al. The Epidemiology of Narcolepsy; Sleep, 2007; Vol. 30, No, 1: 13-26.

[4] Sansa et al. Obstructive sleep apnea in narcolepsy. Sleep Medicine, 2010; 11(1):93-95.

[5] Ohayon MM. Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population. Sleep Medicine, 2013; 14(6): 488-492.

[6] Jennum P, Pickering L, Thorstensen EW, et al. Morbidity of childhood onset narcolepsy: a controlled national study. Sleep Med 2017; 29:13-7.

[7] Challamel MJ, Mazzola ME, Nevisimalova S, et al. Narcolepsy in children. Sleep 1994; 17s:17.

[8] Toss RE and Daly DD. Narcolepsy in Children. Pediatrics 1960; 25:1025-33.

[9] Thorpy MG and Cronin S. Age of onset and time to diagnosis of narcolepsy. Neurology 1999; 52 (Suppl 2):A110.

[10] Mignot EJM. A practical guide to the therapy of narcolepsy and hypersomnia syndromes. Neurotherapeutics 2012; 9(4):739-52.

10.2 Appended Materials

Xyrem REMS Document

Certified Pharmacy Training Program

Patient Counseling Checklist

Patient Quick Start Guide

Prescriber Brochure

Brochure for Pediatric Patients and Their Caregivers

REMS Website Screenshots

120 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) Immediately Following this Page

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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/

YASMEEN I ABOU-SAYED
08/27/2018

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08/27/2018

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21196/S-030

CLINICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21196 (S-030)**
Sponsor:	**Jazz Pharmaceuticals, Inc.**
Drug:	**Xyrem**
Proposed Indication:	(b) (4)
Material Submitted:	**Supplemental New Drug Application**
Correspondence Date:	**4/27/18**
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Reviewer:	**Ranjit B. Mani, M.D.**

TABLE OF CONTENTS

TABLE OF CONTENTS 1
Executive Summary 2
1. Background 7
2. Contents Of Submission 7
3. Contents Of Review 8
4. Final Text Of Pediatric Written Request 9
5. Pre-sNDA Meeting 15
6. Outline Of Main Clinical Study (Study 13-005) Supporting Current Application 16
7. 120-Day Safety Update 78
8. Additional Safety Data Supporting Current Application 89
9. Review Of Proposed Prescribing Information And Related Documents 91
10. Summary Of Statistical Review 91
11. Summary Of Nonclinical Review 92
12. Summary Of Clinical Pharmacology Review 94
13. Summary Of Chemistry Review 95
14. Summary Of Office Of Surveillance And Epidemiology Reviews 96
15. Summary Of Office Of Prescription Drug Promotion (OPDP) Reviews 97
16. Controlled Substances Staff Review 98
17. Financial Disclosure Information 98
18. Site Inspection Report 99
19. Fulfillment Of Terms Of Pediatric Written Request 99
20. Overall Conclusion 100
21. Recommendation 100

Executive Summary

Recommendation

I recommend that this application be approved.

Proposed Indications

The proposed indications for Xyrem®, as stated by the sponsor in the original submission of this application, are as follows:

"Xyrem (sodium oxybate) oral solution is indicated for the treatment of cataplexy in narcolepsy (b) (4)

"Xyrem (sodium oxybate) oral solution is indicated for the treatment of (b) (4)

Currently Approved Indications

The currently approved indications for Xyrem® are as follows:

"Xyrem (sodium oxybate) oral solution is indicated for the treatment of cataplexy in narcolepsy."

"Xyrem (sodium oxybate) oral solution is indicated for the treatment of excessive daytime sleepiness in narcolepsy."

Background To Application

This Supplemental New Drug Application (sNDA), a pediatric efficacy supplement, seeks to expand the approved indication for Xyrem® (sodium oxybate) to include the treatment of children. A priority review of this supplement has been requested and granted. This application is accompanied by a Pediatric Exclusivity Request.

The clinical data subsumed under this application have been submitted in response to a pediatric Written Request from the Agency initially issued on March 10, 2014, and subsequently modified; the Request was finalized on April 25, 2017.

Xyrem® (sodium oxybate oral solution [500 mg/mL]) is currently approved in this country for the treatment of cataplexy and excessive daytime in narcolepsy. Xyrem® was initially approved for marketing in the United States on July 17, 2002. The original approval of Xyrem® was under the Subpart H (21 CFR 314.520) regulations, which have remained applicable to this product. Xyrem® was originally approved for marketing under a restricted distribution program. A formal Risk Evaluation and Mitigation Strategy (REMS) for Xyrem® was approved on February 27, 2015.

Most of the new clinical data that are submitted with this application are derived from the results of Study 13-005, a clinical study conducted in response to the pediatric Written Request.

Summary of Main Clinical Findings

Study 13-005 is the main clinical study supporting this sNDA. Key aspects of this study are summarized below.

Study Design And Significant Amendments

Protocol 13-005 had the following main features:

- The primary objectives of the study were to evaluate the efficacy and safety of Xyrem® in the treatment of pediatric patients (aged 7 to 17 years) who have narcolepsy with cataplexy

- This study had a number of consecutive segments, of which the main randomized, double-blind, placebo-controlled, parallel-arm withdrawal segment was to be the component of the study directed at evaluating the efficacy of Xyrem® in the treatment of cataplexy associated with narcolepsy in children.

- About 100 patients aged 7 to 16 years at study entry were to be enrolled. They would be either Xyrem®-naïve or taking a stable dose of Xyrem® (and a stable dose of stimulants for narcolepsy, if applicable) for at least 2 months prior to study entry. Other key inclusion criteria were as follows: primary diagnosis of narcolepsy with cataplexy meeting International Classification of Sleep Disorders (ICSD)-2 criteria or ICSD-3 criteria, whichever was in effect at the time of the study; positive for the HLA DQB1:0602 haplotype; and history of at least 14 cataplexy attacks in a typical 2-week period and clinically significant symptoms of excessive daytime sleepiness prior to beginning any narcolepsy treatment.

- Throughout the study, all nightly doses of Xyrem® and placebo were to be administered in 2 divided doses, administered 2.5 to 4 hours apart. The starting and maximum doses of Xyrem® as well as the Xyrem® titration regimen (if required) were to be determined based on body weight stratum.

- The consecutive segments of this study were as follows:

    - A screening period lasting up to 30 days.

    - A 3 to 10 week open-label titration period lasting 3 to 10 weeks for patients who were Xyrem®-naïve at study entry.

    - An open-label stable-dose period lasting 2 to 3 weeks. During this phase, a subset of about 24 patients (completers) who were taking a stable dose of Xyrem® at study entry were to participate in an open-label evaluation of the pharmacokinetics of Xyrem®.

    - A double-blind, placebo-controlled withdrawal phase lasting 2 weeks during which period patients were randomized 1:1 to treatment either with Xyrem® in the stable dose established during the preceding 2 weeks or placebo.

    - An open-label safety component which allowed for a total exposure to Xyrem® of up to 1 year.

- The primary efficacy parameter was the change in weekly number of cataplexy attacks during the 2 weeks of the double-blind period, compared with the last 2 weeks of the stable-dose period.

- Key secondary efficacy parameters were the following:

    - Clinical Global Impression of Change for cataplexy severity, comparing the end of the double-blind period with the end of the stable-dose period.

    - Change in the modified Epworth Sleepiness Scale (modified for children and adolescents) score from the end of the stable-dose period to the end of the double-blind period.

- Other secondary efficacy parameters were the following

    - Clinical Global Impression of Change for narcolepsy severity overall comparing the end of the double-blind period with the end of the stable-dose period.

    - Change in quality of life (based on the Short Form-10) from the end of the stable-dose period to the end of the double-blind period.

- Safety monitoring was to comprise assessment of the following during the course of the study: adverse events, vital signs, height, weight, physical examinations, 12-lead electrocardiograms, polysomnographic parameters (including measures of respiration), safety laboratory tests, assessments of growth and precocious puberty (including growth hormone levels), Columbia-Suicide Severity Rating Scale, Children's Depression Inventory 2nd Edition Self-Report Short Version, and Multidimensional Anxiety Scale for Children 10-item Anxiety Index.

- Plasma concentrations of sodium oxybate were measured in the subset of patients participating in the pharmacokinetic analysis, and various pharmacokinetic parameters derived from those data and analyzed further.

- A tiered analysis of the efficacy parameters was conducted beginning with the primary efficacy parameter followed by the two key secondary efficacy parameters (with the Clinical Global Impression of Change in cataplexy severity analyzed first and the change in modified Epworth Sleepiness Scale score analyzed later), and finally the two other secondary efficacy parameters in the same order as stated above.

A pre-specified interim efficacy analysis (on the primary efficacy endpoint) for this protocol that was conducted after 35 subjects completed or discontinued early from the double-blind treatment period led to the Data Safety Monitoring Board for Study 13-005 concluding that Xyrem had demonstrated efficacy in the treatment of cataplexy (it had demonstrated that Xyrem was superior to placebo in the treatment of cataplexy at a p-value ≤ 0.005): the Board then recommended that the double-blind segment of Study 13-005 be discontinued, while the open-label extension (including pharmacokinetic evaluation) continue. The Data Safety Monitoring Board for Study 13-005 also

recommended that patients continue to be enrolled in the open-label pharmacokinetic segment.

The pediatric Written Request under which Study 13-005 was first conducted was amended after the pre-specified interim analysis led to a protocol amendment. The study protocol was also amended to allow for the duration of the open-label safety component to be further extended so that the total duration of Xyrem® treatment for an individual patient could extend up to 3 years; the part of the study originally proposed was then referred to as Part 1 with the newly-proposed extension as Part 2.

Study Results

Study 13-005 was conducted in a manner consistent with the study protocol.

A total of 106 patients were enrolled in this study of whom 104 appear to have received study drug. 99 patients entered the stable-dose period, with 96 of those patients completing that period. Of the 96 patients who completed the stable-dose period, 63 patients participated in the randomized, double-blind, withdrawal phase of the study, whereas the remaining 33 patients continued to take open-label Xyrem. 95 patients then entered the open-label safety period of the study. As of the cut-off date for the 120-day safety update, 85 patients had completed Part 1 of the study and 44 patients had entered Part 2.

During the randomized, double-blind, withdrawal phase, 31 patients were assigned to Xyrem® (30 patients completed that phase) and 32 patients were assigned to placebo (all 32 patients completed that phase).

The primary efficacy analysis (based on an analysis of covariance) indicated that the mean change from baseline over the two -week randomized withdrawal period in the weekly number of cataplexy attacks was 17.37 for the placebo group and 2.52 for the group that continued to take Xyrem® (this change was an increase in cataplexy frequency). This difference was statistically significant ($p < 0.0001$). Statistically significant treatment differences favoring Xyrem® over placebo were seen on the two key secondary efficacy parameters analyzed in the prespecified sequence, the Clinical Global Impression of Change for Cataplexy Severity ($p = 0.0006$) and the change from baseline in modified Epworth Sleepiness Scale score ($p = 0.0001$).

The adverse event profile of Xyrem® seen in this study was not substantially different from that seen in adults. The other safety outcomes did not reveal any data of concern. Safety data for this study that was submitted with the 120-Day Safety Update was not substantially different from that submitted with the original IND for Xyrem®.

The pharmacokinetic completer population consisted of 29 patients, of whom 11 were aged 7 to 11 years, and 18 were aged 12 to 17 years. These data revealed a pharmacokinetic profile for Xyrem® in children that was similar to that seen in adults. A dose-proportionality assessment indicated that while the C_{max} was dose-proportional, the AUC_{0-4} was supra-dose-proportional.

Additional Clinical Findings

Additional safety data for children administered Xyrem® was provided from two sources: postmarketing safety data for Xyrem® comprising data collected since the original approval for Xyrem®; and the published medical literature. The data available indicate a safety profile that is broadly similar to that seen in adults.

Proposed Changes To Labeling

These are described in more detail in the body of this review.

Additional Comments

Study 13-005 has been conducted in accordance with the terms of the pediatric Written Request finalized on April 25, 2017.

The reviews by a number of other Agency staff are also summarized in the body of this review.

Conclusion

This Supplemental New Drug Application has provided sufficient data to support the approval of Xyrem® for the treatment of cataplexy and excessive daytime sleepiness (b) (4)

1. Background

This Supplemental New Drug Application (sNDA), a pediatric efficacy supplement, seeks to expand the approved indication for Xyrem® (sodium oxybate) to include the treatment of children.

This sNDA is also accompanied by a Pediatric Exclusivity Request. A priority review of this supplement has been requested and granted.

Xyrem® (sodium oxybate oral solution [500 mg/mL]) is currently approved in this country for the treatment of cataplexy and excessive daytime in narcolepsy. Xyrem® was originally approved by the Agency on July 17, 2002, for the treatment of cataplexy in narcolepsy, under NDA 21196. A supplemental NDA (an efficacy supplement; S-005) proposing an expansion of the originally approved claim was approved on November 18, 2005; the approved expanded indication was (and still is) as follows: "*The treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy*." Xyrem® was originally approved under the Subpart H (21 CFR 314.520) regulations, which have remained applicable to this product. Xyrem® was originally approved for marketing under a restricted distribution program. A formal Risk Evaluation and Mitigation Strategy (REMS) for Xyrem® was approved on February 27, 2015.

The development of Xyrem® as a treatment for cataplexy in children (i.e., children and adolescents, aged 7 to 17 years) was conducted in response to a pediatric Written Request, initially issued by the Agency on March 10, 2014. After the results of an interim (efficacy) analysis of the double-blind segment of the main study (Study 13-005) conducted under that Written Request became available, an amended Pediatric Written Request was issued by the Agency on February 24, 2017; a few corrections were made to the amended Written Request in a final document issued by the Agency on April 25, 2017.

The clinical data included in this application are largely derived from Study 13-005.

There have been many communications between the Agency and sponsor regarding the development of Xyrem® for use in children, culminating in a Pre-sNDA meeting held on September 6, 2017.

Xyrem® has been investigated for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy in children under IND 49641.

2. Contents Of Submission

This sNDA submission has two main components.

- The original sNDA submission of April 27, 2018, which has been provided in standard electronic Common Technical Document format. This component has five main sections, enumerated and headed as follows:

  Module 1: Regional.
  Module 2: Common Technical Document summaries.
  Module 3. Quality.
  Module 4. Nonclinical study reports.
  Module 5. Clinical study reports.

- A 120-Day Clinical Safety Update submitted on August 23, 2018, which has also been provided in standard electronic Common Technical Document format. This component thus has three main sections, enumerated and headed as follows:

  Module 1: Regional.
  Module 2: Common Technical Document summaries.
  Module 5. Clinical study reports.

Since the original submission of this sNDA, there have a number of additional communications such as, but not limited to, information requests and responses to those requests from the sponsor.

3. Contents Of Review

The contents of this submission have been reviewed under the following main headings and in the same order as below.

- Final text of pediatric Written Request.
- Pre-sNDA meeting.
- Outline of main clinical study (Study 13-005) supporting current application.
- 120-Day Safety Update.
- Additional safety data supporting current application.
- Review of proposed Prescribing Information and related documents.
- Summary of statistical review.
- Summary of nonclinical review.
- Summary of clinical pharmacology review.
- Summary of chemistry review.
- Summary of Office of Surveillance and Epidemiology reviews.
- Summary of Office of Prescription Drug Promotion (OPDP) reviews
- Controlled Substances Staff review.
- Financial disclosure information.
- Site inspection report.
- Fulfilment of terms of pediatric Written Request.
- Overall conclusion.
- Recommendation.

Note that the following are subsumed under this review: primary clinical review, and team leader and cross-disciplinary team leader summary.

4. Final Text Of Pediatric Written Request

The following is the full text of the Amended Written Request that was sent to the sponsor on April 25, 2017. The text is copied verbatim from the letter but has been re-formatted.

Please refer to your correspondence dated October 25, 2016, requesting changes to FDA's March 10, 2014 Written Request for pediatric studies for Xyrem (sodium oxybate) oral solution.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on March 10, 2014 remain the same. (Text added is underlined. Text deleted is strikethrough.)

BACKGROUND:

This Written Request has been amended as a result of an interim analysis of Study 1, described below. The independent Data Safety Monitoring Board conducted a prospectively planned analysis after 35 patients had either completed or discontinued the double-blind segment of that study. The Board reached the conclusion that there were adequate data to support the efficacy of Xyrem in the treatment of cataplexy in children and adolescents aged 7 to 17 years. They recommended: that the double-blind segment of the study be discontinued; that the open-label safety segment of that study be continued; and that patients continue to be enrolled in the open-label pharmacokinetic segment of the study.

This study plan investigates the potential use of sodium oxybate oral solution in the treatment of cataplexy in narcolepsy in children and adolescents aged 7 to 17 years.

Narcolepsy is a lifelong neurological disease estimated to be prevalent in 0.02% of adults worldwide, and in about 1 in 2000 individuals in the United States. The cardinal symptoms of narcolepsy are excessive daytime sleepiness, cataplexy, sleep-related hallucinations, sleep paralysis, and disrupted nighttime sleep. The age of onset of narcolepsy ranges from early childhood to middle age, with a large peak around age 15: thus the first symptoms of narcolepsy commonly manifest during childhood and adolescence.

Cataplexy is a symptom specific to narcolepsy and is characterized by a sudden loss of skeletal muscle tone often triggered by strong emotions such as laughter. The loss of muscle tone in cataplexy may be confined to a limited group of muscles or be more generalized. Localized forms of cataplexy may manifest with symptoms such as head or jaw dropping, buckling of the knees, and slurred speech. Generalized cataplexy with a loss of tone in all voluntary muscles can result in falls. The duration of individual attacks of cataplexy can vary from a second to several minutes. The frequency of attacks of cataplexy can vary from as little as one episode per year to several episodes per day, with attacks occasionally being continual for several hours at a time. Consciousness is fully preserved during attacks of cataplexy. The prevalence of cataplexy in the United States has been estimated to range from 0.05% to 0.067%. Like other symptoms of narcolepsy, cataplexy commonly begins during childhood and adolescence.

As is the case with adults, the symptoms of narcolepsy, including cataplexy, are frequently disruptive of the lives of children and adolescents, both at school and elsewhere. Among several consequences of narcolepsy in that population are impaired academic performance, injury, and emotional disturbances.

Sodium oxybate is the only drug approved for the treatment of cataplexy in narcolepsy. The approval of sodium oxybate for the treatment of cataplexy in narcolepsy is based on studies conducted entirely in adults, as is the approval of that drug for the treatment of excessive daytime sleepiness in narcolepsy. While other drugs such as tricyclics and selective serotonin reuptake inhibitors are used in both adults and children to treat cataplexy, their use for that indication is not evidence-based. Stimulant drugs such as methylphenidate and dextroamphetamine, while prescribed for the treatment of the excessive daytime sleepiness of narcolepsy even in children, are not approved for use in that population and are not known to be effective in cataplexy.

Section 8.4 of the current Prescribing Information for sodium oxybate states the following: "*Safety and effectiveness in pediatric patients has not been established.*" There are also no published randomized, controlled trials of sodium oxybate in pediatric patients. Despite similarities in the symptoms of narcolepsy between children and adults, we do not believe that sodium oxybate can be assumed to have efficacy in children and adolescents based on the extrapolation of efficacy data from adults. There are, however, post-marketing safety data available for about 1500 pediatric patients who were prescribed sodium oxybate off-label.

For the above reasons, the potential use of sodium oxybate as a treatment for cataplexy in narcolepsy in children and adolescents aged 7 to 17 years should be clinically investigated. Narcolepsy is less frequent in children less than 7 years old and has not been reported to occur in neonates; thus, the potential use of sodium oxybate in those populations does not warrant further investigation.

To obtain needed pediatric information on sodium oxybate the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study*:

Based on review of the available nonclinical toxicology data, the following study must be conducted, but may be conducted concurrently with the clinical study in pediatric patients further described below:

A juvenile animal toxicology study in rats.

This study must utilize animals of an age range and stage(s) of development that are comparable to the intended human population, and the animals must be exposed to the drug for a period that will cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study must evaluate effects on growth (including bone growth parameters), reproductive development, and neurological and neurobehavioral development. Reproductive performance must be evaluated following cessation of treatment, after a washout period of appropriate duration (based on half-life). In assessing neurobehavioral development, the effects must be evaluated during treatment and after an appropriate washout period following the cessation of treatment (to evaluate potential long-term effects). To avoid the confounding effect of repeated neurobehavioral testing, separate groups of animals must be used at the two assessment times. However, to avoid unnecessary use of animals, the same group of animals may be used to evaluate neurobehavioral effects during treatment and the effects on reproductive parameters. The neurobehavioral tests must assess sensory function, motor function, and learning and memory. The neuropathological evaluation must include examination of all major brain regions and cellular elements, with particular attention to alterations indicative of developmental insult.

We recommend that dose selection for the pivotal study be based on a preliminary dose-range finding study in juvenile animals, and that a final protocol for the pivotal nonclinical study be submitted to the Division for comment prior to study initiation.

- *Clinical study:*

Study 1: A double-blind, placebo-controlled, randomized withdrawal, multicenter study of the efficacy and safety of sodium oxybate, combined with an open-label evaluation of the pharmacokinetics of sodium oxybate, and an open-label safety evaluation with combined time of sodium oxybate treatment of at least one year in pediatric patients who have narcolepsy with cataplexy.

The efficacy of sodium oxybate in pediatric patients aged 7 to 17 years cannot be extrapolated and will be determined by the studies outlined in this Written Request.

- *Objectives of the study:*

- to evaluate the efficacy of sodium oxybate in the treatment of cataplexy in narcolepsy in pediatric patients aged 7 to 17 years
- to evaluate the safety of sodium oxybate in the treatment of cataplexy in pediatric patients, aged 7 to 17 years, for at least one year.
- to characterize the pharmacokinetics of sodium oxybate given as two doses to children and adolescents, aged 7 to 17 years, who have narcolepsy with cataplexy.
- to compare the pharmacokinetics and dose-proportionality of sodium oxybate in two pediatric age group distributions (7-11 years and 12-17 years), and to further compare those data with corresponding historic data for sodium oxybate in adults.

- *Patients to be Studied:*

- *Age group in which study will be performed*: Patients aged 7 to 17 years.

- *Number of patients to be studied:* At least 100 patients should be enrolled in the study as a whole. At least 8 patients from the 7-11 year age group distribution and 10 patients from the 12-17 year age group distribution should be enrolled in the subset of subjects in whom pharmacokinetic analyses are to be performed.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

- Efficacy Endpoints: The primary efficacy endpoint will be the change in the weekly number of cataplexy attacks during the 2 weeks of double-blind treatment as compared with the weekly number of cataplexy attacks during the 2-week (stable-dose) period immediately preceding the double-blind treatment period.

A key secondary efficacy endpoint must be the Clinical Global Impression of Change in cataplexy severity comparing the end of the double-blind period with the end of the stable- dose period.

Measures of compliance must include measurement of the volume of sodium oxybate remaining at each study visit in each bottle in which that product is dispensed.

- Pharmacokinetic Endpoints: The following pharmacokinetic parameters for sodium oxybate must be evaluated in a subset of patients who are already taking sodium oxybate at a stable dose: AUC0-4, Cmax, and tmax following the first dose; and peak concentration and C4h after the second

dose. Those pharmacokinetic parameters and the dose-proportionality of sodium oxybate in each of the two pediatric age group distributions (7-11 years and 12-17 years) must be assessed and compared with the corresponding historic data in adults.

- Safety Endpoints: Safety outcomes must include an evaluation of adverse events, vital signs, physical examinations, weight, height, 12-lead electrocardiogram, hematology, clinical chemistry, urinalysis, polysomnographic measures (including measures of respiration), assessments of growth and precocious puberty (including measurement of growth hormone), serum pregnancy tests (if appropriate), Columbia-Suicide Severity Rating Scale score, Children's Depression Inventory score, and Multidimensional Anxiety Scale score.

A review of adverse events must be performed at every study visit. Vital signs, height, and weight should also be checked at every study visit using standardized methods. Other assessments should be performed at clinically appropriate intervals, again using standardized methods.

While all adverse events must be reported, patients must be actively monitored for the following adverse events: confusion, somnolence and more pronounced levels of depressed consciousness; respiratory depression; depressed mood and suicidality; anxiety; sleepwalking and other parasomnias; abuse and misuse of sodium oxybate; and weight loss.

A Data Monitoring Committee must be included because of the known safety concerns with sodium oxybate that are listed below. Please refer to the Agency Guidance document entitled "Establishment and Operation of Clinical Trial Data Monitoring Committees" which is available at the following link.

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

- *Known Drug Safety concerns and monitoring:*

Known safety concerns with sodium oxybate include central nervous system depression, respiratory depression, confusion, depressed mood and suicidality, anxiety, parasomnias such as sleepwalking, and abuse and misuse of that drug. The current Prescribing Information for sodium oxybate especially warns of the risk of respiratory and central nervous system depression, and misuse and abuse of that product. Accordingly, patients should be actively monitored for those adverse events. The use of sodium oxybate is contraindicated in combination with sedative hypnotics or alcohol and in individuals with succinic semialdehyde dehydrogenase deficiency. Sodium oxybate is a Schedule III controlled substance and sodium oxybate is available only through a restricted distribution program because of the risks of central nervous system depression, abuse, and misuse.

- *Extraordinary results:*

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

- *dosage form: liquid*
  - *route of administration: oral*
  - *regimen: nightly in two divided doses*

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if
1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,
the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*

The trial must enroll a sufficient number of patients to have at least 80% power to detect a difference between the two treatment groups of 40% in the percentage change in the weekly number of cataplexy attacks during the 2-week randomized withdrawal phase of the study as compared with the weekly number of cataplexy attacks during the last 2 weeks of the immediately preceding stable-dose period, using a two-sided alpha of 0.05. A hypothetical example of such a difference between the treatment groups is illustrated in the following table.

Treatment Group	Weekly number of attacks during last 2 weeks of stable dose	Weekly number of attacks during 2-week randomized withdrawal period	Change in weekly number of attacks	% change in weekly number of attacks*	Difference between treatment groups in
Placebo	10	15	5	+50%	40%
Xyrem	10	11	1	+10%	

*compared with last 2 weeks of stable-dose period
**effect size

Dose proportionality must be assessed using AUC and Cmax values. The AUC and Cmax ratios and their 90% confidence intervals should be presented. Pharmacokinetic parameters will be based on the PK population available.

- *Labeling that may result from the study(ies)*:

You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that sodium oxybate is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*:

You must submit full study reports, not previously submitted to the Agency, that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain Agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):*

Reports of the above studies must be submitted to the Agency on or before September 22, 2018. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:*

Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Reports of the studies that meet the terms of the Written Request dated March 10, 2014, as amended by this letter must be submitted to the Agency on or before September 22, 2018 in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission , via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written

5. Pre-sNDA Meeting

A Pre-sNDA meeting was held with the sponsor on September 6, 2017, at which this then-pending application was discussed. For full details of the items discussed and agreements reached at that meeting, please see the Agency's Minutes.

6. Outline Of Main Clinical Study (Study 13-005) Supporting Current Application

6.1 Outline Of Study Protocol Through Amendment #3

The outline below summarizes the main features of this study protocol as it existed prior to the conduct of an interim analysis described below.

The protocol described below is the version contained in Amendment #3, dated August 5, 2015, which was submitted to IND #49641 on August 11, 2015 (Serial #246). Substantive changes to the protocol were made in Amendment #s 4 and 5 and are summarized later in this review.

Please note that the citations in sponsor tables copied below refer to the items in the study protocol submitted by the sponsor.

6.1.1 Title

A Double-Blind, Placebo-Controlled, Randomized-Withdrawal Multicenter Study Of The Efficacy And Safety Of Xyrem With An Open-Label Pharmacokinetic Evaluation And Safety Extension In Pediatric Subjects With Narcolepsy With Cataplexy.

6.1.2 Objectives

6.1.2.1 Primary Objectives

- To evaluate the efficacy of Xyrem® in the treatment of cataplexy in pediatric patients with narcolepsy.
- To evaluate the safety of Xyrem® in the treatment of cataplexy in pediatric patients with narcolepsy for up to one year.

6.1.2.2 Secondary Objectives

- To evaluate the efficacy of Xyrem® in the treatment of excessive daytime sleepiness in pediatric patients with narcolepsy with cataplexy.
- To characterize the pharmacokinetics of Xyrem® in pediatric patients, aged 7 to 17 years, with narcolepsy with cataplexy.
- To evaluate the safety of titrating Xyrem® in pediatric patients to an effective and tolerable dose.

6.1.3 Design, Dose, Sample Size, And Duration

This study consists of 2 consecutive core components.

1. The key double-blind, placebo-controlled, randomized withdrawal component of the study (with the double-blind, placebo-controlled randomized withdrawal segment forming a phase in that component of the study).

2. An open-label safety extension, following the period of double-blind withdrawal that permits all patients to receive Xyrem® for a total period of up to 1 year.

Patients to be enrolled in the study will be either Xyrem®-naïve or already taking that drug.

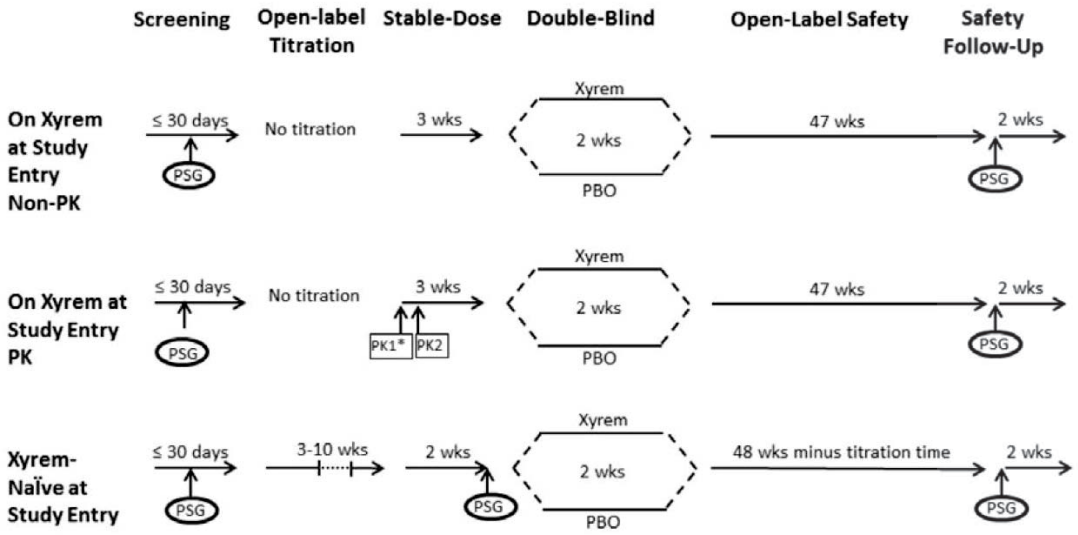
Open-label titration and open-label stable dose periods, in that consecutive order, are to precede the double-blind, placebo-controlled, randomized withdrawal component.

The pharmacokinetics of Xyrem® are to be evaluated in a subset of patients during the first component of the study during the stable-dose period.

Throughout the study, all nightly doses of Xyrem® and (Xyrem®) placebo will be administered in 2 divided doses, administered 2.5 to 4 hours apart.

The Xyrem® product used will be the marketed product, but flavorant may be added to the water used as a diluent if requested by the subject, parent, or guardian for palatability.

The overall study schema is illustrated below in a figure that I have copied from the submission.



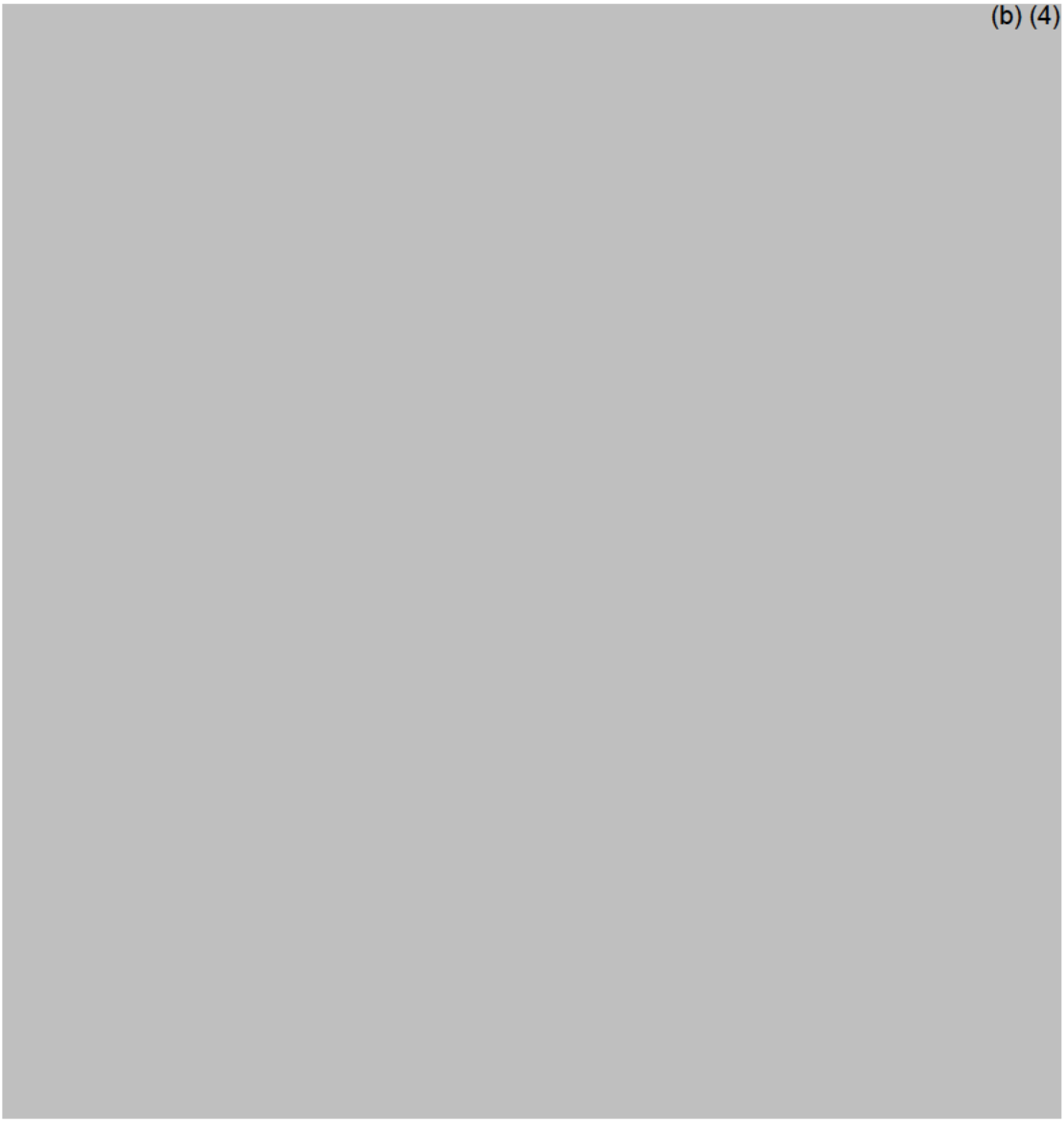
* ½ of usual nightly dose

PK: Pharmacokinetics
PSG: Polysomnogram

Each segment of the study is further described below.

A specific dosing syringe is to be used during the study. An image of that syringe and its gradations is displayed below.

(b) (4)



6.1.3.1 Double-Blind, Placebo-Controlled, Randomized Withdrawal Component

The study will have a screening period lasting up to 30 days.

About 100 patients are to be enrolled in the study. Those enrolled will be:

EITHER

- Xyrem®-naïve.

OR

- Taking a stable dose of Xyrem® (and a stable dose of stimulants for narcolepsy, if applicable) for at least 2 months prior to study entry.

There will be an open-label titration period lasting 3 to 10 weeks for patients who are Xyrem®-naïve at entry. Those patients will have treatment with that drug initiated at a dose that is weight-dependent. The Xyrem® dose will then be titrated until there is maximum benefit in the treatment of cataplexy (and so that the frequency and severity of cataplexy are stable with no further dose adjustments needed) and excessive daytime sleepiness, while tolerability is maintained. Once an optimal dose of Xyrem® is achieved (per the investigator's judgment), patients may enter the open-label stable-dose period of the study. Patients in whom there is no response based on cataplexy frequency compared with study entry will be considered treatment failures and withdrawn from the study. The starting dose, rate of titration, and maximum dose for Xyrem® for the dose titration phase – all of which are weight-dependent – are specified in the following table, which I have copied from the submission.

Subject weight	Initiation dose (taken in two equally divided doses)*	Titration regimen	Maximum total nightly dose
<30 kg	2 g/night	1 g/night/week	6 g/night
≥30 kg – <45 kg	3 g/night	1 g/night/week**	7.5 g/night**
≥45 kg	4.5 g/night	1 or 1.5 g/night/week	9 g/night

*At bedtime and 2.5 to 4 hours later.
**Titration of 1 g/night/week up to 7 g/night and then 0.5 g/night/week final titration permitted.

A reduction in Xyrem® dose on account of poor tolerability will be permitted during the dose-titration phase with any decrement being a multiple of either 1 g/night or 1.5 g/night. Stimulant taper and withdrawal may also be attempted at the discretion of the investigator during the open-label titration phase.

An open-label stable-dose period lasting 2-3 weeks will precede the double-blind, placebo-controlled, randomized withdrawal phase of the study, as follows:

- For patients already taking a stable dose of Xyrem® (and stimulants for narcolepsy, if applicable) for at least 2 months prior to study entry, treatment with the same dose of Xyrem® (and stimulants, if applicable) will be continued for 3 weeks.

- For Xyrem®-naïve patients who have been titrated to an optimal Xyrem® dose (and stimulant dose, if applicable) during the dose-titration phase will remain on the same dose of Xyrem® (and stimulants, if applicable) for 2 weeks during the open-label, stable dose period.

Baseline data will be collected during the last 2 weeks of the stable-dose period.

At the end of the open-label, stable-dose period, patients will be qualified to enter the double-blind treatment period if the following criteria are satisfied:

- Inclusion and exclusion criteria for the study protocol continue to be met.
- The dose of Xyrem® remains unchanged during the stable-dose period.
- No clinically significant worsening in narcolepsy symptoms or clinically significant adverse events attributable to Xyrem® treatment during the stable-dose period as per investigator judgment.

The double-blind, placebo-controlled, randomized withdrawal phase will immediately follow the stable-dose period. This period will last 2 weeks. During this period, patients will be randomized 1:1 to treatment with one of the following regimens:

- Xyrem® continued in the stable dose established during the preceding 2 weeks.
- Placebo that is equivalent in volume to the Xyrem® stable dose established during the preceding 2 weeks.

During the double-blind, placebo-controlled, randomized withdrawal period, patients will remain on the same stimulant dose (if applicable) that was used during the open-label stable-dose period.

Patients who complete the double-blind treatment period will be eligible to continue in the open-label safety component of the study.

During the **open-label stable-dose** phase described above, a subset of patients will participate in the open-label pharmacokinetic evaluation further described below.

6.1.3.1.1 Open-Label Pharmacokinetic Evaluation

Only patients already taking a stable dose of Xyrem® at study entry will be eligible to participate in the pharmacokinetic evaluation section of the study.

Patients enrolled will be stratified into 2 groups by age: 7 to 11 years; and 12 to 17 years. If the variability of Xyrem® pharmacokinetics in children is similar to that in adults, 12 completers in each age group are estimated to be adequate to characterize the pharmacokinetics of Xyrem® in children. When sufficient data are actually available to characterize the pharmacokinetics of Xyrem® in children, enrollment in that component of the study will cease.

Once enrolled in the pharmacokinetic evaluation, patients will spend two nights at the beginning of the stable-dose period (or during the earlier open-label stable dose period) at the study site for the pharmacokinetic evaluation. These two nights are designated (in consecutive order) as Pharmacokinetic Nights 1 and 2.

- On Pharmacokinetic Night 1, subjects will receive one half of their usual and current total nightly Xyrem® dose (administered as two equally divided doses. given at bedtime, and 4 hours later).

- On Pharmacokinetic Night 2 (which will be the next night after Pharmacokinetic Night 1 or within 2 weeks of Pharmacokinetic Night 1), subjects will receive Xyrem® at their usual stable nightly dose (administered as two equally divided doses, given at bedtime, and 4 hours later).

On each of the above nights, pharmacokinetic sampling will be performed as follows:

- At the following times in relation to the first dose: 0 (pre-dose), 0.75, 1.5, 2.5, and 4 hours (pre-second dose)

- 4.75 and 8 hours after the first dose (i.e., 0.75 and 4 hours after the second dose).

6.1.3.2 Open-Label Safety Component

The open-label safety component will follow the randomized withdrawal phase of the study.

This period will allow for a total Xyrem® exposure of up to 1 year in a subset of patients (the 1-year period includes the duration of Xyrem® administration prior to and during the randomized withdrawal phase).

Patients will participate in the open-label safety period itself for the following periods depending on whether they are Xyrem®-naïve or already on Xyrem® at entry into the study, as follows:

- Patients who are already on a stable dose of Xyrem® at entry will participate in the open-label safety period for 47 weeks.

- Patients who are Xyrem®-naïve at study entry will participate in the open-label safety period for 38 to 45 weeks.

On entering the open-label safety period, all subjects will be started at a dose no higher than half the Xyrem® dose administered at the end of the stable-dose period and will then be titrated up to an optimal dose of Xyrem®, as per the judgment of the investigator. The maximum dose used will not exceed that depicted in the table in the previous section.

Patients who withdraw prematurely from the study will undergo a 2-week post-study termination visit.

Measures to assess patient compliance are to be taken consistent with the stipulations in the Written Request of March 10, 2014: data recorded in patient daily diaries and the volume of study drug solution returned at each visit are each to be evaluated.

An age-appropriate formulation of study drug is to be used.

6.1.4 Key Inclusion Criteria For All Patients

- Male or female. Age 7 to 16 years at Visit 2 for subjects on Xyrem® at study entry and at Visit 1.1 for Xyrem®-naïve subjects (to ensure that subjects are < 18 years of age). Please see the study schedule (Section 6.1.7) for further information about the aforementioned visits.

- Primary diagnosis of narcolepsy with cataplexy (Type 1 narcolepsy) meeting International Classification of Sleep Disorders (ICSD)-2 criteria or ICSD-3 criteria, whichever was in effect at the time of the study.

- Positive for the HLA DQB1:0602 haplotype, as determined at screening.

- Documented assent from the patient indicating that he or she is aware of the investigational nature of the study and of the required procedures and restrictions prior to participation in any protocol-related activities.

- Informed consent from parent or guardian.

- History of at least 14 cataplexy attacks in a typical 2-week period and clinically significant symptoms of excessive daytime sleepiness prior to beginning any narcolepsy treatment.

- Willing to spend the required number of nights (2 to 3) in a sleep laboratory for polysomnographic evaluations.

- If currently treated with Xyrem® must have been taking unchanged doses of Xyrem® (twice nightly dosing no higher than 9 g/night) and stimulants, if applicable, for the treatment of narcolepsy symptoms for at least 2 months prior to screening.

- Agreement to abstain from caffeinated-products during nights when a polysomnogram is performed.

- If currently treated with Xyrem®, must have demonstrated clinical improvement of cataplexy per investigator's clinical judgment.

- Has agreed to abstain from caffeinated products during polysomnographic and pharmacokinetic assessment nights.

- If female and of child-bearing potential, must be willing to use a method of contraception that is considered acceptable by the investigator, or agree to abstain from sexual intercourse for the duration of the study and for 30 days after study termination.

- If male and sexually active with a female partner must be willing to use a method of contraception that is considered acceptable by the investigator or agree to abstain from sexual intercourse for the duration of the study and for 30 days after study termination.

6.1.4.1 Additional Inclusion Criteria For Patients Participating In Pharmacokinetic Evaluation Component Of Study

- Must be willing to spend 2 additional nights in a sleep laboratory for polysomnographic evaluations.

- Must have been taking unchanged doses of Xyrem® (and stimulants, if applicable) for the treatment of narcolepsy symptoms for at least 2 months prior to screening.

- Documented assent from the patient indicating that he or she is aware of the investigational nature of the pharmacokinetic component of study and of the required procedures and restrictions before participation in any protocol-related activities.

- Have sufficient blood volume for pharmacokinetic sampling based on body weight in accordance with Seattle Children's Hospital guidelines or, for a particular investigational site, Institutional Review Board eligibility guidelines for pediatric blood collection pertinent to the site.

6.1.5 Key Exclusion Criteria For All Patients

- Inability of patient to understand, assent to, or follow study instructions for any reason, in the opinion of the investigator.

- Inability of parent or guardian to comply with study requirements for any reason, in the opinion of the investigator.

- Previously treated with Xyrem®, but discontinued drug on account of lack of efficacy and/or poor tolerability.

- Narcolepsy secondary to any other medical condition.
- Restless legs syndrome requiring treatment other than iron supplements.
- Succinic semi-aldehyde dehydrogenase deficiency.
- Uncontrolled hypothyroidism.
- History of seizure disorder.
- History of head trauma associated with loss of consciousness.
- Evidence of sleep-disordered breathing, including any one of the following:
    - Presence of clinically significant obstructive or central sleep apnea, as determined by the investigator or documented previously.
    - Obstructive apnea-hypopnea index > 5 for subjects 7 to 11 years of age or obstructive apnea-hypopnea index > 10 for subjects 12 to 17 years of age.
    - Oxygen saturation nadir ≤ 85% at night.
    - Clinically significant hypoventilation.
- Oxygen saturation level < 95% for at least 5 minutes on room air as measured by pulse oximetry, while fully awake during daytime monitoring. If values < 95% are observed at study sites at higher geographic elevations and are acceptable to the investigator, enrollment of the subject requires permission from the Medical Monitor.
- Past or current major thought disorder, e.g., schizophrenia, paranoia, or mania.
- Recent history of clinically significant parasomnia (e.g., sleep walking) that could significantly affect the conduct of the study.
- Current suicide risk as determined from history, Columbia-Suicide Severity Rating Scale, or previous suicide attempt.
- A T-score ≥ 65 on the Children's Depression Inventory 2nd Edition Self-Report Short Version.
- Other documented clinically significant condition (including an unstable medical condition, chronic disease other than narcolepsy with cataplexy, or history or presence of another neurological disorder) that might affect the subject's safety and/or interfere with the conduct of the study in the opinion of the investigator.

- Electrocardiogram with clinically significant deviation from normal or clinically significant physical examination findings, as per the Investigator.

- Clinically significant laboratory abnormality, as per the Investigator.

- Positive pregnancy test at screening (pregnancy tests are to be performed in any woman who reaches menarche).

- Positive urine drug screen for benzodiazepines or drugs of abuse, a positive alcohol test, or a history of substance abuse including alcohol abuse (if the patient takes prescribed amphetamines and has a positive test for those drugs, he will not be excluded).

- Treatment with benzodiazepines, non-benzodiazepine anxiolytics, hypnotics and sedatives, neuroleptics, opioids, barbiturates, diclofenac, valproate, phenytoin, or ethosuximide within 2 weeks prior to enrollment (discontinuation for the purposes of study enrollment is permitted if considered safe by the Investigator and approved by the Medical Monitor).

- Treatment with other drugs for cataplexy (examples provided) within 1 month of screening.

- Current treatment with oral isotretinoin.

- Inability to fast for 2 hours before the first dose through 4 hours following the last dose on nights when polysomnography or pharmacokinetic sampling is performed.

- Lack of a commitment from the parent or guardian that the home situation is safe for Xyrem® use.

- Use of any investigational agent within 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.

- Allergy to local anesthetics that may be used for blood collection.

- Allergy to malic acid, sucralose/maltodextrin, or ingredients in the flavorant if used.

- Unsafe for subject to receive placebo treatment for 2 weeks, in the opinion of the investigator.

6.1.5.1 Additional Exclusion Criteria For Patients Participating In Pharmacokinetic Evaluation Component Of Study

- Hemoglobin below the lower limit of normal for age and gender at screening or at the end of the double-blind period, whichever is closer to pharmacokinetic nights.

- Use of tobacco products or products for smoking cessation within 90 days before screening, including nicotine-containing products, or history of significant use of tobacco (> 10 cigarettes or their equivalent daily) within 3 years prior to the pre-stable-dose-phase polysomnogram.

- Non-compliance with prescribed Xyrem® regimen in the 2 weeks prior to the first Pharmacokinetic Night.

6.1.6 Concomitant Medications

6.1.6.1 Prohibited Medications

- Benzodiazepines, non-benzodiazepine anxiolytics, hypnotics and sedatives, neuroleptics, opioids, barbiturates, diclofenac, valproate, phenytoin, and ethosuximide. If a subject undergoes short-term outpatient procedures during the study and requires opioids or benzodiazepines, study drug must be held for one night while those drugs are administered; if and opioid and/or a benzodiazepine is required for multiple days, the subject must be discontinued from the study.

- Other anti-cataplectic medications such as tricyclic antidepressants, selective serotonin reuptake inhibitors, or tricyclic antidepressants.

- Oral isotretinoin.

- Investigational drugs other than study drug.

6.1.6.2 Permitted Medications

- Stimulant therapy, as long as the dose is stable during the stable-dose and double-blind withdrawal periods.

- Vitamins in normal doses (herbal supplements are prohibited).

- Acetaminophen for fever, headache, or other pain in accordance with the allowable dose limits by age for each country and not to exceed the limits below:

    - For subjects aged 7 to 11 years: no more than 325 mg every 4 to 6 hours, not to exceed 1625 mg in 24 hours.

  - For subjects 12 years and older: no more than 650 mg every 4 to 6 hours, not to exceed 3250 mg in 24 hours.

- Ibuprofen for fever, headache, or other pain in accordance with the allowable dose limits by age for each country and not to exceed the limits below:

  - For subjects aged 7 to 11 years: no more than 100 mg every 6 to 8 hours, not to exceed 400 mg in 24 hours.

  - For subjects 12 years and older: no more than 200 mg every 4 to 6 hours, not to exceed 1200 mg in 24 hours.

- Birth control pills, patches, injections, or implants (all hormonal contraceptives) may be continued.

- Local topical anesthetic agent for placement of indwelling catheter or before any blood draws.

- Non-sedating antihistamines.

- Anti-inflammatories for pain.

- Chronic topical or oral antibiotics for acne.

- Over-the-counter decongestants.

6.1.7 Schedule

The study schedule is depicted in a series of tables which have been copied below from the study protocol in this supplemental NDA and are partly self-explanatory (please refer to the submission itself for further details).

Note that individual episodes of cataplexy are to be recorded in patient diaries.

6.1.7.1 Schedule For Subjects Taking Xyrem® At Study Entry (Including Open-Label Safety Component)

The study schedule for subjects taking Xyrem® at study entry is copied below from the submission.

	Screening Visit	Start Stable-Dose	End Stable-Dose/ Begin Double-Blind Treatment	End Double-Blind/ Begin Open-Label Safety	Open-Label Safety Period with Xyrem										Safety Follow-up
Visits	V1 Day -30 to -1 [a,b]	V2 Day 1	V3 Week 3 ± 3 days	V4 Week 5 +3 days	V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 W 52 ±7 days Or Early Termination	V16 14 days after last treatment +3 days
Informed Consent/Assent	X															
Inclusion/Exclusion Criteria	X	X														
Demographics and Contact Information	X															
Medical History including narcolepsy history, usual bedtime and awakening time	X															
Physical Examination including a brief neurological exam	X			X											X	
Tanner Stage Assessment	X														X	
Height	X	X	X	X	X		X		X			X			X	X
Weight	X	X	X	X	X		X		X			X			X	X
Vital Signs[c]	X	X	X	X	X		X		X			X			X	X

	Screening Visit	Start Stable-Dose	End Stable-Dose/ Begin Double-Blind Treatment	End Double-Blind/ Begin Open-Label Safety	Open-Label Safety Period with Xyrem										Safety Follow-up
Visits	V1 Day -30 to -1 [a,b]	V2 Day 1	V3 Week 3 ± 3 days	V4 Week 5 +3 days	V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 W 52 ±7 days Or Early Termination	V16 14 days after last treatment +3 days
Pulse Oximetry on room air while fully awake	X															
HLA DQB1:0602[d]	X															
Hematology, Chemistry[e]	X			X											X	
TSH	X															
PK subjects only: Coagulation[f]	X[g]				X[h]											
Urinalysis	X			X											X	
Only for Girls <8 years: estradiol, LH, FSH **Only for Boys <9 years:** testosterone, LH, FSH	X														X	
Urine Drug Screen	X	X		X[i]	X		X		X			X			X	
Alcohol Test	X	X		X[i]	X		X		X			X			X	
Serum Pregnancy	X			X												
Urine Pregnancy		X													X	
12-Lead ECG	X			X											X	

	Screening Visit	Start Stable-Dose	End Stable-Dose/ Begin Double-Blind Treatment	End Double-Blind/ Begin Open-Label Safety	Open-Label Safety Period with Xyrem										Safety Follow-up
Visits	V1 Day -30 to -1 [a,b]	V2 Day 1	V3 Week 3 ± 3 days	V4 Week 5 +3 days	V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 W 52 ±7 days Or Early Termination	V16 14 days after last treatment +3 days
Cataplexy Frequency Diary[j]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	
CGIs for Historical Narcolepsy Overall Severity Prior to any Narcolepsy Treatment	X[k]															
CGIs for Historical Cataplexy Severity Prior to any Narcolepsy Treatment	X[k]															
CGIs (narcolepsy overall)	X	X	X													
CGIs (cataplexy severity)	X	X	X													
PGIc (narcolepsy overall)				X												
CGIc (narcolepsy overall)				X												
CGIc (cataplexy severity)				X												
ESS (CHAD)	X	X	X	X	X		X		X			X			X	

	Screening Visit	Start Stable-Dose	End Stable-Dose/ Begin Double-Blind Treatment	End Double-Blind/ Begin Open-Label Safety	Open-Label Safety Period with Xyrem										Safety Follow-up
Visits	V1 Day -30 to -1 [a,b]	V2 Day 1	V3 Week 3 ± 3 days	V4 Week 5 +3 days	V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 W 52 ±7 days Or Early Termination	V16 14 days after last treatment +3 days
Study Drug Dosing Diary[j]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Stimulant Dosing Diary[j]		→	→	→												
Review subject dosing diaries for completeness and compliance		→	→	→												
Review cataplexy frequency diary for completeness			→	→												
SF-10		X	X	X	X		X		X			X			X	
C-SSRS for suicidality[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDI2:SR[S] for depression	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MASC-10 for anxiety scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
School Attendance Diary[m]		→	→													
AE Reporting	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Screening Visit	Start Stable-Dose	End Stable-Dose/ Begin Double-Blind Treatment	End Double-Blind/ Begin Open-Label Safety	Open-Label Safety Period with Xyrem											Safety Follow-up
Visits	V1 Day -30 to -1 [a,b]	V2 Day 1	V3 Week 3 ± 3 days	V4 Week 5 +3 days	V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 W 52 ±7 days Or Early Termination	V16 14 days after last treatment +3 days
Randomize subjects			X													
Dispense Study Drug[n]		X	X	X	X		X		X			X				
Collect study drug, measure compliance			X	X	X		X		X			X			X	
Fasting morning blood sample: GH, IGF-1, prolactin			X	X											See Appendix 1.2[o]	
Breakfast			X	X											See Appendix 1.2[o]	
PSG	See Appendix 1.2														See Appendix 1.2[o]	
PK subjects only: PK Nights 1 and 2		See Appendix 3			Once the subject has been retitrated and is on a stable dose of Xyrem, PK Nights 1 and 2 can be scheduled for a protocol-specified clinic visit or for an additional clinic visit. See Appendix 3											

An arrow (——>) indicates that the assessment is continuous.

a) All subjects will provide their written informed consent prior to the performance of any study-related procedures. The Screening Visit (Visit 1) starts when a subject is assigned a subject number via IVRS/IWRS. If needed, additional screening time may be granted with permission of the Medical Monitor.

b) The Screening Period for subjects with low body weight who are participating in the PK evaluation should be as close as possible to 30 days to minimize the amount of blood drawn over 30 days.

c) Obtain vital signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) after subject has been resting for ≥5 min.

d) HLA DQB1:0602: Collect blood sample unless previous result available.

e) See Table 2.

f) Coagulation: prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (PTT).

g) If PK collection is conducted in the Stable-Dose Period, collect coagulation samples during the Screening Period.

h) If PK collection is conducted during the Open-Label Period, collect coagulation samples within 30 days prior to PK Night 1.

i) Urine drug screen and alcohol test: only for subjects continuing to the Open-label Safety Period.

j) Recorded daily in electronic diary.

k) Impression of severity prior to any narcolepsy treatment.

l) C-SSRS: Use Baseline/Screening Version at Visit 1 and Since Last Visit version at all other visits for subjects ≥12 years of age, and use Children's versions for children <12 years of age.

m) School attendance collected for subjects who attend school during Stable-Dose and Double-Blind Treatment Periods.

n) Study drug quantities dispensed at study visits in accordance with protocol and as required by State or local regulation.

o) If the subject withdraws early from the study during the Open-Label Safety Period, perform a PSG if subject is willing and if the subject is willing to be dosed with study drug for this PSG night. Early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.

6.1.7.2 Schedule For Subjects Who Are Xyrem®-Naïve At Study Entry (Except Open-Label Safety Component)

The study schedule for subjects who are Xyrem®-naïve at study entry is copied below from the submission.

		Open-Label Titration Period (up to 10 weeks) Xyrem-naïve subjects only							Stable-Dose Period		Double-Blind Treatment Period	See Appendix 2.2 for Schedule of Events for the Open-Label Safety Period
Events	Screening	Begin Titration							End Titration Begin Stable-Dose	End of Stable-Dose Begin Double-Blind Treatment	End of Double-Blind Treatment Begin Open-Label Safety	
Visits	V1	V1.1	V1.2	V1.3 Phone Call	V1.4 Phone Call	V1.5	V1.6 Phone Call	V1.7	V2	V3	V4	
Weeks (W)	Day -30 to -1[a]	Day 1	W1 +3 days	W2 +3 days	W3 +3 days	W4 ±7 days	W6 +3 days	W8 ±7 days	W10 ±3 days	W12 +3 day	W14 +3 day	
Informed Consent/Assent	X											
Inclusion/exclusion Criteria	X	X										
Demographics and Contact Information	X											
Medical History including narcolepsy history, usual bedtime and awakening time	X											
Physical Examination including a brief neurological exam	X										X	
Tanner Stage Assessment	X											
Height	X	X	X			X		X	X	X	X	
Weight	X	X	X			X		X	X	X	X	
Vital Signs (blood pressure, pulse/heart rate, body temperature, respiratory rate)[b]	X	X	X			X		X	X	X	X	

		Open-Label Titration Period (up to 10 weeks) Xyrem-naïve subjects only							Stable-Dose Period		Double-Blind Treatment Period	See Appendix 2.2 for Schedule of Events for the Open-Label Safety Period
Events	Screening	Begin Titration							End Titration Begin Stable-Dose	End of Stable-Dose Begin Double-Blind Treatment	End of Double-Blind Treatment Begin Open-Label Safety	
Visits	V1	V1.1	V1.2	V1.3 Phone Call	V1.4 Phone Call	V1.5	V1.6 Phone Call	V1.7	V2	V3	V4	
Weeks (W)	Day -30 to -1[a]	Day 1	W1 +3 days	W2 +3 days	W3 +3 days	W4 ±7 days	W6 +3 days	W8 ±7 days	W10 ±3 days	W12 +3 day	W14 +3 day	
Pulse Oximetry on room air while fully awake	X											
HLA DQB1:0602[c]	X											
Hematology, Chemistry[d]	X										X	
TSH	X											
Urinalysis	X										X	
Only for Girls <8 years: Estradiol, LH, FSH Only for Boys<9 years: Testosterone, LH, FSH	X											
Urine Drug Screen	X	X									X[e]	
Alcohol Test	X	X									X[e]	
Serum Pregnancy Test	X										X	
Urine Pregnancy test		X										
12 Lead ECG	X										X	
Cataplexy Frequency Diary[f]		→										
CGIs for Historical Narcolepsy Overall Severity Prior to any	X[g]											

		Open-Label Titration Period (up to 10 weeks) Xyrem-naïve subjects only							Stable-Dose Period		Double-Blind Treatment Period	See Appendix 2.2 for Schedule of Events for the Open-Label Safety Period
Events	Screening	Begin Titration							End Titration Begin Stable-Dose	End of Stable-Dose Begin Double-Blind Treatment	End of Double-Blind Treatment Begin Open-Label Safety	
Visits	V1	V1.1	V1.2	V1.3 Phone Call	V1.4 Phone Call	V1.5	V1.6 Phone Call	V1.7	V2	V3	V4	
Weeks (W)	Day -30 to -1[a]	Day 1	W1 +3 days	W2 +3 days	W3 +3 days	W4 ±7 days	W6 +3 days	W8 ±7 days	W10 ±3 days	W12 +3 day	W14 +3 day	
Narcolepsy Treatment												
CGIs for Historical Cataplexy Severity Prior to any Narcolepsy Treatment	X[g]											
CGIs (narcolepsy overall)	X	X								X		
CGIs (cataplexy severity)	X	X								X		
PGIc (narcolepsy overall)											X	
CGIc (narcolepsy overall)											X	
CGIc (cataplexy severity)											X	
ESS (CHAD)	X	X								X	X	
Study Drug Dosing Diary[f]		→	→	→	→	→	→	→	→	→	→	
Stimulant Dosing Diary[f]		→	→	→	→	→	→	→	→	→	→	
Review subject dosing diaries for completeness and compliance and cataplexy frequency diary for completeness			→	→	→	→	→	→	→	→	→	
SF-10		X								X	X	
C-SSRS for suicidality[h]	X	X		X		X	X	X	X	X	X	

		Open-Label Titration Period (up to 10 weeks) Xyrem-naïve subjects only							Stable-Dose Period		Double-Blind Treatment Period	See Appendix 2.2 for Schedule of Events for the Open-Label Safety Period
Events	Screening	Begin Titration							End Titration Begin Stable-Dose	End of Stable-Dose Begin Double-Blind Treatment	End of Double-Blind Treatment Begin Open-Label Safety	
Visits	V1	V1.1	V1.2	V1.3 Phone Call	V1.4 Phone Call	V1.5	V1.6 Phone Call	V1.7	V2	V3	V4	
Weeks (W)	Day -30 to -1[a]	Day 1	W1 +3 days	W2 +3 days	W3 +3 days	W4 ±7 days	W6 +3 days	W8 ±7 days	W10 ±3 days	W12 +3 day	W14 +3 day	
CDI2:SR[S] for depression	X	X		X		X	X	X	X	X	X	
MASC-10 for anxiety scale	X	X		X		X	X	X	X	X	X	
School Attendance Diary[i]									→	→	→	
Assess subject and determine if additional dose titration is necessary			X	X	X	X	X	X				
AE Reporting	→	→	→	→	→	→	→	→	→	→	→	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Randomize subjects										X		
Dispense Study Drug[j]		X	X			X		X	X	X	X	
Collect study drug, measure compliance			X			X		X	X	X	X	
Fasting morning blood sample: GH, IGF-1, prolactin[k]										See Appendix 2.3	X	
Breakfast										See Appendix 2.3	X	
PSG	See Appendix 2.3									See Appendix 2.3		

An arrow (⟶) indicates that the assessment is continuous.
Note: A Xyrem naïve subject is defined as a subject who has never been treated with Xyrem or who was previously treated with Xyrem and discontinued Xyrem for at least one month prior to the Screening visit for reasons other than lack of efficacy and/or tolerability issues (e.g., lost insurance coverage, could not afford Xyrem, changed prescribers).

a) All subjects will provide their written informed consent prior to the performance of any study-related procedures. The Screening Visit (Visit 1) starts when a subject is assigned a subject number via IVRS/IWRS. If needed, additional screening time may be granted with permission of the Medical Monitor.
b) Obtain vital signs after subject has been resting for ≥5 min.
c) HLA DQB1:0602: Collect blood sample unless previous result available.
d) See Table 2.
e) Urine drug screen and alcohol test: only for subjects continuing into the Open-Label Safety Period.
f) Recorded daily in electronic diary.
g) Impression of severity prior to any narcolepsy treatment.
h) C-SSRS: Use Baseline/Screening Version at Visit 1 and Since Last Visit version at all other visits for subjects ≥12 years of age and use Children's versions for children <12 years of age.
i) School attendance collected for subjects who attend school during Stable-Dose and Double-Blind Treatment Periods.
j) Study drug dispensed at study visits in accordance with protocol and as required by State or local regulation.
k) See Table 5.

6.1.7.3 Schedule For Polysomnographic Procedures

6.1.7.3.1 Schedule For Patients On Xyrem® At Study Entry

Polysomnographic night procedures for patients taking Xyrem® at study are displayed in the following sponsor table.

	Screening Visit	Open-Label Safety Period with Xyrem
Visits	**V1** **Day -30 to -1**[a]	**Visit 15** **Week 52 (±7 days)** **Or Early Termination**
PSG Night Procedures[b]	Screening PSG	End of Study PSG /Early Termination
Review inclusion/exclusion criteria	X	
Light dinner >2 hours before dosing	X[c]	X[c]
Confirm Parent(s)/ Guardian(s) Contact Information	X	X
Administer or supervise the administration of Study Drug[d]	X	X
PSG	X	X[e]
$EtCO_2$ or $TcCO_2$[f]	X	X
Vital Signs[g]	X	X
Pulse Oximetry[h]	X	X
Record AEs/Concomitant Medications	X	X
Brief neurological exam[i]	X	X
Fasting morning blood sample: GH, IGF-1, prolactin		X
Breakfast (if subject prefers to eat at the study center)	X	X

a) If needed, additional screening time may be granted with permission of the Medical Monitor.
b) Perform all other procedures for the visit prior to the PSG night procedures.
c) Light dinner taken >2 hours prior to dosing. The dinner should be the same or similar on all PSG nights and may be taken at the Sleep Lab or home.
d) Administer the subject's nightly dose of Xyrem divided in two doses, at bedtime and 4 hours later while in bed.
e) Early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.
f) CO_2 monitoring on PSG nights only at sites where monitoring is routinely performed.
g) Obtain vital signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) after subject has been resting for ≥5 min. Obtain at pre-dose and before release from study center. At 1, 4 (pre-2nd dose), 5, and 8 hours after the 1st Xyrem dose, heart and respiratory rates recorded via PSG.
h) SpO_2 monitored continuously from immediately before first dose through 8 hours post-first dose, and recorded pre-dose and at 1 h, 2 h, 4 h (pre-2nd dose), 5 h, 6 h, and 8 h after the first dose. Additional measurement is taken while the subject is awake and before release from the study center.
i) Brief neurological exam before discharge on the morning after PSG.

6.1.7.3.2 Schedule For Patients Who Are Xyrem®-Naïve At Study Entry

Polysomnographic night procedures for patients who are Xyrem®-naïve at study are displayed in the following sponsor table.

	Screening Visit	End Stable-Dose Period Begin Double-Blind Treatment Period	Open-Label Safety Period with Xyrem
Visits	V1 Day -30 to -1[a]	V3 Week 3 (± 3 days)	Visit 15 Week 52 (±7 days) Or Early Termination
PSG Night Procedures[b]	Screening PSG	End of Stable-Dose/Pre-Randomization PSG	End of Study PSG /Early Termination
Review inclusion/exclusion criteria	X		
Light dinner >2 hours before dosing	X[c]	X[d]	X[d]
Confirm Parent(s)/ Guardian(s) Contact Information	X	X	X
Administer or supervise the administration of Study Drug[e]		X	X
PSG	X	X[f]	X[g]
$EtCO_2$ or $TcCO_2$[h]	X	X	X
Vital Signs[i]	X[j]	X[k]	X[k]
Pulse Oximetry	X[l]	X[m]	X[m]
Record AEs/Concomitant Medications	X	X	X
Brief neurological exam[n]	X	X	X
Fasting morning blood sample: GH, IGF-1, prolactin		X	X
Breakfast (if subject prefers to eat at the study center)	X	X	X

Note: A Xyrem naïve subject is defined as a subject who has never been treated with Xyrem or who was previously treated with Xyrem and discontinued Xyrem for at least one month prior to the Screening visit for reasons other than lack of efficacy and/or tolerability issues (e.g., lost insurance coverage, could not afford Xyrem, changed prescribers).

a) If needed, additional screening time may be granted with permission of the Medical Monitor.
b) Perform all other procedures for the visit prior to the PSG night procedures.
c) No food restrictions.
d) Light dinner taken >2 hours prior to dosing. The dinner should be the same or similar on all PSG nights and may be taken at the Sleep Lab or at home.
e) Administer the subject's nightly dose of Xyrem divided in two doses, at bedtime and 4 hours later while in bed.
f) End of Stable-Dose/Pre-Randomization PSG: Perform prior to Randomization.
g) Early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.
h) CO_2 monitoring on PSG nights only at sites where monitoring is routinely performed.
i) Obtain vital signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) after subject has been resting for ≥5 min.
j) Vital signs obtained prior to the start of the PSG and prior to release from study center.
k) Vital signs obtained at pre-dose and before release from the study center. At 1, 4 (pre-2nd dose), 5, and 8 hours after the first Xyrem dose, heart and respiratory rates recorded via PSG.
l) Monitor SpO_2 to determine obstructive sleep apnea status.
m) SpO_2 monitored continuously from immediately before first dose through 8 hours post-first dose, and recorded pre-dose and at 1 h, 2 h, 4 h (pre-2nd dose), 5 h, 6 h, and 8 h after the first dose. Additional measurement is taken while the subject is awake and before release from the study center.
n) Brief neurological exam before discharge on the morning after PSG.

6.1.7.4 Schedule For Open-Label Safety Component (Xyrem®-Naïve At Study Entry)

The schedule for the open-label safety component (extension) is copied below and applies specifically to patients who were Xyrem®-naïve at entry into the study (the schedule for those receiving a stable dose of Xyrem® at study entry is not substantially different).

Events		Open-Label Safety Period with Xyrem										Safety Follow-up
Visits (V) Weeks (W)	V5[a] (4 weeks after end of Double-Blind Treatment Period) ±7 days	V6 W 16 Phone Call ±7 days	V7 W18 ±7 days	V8 W22 ±7 days Phone call	V9 Week 26 ±7 days	V10 W30 ±7 days Phone call	V11 Week 34 ±7 days Phone call	V12 Week 39 ±7 days	V13 Week 43 ±7 days Phone call	V14 Week 48 ±7 days Phone call	Visit 15 Week 52 ±7 days Or Early Termination	V16 14 days after last treatment +3 days
Physical Examination including brief neurological exam											X	
Tanner Stage Assessment											X	
Height	X		X		X			X			X	X
Weight	X		X		X			X			X	X
Chemistry, Hematology											X	
PK subjects only: Coagulation	X[b]											
Urinalysis											X	
Only for Girls ≤8 years: Estradiol, LH, FSH Only for Boys≤9 years: Testosterone, LH, FSH											X	
Urine Drug Screen	X		X		X			X			X	
Alcohol Test	X		X		X			X			X	
Urine Pregnancy test											X	
Study Drug Dosing Diary[c]	→	→	→	→	→	→	→	→	→	→	→	
12-Lead ECG											X	
Vital Signs (blood pressure, pulse/heart rate, body temperature, respiratory rate)[d]	X		X		X			X			X	X
Cataplexy frequency diary[c]	→	→	→	→	→	→	→	→	→	→	→	

Events		Open-Label Safety Period with Xyrem										Safety Follow-up
Visits (V) Weeks (W)	V5[a] (4 weeks after end of Double-Blind Treatment Period) ±7 days	V6 W 16 Phone Call ±7 days	V7 W18 ±7 days	V8 W22 ±7 days Phone call	V9 Week 26 ±7 days	V10 W30 ±7 days Phone call	V11 Week 34 ±7 days Phone call	V12 Week 39 ±7 days	V13 Week 43 ±7 days Phone call	V14 Week 48 ±7 days Phone call	Visit 15 Week 52 ±7 days Or Early Termination	V16 14 days after last treatment +3 days
ESS (CHAD)	X		X		X			X			X	
C-SSRS[e]	X	X	X	X	X	X	X	X	X	X	X	X
Depression scale (CDI2:SR[S])	X	X	X	X	X	X	X	X	X	X	X	X
Anxiety scale (MASC-10)	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life (SF-10)	X		X		X			X			X	
PSG											See Appendix 2.3[f]	
AE Reporting	→	→	→	→	→	→	→	→	→	→	→	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Dispense Study Drug[g]	X		X		X			X				
Collect trial medicine, measure and review compliance	X		X		X			X			X	
PK evaluation	Once the subject has been retitrated and is on a stable dose of Xyrem, PK Nights 1 and 2 can be scheduled for a protocol-specified clinic visit or for an additional clinic visit. See Appendix 3.											

An arrow (→) indicates that the assessment is continuous.

Note: A Xyrem naïve subject is defined as a subject who has never been treated with Xyrem or who was previously treated with Xyrem and discontinued Xyrem for at least one month prior to the Screening visit for reasons other than lack of efficacy and/or tolerability issues (e.g., lost insurance coverage, could not afford Xyrem, changed prescribers).

a) Visit 5 will be conducted 4 weeks after the end of the Double-Blind Treatment Period unless Visit 5 is within 2 weeks of the Week 18 visit. Visits 6-16 will be conducted at Weeks 16, 18, 22, 26, 30, 34, 39, 43, 48, 52, and 54 after Day 1.

b) Coagulation: prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (PTT) collect within 30 days prior to PK Night 1.

c) Recorded daily in electronic diary.

d) Obtain vital signs after the subject has been resting for ≥5 minutes.

e) C-SSRS: Use Since Last Visit version for subjects ≥12 years of age and use Children's versions for children <12 years of age.
f) Early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.
g) Study drug dispensed at study visits in accordance with protocol and as required by State or local regulation.

6.1.7.5 Schedule For Pharmacokinetic Evaluation Procedures

The schedule for pharmacokinetic evaluations (for subjects participating in that component of the study) is below.

Events/Visits	Prior to PK Night 1	PK Night 1[a]	PK Night 2[b]
Informed Consent/Assent for PK evaluation	X		
Coagulation within 30 days prior to PK Night 1[c]	X		
Light dinner >2 hours before dosing[d]		X	X
Confirm Parent(s)/Guardian(s) Contact Information		X	X
Blood samples for PK Assessment[e]		X	X
Vital Signs (blood pressure, pulse/heart rate, body temperature, respiratory rate)[f]		X	X
Pulse Oximetry[g]		X	X
Administer or supervise the administration of Study Drug from subject's study drug supply on PK nights		X[h]	X[i]
Brief neurological exam[j]		X	X
Breakfast (if subject prefers to eat at the study center)		X	X

a) For subjects on Xyrem at study entry participating in PK evaluations during the Stable-Dose Period, PK Night 1 will occur on the night of Day 1. For subjects participating in PK evaluations during the Open-Label Safety Period, PK Night 1 will occur after retitration to a stable dose.

b) For subjects on Xyrem at study entry participating in PK evaluations during the Stable-Dose Period, PK Night 2 will occur within 15 days of PK Night 1. For subjects participating in PK evaluations during the Open-Label Safety Period, there are no restrictions in the timing between PK Nights 1 and 2.

c) Coagulation: prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (PTT).

d) Light dinner taken >2 hours prior to dosing should be the same or similar on both PK Nights. Light meal may be taken at the clinic or at home.

e) Blood samples for sodium oxybate concentrations will be collected at 0 (pre-dose) and 0.75, 1.5, 2.5, 4 (pre-2nd dose), 4.75, and 8 hours after the first dose. Samples taken within ±5 minutes of the protocol specified time points.

f) Obtain vital signs after subject has been resting for ≥5 min. Obtain vital signs at pre-dose. At 1, 4 (pre-2nd dose), 5, and 8 hours after the first Xyrem dose, obtain pulse/heart and respiratory rates.

g) SpO_2 is monitored continuously from immediately before first dose through 8 hours after the first dose, and recorded pre-dose and at 1 h, 2 h, 4 h (pre-2nd dose), 5 h, 6 h, and 8 h after the first dose. An additional measurement will be taken while the subject is awake and before release from the study center.

h) Administer ½ of the subject's usual nightly dose in two equally divided doses, at bedtime and 4 hours later while in bed. Subjects whose equally divided dose does not match a line on the dosing syringe will take the dose that matches the next lower printed line on the dosing syringe (see Section 3.1.7).

i) Administer the subject's nightly dose of Xyrem in two equally divided doses, at bedtime and 4 hours later while in bed. Subjects whose equally divided dose does not match a line on the dosing syringe will take the dose that matches the next lower printed line on the dosing syringe (see Section 3.1.7).

j) Brief neurological exam before discharge on the morning after pharmacokinetic assessment.

6.1.8 Outcome Measures

6.1.8.1 Primary Efficacy Parameter

Change in weekly number of cataplexy attacks during the 2 weeks of the double-blind period, compared with the last 2 weeks of the stable-dose period.

6.1.8.1.1 Further Description Of Primary Efficacy Parameter

The weekly frequency of cataplexy attacks was derived from a diary completed by the patient with the help of a caregiver, if needed.

6.1.8.2 Key Secondary Efficacy Parameters

- Clinical Global Impression of Change for cataplexy severity, comparing the end of the double-blind period with the end of the stable-dose period.

- Change in the modified Epworth Sleepiness Scale score from the end of the stable-dose period to the end of the double-blind period.

6.1.8.2.1 Further Description Of Key Secondary Efficacy Parameters

6.1.8.2.1.1 Clinical Global Impression Of Change For Cataplexy Severity

This parameter was rated based on a 7-point Likert scale, scored as follows

Very much improved: 3.
Much improved: 2.
Minimally improved: 1.
No change: 0.
Minimally worse: -1.
Much worse: -2.
Very much worse: -3.

6.1.8.2.1.2 Epworth Sleepiness Scale For Children And Adolescents

The Epworth Sleepiness Scale for Children and Adolescents is a patient-rated measure of daytime sleepiness. Patients (assisted by their caregivers) are asked to rate their chances of dozing during each of the following 8 activities on a scale from 0-3 (0=never; 1=slight; 2=moderate; 3=high): sitting and reading; sitting and watching TV or a video; sitting quietly in a classroom at school during the morning; sitting or riding as a passenger in a car or bus for about half an hour; lying down to rest or nap in the afternoon; sitting and talking to someone; sitting quietly alone after lunch; and sitting and eating a meal.

6.1.8.3 Other Secondary Efficacy Parameters

- Clinical Global Impression of Change for narcolepsy severity overall comparing the end of the double-blind period with the end of the stable-dose period.

- Change in quality of life (based on the Short Form-10) from the end of the stable-dose period to the end of the double-blind period.

6.1.8.4 Exploratory Efficacy Parameters

- Change in weekly school attendance from the end of the stable-dose period to the end of the double-blind period (if the patient does attend school during that period).

- Patient Global Impression of Change, comparing the end of the double-blind period to the end of the stable-dose period.

6.1.8.5 Safety Measures

Adverse events, vital signs, height, weight, physical examinations, 12-lead electrocardiograms, polysomnographic parameters (including measures of respiration), standard safety laboratory tests (hematology, clinical chemistry, and urinalysis), assessments of growth and precocious puberty (including growth hormone levels), Columbia-Suicide Severity Rating Scale, Children's Depression Inventory 2nd Edition Self-Report Short Version, and Multidimensional Anxiety Scale for Children 10-item Anxiety Index. Serum pregnancy tests.

Plasma carbon dioxide concentrations will also be monitored at sites where such monitoring is routinely performed, and where performance of such monitoring will not have a negative effect on study participation or on polysomnographic data integrity.

A Data Safety Monitoring Board is to review safety data for the study on a regular basis.

6.1.8.6 Pharmacokinetic Measures

Plasma concentrations of sodium oxybate.

6.1.9 Analysis Plan

6.1.9.1 General

The following populations will be used for purposes of analysis.

6.1.9.1.1 Safety Population

This population will consist of all subjects who are dispensed study drug. This population will be used for tabulations and listings of safety data and to summarize efficacy data collected during the double-blind treatment period.

6.1.9.1.2 Pharmacokinetic Half-Dose Population

This population will consist of all subjects who have any pharmacokinetic data for Pharmacokinetic Night 1 when subjects (in the pharmacokinetic analysis subset) receive only half of their usual pre-study dose. This population will be used for listings and for descriptive statistics for the half-dose pharmacokinetic data.

6.1.9.1.3 Pharmacokinetic Full-Dose Population

This population will consist of all subjects who have any pharmacokinetic data for Pharmacokinetic Night 2 when subjects (in the pharmacokinetic analysis subset) receive their usual pre-study dose. This population will be used for listings and descriptive statistics for the full-dose pharmacokinetic data.

6.1.9.1.4 Pharmacokinetic Completer Population

This population will consist of all subjects who have pharmacokinetic data for both pharmacokinetic nights. This population will be used for evaluating within-subject dose proportionality.

6.1.9.2 Efficacy Population

This population will consist of all subjects who are randomized to Xyrem® or Xyrem® placebo and who complete at least 5 days of dosing in the double-blind treatment period. This population will be used as the main analysis population for the primary and secondary efficacy endpoints.

6.1.9.2.1 Randomized Population

This population will consist of all subjects who are randomized to Xyrem® or Xyrem® placebo for the double-blind treatment period of the study. This population will be used to summarize exposure to double-blind treatment and may also be used for summarizing safety data specific to the double-blind treatment period. This population may also be used for an additional analysis of the primary and/or secondary efficacy parameters.

6.1.9.3 Demographic And Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for the safety population, the pharmacokinetic half-dose population, the pharmacokinetic completer population, the randomized population, and the efficacy population. The summaries of data will include numbers and percentages for categorical variables and mean, standard deviation, median, minimum, and maximum for continuous variables.

Tabulations for the randomized and efficacy populations will be by treatment group (as randomized) and for both treatment groups combined. Tables for the randomized population will include a comparison of the treatment groups with categorical variables analyzed by using a Chi-square test and continuous variables analyzed using a one-way analysis of variance model with treatment as the only factor.

6.1.9.4 Handling Of Dropouts And Missing Data

The following methods will be used to handle missing data and data from subjects who discontinue early during double-blind treatment.

- The weekly number of cataplexy attacks will be computed as the average from days with non-missing data, multiplied by 7.
- School attendance will be calculated as the number of missed days, multiplied by 100 and divided by the actual number of school days up to the timepoint of early termination or double-blind treatment period completion.
- The last post-stable-dose period assessment of all other measures will be used as the end-of-double-blind treatment period assessment.

6.1.9.5 Efficacy Parameters

The two treatment groups for the double-blind treatment period will be compared on the efficacy parameters.

Non-categorical efficacy parameters will be analyzed using a non-parametric analysis of covariance. Ordinal categorical parameters will be analyzed using Cochran-Mantel-Haenszel tests for row mean score difference.

To account for multiplicity arising as a consequence of the analysis of the primary endpoint and multiple secondary endpoints, a tiered approach will be used to control the Type 1 family-wise error rate at the two-sided significance level of 0.05 (with an exception for the analysis of the primary endpoint: see below).

Testing will not proceed to the next tier unless Xyrem® is demonstrated to have a statistically significant superiority to placebo as a result of analyses performed at the previous tier level.

The efficacy parameters will be analyzed in the same numerical order as listed below.

6.1.9.5.1 Tier 1: Primary Efficacy Parameter

The primary efficacy parameter is the change in weekly number of cataplexy attacks during the 2 weeks of the double-blind period, compared with the last 2 weeks of the stable dose period.

This parameter will be analyzed at a significance level of 0.048 (two-sided).

6.1.9.5.2 Tier 2: Key Secondary Efficacy Parameter

A key secondary efficacy parameter is the Clinical Global Impression of Change for cataplexy severity comparing the end of the double-blind period with the end of the stable dose period.

This parameter will be analyzed at a significance level of 0.05 (two-sided).

6.1.9.5.3 Tier 3: Key Secondary Efficacy Parameter

Another key secondary efficacy parameter is the change in the modified Epworth Sleepiness Scale score from the end of the stable-dose period to the end of the double-blind period

This parameter will be analyzed at a significance level of 0.05 (two-sided).

6.1.9.5.4 Tier 4: Other Secondary Efficacy Parameter

A secondary efficacy parameter is the Clinical Global Impression of Change for narcolepsy severity overall comparing the end of the double-blind period with the end of the stable dose period

This parameter will be analyzed at a significance level of 0.05 (two-sided).

6.1.9.5.5 Tier 5: Other Secondary Efficacy Parameter

A further secondary efficacy parameter is the change in quality of life (based on the Short Form-10) from the end of the stable-dose period to the end of the double-blind period.

This parameter will be analyzed at a significance level of 0.05 (two-sided).

The analysis of exploratory efficacy endpoints will be conducted without adjustment for multiple comparisons: only the nominal p-value will be reported for those analyses.

6.1.9.6 Pharmacokinetic Parameters

The plasma pharmacokinetic parameters for sodium oxybate are the following: C_{max}, AUC, and T_{max} over the first 4-hour dosing interval. In addition, sodium oxybate concentrations at 4.75 hours and 8 hours after the first nightly dose (0.75 hours and 8 hours after the second dose, respectively) will be measured to estimate peak and residual exposure to sodium oxybate linked to the second nighttime dose.

Plasma sodium oxybate concentrations will be summarized by sampling time point and by pharmacokinetic parameter using descriptive statistics for each age group (i.e., ages 7 to 11 and 12-17) and overall.

Pharmacokinetic parameters will be assessed using analysis of covariance models and natural log-transformed data.

Dose-proportionality is to be assessed based on the ratio of AUC and C_{max} values: the ratios and 90% confidence intervals will be presented. If warranted, regression models will be used to explore the relationship between plasma concentration and dose on a mg/kg basis.

6.1.10 Safety Parameters

Safety data will be summarized using descriptive statistics.

Adverse events will be summarized by treatment group and by dose. Adverse events will be analyzed for sub-populations including the following: Xyrem®-naïve at entry; receiving Xyrem® at entry; 7-11 year age group; and 12-17 year age group.

Safety analyses will also include an evaluation of the nadir oxygen saturation level at each dose and number and duration of confirmed desaturations below 90%, 80%, 70%, 60%, and 50% on polysomnographic nights, excluding the screening polysomnogram.

6.1.10.1 Interim Analysis

An interim analysis is planned to be conducted after 35 subjects complete or discontinue early from the double-blind treatment period. The interim analysis will be conducted by a statistician not directly involved with the design and analysis of the study. The data obtained from the interim analysis will be reviewed by the study's Data Safety Monitoring Board who will recommend whether to continue the study or to halt it early.

Considerations for stopping the study early include the following:

- Treatment success: the O'Brien-Fleming approach will be used with the primary efficacy endpoint which will be tested at a significance level of 0.005 at the interim analysis; if Xyrem® is demonstrated to have a statistically significant superiority to placebo on that analysis, the Data Safety Monitoring Board may then recommend discontinuing the study; however, if the study is not stopped, the final analysis of the primary efficacy parameter will be conducted at a significance level of 0.048 so as to preserve the overall alpha of 0.05.

- Treatment failure: if at the interim analysis, the null hypothesis for the primary efficacy parameter is not rejected at the 0.005 level of significance, a futility analysis will be conducted using a conditional power approach as follows. Assuming that the trend in data observed until the time of the interim analysis will continue until the final analysis, the conditional power of rejecting the null hypothesis at final analysis will be calculated. If the conditional power is less than

15%, it will be concluded that the study is unlikely to demonstrate efficacy and the Data Safety Monitoring Board may then recommend stopping the study. The study may also be discontinued early due to futility.

- Safety concerns: safety data including the incidence of adverse events will be reviewed by the Data Safety Monitoring Board at regular intervals with deaths and serious adverse events getting special scrutiny; based on that review, the Data Safety Monitoring Board may determine if the risk to participating subjects warrants study discontinuation.

An ongoing analysis of pharmacokinetic data will also be conducted to determine if a sufficient number of pharmacokinetic samples have been collected to adequately characterize the pharmacokinetics of Xyrem® in children and adolescents.

6.1.10.2 Sample Size Estimate

At least 100 subjects are to be enrolled in this study so that a minimum of 70 subjects enter the double-blind treatment phase.

A sample size of at least 35 subjects per treatment group entering the double-blind (randomized withdrawal) treatment period is expected to have at least 80% power to detect a difference between treatment groups of 40% in the percentage change in the mean weekly number of cataplexy attacks during the last 2 weeks of the immediately-preceding stable dose period.

6.1.11 Safety Monitoring

The following will be evaluated according to the study schedule outlined earlier: adverse events, vital signs, height, weight, physical examinations, 12-lead electrocardiograms, polysomnographic parameters (including measures of respiration), safety laboratory tests (hematology, clinical chemistry, and urinalysis), assessments of growth and precocious puberty (including growth hormone levels), Columbia-Suicide Severity Rating Scale, Children's Depression Inventory 2nd Edition Self-Report Short Version, and Multidimensional Anxiety Scale for Children 10-item Anxiety Index. Plasma carbon dioxide concentrations will also be monitored at selected sites.

A Data Safety Monitoring Board is to review safety data for the study on a regular basis.

6.2 Results Of Interim Analysis And Subsequent Data Safety Monitoring Board Recommendations

As of November 27, 2015, 35 patients had completed or discontinued early from the double-blind treatment period of this study. The study protocol provided for an interim analysis of efficacy at that timepoint (as already noted above).

For the interim analysis of efficacy, study data were unblinded only for Data Safety Monitoring Board and Clinical Research Organization staff.

The Data Safety Monitoring Board met on February 24, 2016, after reviewing the results of the above interim efficacy analysis and informed the sponsor that the same analysis had demonstrated that Xyrem was superior to placebo in the treatment of cataplexy at a p-value < 0.005. Recommendations were also made by the Data Safety Monitoring Board, as outlined below.

6.2.1 Data Safety Monitoring Board Recommendations Based On Results Of Interim Analysis

The Data Safety Monitoring Board recommended the following based on the results of the interim analysis that was conducted after 35 patients had completed or discontinued the double-blind segment of the study.

- End the double-blind segment of Study 13-005, “as there are adequate data for deriving an inference of benefit in cataplexy.”
- Amend the study protocol to continue the open-label safety segment.
- Continue to enroll subjects in the open-label pharmacokinetic segment (evaluating up to 18 patients in each age-based category).

The results of the above interim analysis led to the original pediatric Written Request being amended and to the issuance of the final pediatric Written Request summarized in Section

6.3 Protocol Amendment (#4) After Interim Analysis

Based on the recommendations of the Data Safety Monitoring Board, the protocol for Study 13-005 was amended in Submission #256 (also submitted on April 18, 2016); this protocol change was designated as Amendment #4 and was dated April 5, 2016.

The main elements of the protocol amendment are below.

6.3.1 Double-Blind Segment Of Study

The double-blind (randomized withdrawal) segment of Study 13-005 is being terminated in accordance with the recommendations of the Data Safety Monitoring Board.

Subjects who have already entered or completed the double-blind segment of the study when the above protocol amendment comes into effect are to follow study procedures for those randomized to double-blind treatment.

The tiered analysis of the secondary efficacy parameters is to be conducted using a one-sided p-value of 0.05, rather than using a two-sided p-value of 0.05 as originally proposed. (Note that in the next protocol amendment, Amendment #5, the tiered analysis of the secondary efficacy parameters reverted to being conducted using a two-sided p-value of 0.05).

Under this amendment, a slight change in the dose-titration regimen for Xyrem®-naïve patients is being instituted. The new regimen is depicted in the table below.

Subject weight	Initiation dose (taken in two equally divided doses)*	Titration regimen	Maximum total nightly dose
<30 kg	≤2 g/night	≤1 g/night/week	6 g/night
≥30 kg – <45 kg	≤3 g/night	≤1 g/night/week	7.5 g/night
≥45 kg	≤4.5 g/night	≤1.5 g/night/week	9 g/night

*At bedtime and 2.5 to 4 hours later. For children who sleep more than 8 hours per night, Xyrem may be given after bedtime, while the child is in bed, in two equally divided doses 2.5 to 4 hours apart.

To facilitate easy comparison, the previous regimen is depicted in the table below.

Subject weight	Initiation dose (taken in two equally divided doses)*	Titration regimen	Maximum total nightly dose
<30 kg	2 g/night	1 g/night/week	6 g/night
≥30 kg – <45 kg	3 g/night	1 g/night/week**	7.5 g/night**
≥45 kg	4.5 g/night	1 or 1.5 g/night/week	9 g/night

*At bedtime and 2.5 to 4 hours later.
**Titration of 1 g/night/week up to 7 g/night and then 0.5 g/night/week final titration permitted.

6.3.2 Open-Label Safety Segment Of Study

The open-label phase of the study will be continued. The study will be continued until at least 100 patients have been enrolled and have had the opportunity to be titrated to an effective Xyrem dose (if Xyrem-naïve) or be treated for at least 1 month at that dose (if receiving Xyrem at study entry).

6.3.3 Open-Label Pharmacokinetic Segment Of Study

The open-label pharmacokinetic segment of the study will continue to enroll patients until the completion of the study. If is not possible to enroll more than 12 patients in each age stratum, the pharmacokinetic analysis is to be conducted using data from additional subjects enrolled at the completion of the study.

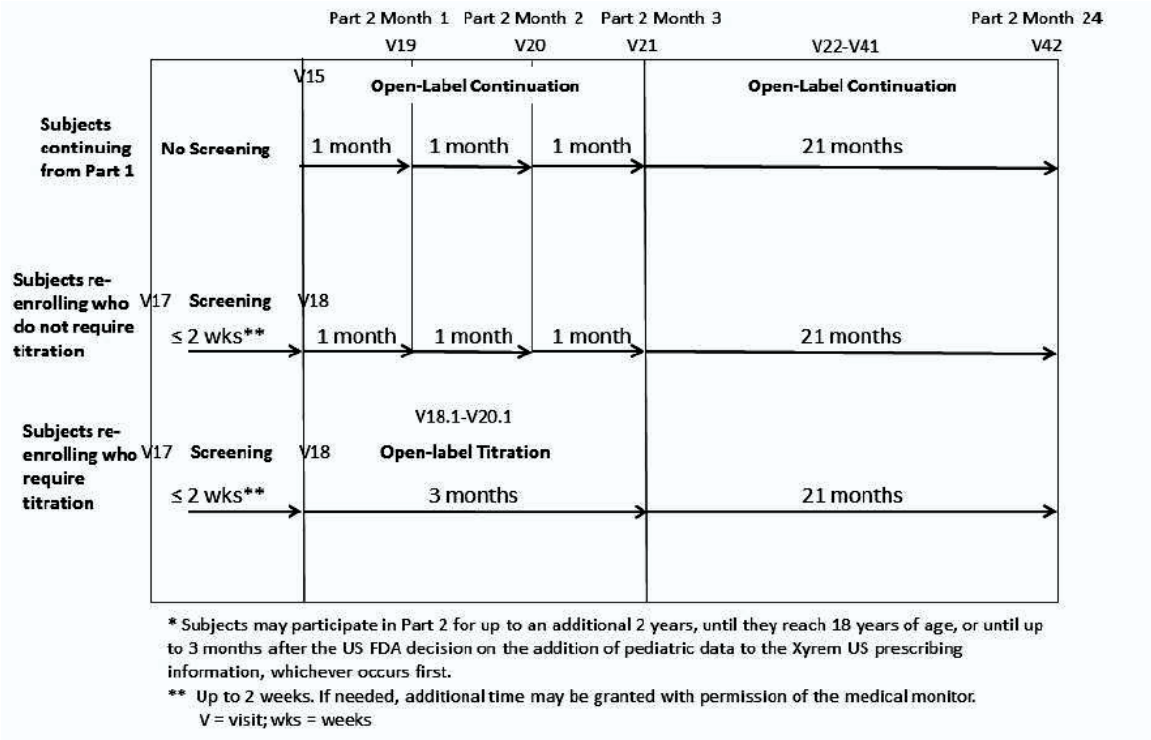
6.4 Subsequent Protocol Amendment: Amendment #5, Dated February 23, 2017 (Submitted To IND 49641 On April 6, 2017, As Serial Number 275)

Under this amendment (set of amendments), this study is divided into 2 parts

- Part 1 lasting up to one year comprises the entire protocol described in Amendment #4 and is the version of the protocol subsumed under the Written Request.

- Part 2 is a further open-label extension to Part 1. In Part 2, , a patient who completes one year of the study in Part 1 will have the opportunity to continue open-label treatment with Xyrem until the first occurrence of any one of the following: an additional 2 years of treatment; the subject reaches 18 years of age; or 3 months have passed after a future Agency decision to add pediatric information to the US Prescribing Information for Xyrem. The total duration of a subject's treatment will thus be up to 3 years. Note that a patient who has earlier completed Part 1 also has the opportunity to complete Part 2; such a patient may or may not require re-titration of Xyrem®.

The schema for Part 2 is summarized below.



Assessments during Part 2 will continue at monthly intervals and will be similar to those for Part 1.

6.5 Study Results

This study was conducted at a total of 30 sites in 5 countries. The countries in which the study was conducted were as follows: the United States (25 sites), France (2 sites), Italy (1 site), the Netherlands (1 site), and Finland (1 site).

6.5.1 Disposition

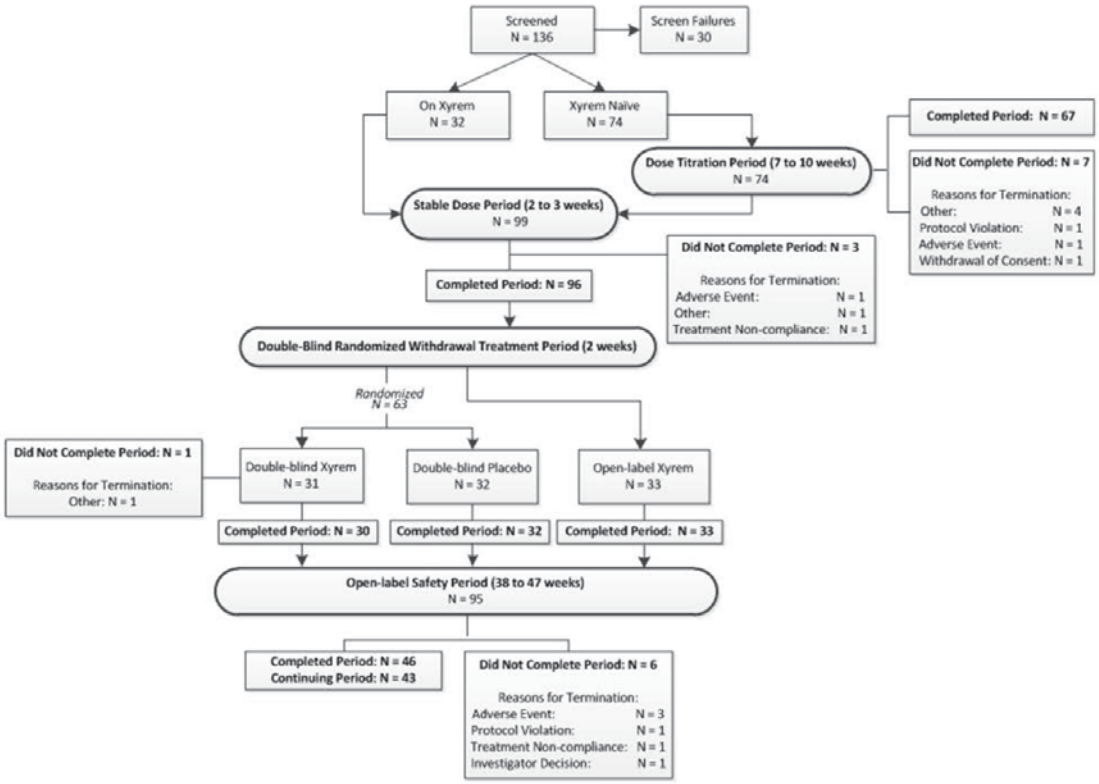
136 patients were screened for this study. 106 patients were then enrolled: of those patients, 74 were Xyrem®-naïve and 32 had previously been exposed to Xyrem®.

99 patients entered the stable-dose period, with 96 of those patients completing that period. Of the 96 patients who completed the stable-dose period, 63 patients participated in the randomized, double-blind, withdrawal phase of the study, whereas the remaining 33 patients continued to take open-label Xyrem.

During the randomized, double-blind, withdrawal phase, 31 patients were assigned to Xyrem® (30 patients completed that phase) and 32 patients were assigned to placebo (all 32 patients completed that phase).

95 patients then entered the open-label safety period (for Part 1 of the study). At the cut-off date (February 10, 2017) for the submission of the report of that study with the original sNDA submission, 46 patients had completed Part 1 of the study, whereas 43 patients were continuing in that phase. As of February 10, 2017, 17 patients had withdrawn from the study.

The disposition of study subjects is summarized in the following graphic which I have copied from the submission.



6.5.2 Protocol Deviations

A total of 42 major protocol deviations were noted in this study. I have reviewed those deviations. None appear to have been significant enough to warrant the exclusion of subjects from the efficacy population.

6.5.3 Study Populations

These are summarized in the following sponsor table.

	Age Group[a]		Xyrem Status[b]		Total
	7 to 11 years	12 to 17 years	Xyrem Naïve	On Xyrem at Entry	
Population	N = 38	N = 68	N = 74	N = 32	N = 106
Safety Population	38 (100.0)	68 (100.0)	74 (100.0)	32 (100.0)	106 (100.0)
PK Population	11 (28.9)	18 (26.5)	18 (24.3)	11 (34.4)	29 (27.4)
PK Half-dose Population	11 (28.9)	18 (26.5)	18 (24.3)	11 (34.4)	29 (27.4)
PK Full-dose Population	11 (28.9)	18 (26.5)	18 (24.3)	11 (34.4)	29 (27.4)
Efficacy Population	26 (68.4)	37 (54.4)	39 (52.7)	24 (75.0)	63 (59.4)
Per Protocol Population	26 (68.4)	37 (54.4)	39 (52.7)	24 (75.0)	63 (59.4)
Randomized Population	26 (68.4)	37 (54.4)	39 (52.7)	24 (75.0)	63 (59.4)

[a] Age in years at the first dispensation of study drug.
[b] Xyrem status at the time of study entry.
Note: The Safety Population consists of all subjects who were dispensed study drug. All 29 subjects completed both night 1 and night 2 of the PK assessments, and therefore the PK Half-dose population, the PK Full-dose population, and the PK Completers population were equivalent; therefore, the PK population is displayed here for simplicity. The Efficacy Population consists of subjects randomized to Xyrem or Placebo who completed at least 5 days of dosing in the Double-blind Treatment Period. The Per Protocol Population includes subjects in the Efficacy Population without a relevant major protocol deviation. The Randomized Population consists of all subjects who were randomized to either Xyrem or Xyrem Placebo for the Double-blind Treatment Period.

6.5.4 Demographic Characteristics For Several Study Populations

The next sponsor table summarizes demographic characteristics for the efficacy, safety, and pharmacokinetic populations. Age was adequately matched across the treatment groups for the efficacy populations.

	Efficacy Population		Safety Population	PK Population
	Placebo[a] N = 32	Xyrem[a] N = 31	N = 106	N = 29
Age (years)[b]				
n	32	31	106	29
Mean (SD)	11.8 (2.48)	11.6 (2.54)	11.9 (2.42)	12.0 (2.35)
Median	12.0	12.0	12.0	12.0
Min, Max	7, 16	7, 16	7, 16	8, 16
Age Group, n (%)				
7 to 11 years	14 (43.8)	12 (38.7)	38 (35.8)	11 (37.9)
12 to 17 years	18 (56.3)	19 (61.3)	68 (64.2)	18 (62.1)
Sex, n (%)				
Male	17 (53.1)	18 (58.1)	63 (59.4)	22 (75.9)
Female	15 (46.9)	13 (41.9)	43 (40.6)	7 (24.1)
Race, n (%)				
Asian	1 (3.1)	1 (3.2)	3 (2.8)	0
Black / African American	7 (21.9)	4 (12.9)	25 (23.6)	1 (3.4)
White	23 (71.9)	25 (80.6)	73 (68.9)	27 (93.1)
Other	1 (3.1)	1 (3.2)	5 (4.7)	1 (3.4)
Ethnicity, n (%)				
Hispanic / Latino	2 (6.3)	0	6 (5.7)	0
Not Hispanic / Latino	30 (93.8)	31 (100.0)	100 (94.3)	29 (100.0)
Country, n (%)				
USA	17 (53.1)	16 (51.6)	62 (58.5)	10 (34.5)
Finland	0	0	1 (0.9)	0
France	3 (9.4)	4 (12.9)	10 (9.4)	0
Italy	9 (28.1)	9 (29.0)	25 (23.6)	19 (65.5)
Netherlands	3 (9.4)	2 (6.5)	8 (7.5)	0

Abbreviations: Max = maximum; Min = minimum; N = the total number of subjects in the population, PK = pharmacokinetic.

[a] Randomized treatment assigned during the Double-blind Treatment Period

[b] Age in years at the first dispensation of study drug.

Note: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who completed at least 5 days of dosing in the Double Blind Treatment Period. The Safety Population consists of all subjects who were dispensed study drug. For the PK population, all 29 subjects completed both Night 1 and Night 2 of the PK assessments; therefore the PK Half-dose population, the PK Full-dose population, and the PK Completers population were equivalent. Data for the PK population is displayed here for simplicity.

6.5.5 Previous Xyrem® Experience

The previous Xyrem® experience at baseline is summarized for various study populations in the table below. The two treatment groups for the randomized, double-blind, placebo-controlled, withdrawal phase were reasonably matched in that respect.

	Efficacy Population		Safety Population	PK Population
	Placebo[a] N = 32	Xyrem[a] N = 31	N = 106	N = 29
Xyrem Status at Entry, n (%)				
Xyrem Naïve	19 (59.4)	20 (64.5)	74 (69.8)	18 (62.1)
On Xyrem at Entry	13 (40.6)	11 (35.5)	32 (30.2)	11 (37.9)
Unequal Nighttime Dosages for Subjects on Xyrem at Study Entry[b]	1 (7.7)	1 (9.1)	4 (12.5)	0
Months of Previous Xyrem Exposure				
n	14[c]	11	33	11
Mean (SD)	19.93 (14.414)	24.64 (19.185)	18.24 (15.953)	17.82 (17.566)
Median	12.50	15.00	12.00	12.00
Min, Max	7.0, 52.0	2.0, 49.0	2.0, 52.0	2.0, 48.0

Abbreviations: Max = maximum; Min = minimum; N = the total number of subjects in the population.
[a] Randomized treatment assigned during the Double-blind Treatment Period.
[b] Subjects on Xyrem at study entry could maintain their typical dosing pattern during the Stable Dose Period, which could include 2 unequal dosages during the night. Percentages are calculated using the number of subjects on Xyrem.
[c] One subject (Subject (b) (6)) received Xyrem prior to entering the study, and due to the amount of time between previous Xyrem exposure and start of the study, the subject was considered to be Xyrem naïve (ADSL dataset).
Note: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who completed at least 5 days of dosing in the Double Blind Treatment Period.

6.5.6 Baseline Disease Characteristics

The sponsor table below summarizes baseline disease characteristics and is self-explanatory. The two treatment groups for the randomized, double-blind, placebo-controlled withdrawal phase were evenly matched for the following more significant characteristics: years since narcolepsy diagnosis, narcolepsy symptoms experienced previously, overall severity of narcolepsy, baseline cataplexy severity, and baseline modified Epworth Sleepiness Scale (ESS) score.

	Efficacy Population		Safety Population	PK Population
	Placebo[a] N = 32	Xyrem[a] N = 31	N = 106	N = 29
Years from Narcolepsy Diagnosis to Screening				
n	32	31	106	29
Mean (SD)	1.94 (1.576)	1.92 (2.169)	1.86 (1.946)	1.42 (1.662)
Median	1.63	0.99	1.21	0.64
Min, Max	0.0, 4.9	0.0, 8.0	0.0, 10.4	0.0, 5.1
Narcolepsy Symptoms Experienced Prior to any Narcolepsy Treatment[b], n (%)				
Cataplexy	32 (100.0)	31 (100.0)	106 (100.0)	29 (100.0)
Excessive daytime sleepiness	32 (100.0)	31 (100.0)	106 (100.0)	29 (100.0)
Hypnagogic and / or Hypnopompic Hallucinations	16 (50.0)	16 (51.6)	60 (56.6)	12 (41.4)
Sleep Paralysis	8 (25.0)	8 (25.8)	37 (34.9)	9 (31.0)
Disrupted Nighttime Sleep	25 (78.1)	27 (87.1)	89 (84.0)	28 (96.6)
Current Narcolepsy Symptoms[b], n (%)				
Cataplexy	30 (93.8)	30 (96.8)	103 (97.2)	29 (100.0)
Excessive daytime sleepiness	31 (96.9)	27 (87.1)	99 (93.4)	26 (89.7)
Hypnagogic and / or Hypnopompic Hallucinations	12 (37.5)	11 (35.5)	44 (41.5)	5 (17.2)
Sleep Paralysis	5 (15.6)	5 (16.1)	28 (26.4)	6 (20.7)
Disrupted Nighttime Sleep	22 (68.8)	20 (64.5)	76 (71.7)	23 (79.3)
Typical Bedtime, n (%)				
20:00 to 21:59	19 (59.4)	20 (64.5)	60 (56.6)	10 (34.5)
22:00 to 23:59	13 (40.6)	11 (35.5)	43 (40.6)	19 (65.5)
00:00 to 02:00	0	0	3 (2.8)	0
Typical Hours of Sleep per Night				
n	32	31	106	29
Mean (SD)	09:16 (00:55)	09:14 (00:57)	09:11 (00:58)	08:50 (00:33)
Median	09:00	09:15	09:00	09:00
Min, Max	07:30, 11:15	07:30, 11:30	06:00, 12:00	07:50, 10:00
CGIs for Historical Condition Prior to any Narcolepsy Treatment				
Narcolepsy Overall Severity, n (%)				
0 = Normal; no signs of illness	0	0	0	0
1 = Borderline ill	0	0	1 (0.9)	0
2 = Slightly ill	0	1 (3.2)	2 (1.9)	0
3 = Moderately ill	5 (15.6)	5 (16.1)	17 (16.0)	1 (3.4)
4 = Markedly ill	19 (59.4)	17 (54.8)	56 (52.8)	22 (75.9)
5 = Severely ill	8 (25.0)	7 (22.6)	25 (23.6)	6 (20.7)
6 = Among the most Extremely ill	0	1 (3.2)	5 (4.7)	0
Mean (SD)	4.1 (0.64)	4.1 (0.81)	4.1 (0.86)	4.2 (0.47)

	Efficacy Population		Safety Population	PK Population
	Placebo[a] N = 32	Xyrem[a] N = 31	N = 106	N = 29
Cataplexy Severity, n (%)				
0 = Normal; no signs of illness	0	0	0	0
1 = Borderline ill	1 (3.1)	0	1 (0.9)	1 (3.4)
2 = Slightly ill	1 (3.1)	1 (3.2)	4 (3.8)	0
3 = Moderately ill	5 (15.6)	5 (16.1)	25 (23.6)	3 (10.3)
4 = Markedly ill	17 (53.1)	15 (48.4)	49 (46.2)	21 (72.4)
5 = Severely ill	7 (21.9)	7 (22.6)	22 (20.8)	4 (13.8)
6 = Among the most Extremely ill	1 (3.1)	3 (9.7)	5 (4.7)	0
Mean (SD)	4.0 (0.97)	4.2 (0.95)	4.0 (0.94)	3.9 (0.75)
Baseline ESS (CHAD)[c]				
n	32	31	106	29
Mean (SD)	13.9 (3.86)	13.2 (4.69)	14.3 (4.18)	13.8 (4.10)
Median	14.0	13.0	14.0	13.0
Min, Max	6, 22	5, 22	5, 22	6, 22
0 to 10 (Normal), n (%)	7 (21.9)	9 (29.0)	21 (19.8)	5 (17.2)
11 to 12 (Mildly Increased), n (%)	3 (9.4)	6 (19.4)	14 (13.2)	8 (27.6)
13 to 15 (Moderately Increased), n (%)	11 (34.4)	7 (22.6)	28 (26.4)	7 (24.1)
≥ 16 (Greatly Increased), n (%)	11 (34.4)	9 (29.0)	43 (40.6)	9 (31.0)
Baseline SF-10 Physical Summary Score				
n	30	30	99	28
Mean (SD)	41.56 (13.802)	43.04 (14.045)	42.61 (13.359)	45.16 (13.069)
Median	46.19	48.47	47.00	48.47
Min, Max	-0.9, 57.2	10.4, 57.2	-0.9, 57.2	-0.9, 57.2
Baseline SF-10 Psychosocial Summary Score				
n	30	30	99	28
Mean (SD)	49.48 (8.043)	50.96 (8.933)	50.35 (8.110)	53.27 (6.393)
Median	51.59	52.93	51.59	54.26
Min, Max	35.5, 59.6	32.9, 62.3	32.9, 62.3	34.7, 62.3

Abbreviations: CHAD = children and adolescents; ESS = Epworth Sleepiness Scale; Max = maximum; Min = minimum; N = the total number of subjects in the population.
[a] Randomized treatment assigned during the Double-blind Treatment Period.
[b] Subjects may have experienced more than one of the narcolepsy symptoms. Subjects are counted in each row according to the symptoms experienced.
[c] Note that some subjects were on Xyrem at baseline and the majority were taking stimulants.
Note: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who completed at least 5 days of dosing in the Double Blind Treatment Period.

6.5.7 Exposure To Xyrem®

The total exposure to Xyrem® over all treatment periods in the safety population during this study is summarized in the next sponsor table.

	Age (years)[a]		Xyrem Status at Study Entry		Total
	7 to 11 N = 38	12 to 17 N = 68	Xyrem Naïve N = 74	On Xyrem N = 32	N = 106
Duration of Xyrem Usage (days)[b]					
n	37	67	72	32	104
Mean (SD)	288.2 (108.09)	256.2 (114.83)	256.7 (122.01)	292.2 (86.21)	267.6 (113.00)
Median	350.0	306.0	331.5	339.0	332.0
Q1, Q3	253.0, 355.0	138.0, 358.0	141.5, 357.0	246.0, 356.0	170.5, 357.0
Cumulative Xyrem Dosage Received (g)[c]					
n	37	67	72	32	104
Mean (SD)	1464.699 (705.8272)	1502.194 (834.3530)	1461.639 (846.4565)	1550.089 (644.3295)	1488.854 (787.7335)
Median	1543.000	1626.000	1592.625	1736.000	1607.250
Q1, Q3	1056.500, 1937.750	801.500, 2246.000	803.000, 2220.625	1154.250, 2019.300	859.250, 2112.875

Abbreviations: Q1 = first quartile; Q3 = third quartile.
[a] Age in years at the first dispensation of study drug.
[b] For subjects who received Xyrem during the Double-blind Treatment Period, this duration was the same as the Total Duration of Dosing. For subjects who received Placebo during the Double-blind Treatment Period, Total Duration of Xyrem Usage equaled the Total Duration of Dosing minus Duration of Treatment during the Double-blind Treatment Period.

The extent of study drug exposure during the stable dose period in the safety population (who had study drug dispensed during that period) is in the next sponsor table. Note that the lowest individual total nightly dose of Xyrem® dispensed during that period was 3 grams.

	Age (years)[a]		Xyrem Status at Study Entry		Total
	7 to 11 N = 36	12 to 17 N = 63	Xyrem Naïve N = 67	On Xyrem N = 32	N = 99
Stable Dose Period Dosage Dispensed (g/night)					
n	36	63	67	32	99
Mean (SD)	6.007 (1.7139)	6.996 (1.4732)	6.922 (1.7458)	6.039 (1.1607)	6.636 (1.6281)
Median	6.000	7.000	7.500	6.000	7.000
Q1, Q3	4.500, 7.250	6.000, 8.000	5.500, 8.500	5.000, 7.000	5.500, 8.000
Min, Max	3.00, 9.00	3.75, 9.00	3.00, 9.00	3.50, 7.50	3.00, 9.00
Stable Dose Period Dosage Dispensed (mg/kg/night)[b]					
n	36	63	67	32	99
Mean (SD)	141.447 (53.3810)	105.669 (30.5447)	117.640 (36.3483)	120.855 (56.6481)	118.679 (43.6711)
Median	127.275	102.612	111.421	110.346	111.317
Q1, Q3	104.818, 176.619	83.519, 127.592	91.019, 142.857	78.265, 139.876	87.940, 142.276
Min, Max	64.81, 304.88	46.51, 182.19	46.58, 239.73	46.51, 304.88	46.51, 304.88

Abbreviations: Q1 = first quartile; Q3 = third quartile.
[a] Age in years at the first dispensation of study drug.
[b] Calculated as Xyrem dosage (g/night) * 1000 / weight (kg), where the weight is the value collected closest to but prior to or on the date of Visit 2 (Start of the Stable Dose Period).
Note: The Safety Population consists of all subjects who were dispensed study drug.

The extent of exposure to individual nightly doses of Xyrem® and its placebo equivalent in those randomized during the double-blind treatment period (and in those who received open-label Xyrem® concurrently) is in the next sponsor table, which is self-explanatory; note that the minimum dose of Xyrem® taken during that period was 3.0 grams/night.

	Treatment Received				
	Randomized Placebo [1] (N=32)	Randomized Xyrem [1] (N=31)	OL Xyrem (N=33)	All Xyrem (N=64)	Total (N=96)
Double-Blind Treatment Period Dose Level Dispensed (g/night)					
n	32	31	33	64	96
Mean (Std. Dev.)	6.672 (1.5534)	6.492 (1.6412)	6.576 (1.7650)	6.535 (1.6932)	6.581 (1.6410)
Median	6.750	7.000	7.000	7.000	7.000
Q1, Q3	5.750, 7.500	5.000, 7.500	5.500, 8.000	5.250, 8.000	5.500, 7.500
Min - Max	3.50 - 9.00	3.00 - 9.00	3.00 - 9.00	3.00 - 9.00	3.00 - 9.00
3 g/night, n (%)	0	1 (3.2)	1 (3.0)	2 (3.1)	2 (2.1)
3.5 g/night, n (%)	2 (6.3)	0	0	0	2 (2.1)
3.75 g/night, n (%)	0	1 (3.2)	1 (3.0)	2 (3.1)	2 (2.1)
4 g/night, n (%)	0	1 (3.2)	3 (9.1)	4 (6.3)	4 (4.2)
4.5 g/night, n (%)	2 (6.3)	2 (6.5)	2 (6.1)	4 (6.3)	6 (6.3)
5 g/night, n (%)	2 (6.3)	3 (9.7)	1 (3.0)	4 (6.3)	6 (6.3)
5.5 g/night, n (%)	2 (6.3)	3 (9.7)	1 (3.0)	4 (6.3)	6 (6.3)
6 g/night, n (%)	4 (12.5)	2 (6.5)	6 (18.2)	8 (12.5)	12 (12.5)
6.25 g/night, n (%)	0	0	1 (3.0)	1 (1.6)	1 (1.0)
6.5 g/night, n (%)	4 (12.5)	2 (6.5)	0	2 (3.1)	6 (6.3)
7 g/night, n (%)	4 (12.5)	5 (16.1)	3 (9.1)	8 (12.5)	12 (12.5)
7.5 g/night, n (%)	6 (18.8)	4 (12.9)	4 (12.1)	8 (12.5)	14 (14.6)
8 g/night, n (%)	0	2 (6.5)	3 (9.1)	5 (7.8)	5 (5.2)
8.5 g/night, n (%)	1 (3.1)	2 (6.5)	3 (9.1)	5 (7.8)	6 (6.3)
9 g/night, n (%)	5 (15.6)	3 (9.7)	4 (12.1)	7 (10.9)	12 (12.5)

Note: The Safety Population consists of all subjects who were dispensed study drug.
N= the total number of subjects in the population. Percentages are calculated using the N value.
[1] Subjects receive randomized treatment of Placebo or Xyrem.
[2] Calculated as Xyrem dosage [g/night] * 1000 / weight (kg), where the weight is the value collected closest to but prior to or on the date of Visit 2 (Start of the Stable-Dose Period).

6.5.8 Extent Of Stimulant Use

The extent of stimulant use during the stable dose phase and the open-label treatment period is in the next sponsor table, which I have copied from the submission.

	Stable Dose Period N = 99	**Double-blind Treatment Period N = 96**
Number of subjects prescribed stimulants, n (%)	55 (56.1)	53 (55.8)
Number of subjects who took all doses of prescribed stimulants, n (%)	39 (70.9)	40 (75.5)
Number of subjects who took a portion of prescribed stimulants, n (%)	14 (25.5)	12 (22.6)
Centrally Acting Sympathomimetics	49 (49.5)	47 (49.0)
Methylphenidate / methylphenidate hydrochloride [a]	18 (18.2)	18 (18.8)
Modafinil	17 (17.2)	16 (16.7)
Armodafinil	7 (7.1)	7 (7.3)
Obetrol / Amfetamine Sulfate [b]	11 (11.1)	10 (10.4)
Lisdexamfetamine mesilate	1 (1.0)	1 (1.0)

[a] One subject (Subject (b) (6) was prescribed Methylphenidate and Methylphenidate hydrochloride (Listing 16.2.4.4).
[b] One subject (Subject (b) (6) was prescribed Obetrol and Amfetamine Sulfate (Listing 16.2.4.4).

Importantly, during the double-blind treatment period, stimulant use occurred in 18/32 (56.3%) of patients who received placebo and 17/31 (54.8%) of patients who received Xyrem®.

6.5.9 Treatment Compliance

Treatment compliance by study period for the safety population is in the next sponsor table. Treatment compliance was matched in the 2 treatment groups during the double-blind withdrawal phase.

	Dose Titration Period	Stable Dose Period	Double-blind Treatment Period			Open-label Safety Period
	Total N = 74	Total N = 99	Randomized Placebo N = 32	Randomized Xyrem N = 31	Open-label Xyrem N = 33	Total N = 95
Percent Compliance[a]						
n	71	98	32	31	32	94
Mean (SD)	83.99 (16.448)	87.77 (15.775)	93.73 (7.836)	92.81 (10.653)	80.82 (17.553)	81.78 (17.202)
Median	89.20	93.30	96.40	100.00	82.70	88.20
Q1, Q3	79.60, 95.00	85.30, 96.70	86.95, 100.00	92.30, 100.00	74.15, 96.90	76.30, 93.10
< 75%, n (%)	14 (18.9)	11 (11.1)	1 (3.1)	3 (9.7)	8 (24.2)	21 (22.1)
≥ 75% to ≤ 90%, n (%)	24 (32.4)	27 (27.3)	9 (28.1)	4 (12.9)	15 (45.5)	34 (35.8)
> 90%, n (%)	33 (44.6)	60 (60.6)	22 (68.8)	24 (77.4)	9 (27.3)	39 (41.1)
Missing, n (%)	3 (4.1)	1 (1.0)	0	0	1 (3.0)	1 (1.1)
Bottle Weight Percent Compliance[b]						
n	68	96	32	31	33	50
Mean (SD)	88.49 (18.100)	100.19 (13.322)	105.46 (5.948)	101.74 (10.324)	98.33 (17.464)	101.51 (12.681)
Median	94.00	101.60	104.70	102.70	101.00	101.85
Q1, Q3	74.70, 102.55	97.05, 104.55	102.60, 109.35	101.20, 107.00	95.20, 104.60	97.60, 104.40
< 75%, n (%)	17 (23.0)	4 (4.0)	0	1 (3.2)	2 (6.1)	1 (1.1)
≥ 75% to ≤ 90%, n (%)	13 (17.6)	5 (5.1)	0	1 (3.2)	4 (12.1)	3 (3.2)
> 90%, n (%)	38 (51.4)	87 (87.9)	32 (100.0)	29 (93.5)	27 (81.8)	46 (48.4)
Missing, n (%)	6 (8.1)	3 (3.0)	0	0	0	45 (47.4)

Abbreviations: Q1 = first quartile; Q3 = third quartile.

[a] Percent compliance was determined using the daily morning diaries. Subjects were expected to take 2 doses of medication per night. Percent compliance was calculated as the number of doses taken during the period and divided by 2 times the number of days in the period, starting from the first dispense to the last date in the treatment period.

[b] Bottle Weight compliance is calculated as the amount taken during the period (measured in mL) based on the amount actually taken, determined by the total amount dispensed and the total amount returned in the bottles dispensed during the period and divided by the expected amount to be taken. Note the required estimation performed to measure amount of study drug returned in the bottles. See Section 9.4.8.

6.5.10 Efficacy Results

All efficacy analyses were conducted according to the study protocol. The results that are summarized below are those of the final efficacy analyses (and do not include those of the interim efficacy analysis, already briefly mentioned above in Section 6.2 and further described below in Section 10.1)

6.5.10.1 Primary Efficacy Analysis

The primary efficacy analysis (or Tier 1 of the hierarchical series of efficacy analyses that were conducted) compared the Xyrem® and placebo groups on the change in weekly frequency of all cataplexy attacks from baseline (the last 2 weeks of the stable dose period) over the randomized, double-blind, placebo-controlled, withdrawal period.

The results of the primary efficacy analysis are in the next sponsor table. As the table indicates, a statistically significant superiority of Xyrem® over placebo was seen on this measure, with a greater increase in cataplexy frequency in those administered placebo than in those continuing Xyrem® during the randomized, double-blind, placebo-controlled withdrawal period.

Weekly Number of Cataplexy Attacks	Placebo N = 32	Xyrem N = 31
Baseline [a] (Last 2 weeks of Stable Dose Period)		
n	32	31
Mean (SD)	16.59 (33.162)	9.60 (13.839)
Median	4.67	3.50
Q1, Q3	1.00, 11.00	0.58, 10.77
Double-blind Treatment Period		
Weekly Number of Cataplexy Attacks[b]		
n	32	31
Mean (SD)	33.96 (46.290)	12.11 (17.361)
Median	21.25	3.77
Q1, Q3	6.93, 26.35	1.50, 17.73
Change from Baseline		
n	32	31
Mean (SD)	17.37 (23.887)	2.52 (7.115)
Median	12.71	0.27
Q1, Q3	3.44, 19.77	-1.00, 2.50
p-value[c]	< 0.0001	

Abbreviations: N= the total number of subjects in the population; Q1 = first quartile; Q3 = third quartile.
[a] Baseline number is calculated from the last 14 days of the Stable Dose Period.
[b] Weekly number is calculated from all days within the Double-blind Treatment Period.
[c] P-value from rank-based analysis of covariance (ANCOVA) with treatment as a factor and baseline count as a covariate.
Notes: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who complete at least 5 days of dosing in the Double-blind Treatment Period. This is the Tier 1 endpoint. Further statistical testing of Tier 2 to Tier 5 endpoints was conditional on meeting statistical significance for the Tier 1 endpoint; see

Subgroup analyses showed that the above effect was also seen within the two age-group categories: 7 to 11 years, and 12 to 17 years. The results of the subgroup analyses are in the next sponsor table.

Weekly Number of Cataplexy Attacks	7 to 11 years N = 26		12 to 17 years N = 37	
	Placebo N = 14	Xyrem N = 12	Placebo N = 18	Xyrem N = 19
Baseline [a] (Last 2 weeks of Stable Dose Period)				
n	14	12	18	19
Mean (SD)	19.14 (34.292)	12.39 (17.968)	14.61 (33.116)	7.83 (10.649)
Median	5.63	3.00	2.80	4.00
Q1, Q3	2.15, 12.92	0.50, 19.36	0.00, 7.50	1.62, 10.00
Double-blind Treatment Period				
Entire Period [b]				
n	14	12	18	19
Mean (SD)	42.58 (49.313)	16.02 (24.138)	27.25 (44.032)	9.64 (11.386)
Median	22.27	3.25	15.50	6.53
Q1, Q3	14.58, 61.00	1.33, 26.75	5.25, 22.50	1.62, 10.00
Change from Baseline				
n	14	12	18	19
Mean (SD)	23.45 (20.765)	3.63 (10.311)	12.64 (25.626)	1.81 (4.249)
Median	18.32	0.13	9.39	0.58
Q1, Q3	7.58, 35.75	-1.15, 2.05	1.08, 16.12	-0.88, 2.58
p-value [c]	0.0001		0.0044	

Abbreviations: N= the total number of subjects in the population; Q1 = first quartile; Q3 = third quartile.
[a] Baseline number is calculated from the last 14 days of the Stable Dose Period.
[b] Weekly number is calculated from all days within the Double-blind Treatment Period. Missing values in the Double-blind Treatment Period are imputed using the value from the Stable Dose Period (baseline observation carried forward).
[c] P-value from rank-based analysis of covariance (ANCOVA) with treatment as a factor and rank baseline count as a covariate. The p-values for the subgroup analyses are considered exploratory.
Notes: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who complete at least 5 days of dosing in the Double-blind Treatment Period.

6.5.10.2 Analysis Of Key Secondary Efficacy Endpoints

6.5.10.2.1 Clinical Global Impression Of Change For Cataplexy Severity

Tier 2 of the hierarchical sequence of efficacy analyses stipulated in the study protocol analyzed scores on the Clinical Global Impression of Change for cataplexy severity. This analysis compared the end of the randomized, double-blind, placebo-controlled withdrawal period with the end of the stable dose period.

The results of the analysis of that measure are summarized in the following table provided by the sponsor. Xyrem® displayed a statistically significant superiority to placebo on that measure: cataplexy became more severe in patients receiving placebo than in those continuing Xyrem® during that period.

	Placebo N = 32		Xyrem N = 31
Response, n (%)			
Total Observed[a]	32		29
Very Much Worse (-3)	4 (12.5)		1 (3.4)
Much Worse (-2)	17 (53.1)		4 (13.8)
Minimally Worse (-1)	7 (21.9)		6 (20.7)
No Change (0)	2 (6.3)		15 (51.7)
Minimally Improved (1)	0		1 (3.4)
Much Improved (2)	2 (6.3)		2 (6.9)
Very Much Improved (3)	0		0
Missing	0		2
Mean (SD)	-1.5 (1.19)		-0.4 (1.12)
p-value[b]		0.0006	
Much Worse or Very Much Worse	21 (65.6)		5 (17.2)
p-value[c]		0.0001	

Abbreviations: CGIc = Clinical Global Impression of Change
[a] Percentages were calculated using the total number of observed values.
[b] P-value from Cochran-Mantel-Haenszel (CMH) test for Row Mean Scores Difference.
[c] P-value from Pearson's chi-square test. P-value is considered exploratory.
Notes: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who complete at least 5 days of dosing in the Double-blind Treatment Period. The CGIc for cataplexy severity is evaluated at the end of the Double-blind Treatment Period. Scores associated with the responses are mapped to 3 for very much improved, to -3 for very much worse.

6.5.10.2.2 Change In Epworth Sleepiness Scale (For Children And Adolescents) Score

Tier 3 of the hierarchical sequence of efficacy analyses stipulated in the study protocol compared the change in modified Epworth Sleepiness Scale score from the end of the stable-dose period to the end of the double-blind randomized withdrawal period between the Xyrem® and placebo groups. The results of that analysis are in the next sponsor table. A statistically significant superiority of Xyrem® over placebo was seen on this parameter for which scores increased in those receiving placebo to a greater extent than in those who continued to receive Xyrem®.

	Placebo N = 32	Xyrem N = 31
Baseline Value[a] (Visit 3 - End of Stable Dose Period)		
n	31	30
Mean (SD)	10.4 (3.80)	8.5 (4.35)
Median	11.0	8.0
Q1, Q3	7.0, 13.0	6.0, 11.0
0 to 10 (Normal), n (%)	15 (48.4)	22 (73.3)
11 to 12 (Mildly Increased), n (%)	6 (19.4)	4 (13.3)
13 to 15 (Moderately Increased), n (%)	8 (25.8)	1 (3.3)
≥ 16 (Greatly Increased), n (%)	2 (6.5)	3 (10.0)
Visit 4 (End of Double-blind Treatment Period)[b]		
Observed Value		
n	31	30
Mean (SD)	13.2 (4.03)	9.2 (4.81)
Median	12.0	9.0
Q1, Q3	11.0, 16.0	6.0, 11.0
0 to 10 (Normal), n (%)	7 (22.6)	21 (70.0)
11 to 12 (Mildly Increased), n (%)	9 (29.0)	3 (10.0)
13 to 15 (Moderately Increased), n (%)	5 (16.1)	3 (10.0)
≥ 16 (Greatly Increased), n (%)	10 (32.3)	3 (10.0)
Change from Baseline		
n	31	30
Mean (SD)	2.8 (3.68)	0.7 (3.22)
Median	3.0	0.0
Q1, Q3	1.0, 5.0	-1.0, 2.0
p-value[c]	0.0004	

Abbreviations: ESS (CHAD) = Epworth Sleepiness Scale for Children and Adolescents; N= the total number of subjects in the population; Q1 = first quartile; Q3 = third quartile.

[a] Baseline value is the value collected at Visit 3 (End of Stable Dose/Start of Double-blind treatment period).

[b] Missing values at the end of the Double-blind Treatment Period are imputed using the value from the Stable Dose Period (baseline observation carried forward).

[c] P-value from rank-based analysis of covariance (ANCOVA) with treatment as a factor and baseline value as a covariate.

Notes: ESS (CHAD) Total score ranges from 0 to 24. The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who complete at least 5 days of dosing in the Double-blind Treatment Period. Percentages are calculated using the total number of observed values.

6.5.10.3 Analysis Of Other Secondary Endpoints And Exploratory Endpoints.

6.5.10.3.1 Clinical Global Impression Of Change For Narcolepsy Overall

Tier 4 of the hierarchical sequence of efficacy analyses stipulated in the study protocol analyzed scores on the Clinical Global Impression of Change for overall narcolepsy severity. These scores compared the end of the randomized, double-blind, placebo-controlled withdrawal period with the end of the stable dose period.

The results of the analysis of that measure are summarized in the following table provided by the sponsor. Xyrem® displayed a statistically significant superiority to placebo on that measure: narcolepsy (overall) became more severe in patients receiving placebo than in those continuing Xyrem® during that period.

	Placebo N = 32		Xyrem N = 31
Response, n (%)			
Total Observed[a]	32		29
Very Much Worse (-3)	2 (6.3)		0
Much Worse (-2)	17 (53.1)		3 (10.3)
Minimally Worse (-1)	9 (28.1)		10 (34.5)
No Change (0)	2 (6.3)		14 (48.3)
Minimally Improved (1)	0		0
Much Improved (2)	2 (6.3)		2 (6.9)
Very Much Improved (3)	0		0
Missing	0		2
Mean (SD)	-1.4 (1.13)		-0.4 (0.95)
p-value[b]		0.0008	
Worsened, n (%)			
Much Worse or Very Much Worse	19 (59.4)		3 (10.3)
p-value[c]		< 0.0001	

Abbreviations: CGIc = Clinical Global Impression of Change
[a] Percentages were calculated using the total number of observed values.
[b] P-value from Cochran-Mantel-Haenszel test for Row Mean Scores Difference.
[c] P-value from Pearson's chi-square test. P-value is considered exploratory.
Notes: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who complete at least 5 days of dosing in the Double-blind Treatment Period. The CGIc for narcolepsy overall is evaluated at the end of the Double-blind Treatment Period. Scores associated with the responses are mapped to 3 for very much improved, to -3 for very much worse.

6.5.10.3.2 Other Endpoints

The Xyrem® and placebo groups for the randomized, double-blind, placebo-controlled withdrawal period were compared on a number of other secondary and exploratory outcome measures: quality of life based on Short Form-10 (physical summary score and psychosocial summary score (Tier 5); weekly school attendance (number of days missed); and Patient Global Impression of Change for narcolepsy severity overall. The differences between treatment groups were not even nominally statistically significant for the measures of quality of life and school attendance.

On the Patient Global Impression of Change for narcolepsy severity overall (which was scored and analyzed in a manner similar to the Clinician Global Impression of Change for cataplexy severity and narcolepsy severity overall), a nominally statistically significant difference between treatment groups was seen as indicated in the table below. This analysis was not part of the hierarchical sequence of analyses specified in the statistical analysis plan.

	Placebo N = 32		Xyrem N = 31
Response, n (%)			
Total Observed[a]	29		30
Very Much Worse (-3)	2 (6.9)		0
Much Worse (-2)	12 (41.4)		5 (16.7)
Minimally Worse (-1)	11 (37.9)		4 (13.3)
No Change (0)	2 (6.9)		13 (43.3)
Minimally Better (1)	2 (6.9)		4 (13.3)
Much Better (2)	0		3 (10.0)
Very Much Better (3)	0		1 (3.3)
Missing	3		1
Mean (SD)	-1.3 (0.97)		0.0 (1.30)
p-value[b]		0.0001	
Worsened, n (%)			
Much Worse or Very Much Worse	14 (48.3)		5 (16.7)
p-value[c]		0.0094	

Abbreviations: PGIc = Patient Global Impression of Change
[a] Percentages were calculated using the total number of observed values.
[b] P-value from Cochran-Mantel-Haenszel (CMH) test for Row Mean Scores Difference.
[c] P-value from Pearson's chi-square test. P-value is considered exploratory
Notes: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who complete at least 5 days of dosing in the Double-blind Treatment Period. The PGIc for narcolepsy overall is evaluated at the end of the Double-blind Treatment Period. Scores associated with the responses are mapped to 3 for very much improved, to -3 for very much worse.

6.5.11 Safety Results

6.5.11.1 Deaths, Serious Adverse Events, And Discontinuations Due To Adverse Events

There were no deaths during this study.

Serious adverse events that occurred during this study are summarized in the next sponsor table.

Subject Number Age[a] / Sex / Race	Treatment Period	System Organ Class *Preferred Term*	Relationship to Study Drug	Severity Outcome
(b) (6)	Dose Titration Period	Psychiatric Disorders	Related	Severe
13 / Male / White		*Acute Psychosis*		Recovered / Resolved
(b) (6)	Dose Titration Period	Psychiatric Disorders	Related	Moderate
14 / Male / White		*Suicidal ideation*		Recovered / Resolved

[a] Age in years at the first dispensation of study drug.

Discontinuations due to adverse events are in the next table taken from the submission.

Subject Number Age[a] / Sex / Race	Treatment Period of Onset	System Organ Class *Preferred Term*	Relationship to Study Drug *Severity; Outcome*
(b) (6)	Dose Titration Period	Psychiatric disorders	Related
15 / Male / White		*Hallucination, tactile*	*Moderate; Recovered / Resolved*
(b) (6)	Dose Titration Period	Psychiatric disorders	Related
14 / Male / White		*Suicidal ideation*	*Moderate; Recovered / Resolved*
(b) (6)	Stable Dose Period	Investigations	Related
13 / Female / White		*Weight decreased*	*Mild; Recovered / Resolved*
(b) (6)	Double-blind Treatment	Respiratory Thoracic and	Related
8 / Male / White	Period; *(Open-label Xyrem)*	Mediastinal Disorders *Sleep apnoea syndrome*	*Moderate; Recovered / Resolved*
(b) (6)	Open-label Safety Period	Psychiatric disorders	Related
14 / Male / Black		*Affect lability*	*Mild; Recovered / Resolved*

I have reviewed the above cases of serious adverse events and/or discontinuations due to adverse events further.

Brief narratives, based on data provided by the sponsor in this submission, are provided below for three of the above patients who had serious adverse events and/or discontinued treatment because of adverse events. They have been selected for further description because of the nature of the adverse events seen. The other adverse events in the above tables do not warrant further description.

Patien (b) (6) (adverse event: acute psychosis) was a 13-year-old boy who had been diagnosed to have narcolepsy over 2 years prior to being enrolled in Study 13-005 and weighed 64 kg. He had cataplexy, excessive daytime sleepiness, and other symptoms of narcolepsy, all of which were marked at study entry. He was Xyrem®-naïve at study entry but was taking methylphenidate in a dose of 75 mg QD. His Xyrem® dose was titrated upwards to 8 g/night over approximately 1 month. After approximately 2 days at that dose, he developed agitation, delusions, and hallucinations (and was diagnosed to have an acute psychosis). A further 2 weeks later, Xyrem® was discontinued, but begun again yet another 2 weeks later at a dose of 4.5 g/night. His symptoms then resolved while continuing to take Xyrem® in that dose for a further 5 months.

Patient (b) (6) (adverse event: suicidal ideation) was a 14-year-old boy who had been diagnosed to have narcolepsy about 1.5 years prior to being enrolled in Study 13-005 and weighed 76 kg. He had cataplexy, excessive daytime sleepiness, and other symptoms of narcolepsy, all of which were marked at study entry. He was Xyrem®-naïve at study entry but was taking methylphenidate in a dose of 10 mg BID. He had no prior personal or family history of depression. 2 days after beginning Xyrem® at a dose of 4.5 g/night, he developed suicidal thoughts which then increased in severity resulting in study medication being discontinued about 12 days after it was first begun. His suicidal thoughts resolved a further 2 days later.

Patient (b) (6) (adverse event: sleep apnea) was an 8-year-old boy who had been diagnosed to have narcolepsy slightly less than 2 years prior to being enrolled in Study 13-005 and weighed 46.9 kg. He had cataplexy, excessive daytime sleepiness, and other symptoms of narcolepsy, all of which were moderate at study entry. He was Xyrem®-naïve at study entry but was taking methylphenidate (controlled-release) in a dose of 27 mg QD. His Xyrem® dose was begun at 4.5 g/night and was titrated upwards to 6 g/night (3 g twice nightly); after taking the latter dose for about 2 weeks. Polysomnography showed episodes of central sleep apnea that occurred mainly after the second nightly dose of Xyrem® with brief periods of oxygen desaturation with a pO2 as low as 83%. Despite a reduction in Xyrem® dose to 4.5 g/night (2.25 g twice nightly) and later to 4 g/night (2 g twice nightly), periods of sleep apnea and oxygen desaturation continued to occur on polysomnography. Xyrem® was then permanently discontinued and follow-up polysomnography revealed no evidence of sleep apnea.

6.5.11.2 All Adverse Events

An overall summary of adverse events across all treatment periods is in the sponsor table below and is self-explanatory.

	Age (years)[a]		Xyrem Status at Entry[b]		Total
	7 to 11 N = 37	12 to 17 N = 67	Xyrem Naïve N = 72	On Xyrem N = 32	N = 104
Any TEAEs	**28 (75.7)**	**47 (70.1)**	**55 (76.4)**	**20 (62.5)**	**75 (72.1)**
Any Related TEAEs[c]	18 (48.6)	34 (50.7)	43 (59.7)	9 (28.1)	52 (50.0)
Any TEAEs Leading to Drug Interruption	3 (8.1)	2 (3.0)	5 (6.9)	0	5 (4.8)
Any TEAEs Leading to Drug Withdrawal	1 (2.7)	4 (6.0)	5 (6.9)	0	5 (4.8)
Any Severe TEAEs	0	4 (6.0)	4 (5.6)	0	4 (3.8)
Any Serious TEAEs	0	2 (3.0)	2 (2.8)	0	2 (1.9)
Any Fatal TEAEs	0	0	0	0	0
Any TEAEs of Special Interest	13 (35.1)	21 (31.3)	25 (34.7)	9 (28.1)	34 (32.7)

Abbreviations: TEAE = treatment emergent adverse event.
[a] Age in years at the first dispensation of study drug.
[b] Xyrem status at the time of study entry.
[c] Related TEAEs included events considered by the Investigator to be related or suspected to be related to study drug.
Note: Percentages are calculated using the N value. This table includes events with onset during any period of the study. Events with onset more than 30 days after the last dose of study drug in the study are excluded.

The overall incidence of adverse events reported in ≥ 5% of subjects in each age group and prior Xyrem®-status category across all treatment periods by system organ class and Preferred Term is in the next sponsor table.

System Organ Class Preferred Term	Age[a] (years)		Xyrem Status at Study Entry		Total
	7 to 11 N = 37	12 to 17 N = 67	Xyrem Naïve N = 72	On Xyrem N = 32	N = 104
Any TEAEs, n (%)	**28 (75.7)**	**46 (68.7)**	**55 (76.4)**	**19 (59.4)**	**74 (71.2)**
Gastrointestinal disorders	**14 (37.8)**	**22 (32.8)**	**31 (43.1)**	**5 (15.6)**	**36 (34.6)**
Nausea	6 (16.2)	12 (17.9)	16 (22.2)	2 (6.3)	18 (17.3)
Vomiting	9 (24.3)	8 (11.9)	15 (20.8)	2 (6.3)	17 (16.3)
Abdominal pain	2 (5.4)	1 (1.5)	3 (4.2)	0	3 (2.9)
Infections and infestations	**9 (24.3)**	**16 (23.9)**	**19 (26.4)**	**6 (18.8)**	**25 (24.0)**
Nasopharyngitis	3 (8.1)	4 (6.0)	7 (9.7)	0	7 (6.7)
Upper respiratory tract infection	2 (5.4)	3 (4.5)	4 (5.6)	1 (3.1)	5 (4.8)
Gastroenteritis	1 (2.7)	3 (4.5)	4 (5.6)	0	4 (3.8)
Pneumonia	2 (5.4)	1 (1.5)	3 (4.2)	0	3 (2.9)
Sinusitis	0	2 (3.0)	0	2 (6.3)	2 (1.9)
Nervous system disorders	**7 (18.9)**	**18 (26.9)**	**19 (26.4)**	**6 (18.8)**	**25 (24.0)**
Headache	4 (10.8)	13 (19.4)	13 (18.1)	4 (12.5)	17 (16.3)
Dizziness	2 (5.4)	4 (6.0)	5 (6.9)	1 (3.1)	6 (5.8)
Psychiatric disorders	**9 (24.3)**	**14 (20.9)**	**17 (23.6)**	**6 (18.8)**	**23 (22.1)**
Nightmare	3 (8.1)	1 (1.5)	2 (2.8)	2 (6.3)	4 (3.8)
Somnambulism	2 (5.4)	2 (3.0)	4 (5.6)	0	4 (3.8)
Confusional arousal	2 (5.4)	1 (1.5)	2 (2.8)	1 (3.1)	3 (2.9)
Anxiety	2 (5.4)	0	2 (2.8)	0	2 (1.9)
Renal and urinary disorders	**7 (18.9)**	**14 (20.9)**	**17 (23.6)**	**4 (12.5)**	**21 (20.2)**
Enuresis	7 (18.9)	12 (17.9)	15 (20.8)	4 (12.5)	19 (18.3)
Investigations	**9 (24.3)**	**9 (13.4)**	**14 (19.4)**	**4 (12.5)**	**18 (17.3)**
Weight decreased	5 (13.5)	7 (10.4)	11 (15.3)	1 (3.1)	12 (11.5)
Respiratory, thoracic and mediastinal disorders	**6 (16.2)**	**7 (10.4)**	**9 (12.5)**	**4 (12.5)**	**13 (12.5)**
Cough	2 (5.4)	2 (3.0)	2 (2.8)	2 (6.3)	4 (3.8)

System Organ Class Preferred Term	Age[a] (years) 7 to 11 N = 37	 12 to 17 N = 67	Xyrem Status at Study Entry Xyrem Naïve N = 72	 On Xyrem N = 32	Total N = 104
Nasal congestion	3 (8.1)	1 (1.5)	4 (5.6)	0	4 (3.8)
Oropharyngeal pain	0	2 (3.0)	0	2 (6.3)	2 (1.9)
Injury, poisoning and procedural complications	**5 (13.5)**	**6 (9.0)**	**6 (8.3)**	**5 (15.6)**	**11 (10.6)**
Contusion	2 (5.4)	1 (1.5)	2 (2.8)	1 (3.1)	3 (2.9)
Procedural pain	1 (2.7)	2 (3.0)	1 (1.4)	2 (6.3)	3 (2.9)
Metabolism and nutrition disorders	**3 (8.1)**	**8 (11.9)**	**11 (15.3)**	**0**	**11 (10.6)**
Decreased appetite	2 (5.4)	6 (9.0)	8 (11.1)	0	8 (7.7)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class.
Note: The summary includes events experienced while receiving Xyrem, excluding events occurring in subjects who received Placebo during the Double-Blind Treatment Period.
Note: Events with onset more than 30 days after the last dose of study drug in the study are excluded.
Note: Subjects may have more than one event with the same SOC. They are counted once in the SOC summary. Subjects may have more than one event with the same PT. They are counted once in the PT summary.
Note: Some SOCs may have achieved the 5% threshold, but if no underlying PTs achieved the 5% threshold, the SOC is not displayed.
[a] Age in years at the first dispensation of study drug.
MedDRA version 17.0.

An overall summary of adverse events that occurred during the double-blind randomized withdrawal period is in the next table taken from the submission and is self-explanatory. Adverse event data for patients who were not randomized but continued to take open-label Xyrem® during that period are also summarized in the table below.

	Treatment Received Randomized Placebo N = 32	 Randomized Xyrem N = 31	 Open-label Xyrem[a] N = 32	 All Xyrem N = 63	Total N = 95
Any TEAEs	**10 (31.3)**	**5 (16.1)**	**5 (15.6)**	**10 (15.9)**	**20 (21.1)**
Any Related TEAEs[b]	7 (21.9)	3 (9.7)	1 (3.1)	4 (6.3)	11 (11.6)
Any TEAEs Leading to Drug Interruption	0	0	1 (3.1)	1 (1.6)	1 (1.1)
Any TEAEs Leading to Drug Withdrawal	0	0	1 (3.1)	1 (1.6)	1 (1.1)
Any Severe TEAEs	0	0	0	0	0
Any Serious TEAEs	0	0	0	0	0
Any Fatal TEAEs	0	0	0	0	0
Any TEAEs of Special Interest	7 (21.9)	2 (6.5)	1 (3.1)	3 (4.8)	10 (10.5)

Abbreviations: TEAE = treatment emergent adverse event
Note: Events with onset on or after the first dose in the Double-blind Treatment Period and prior to the date of first dose in the Open-label Safety Period are presented. Events with onset more than 30 days after the last dose of study drug in the study are excluded.
[a] Subjects entering the Double-blind Treatment Period after the DSMB recommendation to end placebo treatment received open-label Xyrem during this 2-week Treatment Period.
[b] Related TEAEs included events considered by the Investigator to be related or suspected to be related to study drug.

A summary of all adverse events that occurred during the double-blind randomized withdrawal period is in the next table copied from the submission and is self-explanatory. Adverse event data for patients who were not randomized but continued to take open-label Xyrem® during that period are also summarized in the table below. Not surprisingly, in the randomized patients, the incidence of somnolence and cataplexy (as adverse events) was much higher in those who were randomized to placebo than in those randomized to Xyrem®.

	Treatment Received				
	Randomized Placebo N = 32	Randomized Xyrem N = 31	Open-label Xyrem[a] N = 32	All Xyrem N = 63	Total N = 95
Any TEAEs	**10 (31.3)**	**5 (16.1)**	**5 (15.6)**	**10 (15.9)**	**20 (21.1)**
Nervous System Disorders	**7 (21.9)**	**0**	**1 (3.1)**	**1 (1.6)**	**8 (8.4)**
Somnolence	7 (21.9)	0	0	0	7 (7.4)
Cataplexy	6 (18.8)	0	0	0	6 (6.3)
Psychiatric Disorders	**5 (15.6)**	**2 (6.5)**	**0**	**2 (3.2)**	**7 (7.4)**
Sleep disorder	2 (6.3)	1 (3.2)	0	1 (1.6)	3 (3.2)
Skin and Subcutaneous Tissue Disorders	**0**	**2 (6.5)**	**0**	**2 (3.2)**	**2 (2.1)**
Pruritus	0	2 (6.5)	0	2 (3.2)	2 (2.1)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment emergent adverse event
Note: Events with onset on or after the first dose in the Double-blind Treatment Period and prior to the date of first dose in the Open-label Safety Period are presented. Events with onset more than 30 days after the last dose of study drug in the study are excluded.
Note: Subjects may have more than one event with the same SOC; they are counted once in the SOC summary. Subjects may have more than one event with the same PT; they are counted once in the PT summary. SOCs are sorted in descending order of total incidence. PTs within SOC are sorted in descending order of incidence.
Note: Some SOCs may have achieved the 5% threshold, but if no underlying PTs achieved the 5% threshold, the SOC is not displayed.
[a] Subjects entering the Double-blind Treatment Period after the DSMB recommendation to end placebo treatment received open-label Xyrem during this 2-week Treatment Period.
MedDRA Version 17.0.

The incidence of adverse events (reported in ≥ 5% of subjects in each age group and prior Xyrem®-status category) that occurred during the titration, stable dose, and open-label safety periods has also been summarized by the sponsor in separate tables in the submission, but those data have been subsumed under a similar table covering the entire study that is already in the earlier part of this section.

Adverse events of special interest across all study periods in patients receiving Xyrem® and in the safety population are summarized in the next table. The findings in that table are not distinct from those elsewhere in this study report.

	Age (years)[a]		Xyrem Status at Study Entry		Total
	7 to 11 N = 37	12 to 17 N = 67	Xyrem Naïve N = 72	On Xyrem N = 32	N = 104
Any TEAEs of Special Interest	**13 (35.1)**	**17 (25.4)**	**24 (33.3)**	**6 (18.8)**	**30 (28.8)**
Psychiatric disorders	**8 (21.6)**	**11 (16.4)**	**15 (20.8)**	**4 (12.5)**	**19 (18.3)**
Nightmare	3 (8.1)	1 (1.5)	2 (2.8)	2 (6.3)	4 (3.8)
Somnambulism	2 (5.4)	2 (3.0)	4 (5.6)	0	4 (3.8)
Confusional arousal	2 (5.4)	1 (1.5)	2 (2.8)	1 (3.1)	3 (2.9)
Anxiety	2 (5.4)	0	2 (2.8)	0	2 (1.9)
Acute psychosis	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Affect lability	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Confusional state	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Irritability	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Mental status changes	0	1 (1.5)	0	1 (3.1)	1 (1.0)
Mood altered	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Stress	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Suicidal ideation	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Investigations	**5 (13.5)**	**7 (10.4)**	**11 (15.3)**	**1 (3.1)**	**12 (11.5)**
Weight decreased	5 (13.5)	7 (10.4)	11 (15.3)	1 (3.1)	12 (11.5)
Nervous system disorders	**1 (2.7)**	**1 (1.5)**	**2 (2.8)**	**0**	**2 (1.9)**
Somnolence	1 (2.7)	1 (1.5)	2 (2.8)	0	2 (1.9)
Respiratory, thoracic and mediastinal disorders	**1 (2.7)**	**1 (1.5)**	**1 (1.4)**	**1 (3.1)**	**2 (1.9)**
Sleep apnoea syndrome	1 (2.7)	1 (1.5)	1 (1.4)	1 (3.1)	2 (1.9)
General disorders and administration site conditions	**0**	**1 (1.5)**	**1 (1.4)**	**0**	**1 (1.0)**
Feeling jittery	0	1 (1.5)	1 (1.4)	0	1 (1.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment emergent adverse event
[a] Age in years at the first dispensation of study drug.
Note: The summary includes events experienced while receiving Xyrem, excluding events occurring in subjects who received Placebo during the Double-blind Treatment Period.
Note: Events with onset > 30 days after the last dose of study drug in the study were excluded. Subjects with more than one event with the same SOC are counted once in the SOC summary. Subjects with more than one event with the same PT are counted once in the PT summary.
MedDRA Version 17.0.

Further analyses of each of the events in the above table have been presented by the sponsor, but do not reveal any information that is unexpected or distinctive for children.

6.5.11.3 Safety Laboratory Tests

There are no items of concern in the sponsor's display and analysis of the data from standard hematology, clinical chemistry, and urinalysis parameters observed during this study.

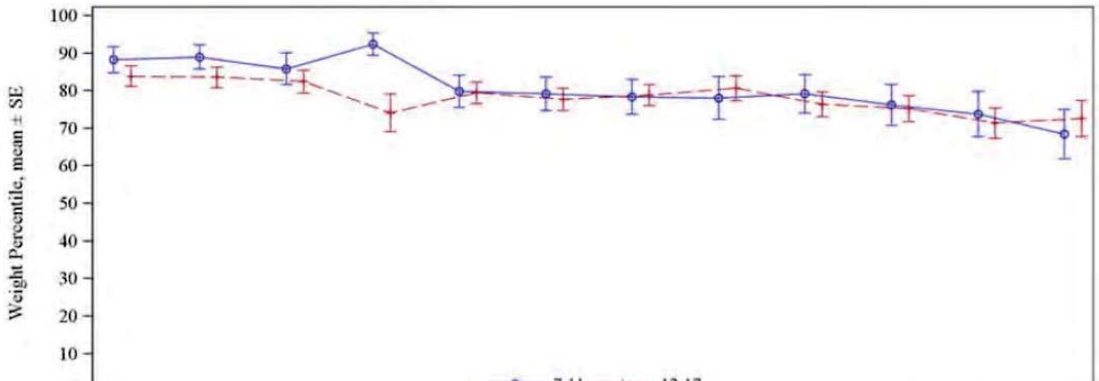
The analysis of growth hormone, insulin-like growth factor 1, and prolactin concentrations obtained over the course of the study revealed no data of significance; neither did the analysis of measures of precocious puberty (luteinizing hormone, follicle-stimulating hormone, testosterone, estradiol, and Tanner staging) conducted in girls < 8 years old and boys < 9 years old.

6.5.11.4 Vital Signs, Height, Weight, And Body Mass Index

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.

No effect of Xyrem® on height were observed during the study.

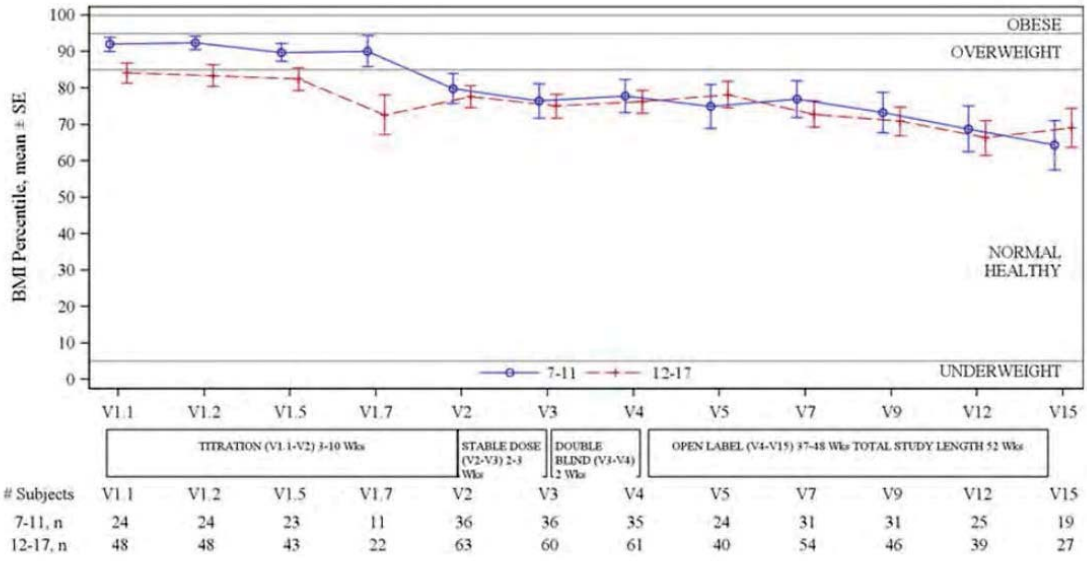
Mean body weight percentile demonstrated a slight decrease over the course of this study. Mean body weight percentile by time data by age category is in the following figure for the safety population which I have taken from the submission.



# Subjects	V1.1	V1.2	V1.5	V1.7	V2	V3	V4	V5	V7	V9	V12	V15
7-11, n	24	24	23	11	36	36	35	24	31	31	25	19
12-17, n	48	48	43	22	63	60	61	40	54	46	39	27

Note: The Safety Population consists of all subjects who were dispensed study drug. Time between visits is not equally spaced. The error bars represent mean - 1 SE to mean + 1 SE.

A trend to a decrease in body mass index percentile was also observed during this study, that was similar for both age-group categories as displayed in the next sponsor figure. The next figure displays body mass index percentile over time in the safety population in both age categories.



# Subjects	V1.1	V1.2	V1.5	V1.7	V2	V3	V4	V5	V7	V9	V12	V15
7-11, n	24	24	23	11	36	36	35	24	31	31	25	19
12-17, n	48	48	43	22	63	60	61	40	54	46	39	27

Note: The Safety Population consists of all subjects who were dispensed study drug. Time between visits is not equally spaced. The error bars represent mean - 1 SE to mean + 1 SE. BMI values less than the 5th percentile are classified as underweight, values between 85 to < 95 are classified as overweight, and values ≥ 95 are classified as obese.

6.5.11.5 Electrocardiograms

No clinically significant findings were noted in the sponsor's analysis of electrocardiographic data obtained during this study.

6.5.11.6 Polysomnograms

No clinically-significant changes in polysomnographic measures of central or obstructive sleep apnea and hypopnea, or oxygen desaturation were seen in this study as is displayed in the following sponsor tables.

Respiratory Parameters Collected during Full Night PSG for Subject who were Xyrem Naïve at Study Entry

Parameters	Screening PSG (without Xyrem) N = 73	End of Stable Dose PSG (with Xyrem) N = 64	Change from Screening – End of Stable Dose N = 63	End of Study PSG (with Xyrem) N = 30	Change from Screening - EoS N = 30	Change from End of Stable Dose - EoS N = 30
			Mean (SD); Median (Q1, Q3)			
Apnea + Hypoapnea index	1.24 (1.180) 1 (0.40, 1.70)	1.924 (4.8115) 1.1 (0.4, 1.65)	0.652 (4.9763) -0.1 (-0.8, 0.6)	0.787 (0.7763) 0.55 (0.3, 0.8)	-0.663 (1.1857) -0.70 (-1.4, 0)	-0.675 (1.6908) -0.20 (-0.960, 0.300)
Apnea index	0.31 (0.483) 0.10 (0.00, 0.40)	1.155 (4.6975) 0.3 (0, 0.7)	0.853(4.7606) 0 (-0.1, 0.3)	0.380 (0.4937) 0 (0, 0.5)	-0.023 (0.6431) 0 (-0.2, 0.2)	-0.0292 (1.5189) 0 (-0.5, 0.2)
Central apnea index	0.27 (0.452) 0.1 (0, 0.40)	1.123 (4.6531) 0.3 (0, 0.675)	0.864 (4.7214) 0 (-0.1, 0.3)	0.293 (0.3732) 0.2 (0, 0.4)	-0.8 (0.6386) 0 (-0.3, 0.1)	-0.338 (1.4855) -0.1 (-0.4, 0.1)
Obstructive apnea + hypoapnea index	0.95 (0.937) 0.7 (0.30, 1.20)	0.797 (0.8989) 0.45 (0.1, 1.150)	-0.205 (0.9494) -0.2 (-0.7, 0.2)	0.473 (0.6373) 0.3 (0.1, 0.6)	-0.59 (0.8953) -0.55 (-1.1, 0)	-0.347 (0.8287) -0.2 (-0.7, 0.1)
Obstructive index	0.03 (0.088) 0 (0, 0)	0.03 (0.092) 0 (0, 0)	-0.01 (0.111) 0 (0, 0)	0.08 (0.315) 0 (0, 0)	0.06 (0.309) 0 (0, 0)	0.05 (0.264) 0 (0, 0)
Percent TST with SpO_2 < 80%	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)
Percent TST with SpO_2 ≤ 85%	0 (0); 0 (0, 0)	0 (0.018) 0 (0, 0)	0 (0.018) 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0.018) 0 (0, 0)
Percent TST with SpO_2 < 90%	0.00 (0.026) 0 (0, 0)	0.03 (0.167) 0 (0, 0)	0.02 (0.171) 0 (0, 0)	0.01 (0.025) 0 (0, 0)	0 (0.032) 0 (0, 0)	-0.01 (0.066) 0 (0, 0)
Total time SpO_2 is ≤ 85% during TST (mins)	0 (0) 0 (0, 0)	0.01 (0.072) 0 (0, 0)	0.01 (0.073) 0 (0, 0)	0 (0.018) 0 (0, 0)	0 (0.018) 0 (0, 0)	-0.01 (0.058) 0 (0, 0)
Total time SpO_2 is < 90% during TST (mins)	0.03 (0.140) 0 (0, 0)	0.13 (0.826) 0 (0, 0)	0.10 (0.851) 0 (0, 0)	0.03 (0.102) 0 (0, 0)	0.01 (0.118) 0 (0, 0)	-0.03 (0.268) 0 (0, 0)
Mean SpO_2 during TST (%)	97.40 (0.944) 97.3 (96.80, 98.00)	97.09 (0.998) 97.1 (96.40, 97.75)	-0.25 (0.917) -0.3 (-0.80, 0.30)	97.41 (0.937) 97.25 (96.90, 97.90)	-0.12 (1.183) 0.05 (-1.0, 0.20)	0.26 (1.150) 0.15 (-0.2, 0.50)

Abbreviations: EoS = end of study; Max = maximum; Min = minimum; mins = minutes; PSG = polysomnogram; SpO_2 = oxygen saturation; TST = total sleep time.

Respiratory Parameters Collected during Full Night PSG for Subjects on Xyrem at Study Entry

Parameters	Screening PSG (with Xyrem) N = 32	End of Study PSG (with Xyrem) N = 17	Change from Screening – EoS N = 17
		Mean (SD); Median (Q1, Q3)	
Apnea + Hypoapnea index	1.16 (1.269); 0.85 (0.25, 1.65)	3.48 (7.187); 0.8 (0.20, 1.80)	1.85 (6.818); -0.1 (-0.90, 0.60)
Apnea index	0.44 (0.750); 0.1 (0.0, 0.65)	2.11 (4.535); 0.3 (0.0, 0.60)	1.51 (4.380); 0 (0.0, 0.60)
Central apnea index	0.42 (0.72); 0.1 (0, 0.65)	1.94 (4.287); 0.1 (0.0, 0.60)	1.36 (4.116); 0 (-0.10, 0.60)
Obstructive apnea + hypoapnea index	0.73 (0.796); 0.45 (0.15, 1.05)	1.53 (4.21); 0.4 (0.0, 1.40)	0.49 (3.732); -0.4 (-0.90, 0.20)
Obstructive index	0.02 (0.072); 0 (0, 0)	0.16 (0.557); 0 (0, 0)	0.15 (0.556); 0 (0, 0)
Percent TST with SpO_2 < 80%	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)
Percent TST with SpO_2 ≤ 85%	0.01 (0.071); 0(0, 0)	0.02 (0.073); 0 (0, 0)	-0.01 (0.125); 0 (0, 0)
Percent TST with SpO_2 < 90%	0.09 (0.512); 0 (0, 0)	0.18 (0.517); 0 (0, 0)	0.01 (0.910); 0 (0, 0)
Total time SpO_2 is ≤ 85% during TST (mins)	0.06 (0.336); 0(0, 0)	0.09 (0.363); 0 (0, 0)	0.02 (0.605); 0 (0, 0)
Total time SpO_2 is < 90% during TST (mins)	0.46 (2.562); 0 (0, 0)	0.78 (2.182); 0 (0, 0)	-0.07 (4.306); 0 (0, 0)
Mean SpO_2 during TST (%)	97.52 (0.828); 97.5 (96.95, 98.20)	97.25 (1.154); 97.2 (96.60, 98.10)	-0.28 (1.048) -0.20 (-0.90, 0.30)

Abbreviations: EoS = end of study; Max = maximum; Min = minimum; mins = minutes; PSG = polysomnogram; SpO_2 = oxygen saturation; TST = total sleep time.

Additional analyses and descriptions of individual patients reported to have arterial oxygen desaturation do not reveal any data of concern.

6.5.11.7 Columbia-Suicide Severity Rating Scale, Children's Depression Inventory, And Multidimensional Anxiety Scale For Children-10

Among subjects who took Xyrem®, two subjects responded positively to the Columbia-Suicide Severity Rating Scale. Those were the 2 subjects with serious adverse events for whom narratives have been provided earlier and are listed in the following table. A further description of those patients is not warranted.

Subject Number Age[a] / Sex / Race	Treatment Period	System Organ Class *Preferred Term*	Relationship to Study Drug	Severity Outcome
(b) (6) 13 / Male / White	Dose Titration Period	Psychiatric Disorders *Acute Psychosis*	Related	Severe Recovered / Resolved
(b) (6) 14 / Male / White	Dose Titration Period	Psychiatric Disorders *Suicidal ideation*	Related	Moderate Recovered / Resolved

[a] Age in years at the first dispensation of study drug.

A slight downward trend in mean Children's Depression Inventory T-scores in both Xyrem® naïve and Xyrem®-treated subjects was observed during the course of the study (higher scores correlate with more severe depression). Scores, however, remained within the average range.

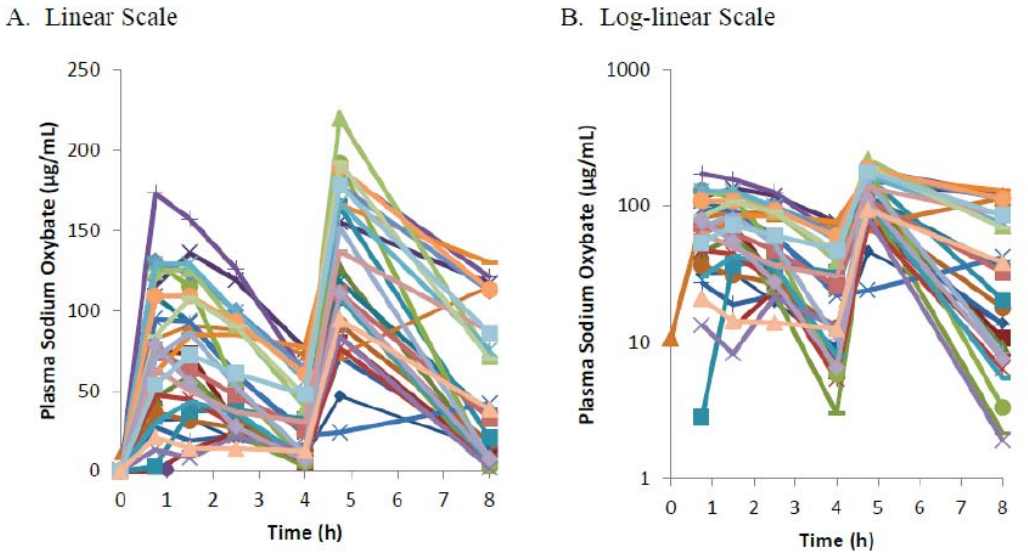
Scores on the Multidimensional Anxiety Scale for Children-10 remained steady during the study.

6.5.12 Pharmacokinetic Results

Pharmacokinetic results for this study came from the pharmacokinetic completer population comprising 29 patients and included 11 patients in the 7 to 11 year age group and 18 patients in the 12 to 17 year age group.

Plasma sodium oxybate concentration-time profiles (using linear and log-linear scales) after the administration of Xyrem® at the full and stable dose in this study is revealed in the following sponsor figure. The profiles represent changes after the first and second nightly doses during the second pharmacokinetic night.

Plasma Sodium Oxybate Concentration-time Profiles for Individual Subjects following Administration of Xyrem during PK Night 2 (PK Population)



The plots correspond to Xyrem doses ranging from 4 to 9 grams per night. Xyrem was administered as 2 evenly divided doses (first and second nightly doses) given 4 hours apart.

Sodium oxybate pharmacokinetic parameters for the first nightly dose of Xyrem® are in the following sponsor table.

First Nightly Dose (g)[a]	Number of Subjects	T_{max} (hours)[a] (Median [Min, Max])	C_{max} (µg/mL) (Mean [CV%])	AUC_{0-4h} (µg/mL*hours) (Mean [CV%])
2	1	0.75 (NC)	79.4 (NC)	143 (NC)
2.25	3	0.82 (0.75-1.50)	72.5 (73%)	195 (83%)
2.5	2	1.66 (0.82-2.50)	65.3 (95%)	156 (92%)
3	1	2.47 (NC)	24.3 (NC)	52.0 (NC)
3.25	3	0.75 (0.75-2.50)	92.5 (36%)	273 (40%)
3.5	8	1.50 (0.75-1.50)	82.9 (60%)	234 (62%)
3.75	3	0.75 (0.75-1.48)	92.7 (35%)	214 (25%)
4	4	0.75 (0.75-1.50)	84.1 (44%)	209 (53%)
4.25	1	0.75 (NC)	47.4 (NC)	114 (NC)
4.5	3	1.50 (0.75-2.50)	82.4 (60%)	233 (67%)

Abbreviations: AUC_{0-4h} = area under the plasma concentration-time curve from time zero to 4 hours postdose; C_{max} = maximum observed plasma concentration; NC = not calculated since only one observation available; T_{max} = time of maximum observed plasma concentration.
[a] Based on half of the planned full nightly dose (Xyrem dosage, g/night).
Note: Results are presented for PK Night 2, on which subjects received their full stable dose of Xyrem.
Note: For T_{max}, median values are reported and the range of observed values (minimum-maximum) are reported in parentheses. For C_{max} and AUC_{0-4h}, mean values are reported and the coefficients of variation (SD / mean expressed as a percentage) are shown in parentheses.

Sodium oxybate pharmacokinetic parameters for the second nightly dose of Xyrem® are in the next sponsor table.

Nightly Dose (g), BID	Number of Subjects	$C_{4.75h}$ (µg/mL) (Mean [CV%])	C_{8h} (µg/mL) (Mean [CV%])
2	1	108 (NC)	2.16 (NC)
2.25	3	125 (43%)	44.9 (129%)
2.5	2	101 (24%)	18.6 (127%)
3	1	83.6 (NC)	8.13 (NC)
3.25	3	157 (11%)	97.5 (29%)
3.5	8	130 (44%)	60.6 (83%)
3.75	3	159 (28%)	33.3 (137%)
4	4	112 (73%)	34.8 (82%)
4.25	1	76.7 (NC)	6.40 (NC)
4.5	3	144 (20%)	56.7 (93%)

Abbreviations: C4.75h = plasma concentration at 4.75 hours postdose; C8h = plasma concentration at 8 hours; NC = not calculated due to only one observation; BID= two times a night.
Results are presented for PK Night 2, on which subjects received their full stable dose of Xyrem.
Mean values are reported the coefficients of variation (SD/mean expressed as a percentage) are shown in parentheses.

The dose proportionality assessment is summarized in the next table from the submission, the footnotes to the table explain that assessment. The sponsor has concluded that while the C_{max} was dose-proportional, the AUC_{0-4} was supra-dose-proportional.

	C_{max}	AUC_{0-4h}
Ratio	1.97	2.53
(90% CI)	(1.67 – 2.31)	(2.18 – 2.94)

Abbreviations: AUC_{0-4h} = area under the plasma concentration-time curve from time zero to 4 hours postdose; CI = confidence interval; C_{max} = maximum observed plasma concentration.
Note: Ratio and confidence interval obtained from a normal distribution and confidence interval for natural log (value on PK Night 2) – natural log (value on PK Night 1). The mean of the difference in logs and confidence intervals are back-transformed to ratio scale.
Note: As described in the text, half of the stable dose was taken on PK night 1, and the full stable dose was taken on PK night 2; therefore, a ratio of 2.00 signifies dose proportionality.

The sponsor has also compared pharmacokinetic data obtained in children with historical pharmacokinetic obtained in adults: while the major pharmacokinetic attributes in children were similar to those obtained in adults, there was greater variability in plasma pharmacokinetic exposure parameters in children.

6.6 Sponsor's Conclusions

The sponsor has drawn the following salient conclusions from the results of Study 13-005.

- Xyrem® had efficacy in the treatment of cataplexy and excessive daytime sleepiness in narcolepsy in pediatric subjects.
- The safety profile of Xyrem® in pediatric subjects was similar to that observed in adults.
- The pharmacokinetics of Xyrem® in children were collectively similar to those seen in adults.

6.7 Reviewer's Summary Comments

6.7.1 Study Design And Significant Amendments

Protocol 13-005 had the following main features:

- The primary objectives of the study were to evaluate the efficacy and safety of Xyrem® in the treatment of pediatric patients (aged 7 to 17 years) who have narcolepsy with cataplexy

- This study had a number of consecutive segments, of which the main randomized, double-blind, placebo-controlled, parallel-arm withdrawal segment was to be the component of the study directed at evaluating the efficacy of Xyrem® in the treatment of cataplexy associated with narcolepsy in children.

- About 100 patients aged 7 to 16 years at study entry were to be enrolled. They would be either Xyrem®-naïve or taking a stable dose of Xyrem® (and a stable dose of stimulants for narcolepsy, if applicable) for at least 2 months prior to study entry. Other key inclusion criteria were as follows: primary diagnosis of narcolepsy with cataplexy meeting International Classification of Sleep Disorders (ICSD)-2 criteria or ICSD-3 criteria, whichever was in effect at the time of the study; positive for the HLA DQB1:0602 haplotype; and history of at least 14 cataplexy attacks in a typical 2-week period and clinically significant symptoms of excessive daytime sleepiness prior to beginning any narcolepsy treatment.

- Throughout the study, all nightly doses of Xyrem® and placebo were to be administered in 2 divided doses, administered 2.5 to 4 hours apart. The starting and maximum doses of Xyrem® as well as the Xyrem® titration regimen (if required) were to be determined based on body weight stratum.

- The consecutive segments of this study were as follows:

    - A screening period lasting up to 30 days.

    - A 3 to 10 week open-label titration period lasting 3 to 10 weeks for patients who were Xyrem®-naïve at study entry.

    - An open-label stable-dose period lasting 2 to 3 weeks. During this phase, a subset of about 24 patients (completers) who were taking a stable dose of Xyrem® at study entry were to participate in an open-label evaluation of the pharmacokinetics of Xyrem®.

    - A double-blind, placebo-controlled withdrawal phase lasting 2 weeks during which period patients were randomized 1:1 to treatment either with Xyrem® in the stable dose established during the preceding 2 weeks or placebo.

    - An open-label safety component which allowed for a total exposure to Xyrem® of up to 1 year.

- The primary efficacy parameter was the change in weekly number of cataplexy attacks during the 2 weeks of the double-blind period, compared with the last 2 weeks of the stable-dose period.

- Key secondary efficacy parameters were the following:

    - Clinical Global Impression of Change for cataplexy severity, comparing the end of the double-blind period with the end of the stable-dose period.

    - Change in the modified Epworth Sleepiness Scale (modified for children and adolescents) score from the end of the stable-dose period to the end of the double-blind period.

- Other secondary efficacy parameters were the following

    - Clinical Global Impression of Change for narcolepsy severity overall comparing the end of the double-blind period with the end of the stable-dose period.

    - Change in quality of life (based on the Short Form-10) from the end of the stable-dose period to the end of the double-blind period.

- Safety monitoring was to comprise assessment of the following during the course of the study: adverse events, vital signs, height, weight, physical examinations, 12-lead electrocardiograms, polysomnographic parameters (including measures of respiration), safety laboratory tests, assessments of growth and precocious puberty (including growth hormone levels), Columbia-Suicide Severity Rating Scale, Children's Depression Inventory 2nd Edition Self-Report Short Version, and Multidimensional Anxiety Scale for Children 10-item Anxiety Index.

- Plasma concentrations of sodium oxybate were measured in the subset of patients participating in the pharmacokinetic analysis, and various pharmacokinetic parameters derived from those data and analyzed further.

- A tiered analysis of the efficacy parameters was conducted beginning with the primary efficacy parameter followed by the two key secondary efficacy parameters (with the Clinical Global Impression of Change in cataplexy severity analyzed first and the change in modified Epworth Sleepiness Scale score analyzed later), and finally the two other secondary efficacy parameters in the same order as stated above.

A pre-specified interim efficacy analysis (on the primary efficacy endpoint) for this protocol that was conducted after 35 subjects completed or discontinued early from the double-blind treatment period led to the Data Safety Monitoring Board for Study 13-005 concluding that Xyrem had demonstrated efficacy in the treatment of cataplexy (it had demonstrated that Xyrem was superior to placebo in the treatment of cataplexy at a p-value ≤ 0.005): the Board then recommended that the double-blind segment of Study 13-005 be discontinued, while the open-label extension (including pharmacokinetic evaluation) continue. The Data Safety Monitoring Board for Study 13-005 also recommended that patients continue to be enrolled in the open-label pharmacokinetic segment.

The pediatric Written Request under which Study 13-005 was first conducted was amended after the pre-specified interim analysis led to a protocol amendment. The study protocol was also amended to allow for the duration of the open-label safety component to be further extended so that the total duration of Xyrem® treatment for an individual patient could extend up to 3 years; the part of the study originally proposed was then referred to as Part 1 with the newly-proposed extension as Part 2.

6.7.2 Study Results

Study 13-005 was conducted in a manner consistent with the study protocol.

A total of 106 patients were enrolled in this study of whom 104 appear to have received study drug. 99 patients entered the stable-dose period, with 96 of those patients completing that period. Of the 96 patients who completed the stable-dose period, 63 patients participated in the randomized, double-blind, withdrawal phase of the study, whereas the remaining 33 patients continued to take open-label Xyrem. 95 patients then entered the open-label safety period of the study. As of the cut-off date for the 120-day safety update, 85 patients had completed Part 1 of the study and 44 patients had entered Part 2.

During the randomized, double-blind, withdrawal phase, 31 patients were assigned to Xyrem® (30 patients completed that phase) and 32 patients were assigned to placebo (all 32 patients completed that phase).

The primary efficacy analysis (based on an analysis of covariance) indicated that the mean change from baseline over the two -week randomized withdrawal period in the weekly number of cataplexy attacks was 17.37 for the placebo group and 2.52 for the group that continued to take Xyrem® (this change was an increase in cataplexy frequency). This difference was statistically significant ($p < 0.0001$). Statistically significant treatment differences favoring Xyrem® over placebo were seen on the two key secondary efficacy parameters analyzed in the prespecified sequence, the Clinical Global Impression of Change for Cataplexy Severity ($p = 0.0006$) and the change from baseline in modified Epworth Sleepiness Scale score ($p = 0.0001$).

The adverse event profile of Xyrem® seen in this study was not substantially different from that seen in adults. The other safety outcomes did not reveal any data of concern.

The pharmacokinetic completer population consisted of 29 patients, of whom 11 were aged 7 to 11 years, and 18 were aged 12 to 17 years. These data revealed a pharmacokinetic profile for Xyrem® in children that was similar to that seen in adults. A dose-proportionality assessment indicated that while the C_{max} was dose-proportional, the AUC_{0-4} was supra-dose-proportional.

7. 120-Day Safety Update

The 120-Day Safety Update for this sNDA was submitted on August 23, 2018.

This Update contains safety data from Parts 1 and 2 of Study 13-005, with a cut-off date of April 30, 2018. (The cut-off date for safety data in the original submission of this sNDA was February 10, 2017).

The safety data included in this update are cumulative for Study 13-005. The data in this update are summarized under the following headings.

7.1 Exposure

As of April 30, 2018, 104 subjects had received Xyrem® for a median duration of 370 days (range: 352 to 492 days) in this study. The distribution of that exposure by duration categories and by cumulative Xyrem® dosage is summarized in the following sponsor table, which is for the safety population.

	Total N = 106
Duration of Xyrem usage (days)[a]	
n	104
Mean (SD)	392.4 (159.77)
Median	370.0
Q1, Q3	352.0, 492.0
Categorized Duration of Study Drug usage	
≥ 6 months	91 (85.8)
≥ 1 year	76 (71.7)
≥ 18 months	20 (18.9)
Cumulative Xyrem dosage received (g)[b]	
n	104
Mean (SD)	2624.355 (1304.8288)
Median	2600.250
Q1, Q3	1807.500, 3690.500

Abbreviations: N = the total number of subjects in the population; n = number of subjects observed; Q1 = first quartile; Q3 = third quartile.

[a] For subjects who received Xyrem during the Double-blind Treatment Period, this duration will be the same as the Total Duration of Dosing. For subjects who received Placebo during the Double-blind Treatment Period, Total Duration of Xyrem Usage equals the Total Duration of Dosing over Part 1 and Part 2 minus Duration of Treatment during the Double-blind Treatment Period.

[b] For subjects who received Xyrem during the Double-blind Treatment Period, this is the cumulative dosage (based on the assigned dosage by the investigator and assuming the subject took the complete assigned dosage every night) used over all periods of study drug exposure. For subjects who received Placebo during the Double-blind Treatment Period, this is the cumulative dosage used over all periods of study drug exposure minus the cumulative dosage used during the Double-blind Treatment Period.

Note: Percentages are calculated using the number of subjects with a duration value in the column.

Note: The Safety Population consists of all subjects who were dispensed study drug.

The duration of Xyrem® use at the maximum nightly dose by age group and weight category at study entry is summarized in the next sponsor table, which is for the safety population.

Subject Weight at Baseline [a]	Maximum Total Nightly Dose	Statistic	Age 7 to 11 [b] N = 37	Age 12 to 17 [b] N = 67	Total N = 104
Xyrem naïve at Study Entry		M [c]	24	48	72
< 30 kg	**6 g/night**	m [c]	2	0	2
		n/m(%) [c]	0/2 (0)	0	0/2 (0)
30 to < 45 kg	**7.5 g/night**	m [c]	9	1	10
		n/m(%) [c]	2/9 (22.2)	0/1 (0)	2/10 (20.0)
		Exposure Days			
		n	2	0	2
		Mean (SD)	262.5 (212.84)	NA	262.5 (212.84)
		Median	262.5	NA	262.5
		Q1, Q3	112.0, 413.0	NA	112.0, 413.0
≥ 45 kg	**9 g/night**	m [c]	13	47	60
		n/m(%) [c]	4/13 (30.8)	14/47 (29.8)	18/60 (30.0)
		Exposure Days			
		n	4	14	18
		Mean (SD)	134.3 (122.00)	307.9 (172.57)	269.3 (175.84)
		Median	128.0	339.0	285.0
		Q1, Q3	32.5, 236.0	143.0, 429.0	85.0, 424.0
On Xyrem at Study Entry		M [c]	13	19	32
< 30 kg	**6 g/night**	m [c]	3	0	3
		n/m(%) [c]	3/3 (100.0)	0	3/3 (100.0)
		Exposure Days			
		n	3	0	3
		Mean (SD)	423.0 (316.31)	NA	423.0 (316.31)
		Median	594.0	NA	594.0
		Q1, Q3	58.0, 617.0	NA	58.0, 617.0
30 to < 45 kg	**7.5g/night**	m [c]	5	1	6
		n/m(%) [c]	1/5 (20.0)	0/1 (0)	1/6 (16.7)
		Exposure Days			
		n	1	0	1
		Mean (SD)	366.0 (NC)	NA	366.0 (NC)
		Median	366.0	NA	366.0
		Q1, Q3	366.0, 366.0	NA	366.0, 366.0

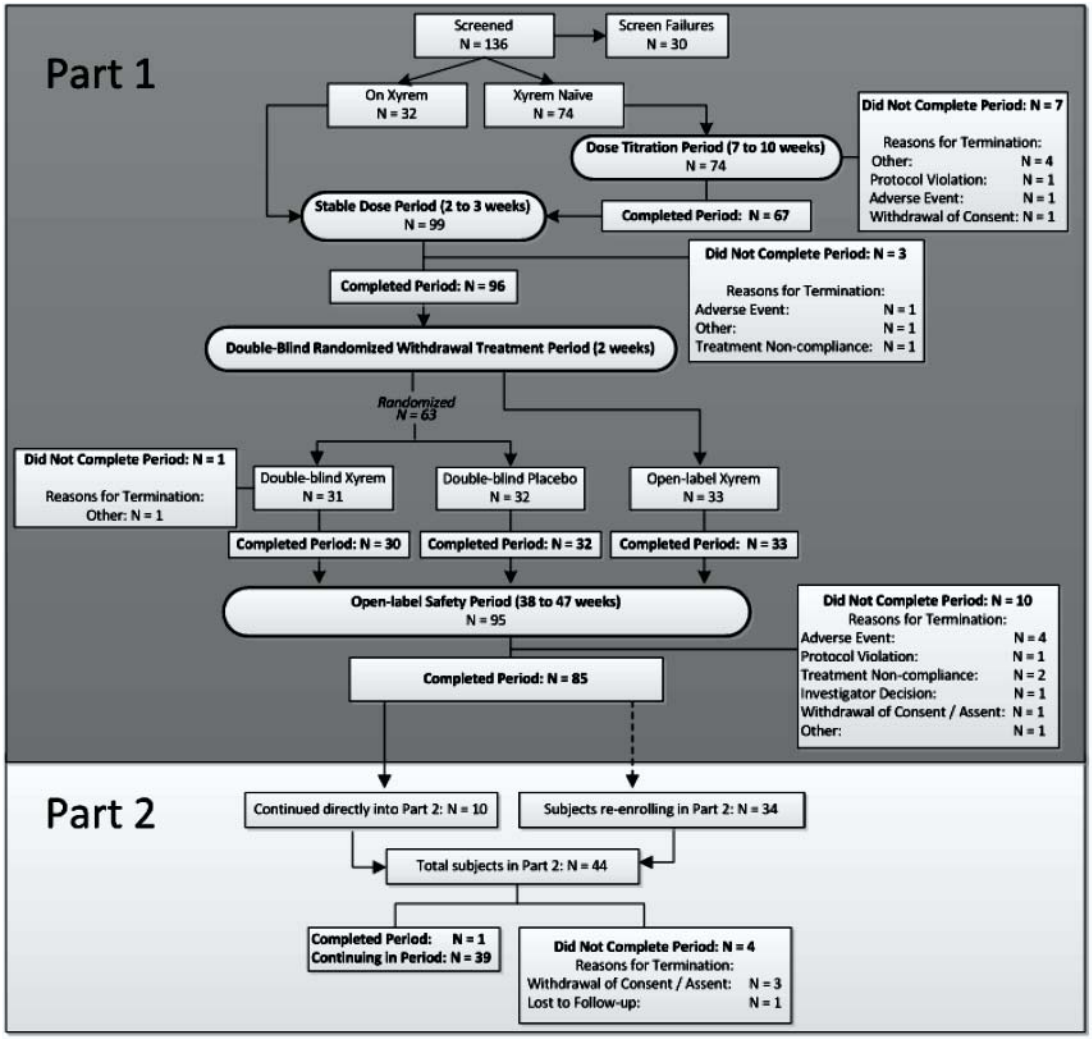
Subject Weight at Baseline [a]	Maximum Total Nightly Dose	Statistic	Age 7 to 11[b] N = 37	Age 12 to 17[b] N = 67	Total N = 104
≥ 45 kg	9 g/night	m [c]	5	18	23
		n/m(%)[c]	0/5 (0)	1/18 (5.6)	1/23 (4.3)
		Exposure Days			
		n	0	1	1
		Mean (SD)	NA	411.0 (NC)	411.0 (NC)
		Median	NA	411.0	411.0
		Q1, Q3	NA	411.0, 411.0	411.0, 411.0

Abbreviations: N = the total number of subjects in the population; NC = not calculated; NA = not available; Q1 = first quartile; Q3 = third quartile.
[a] Baseline weight (kg) refers to the last non-missing value collected prior to or on study Day 1.
[b] Age in years at the first dispense of study drug in Part 1.
[c] M: the number of subjects by each age group and Xyrem status at study entry; m: the number of subjects by each age group, Xyrem status at study entry and weight group; n: the number of subjects by each age group, Xyrem status at study entry, weight group, and met the total maximum nightly Xyrem dose at anytime during the study.
Note: The Safety Population consists of all subjects who were dispensed study drug.
Per protocol, the maximum total nightly dose by weight was only specified for Xyrem naïve subjects and does not apply to on Xyrem subjects. For subjects who received Placebo during the Double-blind Treatment Period, Total Duration of Xyrem Usage equals the Total Duration of Dosing minus Duration of Treatment during the Double-blind Treatment Period.
One subject (b) (6) who was on Xyrem at study entry had a dose that exceeded the maximum total nightly dose in the study allowed for Xyrem-naïve subjects. The subject was < 30 kg at study entry and received a dose of 7.5 g/night.

7.2 Disposition

By April 30, 2018, 85 patients had completed Part 1 and 44 patients were enrolled in Part 2.

The overall disposition of patients for both parts of the study on that date are summarized in the following sponsor figure for the safety population.



Abbreviations: N = the total number of subjects in the population
The Safety Population includes all subjects who were dispensed study drug. Percentages are calculated using the N values.
Note: Discontinuations that occurred during the Open-label Safety Period are included.
Note: For Part 2, "Completed" occurs when either: the subject is followed for an additional 2 years, the subject reaches 18 years of age, or the subject is followed for 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US Prescribing Information.

7.3 Demographics

Demographics for Part 2 are in the next sponsor table.

	Safety Population N = 44
Age, Part 1 (years)[a]	
N	44
Mean (SD)	11.5 (2.24)
Median	12.0
Min, Max	7, 15
Age at first dose taken in Part 2 (years)[b]	
n	44
Mean (SD)	13.1 (2.24)
Median	13.5
Min, Max	8, 17
Age group, Part 2, n (%)	
7 to 11 years	13 (29.5)
12 to 17 years	31 (70.5)
Sex, n (%)	
Male	30 (68.2)
Female	14 (31.8)
Race, n (%)	
Asian	1 (2.3)
Black / African American	12 (27.3)
White	29 (65.9)
Other	2 (4.5)
Ethnicity, n (%)	
Hispanic / Latino	3 (6.8)
Not Hispanic / Latino	41 (93.2)
Country, n (%)	
United States	31 (70.5)
Finland	0
France	0
Italy	12 (27.3)
Netherlands	1 (2.3)

Abbreviations: Max = maximum; Min = minimum; N = the total number of subjects in the population.
[a] Age in years at the first dispensation of study drug.
Note: The Safety Population consists of all subjects who were dispensed study drug. Percentages were calculated using the N value.

7.4 Adverse Events

An overall summary of all treatment-emergent adverse events that occurred during all periods of the study, as of April 30, 2018, is in the following table, which I have copied from the submission. The table is self-explanatory.

	Total N = 104
Any TEAEs	81 (77.9)
Any related TEAEs[a]	57 (54.8)
Any TEAEs leading to drug interruption	8 (7.7)
Any TEAEs leading to drug withdrawal	6 (5.8)
Any severe TEAEs	4 (3.8)
Any serious TEAEs	2 (1.9)
Any fatal TEAEs	0
Any TEAEs of special interest	37 (35.6)

Abbreviations: TEAE = treatment-emergent adverse event.
[a] Related TEAEs included events considered related or suspected to be related to study drug by the Investigator.
Note: Percentages are calculated using the N value. This table includes events with onset on or after the first dose in the study Part 1 or on or after first dose in the Part 2 of the study. Events with onset more than 30 days after the last dose of study drug in Part 1, but before first dose in Part 2, and events with onset more than 30 days after the last dose of study drug in Part 2 are excluded.

The most frequently reported treatment-emergent adverse events by preferred term were enuresis (19.2%), nausea (19.2%), vomiting (18.3%), headache (17.3%), and reduced weight (11.5%).

The total number of treatment-emergent adverse events, and the adverse event rate per 100 days of exposure are in the next sponsor table, which is applicable to all periods of the study through April 30, 2018. The table lists only those events that occurred in ≥ 5% of patients in any treatment group.

System Organ Class Preferred Term	Total N = 104 Total Events / Event Rate per 100 days
Any TEAEs	**426 / 1.044**
Gastrointestinal Disorders	94 / 0.230
Nausea	35 / 0.086
Vomiting	28 / 0.069
Diarrhoea	6 / 0.015
Constipation	6 / 0.015
Abdominal pain upper	5 / 0.012
Abdominal pain	3 / 0.007
Infections and Infestations	**67 / 0.164**
Nasopharyngitis	11 / 0.027
Upper respiratory tract infection	10 / 0.025
Gastroenteritis	6 / 0.015
Sinusitis	5 / 0.012
Pneumonia	3 / 0.007
Impetigo	3 / 0.007
Bronchitis	2 / 0.005
Eye infection	2 / 0.005
Nervous System Disorders	**51 / 0.125**
Headache	31 / 0.076
Dizziness	8 / 0.020
Renal and Urinary Disorders	**40 / 0.098**
Enuresis	35 / 0.086
Psychiatric Disorders	**38 / 0.093**
Nightmare	5 / 0.012
Somnambulism	5 / 0.012
Confusional arousal	5 / 0.012
Anxiety	2 / 0.005
Investigations	**32 / 0.078**
Weight decreased	12 / 0.029
Weight increased	5 / 0.012
Gamma-glutamyltransferase increased	2 / 0.005
Respiratory, Thoracic and Mediastinal Disorders	**19 / 0.047**
Cough	5 / 0.012
Nasal congestion	4 / 0.010
Oropharyngeal pain	2 / 0.005
Injury, Poisoning and Procedural Complications	**18 / 0.044**
Procedural pain	4 / 0.010
Contusion	3 / 0.007
Metabolism and Nutrition Disorders	**14 / 0.034**
Decreased appetite	9 / 0.022

Abbreviations: TEAE=treatment-emergent adverse event.
Note: The summary includes events experienced while receiving Xyrem, excluding events occurring in the Double-blind Treatment Period, for those subjects who received Placebo during that period. Events with onset more than 30 days after the last dose of study drug in the study are excluded.
Note: The event rate was defined as the number of events experienced divided by the number of days of Xyrem exposure as follows: 100 * Total Event Count / total Xyrem Exposure days for all subjects in the population. The Total Event count is the total number of events experienced.

A summary of treatment-emergent adverse events of special interest that occurred during all phases of the study is in the next sponsor table.

	Total N = 104
Any TEAEs of special interest	**33 (31.7)**
Psychiatric Disorders	**20 (19.2)**
Nightmare	5 (4.8)
Somnambulism	5 (4.8)
Confusional arousal	3 (2.9)
Anxiety	2 (1.9)
Acute psychosis	1 (1.0)
Affect lability	1 (1.0)
Confusional state	1 (1.0)
Depression	1 (1.0)
Irritability	1 (1.0)
Mental status changes	1 (1.0)
Mood altered	1 (1.0)
Sleep talking	1 (1.0)
Stress	1 (1.0)
Suicidal ideation	1 (1.0)
Thinking abnormal	1 (1.0)
Investigations	**12 (11.5)**
Weight decreased	12 (11.5)
Respiratory, Thoracic and Mediastinal Disorders	**4 (3.8)**
Sleep apnoea syndrome	3 (2.9)
Cheyne-Stokes respiration	1 (1.0)
Nervous System Disorders	3 (2.9)
Somnolence	2 (1.9)
Hypersomnia	1 (1.0)
General Disorders and Administration Site Conditions	**1 (1.0)**
Feeling jittery	1 (1.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; TEAE = treatment-emergent adverse event
Note: The summary includes events experienced while receiving Xyrem, excluding events occurring in the Double-blind Treatment Period, for those subjects who received Placebo during that period.
Note: This table includes events with onset on or after the first dose in the study Part 1 or on or after first dose in the Part 2 of the study. Events with onset more than 30 days after the last dose of study drug in Part 1, but before first dose in Part 2, and events with onset more than 30 days after the last dose of study drug in Part 2 are excluded.
PTs are sorted in descending order of subject incidence.

There were no deaths or new serious adverse events reported for the period from February 10, 2017, through April 30, 2018.

During the same period from February 10, 2017, through April 30, 2018, a single additional patient who was Xyrem®-naïve withdrew from the study because of a treatment emergent adverse event: a 14-year-old boy (b) (6) withdrew from Part 1 of the study (open-label safety period), on account of headache (which first developed at a Xyrem® dose of 8 g/night) and muscle pain (which first developed at a Xyrem® dose of 9 g/night); these symptoms were mild to moderate in severity and resolved when Xyrem® was discontinued.

7.5 Safety Laboratory Tests

Standard hematology, clinical chemistry, and urinalysis parameters data for this study for the period from February 10, 2017, through April 30, 2018, did not reveal any data of concern.

The analysis of growth hormone, insulin-like growth factor 1, and prolactin concentrations for the period from February 10, 2017, through April 30, 2018, revealed no data of significance; neither did the analysis of measures of precocious puberty (luteinizing hormone, follicle-stimulating hormone, testosterone, estradiol, and Tanner staging) conducted in girls < 8 years old and boys < 9 years old.

7.6 Electrocardiograms

Electrocardiographic data for Study 13-005 for the period from February 10, 2017, through April 30, 2018, were not significantly different from those provided in the original submission of this application and showed no items of concern.

7.7 Vital Signs, Height, Weight, And Body Mass Index

The additional blood pressure, pulse rate, respiratory rate, and temperature reported in this 120-day safety update did not yield any findings of significance.

No effect of Xyrem® on height was observed during the study.

Mean body weight percentile and mean body mass index percentile continued to demonstrate a slight decrease over the course of this study.

7.8 Polysomnographic Data

This 120-Day Safety Update contains cumulative polysomnographic data for the entire study.

Polysomnographic respiratory data for patients already receiving Xyrem® at study entry are in the sponsor table below. These data are based on full-night polysomnograms.

Parameters	Screening PSG (with Xyrem)[a] n = 32	End of Study PSG (with Xyrem) n = 30	Change from Screening – End of Study n = 30
	Mean (SD) Median (Q1, Q3)		
Apnea + Hypoapnea index	1.16 (1.269); 0.85 (0.25, 1.65)	2.54 (5.696); 0.50 (0.20, 1.70)	1.37 (5.331); 0.0 (-0.60, 0.70)
Apnea index	0.44 (0.750); 0.1 (0.0, 0.65)	1.63 (3.779); 0.10 (0.00, 0.50)	1.18 (3.665); 0.0 (0.00, 0.50)
Central apnea index	0.42 (0.72); 0.1 (0, 0.65)	1.53 (3.604); 0.10 (0.00, 0.40)	1.09 (3.485); 0.00 (-0.10, 0.40)
Obstructive apnea + hypoapnea index	0.73 (0.796); 0.45 (0.15, 1.05)	1.00 (3.193); 0.30 (0.00, 0.60)	0.28 (2.791); -0.10 (-0.60, 0.30)
Obstructive index	0.02 (0.072); 0 (0, 0)	0.09 (0.421); 0.00 (0.0, 0.0)	0.09 (0.420); 0.00 (0.0, 0.0)
Percent TST with SpO_2 < 80%	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)
Percent TST with SpO_2 ≤ 85%	0.01 (0.071); 0 (0, 0)	0.01 (0.055); 0.0 (0.0, 0.0)	0.0 (0.093); 0.0 (0.0, 0.0)
Percent TST with SpO_2 < 90%	0.09 (0.512); 0 (0, 0)	0.10 (0.395); 0 (0, 0)	0.00 (0.676); 0 (0,0)
Total time SpO_2 is ≤ 85% during TST (minutes)	0.06 (0.336); 0 (0, 0)	0.05 (0.274); 0 (0, 0)	-0.01 (0.450); 0 (0, 0)
Total time SpO_2 is < 90% during TST (minutes)	0.46 (2.562); 0 (0, 0)	0.44 (1.668); 0 (0, 0)	-0.05 (3.199); 0 (0,0)
Mean SpO_2 during TST (%)	97.52 (0.828); 97.5 (96.95, 98.20)	96.93 (1.471); 97.00 (96.20, 98.00)	-0.58 (1.292); -0.45 (-1.20, 0.30)

Abbreviations: n = number of subjects with a value collected for the test; PSG = polysomnogram; Q1 = first quartile; Q3 = third quartile; SpO_2 = oxygen saturation; TST = total sleep time.

Polysomnographic respiratory data for patients who were Xyrem®-naïve at study entry are in the next sponsor table. These data are also based on full-night polysomnograms.

Parameters	Screening PSG (without Xyrem)[a] n = 73	End of Stable Dose PSG (with Xyrem)[a] n = 64	Change from Screening to End of Stable Dose[a] n = 63	End of Study PSG (with Xyrem) n = 58	Change from Screening – EoS n = 57	Change from End of Stable Dose – EoS n = 58
	Mean (SD); Median (Q1, Q3)					
Apnea + Hypoapnea index	1.24 (1.180); 1 (0.40, 1.70)	1.924 (4.8115); 1.1 (0.4, 1.65)	0.652 (4.9763); -0.1 (-0.8, 0.6)	1.221 (1.6102); 0.6 (0.4, 1.3)	-0.188 (1.7218); -0.3 (-1.0, 0.2)	-0.267 (1.9212); -0.1 (-0.9, 0.4)
Apnea index	0.31 (0.483); 0.10 (0.00, 0.40)	1.155 (4.6975); 0.3 (0, 0.7)	0.853 (4.7606); 0 (-0.1, 0.3)	0.460 (1.0436); 0.2 (0.0, 0.5)	0.125 (0.9869); 0.0 (-0.2, 0.3)	-0.172 (1.5568); -0.1 (0.5, 0.1)
Central apnea index	0.27 (0.452); 0.1 (0, 0.40)	1.123 (4.6531); 0.3 (0, 0.675)	0.864 (4.7214); 0 (-0.1, 0.3)	0.412 (1.0231); 0.1 (0.0, 0.4)	0.118 (0.9765); 0.0 (-0.2, 0.3)	-0.187 (1.5398); -0.1 (-0.4, 0.1)
Obstructive apnea + hypoapnea index	0.95 (0.937); 0.7 (0.30, 1.20)	0.797 (0.8989); 0.45 (0.1, 1.150)	-0.205 (0.9494); -0.2 (-0.7, 0.2)	0.8 (1.1547); 0.4 (0.1, 0.9)	-0.298 (1.2184); -0.2 (-1.0, 0.1)	-0.086 (0.9651); -0.5 (-0.6, 0.4)
Obstructive index	0.03 (0.088); 0 (0, 0)	0.03 (0.092); 0 (0, 0)	-0.01 (0.111); 0 (0, 0)	0.04 (0.229); 0.0 (0, 0)	0.01 (0.243); 0 (0, 0)	0.01 (0.197); 0 (0, 0)
Percent TST with SpO_2 < 80%	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)
Percent TST with SpO_2 ≤ 85%	0 (0); 0 (0, 0)	0 (0.018); 0 (0, 0)	0 (0.018); 0 (0, 0)	0.0 (0.026); 0 (0, 0)	0.0 (0.026); 0 (0, 0)	0.0 (0.030); 0 (0, 0)
Percent TST with SpO_2 < 90%	0.00 (0.026); 0 (0, 0)	0.03 (0.167); 0 (0, 0)	0.02 (0.171); 0 (0, 0)	0.01 (0.080); 0 (0, 0)	0.01(0.087); 0 (0, 0)	0.01 (0.093); 0 (0, 0)
Total time SpO_2 is ≤ 85% during TST (minutes)	0 (0); 0 (0, 0)	0.01 (0.072); 0 (0, 0)	0.01 (0.073); 0 (0, 0)	0.02 (0.132); 0 (0, 0)	0.02 (0.133); 0 (0, 0)	0.01 (0.138); 0 (0, 0)
Total time SpO_2 is < 90% during TST (minutes)	0.03 (0.140); 0 (0, 0)	0.13 (0.826); 0 (0, 0)	0.10 (0.851); 0 (0, 0)	0.07 (0.347); 0 (0, 0)	0.03 (0.388); 0 (0, 0)	0.03 (0.395); 0 (0, 0)
Mean SpO_2 during TST (%)	97.40 (0.944); 97.3 (96.80, 98.00)	97.09 (0.998); 97.1 (96.40, 97.75)	-0.25 (0.917); -0.3 (-0.80, 0.30)	97.12 (0.951); 97.20 (96.70, 97.50)	-0.27 (1.090); -0.20 (-1.10, 0.20)	0.02 (1.083); -0.10 (-0.60, 0.50)

Abbreviations: EoS = End of study; n= number of subjects with a value collected for the test; PSG = polysomnogram; Q1 = first quartile; Q3 = third quartile; SpO_2 = oxygen saturation; TST = total sleep time.

The changes displayed above do not appear to have been clinically significant.

7.9 Columbia-Suicide Severity Rating Scale, Children's Depression Inventory, And Multidimensional Anxiety Scale For Children-10

Among subjects who took Xyrem®, two subjects responded positively to the Columbia-Suicide Severity Rating Scale. Those were the 2 subjects with serious adverse events for whom narratives have been provided earlier and are listed in the following table. A further description of those patients is not warranted.

Subject Number Age[a] / Sex / Race	Treatment Period	System Organ Class *Preferred Term*	Relationship to Study Drug	Severity Outcome
(b) (6)	Dose Titration Period	Psychiatric Disorders	Related	Severe
13 / Male / White		*Acute Psychosis*		Recovered / Resolved
(b) (6)	Dose Titration Period	Psychiatric Disorders	Related	Moderate
14 / Male / White		*Suicidal ideation*		Recovered / Resolved

[a] Age in years at the first dispensation of study drug.

A slight downward trend in mean Children's Depression Inventory T-scores in both Xyrem® naïve and Xyrem®-treated subjects was observed during the course of the study (higher scores correlate with more severe depression). Scores, however, remained within the average range.

Scores on the Multidimensional Anxiety Scale for Children-10 remained steady during the study.

8. Additional Safety Data Supporting Current Application

The sponsor has cited the following sources of data in support of the use of Xyrem® in children: postmarketing data and the published literature.

- Postmarketing data.
- Published literature.

Each of the above items is further addressed below.

8.1 Post-Marketing Data

From the launch of Xyrem® for marketing in September 2002 through October 12, 2017, the following has been the extent of exposure to Xyrem®.

2874 unique pediatric patients initiated treatment with Xyrem® in the United States. These included:

- 422 children < 12 years old (0 - < 12 years of age) and further consisted of 44 children less than 7 years old (0 - < 7 years of age).
- 2452 adolescents aged 12 to < 18 years of age.

The total cumulative exposure to Xyrem® was:

- 488 patient-years for children (< 12 years of age).
- 2309 patient-years for adolescents ranging from 12 to < 18 years of age.

3671 instances of adverse events were reported in pediatric subjects during that subjects, included 378 instances associated with serious adverse events. Further:

- In children, adverse events reported in ≥ 5% of all instances of reports included nausea, somnolence, vomiting, headache, insomnia, and enuresis
- In adolescents, adverse events reported in ≥ 5% of all instances of reports included nausea, somnolence, vomiting, headache, dizziness, fatigue, insomnia, "condition aggravated," and decreased weight.

Serious adverse events reported in ≥ 1% of children have included seizure, sleep apnea syndrome, and vomiting.

6 deaths were reported: 4 in children and 2 in adolescents. None of the deaths seen were attributable to Xyrem® (the brief narratives provided by the sponsor are consistent with that conclusion).

Additional analyses of post-marketing data are also provided by the sponsor who has concluded that the cumulative post-marketing pediatric safety data are consistent with the post-marketing data for Xyrem® in adults and with the existing label for Xyrem® use in adults.

8.2 Published Literature

A summary review of data from 6 published studies has been presented. In those studies, 109 patients have been exposed to Xyrem® for periods ranging from 2 to 90 months.

Reasons for discontinuing study drug in those studies have included increased nightmares, suicidal ideation, dissociative feelings, lack of efficacy, unspecified adverse events, sleep loss, nausea, constipation, body ache, and dizziness.

Adverse events reported in > 10% of patients in any one study include weight loss, headache, nausea, disrupted nighttime sleep, irritability, parasomnias, dry mouth, increased awakenings, dizziness, terminal insomnia, groaning, and sleepiness.

Other safety data are also included. However, the safety data in the published literature for children using Xyrem® indicates a safety profile similar to that observed in adults.

9. 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 (modified) Risk Evaluation and Mitigation Strategy (REMS). The REMS itself is comprised of multiple documents.

That review has been assisted by the input of many 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 section 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. The recommendations that I have been have been consistent with my review of the data in this application.

I am however in agreement with the finalized and agreed-upon versions of the documents listed above that are to accompany the approval letter for this application.

10. Summary Of Statistical Review

The primary statistical review of this sNDA has been performed by Dr. Xiaorong (Sharon) Yan of the Division of Biometrics I. Her review was completed on October 15, 2018.

Her review has been directed mainly at the efficacy results of the randomized, double-blind, placebo-controlled, withdrawal phase of Study 13-005, as derived from the analysis of the primary and key secondary efficacy endpoints for that study.

She has concluded that Study 13-005 has provided sufficient evidence that Xyrem® is effective as compared with placebo in treating cataplexy in patients

with narcolepsy. She has also substantiated the sponsor's main analysis of the two key secondary efficacy endpoints.

Please see the full text of Dr. Yan's review for more details.

10.1 Summary Of Interim Analysis

Dr. Yan's review has also substantiated the results of the interim analysis of the change from baseline in the weekly frequency of cataplexy attacks across the randomized, double-blind, placebo-controlled withdrawal period. As already noted (see Section 6.2), that analysis was conducted when 35 patients had completed or withdrawn early from that period of the study. The interim analysis included 18 patients on placebo and 17 patients on Xyrem®. The results of that analysis are summarized in the following table (Table 4) that I have copied from Dr. Yan's review.

Table 4 Interim Results: Change in the Weekly Number of Cataplexy Attacks

	Placebo N=18	**Xyrem N=17**
Baseline Number of Cataplexy		
Mean (SD)	12.38 (28.69)	11.79 (16.72)
Median	5.31	4.67
Min, Max	0, 125.4	0.0, 51.3
25%, 75% quartile	1.0, 10.0	0.6, 10.8
Double-blind Number of Cataplexy		
Mean (SD)	25.25 (23.86)	13.68 (21.03)
Median	21.25	5.38
Min, Max	2.5, 95.5	0, 75.1
25%, 75% quartile	14.0, 24.7	0.5, 10.0
Change in the Number of Cataplexy		
Mean (SD)	12.87 (17.43)	1.89 (8.03)
Median	12.70	0.0
Min, Max	-29.9, 56.5	-4.5, 32.1
25%, 75% quartile	3.5, 17.6	-1.0, 1.6
p-value (primary)		0.0002

Source: Reviewer's analysis

As has already been noted in this review, Amendment 4 to Study 13-005 provided for the termination of the randomized withdrawal phase of that study. Dr. Yan points out that a total of 63 patients had been randomized to that phase of the study by the time that protocol amendment had become effective at all study sites.

11. Summary Of Nonclinical Review

Dr. Melissa Banks-Muckenfuss was the primary nonclinical (pharmacology-toxicology) reviewer of this submission. Her review has primarily focused on the results of the animal toxicology study (20078509) conducted under the pediatric Written Request finalized on April 25, 2017. She has also reviewed a pilot pharmacokinetic and tolerability study of sodium oxybate in juvenile rats (Study 1301-016). Her review was completed on October 24, 2018.

The animal toxicology study conducted under the above Written Request was a 10-week study (with an 8-week recovery period) in juvenile rats of the following doses of sodium oxybate: 0, 100, 300, and 900 mg/kg orally QD).

Dr. Banks-Muckenfuss has, in summary drawn attention to the following, regarding the results of the 10-week toxicology study conducted in juvenile rats.

- Deaths were observed at doses of 300 mg/kg QD and 900 mg/kg QD, preceded by clinical signs that included uncoordinated gait, reduced activity, reduced respiratory rate, deep breathing, low carriage, partially closed eyes, and other signs; these clinical signs indicated a depressant effect of sodium oxybate on the central nervous system and on respiration. These effects were analogous to the central nervous system and respiratory depressant effects observed in humans administered Xyrem® that are described in the Prescribing Information for that drug. Other clinical signs, such as, but not limited to, reductions in food consumption, were also observed at the above doses of 300 mg/kg QD and 900 mg/kg QD in the juvenile animal study.

- Juvenile animals showed an increased sensitivity to the central nervous system and respiratory depressant effects of Xyrem®.

- The no-observed-adverse-effect level in the juvenile rat toxicity study was 100 mg/kg QD, based on the above.

- Toxicokinetic data indicated that systemic exposure to sodium oxybate increased, generally greater than dose-proportionally, with increasing doses, but also decreased with repeated dosing (i.e., in older rats). There were no sex differences in exposure to sodium oxybate. A tendency for younger rats to show higher exposures was observed in the pilot pharmacokinetic study in juvenile rats. There was considerable variability in pharmacokinetic exposure at the same dose in the juvenile rat toxicology study.

- There is no clear safety margin (based on body surface area-adjusted calculations) between the no-observed-adverse-effect level of 100 mg/kg QD in the juvenile rat toxicity study and the initial total nightly doses proposed by the sponsor for pediatric dosing (ranging from (b) (4) per night to 4.5 grams per night depending on body weight). Inferences that can be drawn from safety margins that are calculated based on comparisons of pharmacokinetic data have a number of limitations that Dr. Banks-Muckenfuss has outlined in her review, but no safety margin can be delineated on that basis either.

Dr. Banks-Muckenfuss has recommended, based on the above-described lack of a safety margin, that Xyrem® **not** be approved for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy.

She does, however, note the following:

- In the juvenile rat toxicity study, dosing was initiated at an age comparable to 2 years in humans (based on the extent of central nervous system development).

On the other hand, Xyrem® is proposed for use in children aged 7 years and older.

- In pediatric subjects, Xyrem® doses are to be titrated and the total nightly dose administered in two divided doses; that was not the case in the juvenile rat toxicology study.

For further details, please see the review by Dr. Banks-Muckenfuss, who has separately concluded that the sponsor has met the terms of the pediatric Written Request finalized on April 25, 2017.

Dr. Lois Freed, supervisory pharmacologist, notes that plasma exposures at the no-adverse effect level dose (100 mg/kg) for adverse effects in juvenile rats are less than that in humans at the maximum recommended human dose of 9 g/night. She however observes that all deaths were preceded by clinical signs consistent with the known pharmacological effects of sodium oxybate and which are monitorable in humans. Dr. Freed further notes that similar adverse central nervous system effects have been observed in adults and are described in labeling. As discussed by Dr. Freed, there has been substantial use of Xyrem in pediatric patients since its approval in 2002. According to the sponsor, during this period, 2874 pediatric patients have received Xyrem® in the U.S., with 422 below the age of 12 years and, of these, 44 below the age of 7 years; no Xyrem®-related deaths have been identified. The sponsor also cited published literature, including six studies reporting safety data in children and adolescents treated with Xyrem® (see Summary of Clinical Safety in current application). In addition, this sNDA includes clinical data in the pediatric population. Dr. Freed concludes that clinical data are arguably the most relevant for determining the safety of a potential therapeutic, and that, if the clinical team concludes that the available data support approval of sodium oxybate for use in pediatric patients for the proposed indication, there is no objection to approval of the application from a nonclinical standpoint.

Additional note from this reviewer. The available clinical safety data for Xyrem®, including data derived from its use in children appear sufficient to offset the safety concerns that have arisen from the results of the juvenile rat toxicity study conducted with sodium oxybate. Thus, the available animal toxicology data do not preclude the approval of Xyrem® for use in children.

12. Summary Of Clinical Pharmacology Review

The main clinical pharmacology reviewers of this supplemental application were Drs. Kevin Krudys and Dawei Li. Their review was completed on October 23, 2018.

Drs. Krudys and Li have summarized the pharmacokinetic data in this application in their review. They have recommended that this application be approved and

have also concluded that the sponsor has met the terms of the pediatric Written Request, finalized on April 25, 2017.

Their main conclusions have been as follows.

- The pharmacokinetics of Xyrem® in children are qualitatively similar to those observed in adults.
- Plasma sodium oxybate concentrations were generally higher after the second nightly dose due to the combined effects of accumulation and food.
- Dose-proportionality assessments suggest dose proportionality in C_{max} and supra-proportionality in AUC, indicating non-linear clearance.

Drs. Krudys and Li have also made recommendations regarding the Prescribing Information proposed by the sponsor.

For further details, please see the review by Drs. Krudys and Li.

13. Summary Of Chemistry Review

The primary chemistry review of this submission was performed by Dr. Rohit Kolhatkar.

Dr. Kolhatkar has concluded that this supplemental application may be approved. He has also recommended a few changes to the Prescribing Information proposed by the sponsor.

Please see Dr. Kolhatkar's review for additional details.

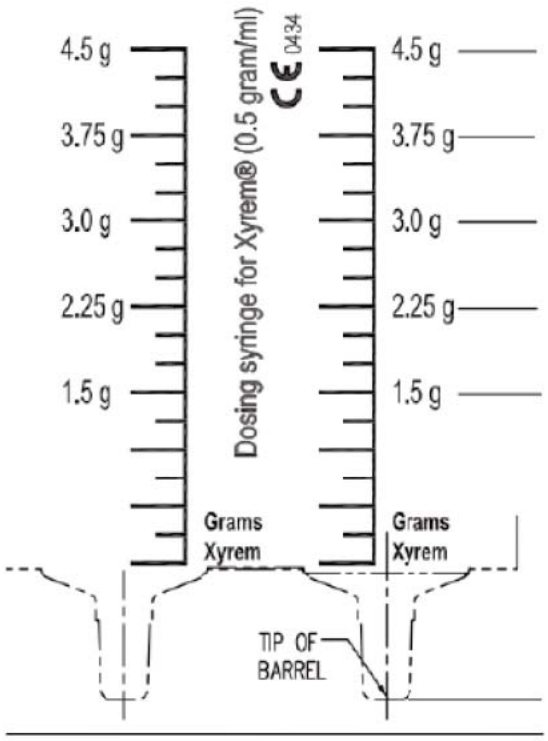
13.1 Currently-Used And Proposed Syringes

Dr. Kolhatkar's review has included a comparison of the syringe currently used for dispensing Xyrem® with the syringe proposed for pediatric use. The dispenser labels for each are in the following figure which I have copied from his review.

(b) (4)

(b) (4)

Current Commercial Dispenser Label



For details of the dispensing and dilution of individual doses of Xyrem®, please refer to the approved and proposed Prescribing Information for that drug.

14. Summary Of Office Of Surveillance And Epidemiology Reviews

Two reviews of this application have been completed by the staff of the Office of Surveillance and Epidemiology. These reviews are described further below.

14.1 Review By Division Of Risk Management (DRISK)

Dr. Yasmeen Abou-Sayed of DRISK has completed a review of the modification to the Risk Evaluation and Mitigation Strategy (REMS) proposed under this application. Her review was completed on October 16, 2018, and contains a full list of the REMS-related documents that she has reviewed.

She concluded her review by stating that the REMS modifications proposed by the sponsor in the original submission of this application, and subsequent submissions are not acceptable. At that time, a number of comments were

conveyed to the sponsor. Communications between the Agency and sponsor regarding the text of the REMS continued after the completion of her review and were continuing at the time of completion of my review.

14.2 Review By Division Of Medication Error Prevention And Analysis (DMEPA)

Dr. Ebony Whaley of DMEPA has completed a consultative review of a human factors validation study report and of labels and labeling submitted with this application; her review was completed on October 4, 2018. The human factors validation study that was conducted by the sponsor was directed at a proposed new Xyrem® dosing syringe, the container label for which has already been depicted in my summary of the Chemistry review of this submission.

Dr. Whaley has concluded that the results of the human factors validation study "*demonstrate that representative users can use the revised oral dosing syringe safely and effectively*." In her review, she has also identified text in the proposed Prescribing Information that may lead to medication errors, and has recommended changes in that text to minimize such errors.

15. Summary Of Office Of Prescription Drug Promotion (OPDP) Reviews

Two reviews have been completed by Christine Bradshaw, Regulatory Review Officer in that Office on the same date

A review completed on October 24, 2018, has responded to a consultation from this Division and the Division of Risk Management (DRISK) for a labeling review from that office regarding (b) (4) components of the proposed modified REMS for Xyrem® associated with this sNDA. In that review, Ms. Bradshaw has acknowledged comments made by DRISK regarding the (b) (4) components of the proposed modified REMS for Xyrem®. She states that OPDP will not be reviewing those materials as part of this supplement. She further recommends that the sponsor may submit those materials to the OPDP in compliance with advertising and promotion regulations.

A second review also completed on October 24, 2018, has responded to a consultation from this Division regarding the proposed Prescribing Information, Medication Guide, and Instructions for Use accompanying this application. That review has been combined with a review from the Office of Medical Policy Programs (by Sharon Williams, MSN) and a number of recommendations made regarding these labeling components.

An internal memorandum to the Division of Risk Management preceded the above reviews.

16. Controlled Substances Staff Review

A review of this application has been completed by Alan Trachtenberg, MD, MPH, of the Controlled Substances Staff. That review was completed on September 25, 2018

Dr. Trachtenberg has recommended that, from the perspective of the Controlled Substances Staff, this sNDA can be approved. He further notes that the proposed changes to Xyrem® labeling do not involve changes to Section 9 (Drug Abuse and Dependence) or any other sections that address drug abuse and dependence.

17. Financial Disclosure Information

Financial disclosure information has been collected only for the single clinical efficacy trial, 13-005, included in this submission.

17.1 Components Of Certification

17.1.1 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 these studies. 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).

17.1.2 Certification Pertinent To Investigators/Sub-Investigators With Disclosable Financial Interests (FDA Form 3455)

The sponsor has listed a single investigator, (b) (4) to whom such certification applied. Further, the sponsor has cited a number of reasons why that investigator that investigator was cleared for participation in Study 13-

005 and why his participation in that study was appropriate and was unlikely to have introduced significant bias into the results of the study.

17.2 Reviewer's Comments

It appears unlikely that the financial arrangements disclosed above introduced significant bias into the results of the single clinical study (13-005) that were submitted with this application.

18. Site Inspection Report

A Clinical Inspection Summary for this application was filed on October 16, 2018 by Roy Blay, PhD, Reviewer, Good Clinical Practice Assessment Branch, Division of Clinical Compliance Evaluation, Office of Scientific Investigations.

Two study sites were inspected. Information for those sites and the conclusions drawn by the inspecting team are in the following table which I have copied from the Clinical Inspection Summary.

Site # Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
(b) (4)	13-005 Subjects: 12	13-17 Aug 2018	NAI
	13-005 Subjects: 25	17-20 Sep 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

19. Fulfillment Of Terms Of Pediatric Written Request

The sponsor has fulfilled the terms of the pediatric Written Request finalized on April 25, 2017.

20. Overall Conclusion

This Supplemental New Drug Application has provided sufficient data to support the approval of Xyrem® (b) (4)

21. Recommendation

This Supplemental New Drug Application may be approved. An approval letter may accordingly be issued accompanied by product labeling that is agreed upon between the Agency and sponsor.

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
10/26/2018

ERIC P BASTINGS
10/26/2018
I concur, and will issue an approval letter for this supplement.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21196/S-030

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/BLA #:	NDA 21,196
Drug Name:	Xyrem® (sodium oxybate)
Indication(s):	(b) (4)
Applicant:	Jazz Pharmaceuticals
Date(s):	Date of Submission: April 27, 2018 PDUFA Date: October 27, 2018
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Sharon Yan
Concurring Reviewers:	Kun Jin, Team Leader Jim Hung, Director
Medical Division:	Neurology
Clinical Team:	Ranjit Mani, Clinical Reviewer Eric Bastings, Deputy Director Billy Dunn, Director
Project Manager:	Vandna Kishore

Table of Contents

1 EXECUTIVE SUMMARY 4

2 INTRODUCTION 4

2.1 OVERVIEW 4
SOURCE: REVIEWER'S SUMMARY 5
2.2 DATA SOURCES 5

3 STATISTICAL EVALUATION 5

3.1 DATA AND ANALYSIS QUALITY 5
3.2 EVALUATION OF EFFICACY 5
3.2.1 Evaluation of Efficacy for Study 13-005 5
3.2.1.1 Study Design 5
3.2.1.2 Study Endpoints 7
3.2.1.3 Statistical Methodologies 7
3.2.1.3.1 General Consideration 7
3.2.1.3.2 Analyses of the Primary Endpoints 7
3.2.1.3.3 Analysis of Secondary Endpoints 8
3.2.1.3.4 Handling of Missing Values 8
3.2.1.3.5 Interim Analysis 9
3.2.1.4 Study Results 9
3.2.1.4.1 Patient Disposition 9
3.2.1.4.2 Patient Baseline Disease Characteristics 11
3.2.1.5 Efficacy Results 12
3.2.1.5.1 Primary Endpoint – Change in the Weekly Number of Cataplexy Attacks 12
3.2.1.5.2 Secondary Endpoints 14
3.3 EVALUATION OF SAFETY 15

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS 15

4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION 15
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS 16

5 SUMMARY AND CONCLUSIONS 17

5.1 STATISTICAL ISSUES 17
5.2 COLLECTIVE EVIDENCE 17
5.3 CONCLUSIONS AND RECOMMENDATIONS 17

LIST OF TABLES

Table 1 List of All Studies Included in This Review..... 5
Table 2 Demographic Characteristics (Randomized Subjects) 11
Table 3 Baseline Disease Characteristics 11
Table 4 Interim Results: Change in the Weekly Number of Cataplexy Attacks 12
Table 5 Final Results of Weekly Number of Cataplexy Attacks..... 13
Table 6 CGIc for Cataplexy Severity..... 14
Table 7 Change from Baseline in ESS (CHAD) Score at the End of Doub-blind Period..... 15
Table 8 Change in the Weekly Number of Cataplexy Attacks by Subgroup 15
Table 9 Change in the Weekly Number of Cataplexy Attacks by Xyrem Status at Entry 17

LIST OF FIGURES

Figure 1 Study Schema 7
Figure 2 Patient Disposition..... 10

1 EXECUTIVE SUMMARY

This pediatric supplemental NDA is to support the expansion of the labeling to include the pediatric use of Xyrem (sodium oxybate) oral solution for the treatment of cataplexy in patients with narcolepsy.

The Xyrem pediatric clinical program consists of a single Phase 2/3 study (Study 13-005) of Xyrem in the treatment of pediatric subjects, ages 7 to 17, with narcolepsy with cataplexy. The study was conducted under Pediatric Written Request (PWR), as amended on 25 April 2017.

Study 13-005 was a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of Xyrem.

After reviewing the results from a pre-planned interim analysis based on 35 subjects, the Data Safety Monitoring Board (DSMB) recommended that the placebo treatment in the Double-blind Treatment Period of the trial be stopped as the prespecified stopping criterion ($p < 0.005$) was met. The interim results showed an increase of 12.7 in the median of weekly number of cataplexy attacks in patients withdrew from Xyrem and received placebo, compared to no change in patients continued in Xyrem treatment during the double-blind period with a p-value of 0.0002 in the treatment difference.

The results from the final analysis on the primary efficacy endpoint of change in weekly number of cataplexy attacks were similar to the ones from the interim analysis.

2 INTRODUCTION

2.1 Overview

Xyrem® (sodium oxybate) oral solution (NDA 21-196) is approved in the United States (US) for the treatment of cataplexy in patients with narcolepsy (2002) and for the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy (2005).

Jazz Pharmaceuticals conducted one efficacy and safety study (Protocol 13-005) with Xyrem in pediatric patients with narcolepsy with cataplexy to support the application. Study 13-005 was conducted under the Pediatric Written Request.

Study 13-005 was a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of Xyrem (sodium oxybate) oral solution in pediatric subjects with narcolepsy with cataplexy.

On February 24, 2016, the Data and Safety Monitoring Board (DSMB) for this study reviewed the results from a pre-planned interim analysis of the primary efficacy based on 35 subjects

having completed or discontinued from the Double-blind Treatment Period of the study. The results of this analysis showed positive efficacy on the primary endpoint, the change in the weekly number of cataplexy attacks, at a significance level of $p < 0.005$. Since this met the prespecified criterion for success, the DSMB recommended that the placebo treatment in the Double-blind Treatment Period of the trial be stopped. The DSMB further recommended that the open-label portion of the study be continued, so as not to further expose subjects to placebo treatment.

The following table presents a summary of the study.

Table 1 List of All Studies Included in This Review

	Phase and Design	Treatment Period	Comparator	# of Subjects per Arm	Study Population
13-005	Phase 3, double-blind, placebo-controlled, 2-arm, randomized withdrawal	open-label Stable Dose Period (2 weeks) and Double-Blind Withdrawal (2 weeks)	Placebo	Placebo: 32 Xyrem: 31	Pediatric patients with narcolepsy with cataplexy

Source: Reviewer's summary

2.2 Data Sources

All documents reviewed for this BLA supplement submission are in electronic form. The path to the original submission on 4/27/2018 is \\CDSESUB1\evsprod\NDA021196\0278.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No major issues were identified in the submission of data and study documents.

3.2 Evaluation of Efficacy

3.2.1 Evaluation of Efficacy for Study 13-005

3.2.1.1 Study Design

The primary objectives of Study 13-005 were to evaluate the efficacy and safety of Xyrem (sodium oxybate) oral solution in the treatment of cataplexy in pediatric subjects with narcolepsy.

The study was a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of Xyrem (sodium oxybate) oral solution.

Children and adolescents aged 7 to 16 years diagnosed with narcolepsy with cataplexy who were being treated with Xyrem or who were Xyrem naïve, with or without concomitant stable stimulant use, were eligible to enter the study. For this study, a Xyrem-naïve subject was defined as a subject who had never been treated with Xyrem or who was previously treated with Xyrem and discontinued Xyrem for at least 1 month prior to the Screening visit for reasons other than lack of efficacy and / or tolerability.

Following Screening, subjects who were Xyrem naïve entered the open-label Dose Titration Period of up to 10 weeks. Once the Xyrem dose had been optimized per the Investigator's judgment, these subjects entered the open-label Stable Dose Period with that dose. Subjects who were on Xyrem at study entry remained on their stable dose and regimen and entered the Stable Dose Period following screening. Subjects were eligible to enter the Double-blind Treatment Period if the dose and regimen of Xyrem remained unchanged during the Stable Dose Period and, in the judgment of the Investigator, no clinically significant worsening in narcolepsy symptoms or clinically significant adverse events due to Xyrem treatment had occurred.

Subjects entering the Double-blind Treatment Period were randomized 1:1 to receive one of the following 2 treatments during the 2-week Double-blind Treatment Period (randomized-withdrawal):

- Xyrem: Active Xyrem was continued as a double-blind treatment at the stable dose taken and regimen used in the prior 2 weeks
- Xyrem placebo: Xyrem placebo was initiated as a double-blind treatment at a volume and regimen equivalent to the Xyrem dose taken in the prior 2 weeks.

At least 100 subjects were to be enrolled in approximately 70 sites globally. It was planned to have 70 subjects entering the double-blind treatment period.

As a result of a preplanned interim analysis, which showed positive efficacy results on the primary efficacy endpoint, the protocol was amended (Amendment 4) to replace the placebo treatment in the Double-blind Treatment Period with open-label Xyrem treatment. After Amendment 4 became effective (effective date from May 17, 2016), all subjects entering the Double-blind Treatment Period received open-label Xyrem treatment. An amended Written Request was issued on April 25, 2017, reflecting this change. For administrative reasons, the term "Double-blind Treatment Period" continued to be used throughout the protocol.

A schematic description of the study design is presented in Figure 1.

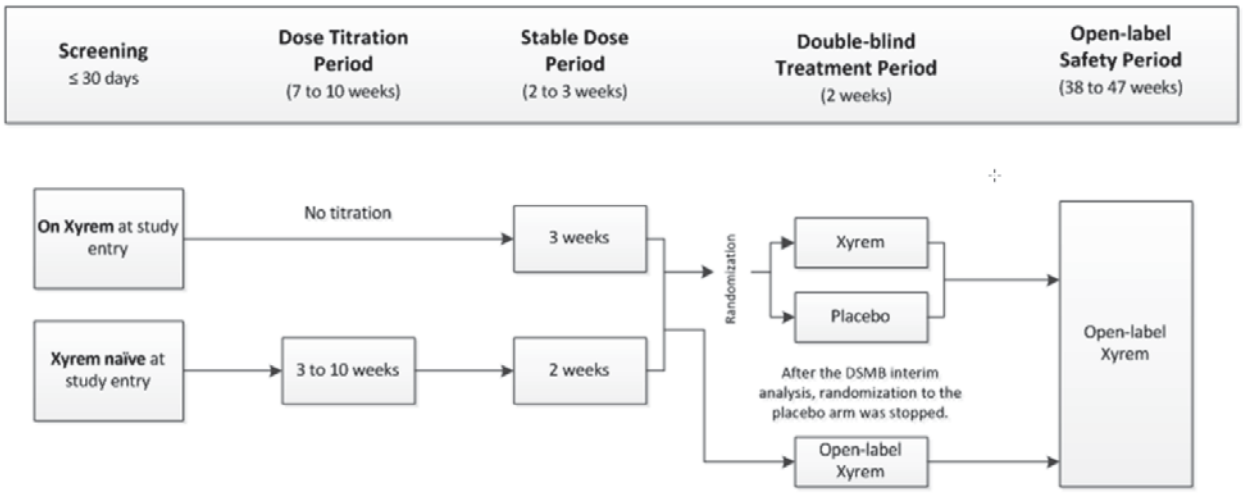


Figure 1 Study Schema
Source: Figure 1 of Clinical Study Report

3.2.1.2 Study Endpoints

The primary endpoint (Tier 1) is the change in weekly number of cataplexy attacks from the last 2 weeks of the Stable Dose Period to the 2 weeks of the Double-blind Treatment Period.

Subjects (if needed, with the help of caregiver) were to complete a cataplexy frequency diary daily in the evening to record the daily frequency of the subject's cataplexy attacks.

Key secondary endpoints (Tiers 2 and 3) are:

1. CGIc for cataplexy severity from the end of the Stable Dose Period to the end of the Double-blind Treatment Period
2. Change in the ESS (CHAD) score from the end of the Stable Dose Period to the end of Double-blind Treatment Period

3.2.1.3 Statistical Methodologies

3.2.1.3.1 General Consideration

The Efficacy Population consisted of all subjects who were randomized and who completed at least 5 days of dosing in the Double-blind Treatment Period. This population was used as the main analysis population for tables of the primary and secondary efficacy endpoints.

3.2.1.3.2 Analyses of the Primary Endpoints

For the assessment of the primary efficacy endpoint, the number of weekly cataplexy attacks was determined in each period (last 14 days of the Stable Dose Period or during the Double-Blind Period) by taking the total number of cataplexy attacks reported during the period and dividing by the number of days during the period where a diary was completed. This ratio was then multiplied by 7 to determine the weekly number of attacks. Change in the weekly number of cataplexy attacks was calculated as the weekly number of cataplexy attacks during the Double-blind Treatment Period minus the weekly number of cataplexy attacks during the last 2 weeks of the Stable Dose Period (baseline).

The primary efficacy analysis compared Xyrem and Placebo using a non-parametric analysis of covariance (ANCOVA) by ranking both the baseline covariate and the change from baseline value without regard to assigned treatment group. The ANCOVA was performed with the rank for the change from baseline as the dependent variable, treatment as a factor, and the rank for the baseline value as the covariate. A sensitivity analysis was performed adjusting for age group (7 to 11 years of age and 12 to 17 years of age).

3.2.1.3.3 Analysis of Secondary Endpoints

Key Secondary Endpoints Analyses

CGIc for cataplexy severity was completed at the end of the Double-blind Treatment Period and investigators rated their impression of any change in the severity of the subject's cataplexy since baseline (defined as the end of the stable dose period) on a 7-point scale. The analysis assigned a value to each ordinal category, ranging from -3 to 3 (Very Much Worse to Very Much Improved), and the overall distribution was compared between Xyrem and Placebo by the Cochran-Mantel-Haenszel (CMH) test for row mean score difference.

An exploratory analysis compared the percent of subjects who worsened, defined as "much worse" or "very much worse", between treatments using a chi square test.

For the ESS (CHAD) endpoint, the change in score from the Stable Dose Period to the end of the Double-blind Treatment Period was compared between treatment groups using the nonparametric ANCOVA model, as described in the primary endpoint analyses. A sensitivity analysis was performed adjusting for use of stimulants in the Stable Dose Period.

3.2.1.3.4 Handling of Missing Values

For the ESS (CHAD) endpoint, a missing value in the Double-blind Treatment Period was imputed using the last available value from the Stable Dose Period (i.e., baseline value carried forward).

3.2.1.3.4.1 Multiplicity Adjustment

A tiered approach was planned to control the Type 1 family-wise error rate at the two-sided 0.05 significance level. At the pre-specified interim analysis, the DSMB recommended stopping Placebo treatment during Double-blind Treatment Period due to the positive primary efficacy Results. Statistical testing of the secondary endpoints was performed after all randomized subjects completed the Double-blind Treatment Period, starting with Tier 2 in sequential order by tier (as noted in the section above, at the 0.05 significance level). If Xyrem was significantly better than Placebo, then testing continued with the next tier.

3.2.1.3.5 Interim Analysis

An interim analysis was conducted as planned after 35 subjects completed or discontinued early from the Double-blind Treatment Period. The data were reviewed by a DSMB that recommended stopping placebo treatment in the Double-blind Treatment Period and continuing the study as an open-label safety study.

Considerations for stopping the study early included the following as initially planned.

For stopping the study early because of treatment success, so that fewer subjects would be exposed to placebo: The O'Brien-Fleming approach was to be used with the primary efficacy endpoint. This endpoint was to be tested at a significance level of 0.005 at the interim analysis. If statistical significance was shown, the DSMB could recommend stopping the study considering the overall study objectives and subject's safety. If the study was not stopped, to maintain an overall alpha of 0.05, the final analysis was to be conducted at a significance level of 0.048, based on one prior look at the data.

Stopping rules for futility and safety were also pre-specified in the protocol and assessed by the DSMB.

3.2.1.4 Study Results

3.2.1.4.1 Patient Disposition

Of the 136 subjects screened, 106 subjects were enrolled: 74 subjects were Xyrem naïve and 32 subjects were on Xyrem at study entry. Xyrem naïve subjects who entered the study underwent dose titration based on body weight category during the Dose Titration Period. About 90% of subjects achieved a tolerable and efficacious dose and entered the Stable Dose Period. Subjects on Xyrem at study entry immediately entered the Stable Dose Period. After completing the Stable Dose Period, eligible subjects entered the Double-blind Treatment Period followed by the Open-label Safety Period.

Overall, as of 10 February 2017 (primary database cutoff date), a total of 17 subjects discontinued from the study during various study periods (7 subjects discontinued from the Dose Titration Period; 3 subjects discontinued from the Stable Dose Period; 1 subject discontinued from the Double-blind Treatment Period; 6 subjects discontinued from the Open-label Safety Period).

Note that the primary endpoint was met in the interim analysis, which included 35 randomized subjects. The randomization to Placebo or Xyrem during the Double-blind Treatment Period continued until Protocol Amendment 4 became effective. Therefore, additional subjects were randomized after the interim analysis and the final Efficacy population consisted of 63 subjects randomized to Xyrem (31 subjects) or Placebo (32 subjects) who completed at least 5 days of dosing in the Double-blind Treatment Period.

Subject disposition at the time of the data cut off on 10 February 2017 is depicted in Figure 2.

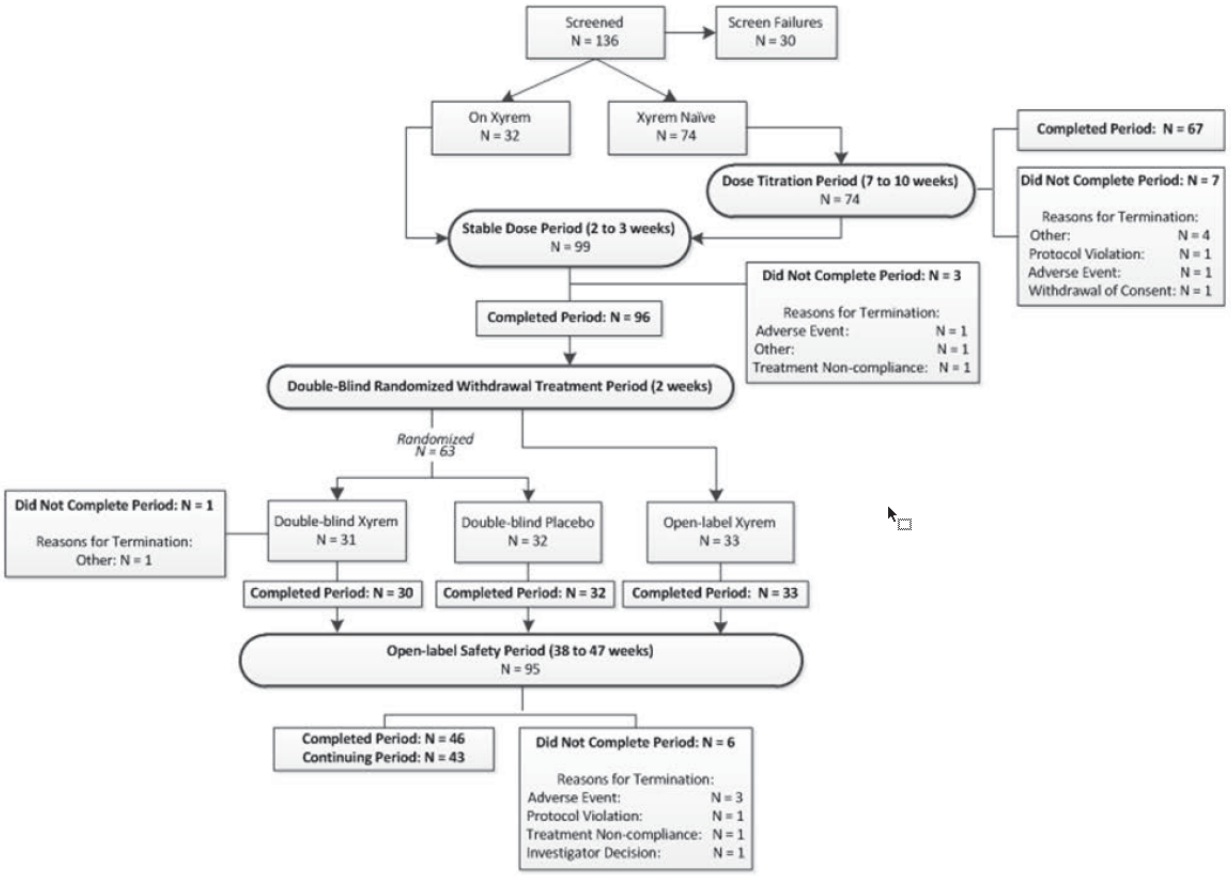


Figure 2 Patient Disposition
Source: Figure 3 of Clinical Study Report

No randomized subjects were excluded from the Efficacy population due to major deviations; therefore, the Randomized population, the Per Protocol population and the Efficacy population were equivalent.

Patient Demographics

Overall, the median age was 12 years (range: 7 to 16). More subjects were enrolled in the 12 to 17-year age group (68/106 subjects, 64.2%) than in the younger 7 to 11-year age group (38/106 subjects, 35.8%). Most subjects (59.4%) were male and White (68.9%). Baseline demographic characteristics were generally balanced between treatment groups in the randomized population (Table 2).

Table 2 Demographic Characteristics (Randomized Subjects)

	Placebo N=32	**Xyrem N=31**
Age (years)		
Mean (SD)	11.8 (2.48)	11.6 (2.54)
Median	12.0	12.0
Min, Max	7, 16	7, 16
Sex, n (%)		
Male	14 (43.8)	12 (38.7)
Female	18 (56.3)	19 (61.3)
Race, n (%)		
Asian	1 (3.1)	1 (3.2)
Black / African American	7 (21.9)	4 (12.9)
White	23 (71.9)	25 (80.6)
Other	1 (3.1)	1 (3.2)
Country, n (%)		
USA	17 (53.1)	16 (51.6)
France	3 (9.4)	4 (12.9)
Italy	9 (28.1)	9 (29.0)
Netherland	3 (9.4)	2 (6.5)

Source: Reviewer's Summary and Table 8 of Clinical Study Report

3.2.1.4.2 Patient Baseline Disease Characteristics

The mean years from diagnosis for the subjects was near 2 years at the screening. About 41% of the subjects in the placebo group and 36% of subjects in the Xyrem group were on Xyrem at the entry. Most subjects (near 90%) had cataplexy severity of moderately ill to severely ill. Subjects baseline disease characteristics were generally balanced between treatment groups (Table 3).

Table 3 Baseline Disease Characteristics

	Placebo N=32	**Xyrem N=31**
Years from Diagnosis		
Mean (SD)	1.94 (1.58)	1.92 (2.17)
Median	1.63	0.99
Xyrem Status at Entry, n (%)		
Xyrem naïve	19 (59.4)	20 (64.5)
On Xyrem at Entry	13 (40.6)	11 (35.5)

Cataplexy Severity, n (%)		
0=Normal, no sign of illness	0	0
1=Borderline ill	1 (3.1)	0
2=Slightly ill	1(3.1)	1 (3.2)
3=Moderately ill	5 (15.6)	5 (16.1)
4=Markedly ill	17 (53.1)	15 (48.4)
5=Severely ill	7 (21.9)	7 (22.6)
6=Most extremely ill	1 (3.1)	3 (9.7)
Mean (SD)	4.0 (0.97)	4.2 (0.95)
Baseline ESS (CHAD)		
Mean (SD)	13.9 (3.86)	13.2 (4.69)
Median	14.0	13.0

Source: Table 10 of Clinical Study Report

3.2.1.5 Efficacy Results

3.2.1.5.1 Primary Endpoint – Change in the Weekly Number of Cataplexy Attacks

The double-blind treatment period was stopped after protocol amendment 4. As a result, the interim analysis is the primary analysis for determining the efficacy.

The interim analysis included 35 subjects, 18 in the placebo group and 17 in the Xyrem group. The primary analysis of the change in the weekly number of cataplexy attacks was the analysis of covariance in ranked data.

At the baseline, the mean and median of the weekly number of cataplexy attacks were similar in the two treatment groups. During the double-blind treatment period, the weekly number of cataplexy attacks was more than doubled in the placebo group and was little changed in the Xyrem group. The mean and median change were 12.87 and 12.70, respectively, in the placebo group, compared to 1.89 and 0, respectively, in the Xyrem group. The treatment difference was statistically significant with a p-value of 0.0002, which triggered the stopping rule.

Table 4 Interim Results: Change in the Weekly Number of Cataplexy Attacks

	Placebo N=18	**Xyrem N=17**
Baseline Number of Cataplexy		
Mean (SD)	12.38 (28.69)	11.79 (16.72)
Median	5.31	4.67
Min, Max	0, 125.4	0.0, 51.3
25%, 75% quartile	1.0, 10.0	0.6, 10.8
Double-blind Number of Cataplexy		
Mean (SD)	25.25 (23.86)	13.68 (21.03)
Median	21.25	5.38
Min, Max	2.5, 95.5	0, 75.1
25%, 75% quartile	14.0, 24.7	0.5, 10.0
Change in the Number of Cataplexy		
Mean (SD)	12.87 (17.43)	1.89 (8.03)
Median	12.70	0.0

Min, Max	-29.9, 56.5	-4.5, 32.1
25%, 75% quartile	3.5, 17.6	-1.0, 1.6
p-value (primary)		0.0002

Source: Reviewer's analysis

Based on the positive interim results, the DSMB recommended to stop the placebo treatment. The protocol was amended (Amendment 4). The effective date of the amendment 4 varied at different sites with the earliest effective date in May 2016. A total of 63 subjects were randomized before Amendment 4 became effective.

The final efficacy data set included all 63 subjects who were randomized: 32 to the placebo group and 31 to the Xyrem group.

During the Double-blind Treatment Period, the number of weekly cataplexy attacks was more than doubled in the placebo group but was little changed in the Xyrem group - results that were similar to what were observed in the interim analysis. The median change from baseline (the last 2 weeks of the Stable Dose Period) in the weekly number of cataplexy attacks was 12.71 for subjects randomized to Placebo and 0.27 for subjects randomized to Xyrem. The comparison of the ranked change from baseline between treatments was statistically significant ($p < 0.0001$) when analyzed by ANCOVA using ranked data, adjusted by ranked baseline.

Most subjects completed 14 days of diary used for the calculation of weekly number of cataplexy attacks. The mean, median as well as the middle 50% of the number of diaries were about 14 days.

Table 5 presents a summary of the results at final analysis of the primary endpoint.

Table 5 Final Results of Weekly Number of Cataplexy Attacks

	Placebo N=32	**Xyrem N=31**
Baseline Number of Cataplexy		
Mean (SD)	16.59 (33.16)	9.60 (13.84)
Median	4.67	3.50
Min, Max	0.0, 125.4	0.0, 51.3
25%, 75% quartile	1.0, 11.0	0.6, 10.8
Double-blind Number of Cataplexy		
Mean (SD)	33.96 (46.29)	12.11 (17.36)
Median	21.25	3.77
Min, Max	0.0, 183.0	0.0, 75.0
25%, 75% quartile	6.9, 26.4	1.5, 17.7
Change in the Number of Cataplexy		
Mean (SD)	17.37 (23.89)	2.52 (7.12)
Median	12.71	0.27
Min, Max	-29.9, 103.0	-4.5, 32.1
25%, 75% quartile	3.4, 19.8	-1.0, 2.5
p-value (primary)		<0.0001

Number of Diaries, days		
Mean (SD)	13.56 (1.48)	14.00 (2.03)
Median	14.0	14.0
Min, Max	10, 17	7, 18
25%, 75% quartile	13.5, 14.0	13.0, 15.0

Source: Reviewer's analysis

Sensitivity analysis by adjusting the age group yielded similar results with a p-value of <0.0001.

3.2.1.5.2 Secondary Endpoints

CGIc for Cataplexy Severity

Two subjects in the Xyrem group did not have CGIc ratings and were not included in the analysis. The analysis of the overall ratings on the 7-point scale using Cochran-Mantel-Haenszel (CMH) test (the primary test) showed a statistically significant treatment difference with a p-value of 0.0006.

At the end of the double-blind period about 66% of the subjects in the placebo group had CGIc ratings of much worse or very much worse, compared to about 17% of the subjects in the Xyrem group with the same ratings.

Table 6 CGIc for Cataplexy Severity

	Placebo N=32	**Xyrem N=31**
CGIc Ratings, n (%)		
Total Observed	32	29
Very Much Worse (-3)	4 (12.5)	1 (3.4)
Much Worse (-2)	17 (53.1)	4 (13.8)
Minimally Worse (-1)	7 (21.9)	6 (20.7)
No Change (0)	2 (6.3)	15 (51.7)
Minimally Improved (1)	0	1 (3.4)
Much Improved (2)	2 (6.3)	2 (6.9)
Very Much Improved (3)	0	0
Missing	0	2
p-value		0.0006
CGIc Worsening[1], n (%)		
Yes	21 (65.6)	5 (17.2)
No	11 (34.3)	24 (82.8)
p-value[2]		0.0001

1. Worsening = CGIc rating much worse or very much worse
2. P-value is from chi square test of proportion of patients with worsening for sensitivity analysis.

Source: Reviewer's analysis

Change in ESS (CHAD) Score

One subject in each of the treatment group did not have baseline ESS score available and were not included in the analysis. An additional subject who was randomized to placebo group did not

have assessment value in the double-blind withdrawal period and had the baseline value carried forward, i.e., with 0 change. At the end of Stable-Dose period (baseline), the median ESS score was 11.0 for the placebo group and 8.0 for the Xyrem group. At the end of the double-blind treatment period, the median ESS score increased by 3 points in the placebo group and was flat in the Xyrem group. The difference in the change from baseline in the ESS core was statistically significant based on the ANCOVA with the ranked score adjusted by ranked baseline score.

Table 7 Change from Baseline in ESS (CHAD) Score at the End of Doub-blind Period

	Placebo N=31	**Xyrem N=30**
Baseline (Visit 3 – End of Stable Dose)		
Mean (SD)	10.4 (3.80	8.5 (4.35)
Median	11.0	8.0
Visit 4 (End of Double-blind)		
Mean (SD)	13.2 (4.03)	9.2 (4.81)
Median	12.0	9.0
Change from Baseline		
Mean (SD)	2.8 (3.68)	0.7 (3.22)
Median	3.0	0.0
p-value		0.0004

Source: Reviewer's analysis

Sensitivity analysis adjusting for the use of stimulants in the Stable Dose Period yielded similar results with a p-value of 0.0009.

3.3 Evaluation of Safety

Please refer to Evaluation of Safety by Dr. Ranjit Mani.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Analysis of the primary endpoint by gender, race, age and geographic region were performed. Differences among the subgroups in the change of weekly number of cataplexy attacks appear to be mostly due to the difference in the baseline weekly number of cataplexy attacks. The treatment effects were consistent among the subgroup populations.

Table 8 Change in the Weekly Number of Cataplexy Attacks by Subgroup

	Placebo N=32	**Xyrem N=31**

Sex		
Female		
N	15	13
Baseline Mean (Median)	25.06 (5.25)	5.85 (1.50)
Change in Mean (Median)	19.79 (16.00)	0.47 (0.00)
Male		
N	17	18
Baseline Mean (Median)	9.12 (2.69)	12.30 (7.75)
Change in Mean (Median)	15.23 (11.00)	4.00 (0.43)
Age Group		
7-11 Years		
N	14	12
Baseline Mean (Median)	19.14 (5.63)	19.39 (3.00)
Change in Mean (Median)	23.45 (18.32)	3.63 (0.13)
12-17 Years		
N	18	19
Baseline Mean (Median)	14.61 (2.80)	7.83 (4.00)
Change in Mean (Median)	12.64 (9.39)	1.81 (0.58)
Race		
White		
N	23	25
Baseline Mean (Median)	21.92 (5.38)	9.66 (4.00)
Change in Mean (Median)	20.68 (16.00)	1.92 (0.58)
Black		
N	7	4
Baseline Mean (Median)	2.00 (0.00)	2.50 (1.25)
Change in Mean (Median)	9.38 (4.21)	-1.15 (-0.44)
Region		
USA		
N	17	16
Baseline Mean (Median)	5.80 (5.38)	12.39 (6.08)
Change in Mean (Median)	13.68 (12.00)	1.97 (0.00)
Non-USA		
N	15	15
Baseline Mean (Median)	28.82 (2.92)	6.62 (3.00)
Change in Mean (Median)	21.55 (16.00)	3.10 (1.27)

Source: Reviewer's analysis

4.2 Other Special/Subgroup Populations

Analysis of the change in weekly number of cataplexy attacks by Xyrem status at the study entry was performed. At the entry of the study, 13 subjects randomized to placebo and 11 subjects randomized to Xyrem were on Xyrem. Nineteen (19) subjects randomized to placebo and 20 subjects randomized to Xyrem were considered Xyrem naïve (had never been treated with ZXyrem or had discontinued Xyrem for at least one month). Treatment effect is consistent between the two subgroups.

Table 9 Change in the Weekly Number of Cataplexy Attacks by Xyrem Status at Entry

	Placebo N=32	Xyrem N=31
Xyrem Status at Entry		
On Xyrem		
N	13	11
Baseline Mean (Median)	14.28 (4.50)	11.38 (3.00)
Change in Mean (Median)	13.17 (12.00)	2.43 (1.17)
Xyrem Naive		
N	19	20
Baseline Mean (Median)	18.17 (4.85)	8.62 (3.75)
Change in Mean (Median)	20.24 (13.42)	2.57 (0.13)

Source: Reviewer's analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No significant statistical issues were found to be deemed having significant impact on the efficacy results.

5.2 Collective Evidence

Study 13-005 has showed efficacy that is consistent at the interim and final analyses and across subgroup populations. Patients who withdrew from Xyrem had a median increase of over 12 cataplexy attacks compared to no increase in patients who continued Xyrem treatment during the double-blind treatment period. The treatment difference highly statistically significant.

5.3 Conclusions and Recommendations

Study 13-005 has provided sufficient evidence that Xyrem is effective as compared to placebo in treating cataplexy in patients with narcolepsy.

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/

XIAORONG YAN
10/15/2018

KUN JIN
10/15/2018
I concur with the review.

HSIEN MING J HUNG
10/15/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21196/S-030

CLINICAL PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	21196
Supporting document:	1069
Applicant's letter date:	4/27/18
CDER stamp date:	4/27/18
Product:	Xyrem® (sodium oxybate)
Indication:	(b) (4)
Applicant:	Jazz Pharmaceuticals
Review Division:	DNP
Reviewer:	Melissa Banks-Muckenfuss, PhD
Supervisor:	Lois Freed, PhD
Division Director:	Billy Dunn, MD
Project Manager:	Vandna Kishore, RPh

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 3

1.1 INTRODUCTION 3

1.2 Brief Discussion of Nonclinical Findings 3
1.3 Recommendations 3

2 DRUG INFORMATION 4

2.1 Drug 4
2.2 Relevant INDs, NDAs, BLAs and DMFs 4
2.3 Drug Formulation 4
2.4 Comments on Novel Excipients 4
2.5 Comments on Impurities/Degradants of Concern 4
2.6 Proposed Clinical Population and Dosing Regimen 4
2.7 Regulatory Background 5

3 STUDIES SUBMITTED 5

3.1 Studies Reviewed 5
3.2 Studies Not Reviewed 5
3.3 Previous Reviews Referenced 5

5 PHARMACOKINETICS/ADME/TOXICOKINETICS 6

5.1 PK/ADME 6

10 SPECIAL TOXICOLOGY STUDIES 9

11 INTEGRATED SUMMARY AND SAFETY EVALUATION 29

12 APPENDIX/ATTACHMENTS 32

1 Executive Summary

1.1 Introduction

Xyrem® is currently marketed for the treatment of excessive daytime sleepiness and cataplexy in narcolepsy in adults. This supplemental NDA addresses an outstanding PWR to assess the use of Xyrem in the pediatric population.

1.2 Brief Discussion of Nonclinical Findings

The sponsor conducted a 10-week study of sodium oxybate (0, 100, 300, and 900 mg/kg PO QD) in juvenile rats, with an 8-week recovery period. In the study, the NOAEL was 100 mg/kg/day based on mortality preceded by clinical signs at ≥300 mg/kg/day; there was no safety margin to the NOAEL on a mg/m^2 basis. Compared to adults, young animals showed increased sensitivity to the depressant effects of sodium oxybate. At 900 mg/kg/day, the following were also observed: reduced body weight gain over the dosing period (approximately 6% in females and 12% in males, with a slight difference in mean body weight compared to controls persisting at recovery), delayed sexual maturation (correlating with reduced body weight) in males, and slight increases in bone mineral content and density. Clear changes in body weight gain and bone content and density were not observed after the recovery period.

Systemic exposure increased, generally greater than dose-proportionally, with increasing doses, and decreased with repeated dosing. No clear sex difference was observed, and exposures tended to be higher at the initiation of dosing on PND21 compared to PND49 and PND90. A tendency for young rats (e.g., PND4 compared to PND21) to show higher exposures was also observed in the sponsor's pilot single dose PK study.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, Xyrem is not recommended for approval for the treatment of cataplexy and excessive daytime sleepiness in pediatric patients with narcolepsy. Juvenile animals showed increased sensitivity to the depressant effects of Xyrem, presumably resulting in the observed mortalities, without a clear safety margin.

1.3.2 Additional Nonclinical Recommendations

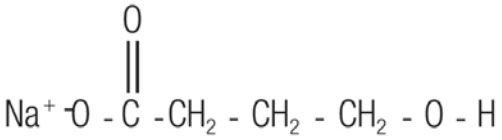
None.

1.3.3 Labeling

Recommendations for the wording in Section 8.4, Pediatric Use are under discussion.

2 Drug Information

2.1 Drug

Generic Name	sodium oxybate
Tradename	Xyrem
Chemical Name	sodium 4-hydroxybutyrate
Molecular Formula and Weight	$C_4H_7NaO_3$; 126.09 g/mole
Structure or Biochemical Description	
Pharmacologic Class	central nervous system depressant

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 49,641 sodium oxybate
NDA 21-196 Xyrem Cataplexy and EDS in Narcolepsy in adults

2.3 Drug Formulation

As described in the Xyrem labeling, “Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. Each mL of Xyrem contains 0.5 g of sodium oxybate (equivalent to 0.413 g/mL of oxybate) in USP Purified Water, neutralized to pH 7.5 with malic acid.”

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

None of concern identified.

2.6 Proposed Clinical Population and Dosing Regimen

Xyrem is proposed for treatment of both cataplexy and excessive daytime sleepiness (EDS) in pediatric patients with narcolepsy, with the proposed dosing regimen below (from the sponsor).

(b) (4)

2.7 Regulatory Background

In 2002, NDA 21-196 for Xyrem® (sodium oxybate) oral solution was approved for the treatment of cataplexy and excessive daytime sleepiness (EDS) in patients with narcolepsy. A pediatric Written Request (WR) for Xyrem was issued by the Agency on March 10, 2014 and amended on April 25, 2017.

3 Studies Submitted

3.1 Studies Reviewed

Study 20078509: A 10-Week Juvenile Toxicity Study of Xyrem (Sodium Oxybate) by Oral (Gavage) in Rats with an 8-Week Recovery Period

Study 1301-016: A Pilot Pharmacokinetic/Tolerability Study of Xyrem® (Sodium Oxybate) Following a Single Oral (Gavage) or Intravenous Dose in Juvenile Rats with a Lactational Exposure Evaluation in F_0 Dams

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

P/T review for SDN290, Dose-ranging juvenile animal study #20078508 and protocol for the pivotal juvenile toxicology study #20078509

PT Review for Xyrem, N21196, Dr. Rosloff

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study 1301-016: A Pilot Pharmacokinetic/Tolerability Study of Xyrem® (Sodium Oxybate) Following a Single Oral (Gavage) or Intravenous Dose in Juvenile Rats with a Lactational Exposure Evaluation in F_0 Dams

Conducted by (b) (4)

Non-GLP, initiated 5/12/15

Each animal was administered a single dose of Xyrem, according to the schedule described in the sponsor's Tables A and B (below).

Table A: Group Assignments

Group Number	Treatment	Route	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Number of Animals	
					Male	Female
1	LD 12 Dams	PO	2000	500	-	15
2	PND 4 Pups	PO	200	50	60	60
3	PND 4 Pups	PO	2000	500	60	60
4	PND 21 Pups	PO	200	50	30	30
5	PND 21 Pups	PO	2000	500	30	30
6	PND 28 Pups	IV	120	30	30	30
7	PND 28 Pups	PO	200	50	15	15
8	PND 28 Pups	PO	2000	500	15	15
9	PND 49 Pups	PO	200	50	15	15
10	PND 49 Pups	PO	2000	500	15	15
11	PND 5 Pups	PO	1000	250	60	60

LD – Lactation Day; PND – Postnatal Day; PO – Oral Gavage; IV – intravenous via the lateral tail vein administered as a slow bolus injection over 2 minutes ±15 seconds
- Not Applicable

Table B: F_0 Dam Blood and Milk Sample Collection			
Group(s)	Animals/Time point	Day of Dose	Blood/Milk Collection Time points (Hours Postdose)
1	5	LD 12	0.5, 1, and 2

Table C: Juvenile Blood Sample Collection			
Group(s)	Animals/ Time point	Day of Dose	Blood Collection Time points (Hours Postdose)
2 and 3	12/sex[a]	PND 4	0.083, 0.25, 0.5, 1, and 2
11	12/sex[a]	PND 5	0.083, 0.25, 0.5, 1, and 2
4	6/sex[b]	PND 21	0.083, 0.25, 0.5, 1, and 2
5	6/sex[b]	PND 21	0.083, 0.25, 0.5, 1, and 2
6	3 or 4/sex[c]	PND 28	0.083, 0.167, 0.25, 0.5, 0.75, 1, 1.5, and 2[e]
7 and 8	3/sex	PND 28	0.083, 0.25, 0.5, 1, and 2
9 and 10	3/sex[d]	PND 49	Predose and 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, and 4

[a]At each time point, blood was collected from four pups/sex and pooled, resulting in three samples/group/time point.
[b]At each time point, blood was collected from two pups/sex resulting in three pooled samples/time point with the exception of the 2 hour time point where samples were collected individually.
[c]Blood samples were collected from four animals/sex at 0.083, 0.167, 0.25, 0.5, 0.75, and 1 hour postdose and from three animals/sex at 1.5 and 2 hours postdose.
[d]Blood samples were collected from five cohorts of three animals/sex/group were bled at alternating time points; samples were collected from each animal three times.
[e]Collection times were based on the end of IV administration. Time points for PK analysis were not adjusted based on the duration of IV bolus injection.

The dose volume was 4 mL/kg. Observations included mortality/morbidity and clinical signs. TK parameters were determined using "mean composite plasma concentration-time data." Sodium oxybate concentration in milk was calculated as "the total amount of Sodium Oxybate secreted into the milk… at each time point based on the total volume of milk collected."

Drug-related mortality and/or moribundity occurred at 2000 mg/kg (8 male and 9 female PND4 pups, and all PND21 pups [moribund at 1 hr postdose, with one female found dead prior to 2 hr postdose]). Mortality did not occur at 200 mg/kg PO or 120 mg/kg IV.

Following PO administration of 2000 and 1000 mg/kg, PND4 and PND5 pups showed decreased activity and pale, discolored skin, which occurred in all animals and lasted > 2 hr in survivors. PND21 pups showed decreased activity that persisted. PND28 pups also showed splayed limbs and slow breathing (at 30 minutes postdose), with 2 of 6 also showing hypersensitivity to touch at 1 hr postdose. Decreased activity was reported in PND49 animals and LD12 dams with prostration reported in one female PND49 animal. IV administration in PND28 pups produced decreased activity within 15 minutes, and behavior had normalized by 1 hr postdose.

Sodium oxybate plasma exposures increased with increasing dose. At a given dose, sodium oxybate plasma exposures often tended to be higher in younger animals (particularly PND4 compared to PND21). Exposures achieved were generally independent of sex. See the sponsor's summary Tables 3 and 4, below. Sodium oxybate bioavailability decreased with increasing dose (i.e., approximately 50% at 200 mg/kg PO and 34% at 2000 mg/kg PO).

Table 3: Sodium Oxybate Plasma Pharmacokinetic Parameters Following a Single Oral Gavage Administration of 200, 1000, and 2000 mg/kg XYREM® on PND 4, 5, 21, and 28 or a Single Intravenous Bolus Injection of 120 mg/kg XYREM® on PND 28 to Male and Female Juvenile Rats

PND	Dose (mg/kg)	Group	Route	Gender	C_0 (µg/mL)	C_0/Dose (kg*µg/mL/mg)	C_{max} (µg/mL)	C_{max}/Dose (kg*µg/mL/mg)	T_{max} (hr)	T_{last} (hr)	AUC_{Tlast} (hr*µg/mL)	$AUC_{0\text{-}2hr}$ (hr*µg/mL)	$AUC_{0\text{-}2hr}$/Dose (hr*kg*µg/mL/mg)	F:M[a]	F:M[b]	$T_{1/2}$ (hr)	F (%)[c]
4	200	2	Oral	Female	NA	NA	382	1.91	2	2	364	364	1.82	1.31	1.28	NA[d]	NA
4	200	2	Oral	Male	NA	NA	291	1.46	2	2	285	285	1.42	NA	NA	NA[d]	NA
4	2000	3	Oral	Female	NA	NA	3210	1.61	2	2	3710	3710	1.85	1.35	1.16	NA[d]	NA
4	2000	3	Oral	Male	NA	NA	2390	1.19	2	2	3200	3200	1.60	NA	NA	NA[d]	NA
5	1000	11	Oral	Female	NA	NA	1000	1.00	2	2	1110	1110	1.11	0.998	1.01	NA[d]	NA
5	1000	11	Oral	Male	NA	NA	1000	1.00	2	2	1100	1100	1.10	NA	NA	NA[d]	NA
21	200	4	Oral	Female	NA	NA	89.9	0.449	0.5	2	108	108	0.538	0.712	0.730	NA[d]	NA
21	200	4	Oral	Male	NA	NA	126	0.631	1	2	147	147	0.736	NA	NA	NA[d]	NA
21	2000	5	Oral	Female	NA	NA	1120	0.562	2	2	1340	1340	0.672	0.973	0.945	NA[d]	NA
21	2000	5	Oral	Male	NA	NA	1160	0.578	2	2	1420	1420	0.711	NA	NA	NA[d]	NA
28	120	6	IV Bolus	Female	307	2.56	264	2.20	0.083	1	139	143	1.19	1.01	1.07	0.165	NA
28	120	6	IV Bolus	Male	301	2.51	263	2.19	0.083	1	132	134	1.12	NA	NA	0.209	NA
28	200	7	Oral	Female	NA	NA	91.2	0.456	0.5	2	115	115	0.576	0.997	0.983	NA[d]	48.4
28	200	7	Oral	Male	NA	NA	91.4	0.457	1	2	117	117	0.586	NA	NA	NA[d]	52.3
28	2000	8	Oral	Female	NA	NA	861	0.431	2	2	826	826	0.413	1.51	1.11	NA[d]	34.7
28	2000	8	Oral	Male	NA	NA	569	0.284	2	2	741	741	0.371	NA	NA	NA[d]	33.1

NA - Not applicable
a: F:M = $C_{max\ Female}/C_{max\ Male}$
b: F:M = $AUC_{0\text{-}2hr\ Female}/AUC_{0\text{-}2hr\ Male}$
c: $F = [(AUC_{0\text{-}2hr}/Dose_{PO})/(AUC_{0\text{-}2hr}/Dose_{IV})]*100$
d: $T_{1/2}$ not calculated due to insufficient concentration-time data

Table 4: Sodium Oxybate Plasma Pharmacokinetic Parameters Following a Single Oral Gavage Administration of 200, 1000, and 2000 mg/kg XYREM® on PND 49 to Male and Female Juvenile Rats

PND	Dose (mg/kg)	Group	Route	Gender	C_{max} (µg/mL)	C_{max}/Dose (kg*µg/mL/mg)	T_{max} (hr)	T_{last} (hr)	AUC_{Tlast} (hr*µg/mL)	$AUC_{0\text{-}4hr}$ (hr*µg/mL)	$AUC_{0\text{-}4hr}$/Dose (hr*kg*µg/mL/mg)	F:M[a]	F:M[b]	$T_{1/2}$ (hr)
49	200	9	Oral	Female	166	0.830	0.5	3	112	113	0.563	2.12	1.51	0.217
49	200	9	Oral	Male	78.1	0.391	0.75	3	74.0	74.4	0.372	NA	NA	0.385
49	2000	10	Oral	Female	406	0.203	4	4	1040	1040	0.522	1.15	1.33	NA[c]
49	2000	10	Oral	Male	354	0.177	4	4	786	786	0.393	NA	NA	NA[c]

NA - Not applicable
a: F:M = $C_{max\ Female}/C_{max\ Male}$
b: F:M = $AUC_{0\text{-}4hr\ Female}/AUC_{0\text{-}4hr\ Male}$
c: $T_{1/2}$ not calculated due to insufficient concentration-time data

Relatively high variability (approximately 30-50%) in both plasma and milk concentrations was observed on LD12. Milk concentrations were lower than plasma concentrations at all sampling times. See Table 1 from the sponsor, below.

Table 1: Sodium Oxybate Milk and Plasma Concentration Ratios Following a Single Oral Gavage Administration of 2000 mg/kg XYREM® on LD 12 to Lactating Dams

				Milk	Plasma	
Animal Group	Dose (mg/kg)	LD	Time (hr)	Mean (µg/mL)		Concentration Ratio[a]
1	2000	12	0.5	91.8	470	0.195
			1.0	194	601	0.323
			2.0	108	347	0.311
a: Concentration ratio = Mean $Concentration_{Milk}$/Mean $Concentration_{Plasma}$						

10 Special Toxicology Studies

The sponsor previously submitted a dose-ranging study (Study 20078508) to support submission of the proposed protocol for the pivotal juvenile toxicology study (Study 20078509). The Division provided the following advice on the protocol:

We have reviewed the protocol for a pivotal juvenile animal toxicology study (Study #20078509), submitted to IND 49641 on December 18, 2015, and have the following comments:

1. Dosing to PND 111, as you propose, may make study interpretation difficult; therefore, we recommend that animals be dosed only up to PND 70-90.
2. Neurobehavioral testing should be conducted during the dosing period and after an appropriate wash-out period in a separate group of animals (15-20/sex/group at each time point).
3. There is no need to conduct an FOB in addition to the other neurobehavioral tests.
4. Histopathological assessment should include a standard battery of tissues (cf. Bregman et al. Toxicol Pathol, 2003, 31(2): 252–253; Jacobs et al. Toxicol Pathol, 2003, 31: 571), not limited to brain, in 10/sex/group at the end of the dosing and recovery periods. An expanded neurohistopathological evaluation should be included (Bolon et al. Toxicol Pathol, 2006, 34:296-313).
5. Reproductive function does not need to be evaluated at the end of the dosing period. It should be conducted in 15-20/sex/group in recovery animals, after the neurobehavioral evaluation is completed.
6. We are concerned that the proposed high dose (900 mg/kg) may result in unacceptable toxicity, based on the deaths observed at 1000 mg/kg in the dose-ranging study in juvenile animals.

Study title: A 10-Week Juvenile Toxicity Study of Xyrem (Sodium Oxybate) by Oral (Gavage) in Rats with an 8-Week Recovery Period

Study no.:	20078509
Study report location:	(b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	3/15/16
GLP compliance:	Yes (FDA), except characterization and stability of the drug (GMP)
QA statement:	Yes
Drug, lot #, and % purity:	Sodium oxybate, Batch (b) (4), 97.6% pure

Key Findings

NOAEL= 100 mg/kg, based on mortality preceded by clinical signs at ≥300 mg/kg/day.

At 900 mg/kg, the following were observed:

- Mortality (preceded by clinical signs)
- Reduced body weight (M > F; slight difference persisted after recovery)
- Delayed sexual maturation in males
- Increased bone mineral content and density

Methods (see the sponsor's Text Tables 1 and 3, below)

Frequency of dosing:	QD, from PND21 to PND90
Route of administration:	PO (gavage)
Formulation/Vehicle:	Reverse osmosis (R.O.) membrane-processed deionized water
Species/Strain:	(b) (4):CD(SD) Sprague-Dawley rats (b) (4)
	19 to 45 g

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	No. of Animals					
					Main[a] (Cohort 1)		Recovery[b] (Cohort 2)		TK[c] (Cohort 3)	
					M	F	M	F	M	F
1	Control Article	0 (Control)	0	2.0	20	20	28	28	6	6
2	Sodium oxybate oral solution	100	50	2.0	20	20	28	28	27	27
3	Sodium oxybate oral solution	300	150	2.0	20	20	28	28	27	27
4	Sodium oxybate oral solution	900	450	2.0	20	20	28	28	27	27

TK = Toxicokinetic; M = Male; F = Female; - = Not applicable.
[a] Twenty (20) rats/sex/dose group were assigned to Cohort 1 (main study).
[b] Twenty-eight (28) rats/sex were assigned to Cohort 2 (recovery study) and were given an approximately 8 week treatment-free period after the completion of dose administration.
[c] Three (3) rats/sex in Group 1 and 18 rats/sex in Groups 2 through 4 were assigned for terminal blood sample collection following first dose (PND 21). An additional, three (3) rats/sex in Group 1 and 9 rats/sex in Groups 2 through 4 were assigned for blood sample collection on PND 49 and again on PND 90 (terminal), when possible.

Text Table 3
Number of Animals Assigned to Study

Group No.	Main Study				Recovery Study				TK Study	
	Cohort 1a		Cohort 1b		Cohort 2a		Cohort 2b		Cohort 3	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
1	10	10	10	10	10	10	18	18	6	6
2	10	10	10	10	10	10	18	18	27	27
3	10	10	10	10	10	10	18	18	27	27
4	10	10	10	10	10	10	18	18	27	27
	80 Male + 80 Female				112 Male + 112 Female				87 Male + 87 Female	

TK = Toxicokinetic
- Ten (10) rats/sex/group were assigned to Cohorts 1a and 2a for behavior evaluation and brain neurohistopathology evaluations.
- Ten (10) or 18 rats/sex/group were assigned to Cohorts 1b and 2b for clinical pathology blood and urine collections, sperm evaluation (as applicable) and histopathology evaluations.

Observations and Results

Survival [Twice daily]

There were four clearly drug-related early mortalities; two HDM and one HDF were found dead between PND21 and PND23, and one MDF was found dead on PND27. These deaths were dose-related and preceded by drug-related clinical signs (e.g., uncoordinated gait, decreased activity, decreased respiratory rate, low carriage, deep breathing, partially closed eyes, and/or lack of or impaired righting reflex). Cause of death was not determined (tissues were reportedly normal at necropsy, except minimal nephropathy in the MDF) but appeared consistent with CNS/respiratory depression.

Additionally, one MDM was found dead on PND99; no clinical signs were observed prior to death and only slight dilatation of the right renal pelvis was observed at necropsy.

The death of this MDM is of uncertain relationship to drug; the sponsor noted that no other drug-related deaths occurred outside of the dosing period.

Two other early mortalities that occurred in the study were not drug-related; one control female was sacrificed on PND53 because of a tail injury and one HDF was found dead on PND37 with macroscopic and microscopic findings consistent with gavage accident.

Clinical Signs [Daily, and 1 hr (first through 21st day of dosing) or 2 hr (from 22nd dosing day on) postdose]
Dose-related clinical signs occurred at MD and HD and generally were observed postdose for the first 2 or 3 weeks, respectively. At MD, decreased activity, uncoordinated, abnormal gait, partially closed eye(s), deep breathing, low carriage, reduced respiratory rate and/or splayed limbs were observed (resolving within 24 hr). At HD, increased activity, lying on side, erect fur, prostrate, closed eye(s), lack of/impaired righting reflex, hyperreactive, and/or labored breathing also occurred.

Body Weight [Daily, twice weekly during recovery]
At PND21 (initiation of dosing), mean body weights were approximately 5% and 7% lower in MD and HD animals compared to controls. Mean body weight reductions of approximately 6% (adjusting for the baseline difference), compared to controls, occurred over the first week and continued through the second (F) and fourth (M) week of dosing, partially resolving in females but persisting to PND90/91 in HDM. See the sponsor's Figures 1 and 2, below. Statistically significant reductions in mean body weight gains occurred for approximately 2 and 5 weeks in HDF and HDM, respectively. Overall, mean body weight gain was reduced approximately 6% and 12% over the dosing period in HDF and HDM, respectively.

Figure 1

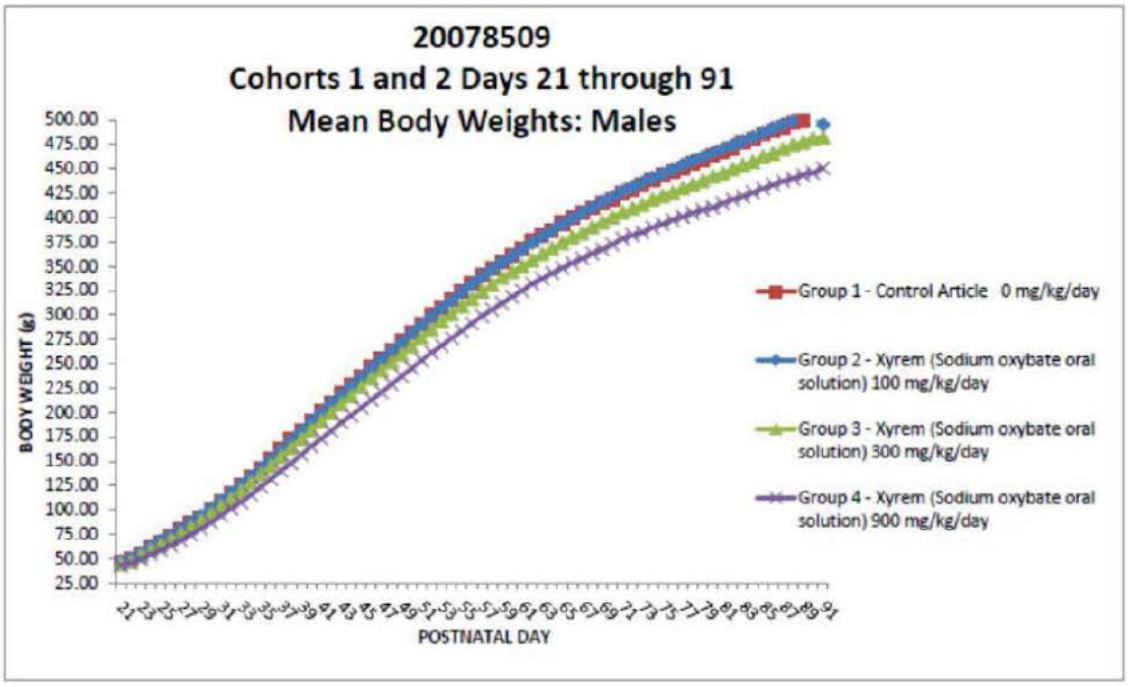
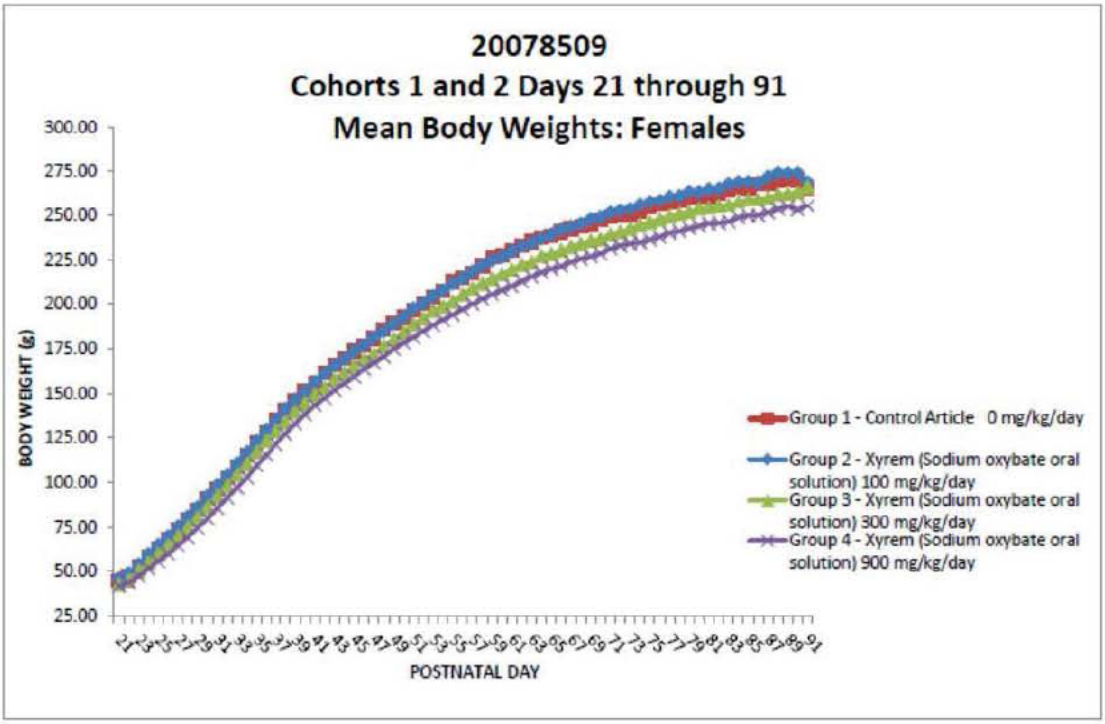


Figure 2



During the recovery period, reduced mean body weights compared to controls were observed in HDM and HDF (approximately 10%, on average across cohorts, including females during gestation). A slight reduction was suggested in MDM and MDF (up to 5%). It is unclear whether these observations were influenced by the baseline body weight differences among the groups (i.e., 5% and 7% lower than controls at MD and HD, respectively) at PND21. No clear effects on body weight gain were reported during the recovery period.

Food Consumption [weekly, GD0, 7, 10 and 12 in females]
Dose-related reductions in food consumption were observed at MD and HD (up to 17% over the dosing interval at HD). The reductions were greatest over the first two (MD) to three (HD) weeks. Overall, food consumption was reduced 6% and 15-17% at MD and HD during the dosing period. No effects were reported for the recovery period, including the gestation period in females.

Ophthalmic Observation [PND 80 or 83/86 and PND140 or 143-146)]
Evaluations were performed by (b) (4) using an indirect ophthalmoscope in conjunction with a hand-held lens.

No drug-related ophthalmic findings were reported.

Physical Development

Sexual Maturation [Cohorts 1 and 2, beginning PND35]
Balano-preputial separation was delayed in HDM, and correlated with reduced mean body weights. See the sponsor's summary Table 5, below. No clear effect on vaginal patency was observed.

Table 5

Summary of Sexual Maturation Data: Cohorts 1 and 2

Group 1 - Control Article
Group 2 - Xyrem (Sodium oxybate oral solution) 100 mg/kg/day
Group 3 - Xyrem (Sodium oxybate oral solution) 300 mg/kg/day
Group 4 - Xyrem (Sodium oxybate oral solution) 900 mg/kg/day

		GROUP			
		1	2	3	4
MALES					
Day of Balano-Preputial Separation	Mean	43.8	43.7	43.0	45.8 b
	SD	2.7	2.7	2.5	2.9
	N	48	48	42	43
Body Weight	Mean	225.7	225.6	213.4 c	212.7 c
	SD	30.1	24.0	21.2	25.7
	N	48	48	42	43
FEMALES					
Day of Vaginal Patency	Mean	33.4	33.0	32.9	34.7
	SD	2.4	2.0	1.5	2.6
	N	46	48	46	47
Body Weight	Mean	110.1	110.6	103.7 c	107.8
	SD	13.4	12.6	12.5	13.7
	N	46	48	46	47

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01 (Dunn);c=p≤0.05,d=p≤0.01 (Dunnett)
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Sperm Analysis
Sperm was unaffected at the end of the recovery period.

Estrous Cycles
No drug-related effects were observed.

Neurological Assessment
Motor Activity [sponsor's Text Table 5, below]

Text Table 5
Motor Activity Schedule

Cohort	Day of Study	Number of Rats (if possible)
1a	PND 60 ± 2 days (Day 40 ± 2 of dosing)	All rats
1b	PND 60 ± 2 days (Day 40 ± 2 of dosing)	All rats
2a	PND 120 ± 2 days	All rats
2b	PND 120 ± 2 days	10 rats/sex/group (the same rats used for acoustic startle habituation and Morris water maze)

Motor activity was evaluated prior to dosing on the scheduled day. Each animal was monitored a for 60-minute session (6 intervals of 10 minutes each), with detection of movement in two dimensions and differentiated as fine movement or ambulation. Overall, the data were highly variable. Statistically significant increases in ambulation [ss] were observed in LDM and HDM during the recovery period. However, no clearly drug-related patterns in performance emerged.

Acoustic Startle Habituation [sponsor's Text Table 6, below]

Text Table 6
Acoustic Startle Habituation Schedule

Cohort	Day of Study	Number of Rats (if possible)
1a	PND 65 ± 2 days (Day 45 ± 2 of dosing)	All rats
1b	PND 65 ± 2 days (Day 45 ± 2 of dosing)	All rats
2a	PND 125 ± 2 days	All rats
2b	PND 125 ± 2 days	10 rats/sex/group (the same rats were used for motor activity and Morris water maze)

Each session consisted of a series of "blank" baseline trials, followed by 50 stimulus trials, and then another five "blank" trials. Data were analyzed in blocks of five trials each. No drug-related differences were reported. The "Max Time" data were highly variable.

Morris Water Maze [sponsor's Text Table 6, below]

Text Table 7
Morris Water Maze Schedule

Cohort	Day of Study	Number of Rats (if possible)
1a	Between PNDs 70 and 90 (Between Days 50 and 70 of dosing)	All rats
1b	Between PNDs 70 and 90 (Between Days 50 and 70 of dosing)	All rats
2a	Between PNDs 130 and 150	All rats
2b	Between PNDs 130 and 150	10 rats/sex/group (the same rats were used for motor activity and acoustic startle habituation)

Testing consisted of three sessions on consecutive days. The first two sessions were comprised of 9 trials, measuring the latency to reach the platform (up to a maximum of 60 seconds). The third session consisted of a probe trial, in which the platform was removed and movement was recorded for 30 seconds; the relative proportion of time spent in the quadrant where the platform was located in the previous sessions was measured.

Individual trial results were presented for each of the 9 trials in the first session, but only interval data (i.e., trials 1-3, trials 4-6, and trials 7-9) was provided for the second session. The summary results for the first two sessions were calculated in three "intervals" which combined the measures of three trials each into a (least squares) mean (i.e., trials 1-3, trials 4-6, and trials 7-9, as well as a "combined interval" which was the mean of the 3 intervals). The statistical analysis used the least square means as the basis for analysis. No clearly drug-related differences were observed, as presented.

Reproduction [Cohort 2b, with cohabitation PND147-153]

No drug-related effects were reported (see sponsor's Table 8, below); however, it is noted that the pregnancy rate was fairly low in most groups (including controls). There were no clearly drug-related effects on ovarian and uterine findings.

Table 8

Summary of Mating, Fertility and Maternal Performance: Cohort 2b

Group 1 - Control Article
Group 2 - Xyrem (Sodium oxybate oral solution) 100 mg/kg/day
Group 3 - Xyrem (Sodium oxybate oral solution) 300 mg/kg/day
Group 4 - Xyrem (Sodium oxybate oral solution) 900 mg/kg/day

		GROUP			
		1	2	3	4
Mating and Fertility (Pairing Dates 1 to 7)					
Pre-coital Interval	Mean	2.1	2.7	3.1	2.5
	SD	1.1	1.5	1.5	1.2
	N	15	18	16	14
Mated	N	15	18	16	14
No Mated Date	N	3	0	1	2
Mating Index	N/N	15/18	18/18	16/17	15/16
	%	83.3	100.0	94.1	93.8
Pregnancy Rate	N/N	13/18	17/18	12/17	14/16
	%	72.2	94.4	70.6	87.5
Fertility Index	N/N	13/15	17/18	12/16	14/15
	%	86.7	94.4	75.0	93.3
Maternal Performance					
Pregnant	N	13	17	12	14
Preterminally Euthanized	N	0	0	0	0
Females with Live Conceptuses	N	13	17	12	14
Females with all conceptuses nonviable	N	0	0	0	0

Mated - Includes pregnant with no mated date; Mating Index - Number Mated (includes pregnant - no mated date as Mated)/Number Paired
Pregnancy Rate - Number Pregnant/Number Paired; Fertility Index - Number Pregnant/Number Mated (includes pregnant - no mated date as Mated)
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Clinical Pathology [sponsor's Text Table 8, below]

Text Table 8
Samples for Clinical Pathology Evaluation (Cohorts 1b and 2b)

Group Nos.	Cohort	Time Point	Hematology	Coagulation	Clinical Chemistry	Urinalysis
1 to 4	Cohort 1b	Scheduled	X	X	X	X
1 to 4	Cohort 2b	Euthanasia	X	X	X	X
Unscheduled euthanasia	Cohorts 1	Before euthanasia	X	X	X	-

X = Sample collected; - = Not applicable.

Hematology [parameters from the sponsor, below]

Red blood cell count Hemoglobin concentration Hematocrit Mean corpuscular volume Red blood cell distribution width Mean corpuscular hemoglobin concentration Mean corpuscular hemoglobin Reticulocyte count (absolute) Platelet count	White blood cell count Neutrophil count (absolute) Lymphocyte count (absolute) Monocyte count (absolute) Eosinophil count (absolute) Basophil count (absolute) Large unstained cells Other cells (as appropriate)

Note: Blood smear slides were prepared for all animals for possible RBC morphology evaluation. Two slides per animal were prepared at the Testing Facility and stained by (b) (4) Slide review was only performed on samples that met flagging criteria to confirm accurate hematology data.

Activated partial thromboplastin time Fibrinogen	Prothrombin time

Slight reductions in WBC counts, particularly neutrophils and lymphocytes, were observed in treated animals. WBC counts, specifically neutrophils, monocytes, and eosinophils in males, were reduced at HD (approximately 40% in HDM [ss]; approximately 20-30% in HDF [nss] except monocytes). Slight reductions in RBC parameters were also observed in MD and HD females. APTT was observed to be slightly increased in HDM (7%, [ss]). See Text Table 3 from the Clinical Pathology Interpretation report, below. Slight reductions in WBC and/or RBC parameters were reported at termination in the adult rat chronic toxicity study, as described in the original Xyrem NDA review.

Text Table 3
Xyrem-related Hematology[a] Changes in Juvenile Rats on PND 91

Group	2		3		4	
Dose (mg/kg/day)	100		300		900	
Sex	M	F	M	F	M	F
Parameter						
WBC	–19	–	–	–	–22	–19
NEUT	–8	–11	–25	–32	**–41**[a]	–31
LYMPH	–21	–	–	–	–19	–18
RBC	–	–	–	–2	–	–7
HGB	–	–	–	–2	–	–3
HCT	–	–	–	**–4**[a]	–	**–5**[b]

[a] Changes are expressed as percentage from mean control value.
'–': indicates results were not considered to be meaningfully different from mean control value.
Bolded values were statistically significant: [a]: $p \leq 0.05$; [b]: $p \leq 0.01$

During the recovery period, WBC remained reduced approximately 10% to 30% (e.g., neutrophils 30% in HDM [ss]). Slight reductions in platelets and reticulocytes (10-20% not d-r) were also observed in males. See the clinical pathologist's summary Text Table 4, below.

Text Table 4
Xyrem-related Hematology[a] Changes in Juvenile Rats administered on PND 160 to 162 (males) and DG 13 (females)

Group	2		3		4	
Dose (mg/kg/day)	100		300		900	
Sex	M	F	M	F	M	F
Parameter						
WBC	–	–	–11	–	–13	–
NEUT	–	–	–19	–	**–34**[a]	–
RETIC	**–21**[a]	–	**–22**[a]	–	–15	–

[a] Changes are expressed as percentage from mean control value.
'–': indicates results were not considered to be meaningfully different from mean control value.
Bolded values were statistically significant: [a]: $p \leq 0.05$; [b]: $p \leq 0.01$

Clinical Chemistry [parameters from the sponsor, below]

Alanine aminotransferase	Total protein
Aspartate aminotransferase	Albumin
Alkaline phosphatase	Globulin (calculated)
Gamma-glutamyltransferase	Albumin/globulin ratio
Creatine kinase	Glucose
Total bilirubin[a]	Cholesterol
Urea nitrogen	Triglycerides
Creatinine	Sodium
Calcium	Potassium
Phosphorus	Chloride

[a] When total bilirubin was >0.5 mg/dL, indirect and direct bilirubin was also measured.

"Non-reversible, minimal to moderate" increases in aspartate aminotransferase and creatine kinase activity were reported in treated females; the clinical pathology interpretation report indicated these changes were "suggestive of a muscular effect." See the Text Table 5, below, from the Clinical Pathology Interpretation report. CK was increased in MDF and HDF (1.5-2.5 fold [ss], not d-r), and AST was slightly increased (~30% [nss]), not d-r) in treated females. ALP was slightly increased (15 -20% [nss]) in MDM, HDM, and HDF. The report also discussed "reversible, minimal increases in glucose concentration" in treated males. Serum phosphorus (~10% [nss]) was slightly increased in treated males. Total bilirubin was slightly reduced (15-20%) in MDF and HDF.

Text Table 5
Xyrem-related Clinical Chemistry[a] Changes in Juvenile Rats on PND 91

Group	2		3		4	
Dose (mg/kg/day)	100		300		900	
Sex	M	F	M	F	M	F
Parameter						
AST	–	+27	–	+36	–	+31
CK	–	+55	–	**+138**[a]	–	**+118**[a]
GLUC	+25	–	+30	–	+24	–

[a] Changes are expressed as percentage from mean control value.
'–': indicates results were not considered to be meaningfully different from mean control value.
Bolded values were statistically significant: [a]: $p \leq 0.05$; [b]: $p \leq 0.01$

During the recovery period (i.e., tested at PND 160-162 in males and GD13 in females), CK was still increased (approximately 2- to 3-fold) and AST remained slightly increased (30%) in treated females. Slight increases in urea concentration in treated females and in phosphorus in MD and HD females, but the Clinical Pathology Interpretation report attributed these observations to possible "subclinical dehydration." See Text Table 6 from the Interpretation report, below. Total bilirubin was slightly increased (15-30% [ss]) in treated males, and triglycerides were slightly reduced (15-40% [nss]) in treated males and HDF.

Text Table 6
Xyrem-related Clinical Chemistry [1] Changes in Juvenile Rats on PND 160 to 162 (males) and DG 13 (females)

Group	2		3		4	
Dose (mg/kg/day)	100		300		900	
Sex	M	F	M	F	M	F
Parameter						
AST	–	+34	–	+30	–	+31
CK	–	+94	–	+164	–	+175
UREAN	–	+12	–	+5	–	+10
PHOS	–	–	–	+8	–	**+20**

1) Changes are expressed as percentage from mean control value.
2) '–': indicates results were not considered to be meaningfully different from mean control value.
3) Bolded values were statistically significant.

Urinalysis [parameters from the sponsor, below]

Color	Glucose
Clarity	Bilirubin
Specific gravity	Ketones
Total Volume	Nitrites
pH	Leukocytes
Protein	Blood
	Urobilinogen

Urine pH was slightly more basic in HD animals compared to controls. This was also reported in the adult rat chronic toxicity study in original Xyrem NDA review. The presence of leukocytes in the urine was reduced in HDM.

Pathology

Organ Weights

A few organ weights showed slight changes. Absolute adrenal gland weight was increased in HDM (27%, [ss]) compared to controls but reduced (14%) in HDF. Absolute spleen weight was reduced (10-20%, [ss] in M) in drug-treated animals. Absolute heart weight was reduced 6% [nss] in HDM and 11% [ss] in HDF. Absolute thyroid weight was reduced 13% in HDM and 15% in HDF. Absolute prostate and seminal vesicle weights were reduced 7 to 12% (similar to the BW reductions) in HDM, but testis weight was similar to controls. Absolute uterus weight was increased 41% in HDF.

After the recovery period, adrenal gland weight (absolute and/or relative to BW) was increased 9% to 14% in MD and/or HD animal compared to controls. Absolute

thyroid weight was still reduced 12% in HDM compared to controls. Absolute kidney, liver, and spleen weights tended to reflect the reduced body weights observed in MD and/or HD animals. Absolute ovary weight was reduced 13% in HDF.

Gross Pathology
No clearly drug-related findings were reported.

Histopathology

Adequate Battery	Yes (see Histopathology Inventory) Control and HD only (LD and/or MD assessed based on HD) – Cohort 1b, as well as 3 early mortalities from Cohort 2b
Separate, Signed Report	Yes
Histopathology	(b) (4)
Neurohistopathology	(b) (4)
Peer Review	No

Histopathology Findings (Appendices 25 and 26)
The pathologist stated that all animals were sexually mature, based on "the presence of active spermatogenesis in the testes and the presence of corpora lutea in the ovaries" and added that "the growth plate in the femur was open in all animals."

The pathologist reported no drug-related alterations; few potentially drug-related alterations were observed in the study (see selected tissues from the sponsor's table, below). A very low incidence of minimal-mild vacuolation or minimal hepatocellular necrosis was observed in the liver at HD. Increased incidences of minimal mononuclear cell infiltration in the lacrimal gland and alveolar histiocytic infiltration in the lung were also observed. It is noted that parathyroid was not present in half of the HDF samples. There were no drug-related findings in skeletal muscle or heart, which was of concern based on increases in CK and AST in the clinical pathology assessment.

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Histopathology was not conducted for recovery animals because no drug-related findings were identified in the main study animals.

Neurohistopathology
Brain and spinal cord tissues were stained with H&E, Luxol fast blue/cresyl violet (LFB/CV), and Bielschowsky's silver stain. Trigeminal nerves and ganglia and dorsal root ganglia and dorsal nerve roots were stained with H&E and Bielschowsky's silver stain. Eyes, optic nerves, and skeletal muscle (gastrocnemius and soleus) were stained with H&E. Peripheral nerves (sciatic, tibial, peroneal, and sural) and ventral nerve roots were stained with H&E, toluidine blue, and Bielschowsky's silver stains. The following subanatomic sites were assessed (see sponsor's Text Table 2, below).

Text Table 2
Subanatomic Sites of the Brain

Olfactory bulb	Pontine nuclei
Frontal, parietal and temporal cortex	Cerebral peduncle
Cingulate and retrosplenial cortex	Medial geniculate nucleus
Septal nucleus	Posterior collicular nuclei
Piriform cortex	Lateral anterior olivary nucleus
Anterior commissure	Red nucleus
Bed nucleus stria terminalis	Substantia nigra
Caudate, putamen and globus pallidus	Raphe nuclei
Internal capsule	Cerebellar cortex
Amygdaloid nucleus	Cerebellar roof nuclei
Thalamus	Medial and Lateral vestibular nuclei
Hypothalamus	Reticular gray matter
Habenular nuclei	Posterior olivary nuclei
Subiculum	Trigeminal motor nucleus and spinal sensory tract
Hippocampal sites CA1,2 &3	Cuneate and gracile nuclei
Hippocampal dentate gyrus	Hypoglossal nucleus
Anterior colliculi	Pyramids

The pathologist reported no drug-related gross observations or brain weight and morphometry alterations. Several brain morphometry measurements were excluded (i.e., 51 of 440 total) based on problems with the sections/measurements; the pathologist noted that the decisions to exclude data were made in a blinded fashion.

The pathologist stated that the only finding was "isolated (minimal) myofiber degeneration in the gastrocnemius or soleus skeletal muscles in a few individual animals," which was reported in both control and HD animals. The finding was described as "characterized by a single myofiber with proliferation of satellite cells obscuring the sarcoplasm." One HDF showed mild fibrosis of the gastrocnemius muscle (clinical pathology was not available for this animal).

Because no drug-related findings were observed, neurohistopathology was not conducted for recovery animals.

Bone (Length and Densitometry)
Mean femur length was generally similar to controls. Treated males showed a dose-dependent very slight reduction (maximum of approximately 3.5%) at the end of the dosing period, which may correlate with the slight developmental delay. The slightly increased femur length in the LD animals (approximately 3%, [ss]) at the end of recovery is of unclear biological significance.

Bone densitometry by pQCT analysis showed slight changes at HD. Slight to mild increases in bone mineral content (total and trabecular, +13% and +57%, respectively) and bone mineral density (total and trabecular, +11% and +53%, respectively) were observed in the distal metaphysis of the femur in HDM [ss]. Bone size at the diaphysis of the femur was slightly increased in HD animals. Minimal increases in total area (+8% and +9%, respectively, in HDM and HDF [nss]) were observed, and were associated with minimal increases in both the cortical area (+7% and +9%, respectively) and bone mineral content (+7% and +9%, respectively), in HDM [nss] and HDF [ss]. Slight increases in cross-sectional moment of inertia (+15% [nss] and +20% [ss] in HDM and HDF, respectively), an estimator of the resistance of bone to bending, were also observed; the sponsor associated this change with the observed changes in bone size and geometry at the diaphysis.

The sponsor reported that the alterations were small and not associated with changes in bone length, bone histology, alkaline phosphatase (ALP; although some slight changes were observed, see **Clinical Chemistry**); no clinical signs indicative of fracture were observed. The alterations were not observed at the end of the recovery period.

Toxicokinetics [PND 21 (first dosing day), PND49, and PND90]
Sodium oxybate was BQL in all control plasma samples. Systemic exposure increased, generally greater than dose-proportionally, with increasing doses. T_{max} ranged between 0.5 and 4 hr, and the half-life ranged from 0.36 to 1.54 hr; plasma sodium oxybate concentrations were quantifiable until approximately 2 hr at LD, and 4 hr at MD an HD. Exposures tended to be decreased with repeated dosing. No clear sex difference was observed. Accumulation ratios ranged from (b) (4) (see sponsor's Table 2.5, below). See the sponsor's summary (b) (4) Tables 2.1, 2.2, 2.3, and 2.5, below.

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11 Integrated Summary and Safety Evaluation

The sponsor conducted a 10-week study of sodium oxybate (0, 100, 300, and 900 mg/kg PO QD, from PND21 to PND90) in juvenile rats, with an 8-week recovery period. In the study, mortality that was preceded by clinical signs of CNS/respiratory depression occurred at ≥ 300 mg/kg/day. Alterations in clinical pathology (CK and AST) occurred in females, but clear histopathologic correlates were not observed. At 900 mg/kg/day, the following were also observed: reduced body weight gain over the dosing period (approximately 6% in females and 12% in males, with a mean body weight reduction of approximately 10% compared to controls after the recovery period), delayed sexual maturation (correlated with reduced body weight in males), and slight increases in bone mineral content and density. Clearly drug-related adverse effects on neurobehavior, reproductive capacity, organ weights, macroscopic and microscopic anatomical pathology, or neurohistopathology at doses up to 900 mg/kg/day were not observed.

Systemic exposure increased, generally greater than dose-proportionally, with increasing doses, and tended to decrease with repeated dosing. No clear sex difference was observed. The average C_{max} was approximately 20-35 μg/mL at 100 mg/kg, approximately 100-150 μg/mL at 300 mg/kg, and approximately 400-600 μg/mL at 900 mg/kg. On average, AUC_{0-t} (with t= time after dosing at which the last quantifiable concentration was observed; the last sampling at 4 hr) was approximately 25-30 μg·hr/mL at 100 mg/kg, approximately 150 μg·hr/mL at 300 mg/kg, and 1160 μg·hr/mL at 900 mg/kg.

In the pediatric PK study (Study 13-005; included subjects 7 to 17 years old), the sponsor stated that there was no clear association between the dose and the C_{max} or AUC_{0-4h} (see the sponsor's Clinical Overview). The sponsor attributed the absence of a clear relationship to the wide range of body weights in the pediatric patients for which PK was obtained, which resulted in a variable mg/kg dose administered. In pediatric patients, T_{max}, C_{max}, and AUC_{0-4h} after the first nightly dose of 4.5 g were 1.5 hr, 82.4 μg/mL, and 233 μg·hr/mL, respectively; see the sponsor's table below, from the Clinical Pharmacology review.

From the Clinical Pharmacology review

Table 7: Sodium Oxybate PK Parameters for the First Nightly Dose of Xyrem (PK Night 2, PK Population)

First Nightly Dose (g)[a]	Number of Subjects	T_{max} (hours)[a] (Median [Min, Max])	C_{max} (µg/mL) (Mean [CV%])	AUC_{0-4h} (µg/mL*hours) (Mean [CV%])
2	1	0.75 (NC)	79.4 (NC)	143 (NC)
2.25	3	0.82 (0.75-1.50)	72.5 (73%)	195 (83%)
2.5	2	1.66 (0.82-2.50)	65.3 (95%)	156 (92%)
3	1	2.47 (NC)	24.3 (NC)	52.0 (NC)
3.25	3	0.75 (0.75-2.50)	92.5 (36%)	273 (40%)
3.5	8	1.50 (0.75-1.50)	82.9 (60%)	234 (62%)
3.75	3	0.75 (0.75-1.48)	92.7 (35%)	214 (25%)
4	4	0.75 (0.75-1.50)	84.1 (44%)	209 (53%)
4.25	1	0.75 (NC)	47.4 (NC)	114 (NC)
4.5	3	1.50 (0.75-2.50)	82.4 (60%)	233 (67%)

Abbreviations: AUC_{0-4h} = area under the plasma concentration-time curve from time zero to 4 hours postdose; C_{max} = maximum observed plasma concentration; NC = not calculated since only one observation available; T_{max} = time of maximum observed plasma concentration.

[a] Based on half of the planned full nightly dose (Xyrem dosage, g/night).

Note: Results are presented for PK Night 2, on which subjects received their full stable dose of Xyrem.

Note: For T_{max}, median values are reported and the range of observed values (minimum-maximum) are reported in parentheses. For C_{max} and AUC_{0-4h}, mean values are reported and the coefficients of variation (SD / mean expressed as a percentage) are shown in parentheses.

Estimation of a PK-based safety margin from the NOAEL in the juvenile animal toxicology study to the recommended pediatric doses, minimum age and weight-based factors aside, is complicated by the fact that dosing in the juvenile animal toxicology study was conducted differently; that is, animals were dosed once daily at a given dose, but pediatric subjects will initiate dosing at lower than the maximum recommended nightly dose (which is to be taken in two divided doses) and the dose is slowly titrated (see below from the sponsor's proposed labeling). The pediatric PK data available (see above) do not include doses listed in the (b) (4) ranges proposed.

(b) (4)

The variability in the pediatric PK data complicate its use as a basis for comparison with the observed juvenile animal exposures. Generally, the available pediatric PK data (i.e., at doses up to 4.5 g, half of the maximum recommended nightly dose) showed C_{max} and AUC exposures approximately comparable to that at the 300 mg/kg dose in juvenile animals. It is noted that the juvenile animal exposures also showed variability in exposures, particularly at MD and HD (e.g., Cmax, T_{max}).

Conclusion

Overall, the results of the juvenile animal toxicology study demonstrated severe toxicity (i.e., mortalities early in the dosing period preceded by CNS and respiratory clinical signs) related to higher doses at the initiation of dosing. Based on the nonclinical data, juvenile animals show an increased sensitivity to the CNS (and respiratory) depressant effects of sodium oxybate, effects known to occur in adults and for which a Black Box Warning exists in the current Xyrem label. There is no clear safety margin (on either a PK or a body surface area-adjusted exposure basis) to the to the first nightly dose (at the initial dose, of two nightly doses) and/or the MRHD. Other toxicities (i.e., reduced body weight gain, delayed sexual maturation in males, and slight alterations [i.e., increases] in bone content and density) were also observed at the HD. Body weight gains (although a slight difference in mean body weight compared to controls persisted at recovery) and bone content and density were not clearly altered after the recovery period.

Although the juvenile animal data show increased sensitivity and toxicity to sodium oxybate, it is notable that dosing was initiated in the juvenile rats at a CNS developmentally-comparable age of approximately 2 years in humans (Kim et al., 2017), and that age-dependent exposures (i.e., younger > older rats, both C_{max} and AUC) have been observed. Based on the population defined in the PWR, the pediatric population proposed includes children 7 years of age and older. Additionally, dosing was neither titrated nor divided in the juvenile animal study; both dose titration and divided dosing are used in adults and are proposed in children.

12 Appendix/Attachments

Histopathology inventory

Study	Juvenile Toxicology Study 20078509
Species	Rat
Adrenals	X*
Aorta	X
Bone Marrow smear	X (femur)
Bone (femur)	X (and sternum)
Brain	X*
Cecum	X
Cervix	X*
Colon	X
Duodenum	X
Epididymis	X*
Esophagus	X
Eye	X
Fallopian tube	X* (oviduct)
Gall bladder	n/a
Gross lesions	X
Harderian gland	X
Heart	X*
Ileum	X
Injection site	n/a
Jejunum	X
Kidneys	X*
Lachrymal gland	X
Larynx	
Liver	X*
Lungs	X
Lymph nodes, cervical	
Lymph nodes mandibular	X
Lymph nodes, mesenteric	X
Mammary Gland	X
Nasal cavity	
Optic nerves	X
Ovaries	X*
Pancreas	X

Parathyroid	X*
Peripheral nerve	(see sciatic nerve)
Pharynx	
Pituitary	X*
Prostate	X*
Rectum	X
Salivary gland	X
Sciatic nerve	X
Seminal vesicles	X*
Skeletal muscle	X
Skin	
Spinal cord	X
Spleen	X*
Sternum	(see bone)
Stomach	X
Testes	X*
Thymus	X*
Thyroid	X*
Tongue	X
Trachea	X
Ureter	X
Urinary bladder	X
Uterus	X*
Vagina	X
Zymbal gland	

X, histopathology performed
*, organ weight obtained

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/s/

MELISSA K BANKS-MUCKENFUSS
10/24/2018

LOIS M FREED
10/24/2018

Office of Clinical Pharmacology Review

NDA Number	21196 S30
Link to EDR	\\CDSESUB1\evsprod\NDA021196\0278\
Submission Date	04/27/2018
Submission Type	Pediatric Efficacy Supplement
Brand Name	Xyrem
Generic Name	Sodium Oxybate oral solution
Dosage Form and Strength	Oral Solution: (b) (4)
Route of Administration	Oral
Proposed Indication	Cataplexy or excessive daytime sleepiness (EDS) in narcolepsy in patients 7 years of age and older
Applicant	Jazz Pharmaceuticals
OCP Review Team	Kevin Krudys, Ph.D., Dawei Li, Ph.D., Angela Men, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY 3
1.1 Recommendations 3
1.2 Post-Marketing Requirements and Commitments 3
2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT 3
2.1 Pharmacology and Clinical Pharmacokinetics 3
2.2 Summary of Labeling Recommendations 5
3. Question Based Review 6
3.1 Pertinent Regulatory Background 6
3.2 Clinical Pharmacology Review Questions 6
3.2.1 Is the proposed dosing regimen appropriate for the pediatric population for which the indication is begin sought? 6
4. APPENDICES 8
4.1 Population PK Analysis 8
4.2 Indivudal Study Reivew 13

1. EXECUTIVE SUMMARY

In this pediatric efficacy supplement, Jazz Pharmaceuticals is seeking approval of Xyrem® for treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older. The submission is in response to a pediatric Written Request issued on March 10, 2014 and amended on April 25, 2017.

Xyrem® is a CNS depressant currently approved for treatment of cataplexy or excessive daytime sleepiness in the adult population. In adults the recommended starting dose 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 can be increased to a total of 9 g per night.

The current submission includes the results from the pivotal pediatric clinical trial 13-005, a double-blind, placebo-controlled, randomized withdrawal study of Xyrem® in pediatric subjects with narcolepsy with cataplexy. In addition, a population PK analysis was conducted to describe the pharmacokinetics in the pediatric population and to support the proposed dosing regimen. The primary focus of this review is the evaluation of the proposed pediatric dosing regimen.

1.1 Recommendations

The submission is acceptable from a clinical pharmacology perspective and we recommend approval for the proposed indications in pediatric patients 7 years of age and older. From a clinical pharmacology perspective, the applicant has met the terms of the Pediatric Written Request. The applicant should include appropriate labeling, described below, in the pediatric population.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

The pharmacokinetics of sodium oxybate in the adult population are summarized in the product label. Briefly, sodium oxybate pharmacokinetics are nonlinear and are similar following single or repeat dosing of Xyrem. Following oral administration, absolute bioavailability is 88% and the average time to peak plasma concentration ranges from 0.5 to 1.25 hours. Administration of Xyrem immediately after a high-fat meal results in delayed absorption and reduction in exposure. Metabolism is the major pathway for elimination, producing carbon dioxide and water via the Krebs cycle and secondarily by beta-oxidation. Plasma levels of sodium oxybate have been demonstrated to increase more than dose-proportionally.

Pediatric PK data were collected in Study 13-005, a double-blind, placebo-controlled, randomized withdrawal, efficacy and safety study of Xyrem with an open-label PK evaluation and safety extension. Pediatric patients between the ages of 7 and 16 years who were diagnosed with narcolepsy with cataplexy, who were being treated with Xyrem or who were Xyrem naïve, were eligible to enter the

study. Dosing in subjects who were Xyrem naïve is provided in Table 1. Subjects who were on Xyrem at study entry remained on their stable dose and regimen.

Table 1: Study 13-005 Xyrem Dose Initiation and Titration

Subject Weight (kg)	Initiation Dose (Taken in 2 divided doses)[a]	Titration Regimen	Maximum Total Nightly Dose
< 30	≤ 2 g/night	≤ 1 g/night/week	6 g/night
≥ 30 to < 45	≤ 3 g/night	≤ 1 g/night/week	7.5 g/night
≥ 45	≤ 4.5 g/night	≤ 1.5 g/night/week	9 g/night

[a] At bedtime and 2.5 to 4 hours later. For children who slept more than 8 hours per night, Xyrem could be given after bedtime, while the child was in bed, in 2 equally divided doses 2.5 to 4 hours apart.

After a dose stabilization period, patients were randomized to continue double-blind treatment at the stable dose or to receive placebo at a volume and regimen equivalent to the stable Xyrem dose. Following an interim analysis, which demonstrated positive efficacy results on the primary endpoint, the protocol was amended to replace the placebo arm with open-label Xyrem treatment.

Once subjects were taking a stable dose of Xyrem, they were eligible to participate in an open-label PK evaluation. PK sampling was performed on PK Nights 1 and 2. The first nightly dose was taken at least 2 hours after a meal and the second dose was taken 4 hours after the first dose. On PK Night 1, Xyrem was administered at half the stable dose and on PK Night 2, Xyrem was administered at the full dose. Blood samples were obtained at the following times relative to the first Xyrem dose: 0, 0.75, 1.5, 2.5, 4, 4.75 and 8 hours. The PK population (N=29) consisted of 2 age groups, 7 to 11 years (N=11) and 12 to 17 years (N=18).

Noncompartmental Results

The pharmacokinetics of sodium oxybate was characterized in study 13-005. Dose proportionality assessments suggested sodium oxybate exhibited proportionality in Cmax, and supra-proportional increases in AUC, indicating nonlinear clearance. The combined effects of accumulation and food effect led to sodium oxybate plasma concentrations that were generally higher after the second nightly dose than the first nightly dose. Overall, the PK of sodium oxybate in pediatric subjects was similar to that previously observed in adults.

Analytical Section

Plasma sodium oxybate concentrations obtained in Study 13-005 were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) analytical method.

The lower limit of quantitation was 1.00 mcg/mL and the upper limit of quantitation was 160.00 mcg/mL. Accuracy and precision of QC samples were (b) (4) at LLQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits. Summary of bioanalytical methods used in Study 13-005 is provided in the table below:

(b) (4)

Population PK Model Results

Population PK analysis was performed with pooled pediatric and adult data. The results of the analysis are provided in greater detail in Appendix 4.1. Briefly, the final model was a two-compartment model with Michaelis-Menten elimination. The final model included a proportional food effect (meal within 2 hours) on ka, allometric scalars on Vc and Vmax (centered on a body weight of 70 kg), pediatric and child age category effects on Vc and a proportional diurnal effect (AM vs. PM dosing) on Vmax. Body weight was found to be the most significant factor on oxybate kinetics. When Xyrem is dosed as mg/kg, similar PK is predicted between adult and pediatric subjects.

2.2 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following dosing in pediatric patients 7 years of age and older:

(b) (4)

Patient Weight	Initial Dose		Maximum Recommended Dose	
	Take at Bedtime:	Take 2.5 to 4 Hours Later:	Take at Bedtime:	Take 2.5 to 4 Hours Later:
20 kg to <30 kg	≤ 1 g	≤ 1 g	≤ 3 g	≤ 3 g
30 kg to <45 kg	≤ 1.5 g	≤ 1.5 g	≤ 3.75 g	≤ 3.75 g
≥45 kg	≤ 2.25 g	≤ 2.25 g	≤ 4.5 g	≤ 4.5 g

3. Question Based Review

3.1 Pertinent Regulatory Background

Xyrem (sodium oxybate) was first approved for the treatment of cataplexy in patients with narcolepsy in 2002. In 2005, Xyrem was also approved for the treatment of excessive daytime sleepiness in patients with narcolepsy. Xyrem is a controlled substance and is only available through a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use. A pediatric Written Request (WR) was issued on March 10, 2014 to investigate the use of sodium oxybate oral solution in the treatment of cataplexy in narcolepsy in children and adolescents aged 7 to 17 years. The WR required PK assessment, including an analysis of dose proportionality, as part of the required efficacy and safety study. The WR was amended on April 25, 2017 in response to an interim analysis of Study 1, which concluded that there were adequate data to support the efficacy of Xyrem in the pediatric population. At that time, the Office of Clinical Pharmacology agreed to remove a requirement from the WR for an ongoing analysis of PK data to determine if a sufficient number of subjects have been enrolled to adequately characterize the PK of sodium oxybate in the pediatric population.

3.2 Clinical Pharmacology Review Questions

3.2.1 Is the proposed dosing regimen appropriate for the pediatric population for which the indication is begin sought?

In general, the recommended dosing regimen is acceptable, (b) (4) The dosing regimen for which efficacy and safety was demonstrated in Study 13-005 is displayed in Table 1. (b) (4)

(b) (4)

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4. APPENDICES

4.1 Population PK Analysis

The applicant performed a population PK analysis of plasma oxybate concentrations following administration of Xyrem in healthy adult subjects and pediatric and adult subjects with narcolepsy. The purpose of the analysis was to assess sources of variability and to support the proposed dosing recommendations.

Data from the following clinical studies were included in the analysis:

Table 3: Studies Included in the Population PK Analysis

Study #	Patient Population	Study Design	Doses Administered	Dosing Regimen	Blood Sample Collection
13-005	Pediatric subjects with narcolepsy with cataplexy	Double-blind, placebo controlled, randomized-withdrawal study of efficacy, safety, and PK of Xyrem	1 – 4.5 g BID	Titration of Xyrem-naïve patients to a stable nightly dose or stable nightly dose of patients already taking Xyrem (steady-state dosing)	0 (pre-dose), 0.75, 1.5, 2.5, 4 hours (pre-2nd dose), 4.75, and 8 hours following the first dose
OMC-SXB-9	Healthy adult volunteers	Open label, two period, two treatment, crossover randomized study of Xyrem PK	2 doses of 2.25 g or 2 doses of 4.5 g	2 doses of Xyrem administered 4 hours apart on Study Days 1 and 8	Pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 4.17 4.33, 4.5, 4.75, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9 and 10 hours after the first dose
09-002 (Treatment A Only)	Healthy adult volunteers	Open label, randomized, relative bioavailability crossover study of Xyrem sustained-release tablet versus Xyrem oral solution	Treatment A: 2 doses of 3 g	Administration of 2 doses of Xyrem 4 hours apart	Treatment A: pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.25, 4.5, 4.75, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, and 12 hours after administration of the first 3 g dose of solution
OMC-SXB-10	Narcoleptic adult subjects	Open label, two period study to compare single dose versus 8-week dosing of Xyrem	4.5 g Xyrem qhs for 8 weeks	Single and steady-state administration of Xyrem	Pre-dose and 0.17 (10 minutes), 0.33 (20 min), 0.5 (30 minutes), 0.75 (45 min), 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, and 7 hours after administration of each of the two 4.5 g test dose of solution.
13-010	Healthy adult volunteers	Open label, randomized crossover study of PK, bioavailability, bioequivalence, and food effect of Xyrem	Treatment C: 4.5 g Xyrem oral solution fasted Treatment D: 4.5 g Xyrem oral solution fed Treatment G: 4.5 g Xyrem oral solution fasted	Administration of 2 doses of Xyrem 4 hours apart	Pre-dose and at 0.17 (10 minutes), 0.33 (20 min), 0.5 (30 minutes), 0.75 (45 min), 1 (60 min), 1.25 (75 min) 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7 and 8 hours after administration of a single 4.5 g Xyrem dose

Source: Population Pharmacokinetics Report, Appendix 1, Page 49

The PK dataset included PK samples from 174 subjects, including 29 (16.7%) pediatric subjects and 145 (83.3%) adult subjects. There were a total of 3775 observations, including 333 (8.8%) from pediatric

subjects and 3442 (91.2%) from adult subjects. The median age of the pediatric subjects was 12 years (range: 8 to 16 years) and the median body weight was 60.8 kg (range: 31 to 129 kg). One subject (b) (6) from Study 13-005 was removed from the analysis because the subject had a quantifiable pre-dose concentration and had a PK profile inconsistent with the expected PK of oxybate.

Population PK Model

Structural model: Two-compartment model with first-order absorption and Michaelis-Menten clearance. PK parameters include Vmax, Km, Vc, Vp, ka, k23 and k32

Interindividual variability: Proportional. The data supported variability on Vmax, Km (block), Vc and ka

Residual Variability: Proportional error model

Interoccasion variability: included on Vmax and Km

Covariates: A forward ($p<0.05$) and backward ($p<0.001$) elimination process was used to evaluate covariate effects. Measures of body size, age, sex, race, disease status, prandial status, diurnal factors and bioanalytical methods were assessed. The potential relationship was characterized using linear, power or dichotomous models, depending on the covariate. The final model included a proportional food effect (meal within 2 hours) on ka, allometric scalars on Vc and Vmax (centered on a body weight of 70 kg), pediatric and child age category effects on Vc and a proportional diurnal effect (AM vs. PM dosing) on Vmax

Final parameter estimates are shown in Table 4.

Table 4: PK Parameter Estimates for the Final Pop PK Model

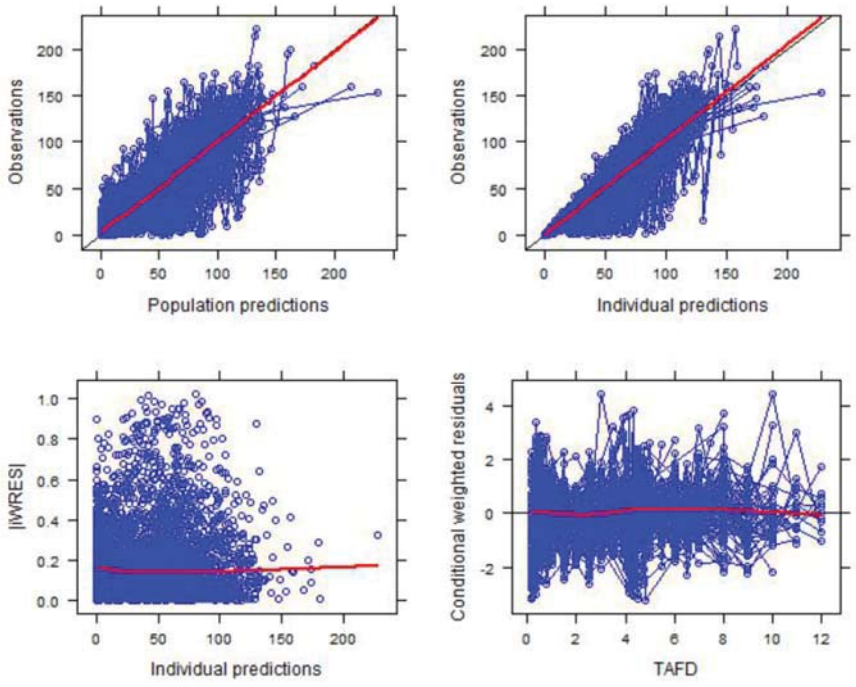
	NONMEM			Bootstrap	
Parameter (units)	**Estimate**	**IIV**	**IOV**	**Median**	**2.5th to 97.5th Percentile**
Vmax (mg/h)	1508	37.7%	10.2%	1503	(1357, 1699)
Km (mg/L)	22.0	41.4%	24.5%	22.0	(17.74, 26.78)
Central Compartment Volume of Distribution (VC) (L)	29.5	11.8%	NA	29.4	(28.35, 30.51)
Peripheral Volume of Distribution (VP) (L)	5.33	NA	NA	5.31	NA
Ka (1/hr)	4.12	47.2%	NA	4.08	(3.57, 4.76)
F (NA)	1.00 (Fixed)	NA	NA	1	Fixed
K23 (1/hr)	0.0968	NA	NA	0.0969	(0.0655, 0.1407)
K32 (1/hr)	0.536	NA	NA	0.536	(0.449, 0.633)
Food Effect on Ka (NA)	-0.681	NA	NA	-0.682	(-0.741, -0.61)
AS Exponent on VC (NA)	0.650	NA	NA	0.649	(0.506, 0.812)
AS Exponent on Vmax (NA)	0.633	NA	NA	0.619	(0.434, 0.801)
Diurnal Effect on Vmax (NA)	-0.177	NA	NA	-0.177	(-0.2438, -0.1106)
Pediatric Age Category on VC	0.201	NA	NA	0.193	(0.0897, 0.3213)
Child Age Category on VC	-0.328	NA	NA	-0.318	(-0.518, -0.124)
Proportional Error (%CV)	28.1	NA	NA	28.1	(26.6, 29.5)

NOTE: Child age category = 7-11 years; pediatric age category = <18 years; Peripheral volume of distribution calculated as (K23/K32)*VCNA=Not available; AS = Allometric scaling

Source: Population Pharmacokinetics Report, Table 3-2, Page 30.

Basic goodness-of-fit plots and visual predictive checks are illustrated in Figure 2 and Figure 3, respectively.

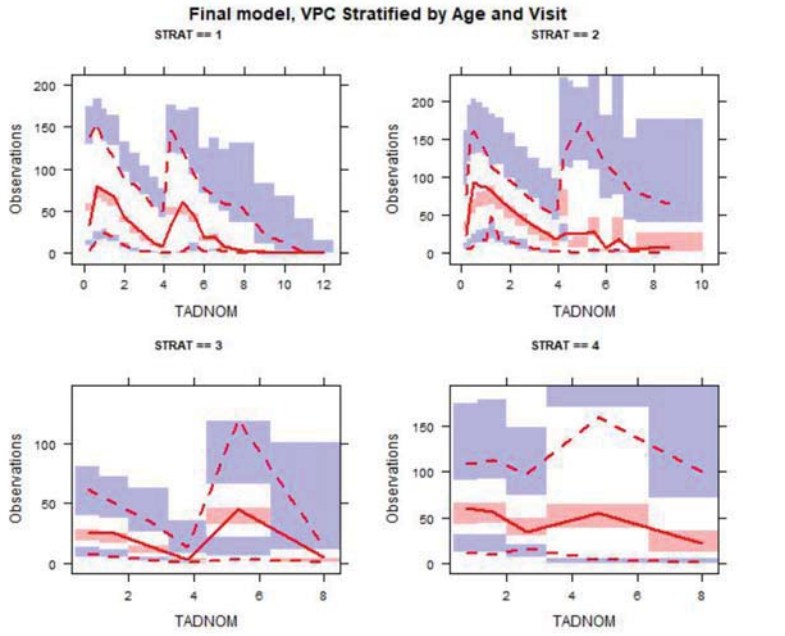
Figure 2: Basic Goodness-of-Fit Plots for Final Model



Upper Left plot is Predicted (PRED) vs Observed (DV), upper right is Individual Predicted (IPRED) vs DV, lower left plot is Individual Weighted Residuals (IWRES) vs IPRED, and lower right plot is Conditional Weighted Residuals (CWRES) vs Time After First Dose (hours) for the Final Pharmacokinetic Model of Oxybate

Source: Population Pharmacokinetics Report, Figure 3-2, Page 27.

Figure 3: Visual Predictive Check for Final PK Model



TADNOM (x axis) is nominal time after dose; y axis is concentration (µg/mL). The upper left plot (Stratum [STRT] 1) is adult population visit 1, the upper right plot (Stratum 2) is adult population visit 2, the lower left (Stratum 3) is pediatric population visit 1, and the lower right plot (Stratum 4) is pediatric population visit 2. The solid red line is the median of the observed data vs time after nominal dose time (TADNOM), the dashed red line is the upper and lower 95% range for the observed data. The red shaded are is the 95% prediction interval (PI) for the median, based on the simulations, and the blue shaded areas are the 95% PI for the upper and lower 95% range of the simulated data. Visit 1 is PK night 1 in Study 13-005 and the first period for the remaining studies. Visit 2 is PK night 2 in Study 13-005 and the second period for the remaining studies.

Source: Population Pharmacokinetics Report, Figure 305, Page 31.

The applicant concludes that body weight is the most significant factor on oxybate kinetics and that when Xyrem is dosed as mg/kg, similar PK is predicted between adult and pediatric subjects. Simulations were performed for different mg/kg doses, but not for the proposed doses.

Reviewer's Comments: The structure of the applicant's final Pop PK model is generally aligned with previous knowledge of oxybate pharmacokinetics. The Michaelis-Menten parameterization is reasonable as pharmacokinetics are known to be nonlinear and show greater than dose proportionality. According to the label, administration of Xyrem after a high-fat meal resulted in delayed absorption and reduction in exposure. The diurnal covariate estimated in the model is not relevant for the pediatric data because all data was collected at night in this population. The categorical age-based covariate on Vc does not appear to be supported by a mechanistic basis, although the reviewer agrees with the applicant that this covariate is not clinically significant. Based on parameter estimates and goodness-of-fit plots, it appears that the model provides an adequate description of the time course of oxybate concentrations.

The applicant does not provide simulated exposure for the proposed dosing regimens. It is worth noting that the youngest pediatric subject in the PK database weighed 31 kg, yet the applicant is proposing dosing down to (b) (4)*. For simulations, the applicant samples from the 13-005 population, so none of the virtual subjects in their simulations cover the lower weight range.*

4.2 Individual Study Review

Study 13-005: A Double-blind, Placebo-Controlled, Randomized-Withdrawal, Multi-center Study of the Efficacy and Safety of Xyrem with an Open-label Pharmacokinetic Evaluation and Safety Extension in Pediatric Subjects with Narcolepsy with Cataplexy.

Objectives:

The primary objectives of this study are:

- Evaluate the efficacy of Xyrem (sodium oxybate) oral solution in the treatment of cataplexy in pediatric subjects with narcolepsy.
- Evaluate the safety of Xyrem in the treatment of cataplexy in pediatric subjects with narcolepsy for up to 1 year.

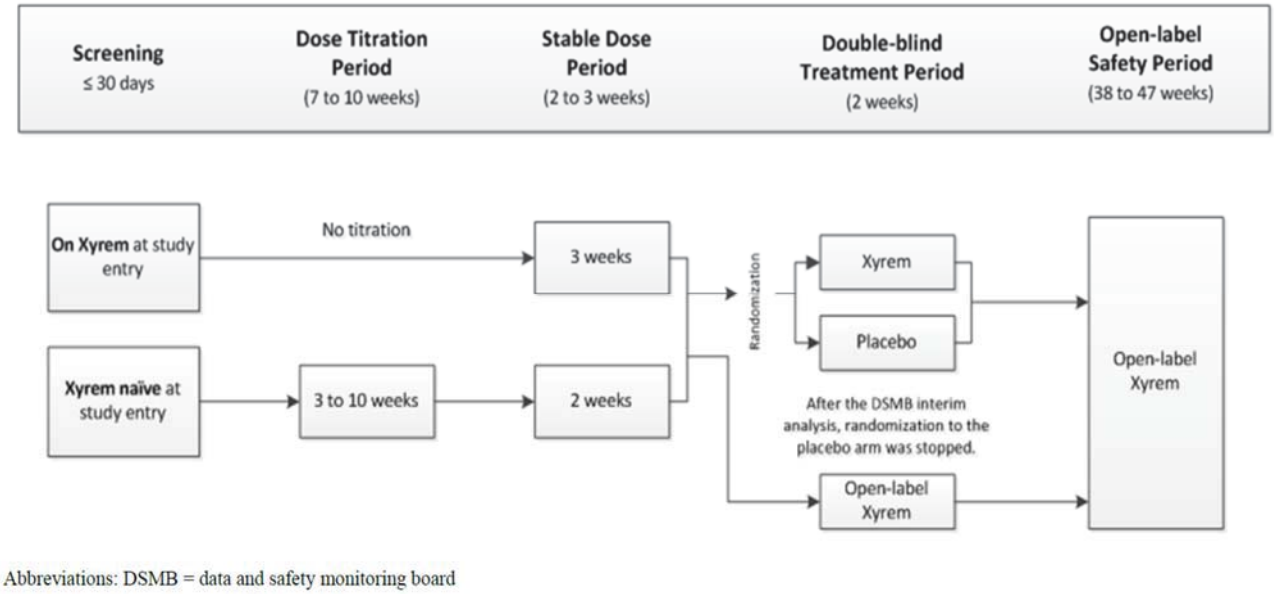
The secondary objectives of this study are:

- Evaluate the efficacy of Xyrem in the treatment of EDS in pediatric subjects with narcolepsy with cataplexy.
- Characterize the PK of Xyrem in pediatric subjects (ages 7 to 17 years) with narcolepsy with cataplexy.
- Evaluate the safety of titrating Xyrem in pediatric subjects to an effective and tolerable dose.

Study Design:

This study was a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of Xyrem (sodium oxybate) oral solution (See Figure 4). Pediatric subjects between the ages of 7 and 17 who were diagnosed with narcolepsy with cataplexy, who were being treated with Xyrem or who were Xyrem naïve, were eligible to enter the study.

Figure 4. Study Schema



Abbreviations: DSMB = data and safety monitoring board

Study Population:

100 subjects planned, 63 subjects randomized in the Efficacy population, 106 subjects in the Safety population.

Key Inclusion Criteria:

- Male or female subjects aged 7 to 16 years at study entry
- Had a primary diagnosis of narcolepsy with cataplexy
- Was positive for the Human Leukocyte Antigen (HLA) DQB1:0602 haplotype
- Had a history of having at least 14 cataplexy attacks in a typical 2-week period and clinically significant symptoms of EDS prior to any narcolepsy treatment

Key Exclusion Criteria:

- Narcolepsy secondary to another medical condition, e.g., CNS injury or lesion
- Succinic semi-aldehyde dehydrogenase deficiency (SSADH)
- Evidence of sleep-disordered breathing
- Oxygen saturation level < 95% for at least 5 minutes on room air, or subjects with known or suspected respiratory difficulty, or any condition that could have compromised a subject's breathing
- Positive urine drug screen for benzodiazepines or drugs of abuse, a positive alcohol test, a history of substance abuse including alcohol abuse, or unwillingness to refrain from consuming alcohol during the study

Study Treatment:

For subjects who were Xyrem naïve, Xyrem therapy was initiated based on the subjects' weight as shown in the table below. Xyrem doses were administered in two equally divided doses. Subjects were titrated on Xyrem to achieve maximum clinical benefit in cataplexy and EDS while maintaining tolerability. Dose adjustment during the open-label Dose Titration Period occurred based on the subject's weight to a dose level targeted to be no higher than the maximum dose described in the Table below in up to 10 weeks.

The study drug titration rate was ≤ 1 g/night/week for subjects < 45 kg, and ≤ 1.5 g/night/week for subjects ≥ 45 kg. The dose could have been incrementally titrated more frequently than weekly, as long as the total weekly increase was no more than 1 g/night/week in subjects < 45 kg and no more than 1.5 g/week in subjects >45 kg. All injections were administered in the same thigh but at different locations.

Table 5. Xyrem Dose Initiation and Titration for Xyrem Naïve Subjects

Subject weight	Initiation dose (taken in two equally divided doses)*	Titration regimen	Maximum total nightly dose
< 30 kg	≤ 2 g/night	≤ 1 g/night/week	6 g/night
≥ 30 kg – < 45 kg	≤ 3 g/night	≤ 1 g/night/week	7.5 g/night
≥ 45 kg	≤ 4.5 g/night	≤ 1.5 g/night/week	9 g/night

*At bedtime and 2.5 to 4 hours later. For children who slept more than 8 hours per night, Xyrem could be given after bedtime, while the child was in bed, in two equally divided doses 2.5 to 4 hours apart.

Pharmacokinetics:

Pharmacokinetic parameters were derived from individual plasma sodium oxybate concentration-time data over 4 hours following the first nightly dose. The PK parameters for plasma sodium oxybate concentrations included: the area under the plasma concentration time curve (AUC), AUC0-4 and AUC0-infinity, maximum plasma drug concentration (Cmax), half-life (t1/2), and time to maximum plasma drug concentration (Tmax), over the first 4-hour dosing interval. In addition, sodium oxybate concentrations at 4.75 hours (0.75 hours after the 2nd dose) and 8 hours (4 hours after 2nd dose) were measured to estimate peak and residual exposure associated with the second nighttime dose. Dose proportionality was based on the ratio between PK Night 2 (full stable dose) vs PK Night 1 (half of the stable dose) for AUC0-4 and Cmax values.

(b) (4)

Safety Evaluations:

Safety was assessed by the incidence of TEAEs, and descriptively for vital signs, 12-lead ECG, PSG parameters, clinical laboratory results, assessments of growth and precocious puberty, and the C-SSRS, CDI 2: SR[S], and MASC-10 assessments.

Statistical Methods:

Pharmacokinetics were assessed and summarized by age group (7 to 11 and 12 to 17 years old) and overall.

Sodium Oxybate Concentration

For each PK Night, sodium oxybate concentrations were summarized by sampling time point: predose (0), 0.75, 1.5, 2.5, 4 (before the second dose), 4.75, and 8 hours following the first dose. Assessments at 4.75 and 8 hours represent the peak concentration and C4h after the second dose. All sodium oxybate concentrations recorded below the limit of quantification (BLQ) were imputed with a concentration of 0.

Descriptive summary statistics along with the coefficient of variation (CV%) were presented for each age group and overall for each Xyrem dose by time point.

PK Parameters

PK parameters such as Tmax, Cmax, AUC0-4, AUC0-infinity and half-life (t1/2) were derived based on individual plasma sodium oxybate concentration-time data following the first dose. Descriptive summary statistics along with CV%, geometric mean, and geometric standard deviation were presented for each age groups and overall for each Xyrem dose.

Dose Proportionality

For subjects in the PK Completer population, analyses for dose proportionality were performed for AUC0-4 and Cmax. The analyses were based on the ratio between PK Night 2 vs PK Night 1 for AUC0-4 and Cmax values. For each parameter, the natural log transformed value on PK Night 2 minus the natural log transformed value on PK Night 1 was the response variable. The estimated mean difference and 90% confidence interval were back-transformed to ratio scale by exponentiation in order to interpret the results in ratio scale. If a value of 2 was contained within the 90% confidence interval, it indicated proportionality.

RESULTS

Pharmacokinetics:

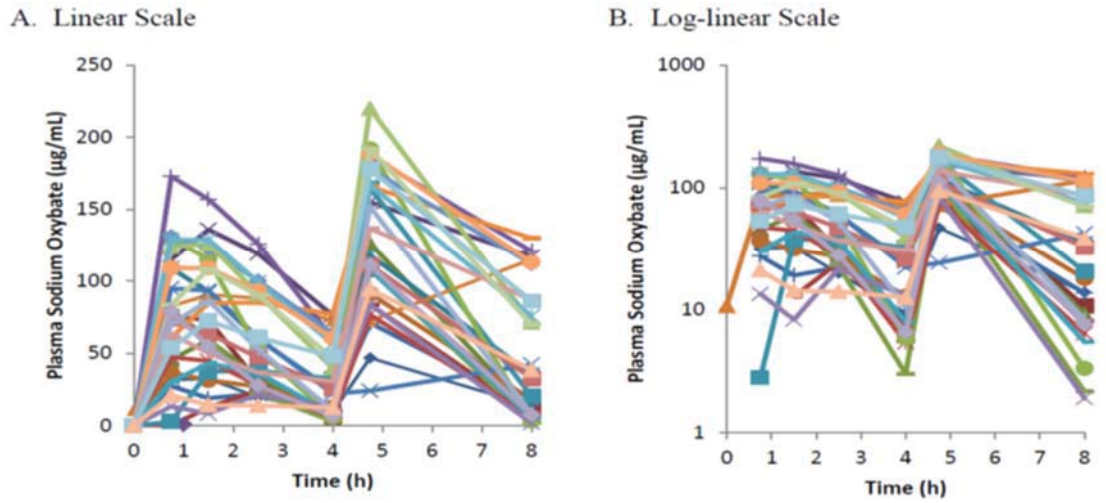
Pharmacokinetic results were obtained for the PK Completer population (N = 29), which comprised the two age groups, 7 to 11 years (N = 11; 37.9%) and 12 to 17 years (N = 18; 62.1%). There were no apparent differences in Xyrem PK characteristics between the 2 age groups.

PK sampling was performed on PK Nights 1 and 2, both of which occurred while subjects were receiving a stable dose of Xyrem. On PK Night 1, Xyrem was administered at approximately half of the stable dose, and on PK Night 2 Xyrem was administered at the full stable dose. Data from PK Night 1 (half of stable dose) informed dose proportionality, while data from PK Night 2 (full stable dose) informed exposure to drug at the stable dose. As exposure at the full stable dose is more relevant to safety and efficacy, the summary of PK results focuses mainly on the results from PK Night 2.

Sodium Oxybate Plasma Concentration-Time Profiles

Sodium oxybate plasma concentration-time profiles following administration of Xyrem at the full stable dose are shown in Figure 5. The plasma concentration-time profile presented on a log-linear scale (Figure 5, panel B) shows large variation in the terminal slopes.

Figure 5. Plasma Sodium Oxybate Concentration-time Profiles (Individual subject)



Xyrem Pharmacokinetic Parameters

For the first nightly dose on PK Night 2, the median Tmax ranged from 0.75 to 2.5 hours, and the mean Cmax and AUC0-4h values ranged from 24.3 to 92.7 µg/mL and 52.0 to 273 µg•mL/h, respectively (Table 7).

Table 7: Sodium Oxybate PK Parameters for the First Nightly Dose of Xyrem (PK Night 2, PK Population)

First Nightly Dose (g)[a]	Number of Subjects	T_{max} (hours)[a] (Median [Min, Max])	C_{max} (µg/mL) (Mean [CV%])	AUC_{0-4h} (µg/mL*hours) (Mean [CV%])
2	1	0.75 (NC)	79.4 (NC)	143 (NC)
2.25	3	0.82 (0.75-1.50)	72.5 (73%)	195 (83%)
2.5	2	1.66 (0.82-2.50)	65.3 (95%)	156 (92%)
3	1	2.47 (NC)	24.3 (NC)	52.0 (NC)
3.25	3	0.75 (0.75-2.50)	92.5 (36%)	273 (40%)
3.5	8	1.50 (0.75-1.50)	82.9 (60%)	234 (62%)
3.75	3	0.75 (0.75-1.48)	92.7 (35%)	214 (25%)
4	4	0.75 (0.75-1.50)	84.1 (44%)	209 (53%)
4.25	1	0.75 (NC)	47.4 (NC)	114 (NC)
4.5	3	1.50 (0.75-2.50)	82.4 (60%)	233 (67%)

Abbreviations: AUC_{0-4h} = area under the plasma concentration-time curve from time zero to 4 hours postdose; C_{max} = maximum observed plasma concentration; NC = not calculated since only one observation available; T_{max} = time of maximum observed plasma concentration.

[a] Based on half of the planned full nightly dose (Xyrem dosage, g/night).

Note: Results are presented for PK Night 2, on which subjects received their full stable dose of Xyrem.

Note: For T_{max}, median values are reported and the range of observed values (minimum-maximum) are reported in parentheses. For C_{max} and AUC_{0-4h}, mean values are reported and the coefficients of variation (SD / mean expressed as a percentage) are shown in parentheses.

There was no apparent association between the magnitude of the gram dose of Xyrem and either Cmax and AUC0-4h. The absence of a relationship was most likely attributable to the wide range of body weights in the PK population, which resulted in a large variation in the mg/kg doses.

Dose Proportionality

Dose proportionality assessments were based on within-subject comparisons of the 2 PK Nights, where Cmax and AUC0-4h values were expressed as ratios between PK Night 2 (full stable dose) and PK Night 1 (half of the stable dose). As PK Night 2 used a 2-fold higher dose, a mean ratio of 2.00 would suggest dose proportionality. For Cmax, the mean ratio was 1.97 and the 90% CI was 1.67 to 2.31. As the 90% CI included 2.00, the assessment suggested that Cmax was dose proportional. For AUC0-4h, the mean ratio was 2.53 and the 90% CI was 2.18 to 2.94. As the lower bound of the 90% CI was greater than 2.00, AUC0-4h was concluded to be supra-proportional.

Comparison with Historic PK Results in Adults

In both the pediatric and adult populations, the PK is nonlinear (concentration-dependent), plasma exposure increases supra-proportionally with dose, and plasma concentrations are higher with the secondly nightly dose than after the first owing largely to the effect of food on the rate of absorption. However, the PK results for pediatric subjects in Study 13-005 were generally more variable as compared to PK results for Xyrem in adults. This is due to differences in study design for adult and pediatric PK investigations, as well as the extent of variation in body weights, both of which affected the extent of variation in dose range.

Safety:

Safety assessments conducted during Study 13-005 demonstrated Xyrem was tolerated by pediatric subjects with narcolepsy. The types of TEAEs that occurred in this study were similar to previous reports in studies of narcolepsy in adults. No new safety concerns with regard to death, SAEs, or other significant AEs were identified.

CONCLUSIONS:

The PK of Xyrem in pediatric subjects was qualitatively similar to that observed in adults. The combined effects of accumulation and food effect led to sodium oxybate plasma concentrations that were generally higher after the second nightly dose than the first nightly dose. Dose proportionality assessments suggest Xyrem exhibited proportionality in Cmax, and supra-proportional increases in AUC, indicating nonlinear clearance.

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/

KEVIN M KRUDYS
10/21/2018

DAWEI LI
10/22/2018

YUXIN MEN
10/23/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21196/S-030

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone: 301-796-2200
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MEMORANDUM TO FILE

Pediatric Labeling Review

From:	Carolyn L. Yancey, MD, DPMH Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Hari Cheryl Sachs, MD, Team Leader, DPMH John J. Alexander, MD, MPH, Deputy Director, DPMH
NDA Number:	021196/Supplement (S) S-030
Sponsor:	Jazz Pharmaceuticals, Incorporated
Drug:	Xyrem (sodium oxybate) oral solution, Schedule III controlled substance
Dosage Form and Route of Administration:	Oral solution, 0.5 g per milliliter (mL). Initial dose at 4.5 grams (g) per night orally in two equal, divided doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later.
Approved Indication:	**Adult**: Treatment of - cataplexy in narcolepsy - excessive daytime sleepiness (EDS) in narcolepsy
Proposed Indication:	**Pediatric**: Treatment of cataplexy or EDS in patients 7 years and older with narcolepsy.
Consult Request:	The Division of Neurology Products (DNP) requests the DPMH collaboration for the new drug application (NDA) 021196 efficacy supplement (S-030) for Xyrem (sodium oxybate) oral solution proposed for treatment of cataplexy or EDS in narcolepsy in pediatric patients 7 years to 17 years of age. The Xyrem pediatric efficacy supplement includes the study report on a Phase 3 clinical trial #13-005 entitled, "A Double-Blind, Placebo-controlled, Randomized-Withdrawal, Multicenter Study of the Efficacy and Safety of Xyrem with an Open-Label Pharmacokinetic Evaluation and Safety Extension in Pediatric Subjects with Narcolepsy with Cataplexy" conducted pursuant to the Xyrem pediatric Written Request (WR). The applicant also submits a

request for six months pediatric exclusivity based on the completed clinical trial report cited above. DNP requests DPMH review of the proposed labeling and support on preparation for discussion with the Pediatric Review Committee (PeRC). The DPMH Consult is dated May 3, 2018.

Background

The efficacy supplement under review is from Jazz Pharmaceuticals for Xyrem (sodium oxybate) oral solution proposed for the treatment of cataplexy or EDS in narcolepsy in pediatric patients 7 years to 17 years of age. Proposed labeling for this supplement addresses addition of the new pediatric patient population for the same two adult approved sodium oxybate indications. Xyrem was approved by the Food and Drug Administration (FDA) on July 17, 2002 under the restricted distribution regulations contained in 21 Code of Federal Regulations (CFR) 314.500 (Subpart H) to assure safe use of the product. Xyrem was approved with a risk management program (RMP) including a restricted distribution program to educate physicians and patients about the risks and benefits of Xyrem, including critical information necessary for safe use and handling of the drug, maintenance of a registry of all participating patients, and a record of all prescribers.

The most recent FDA-approved labeling for Xyrem (dated November16, 2017) conforms with the Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) format. The applicant's proposed Xyrem (sodium oxybate) oral solution labeling includes revisions reflecting the data on the pediatric study, including pharmacokinetic (PK) and safety data. The RMP was revised to be a risk evaluation and mitigation strategy (REMS) program on January 26, 2017 and will need to be modified to add pediatric patients (7 years through 17 years of age) including any new risk information reported in pediatric patients.

Regulatory History of NDA 021169

- **July 17, 2002**: Xyrem was approved by FDA for treatment of adult cataplexy associated with narcolepsy under the restricted distribution regulations contained in 21 CFR 314.50, Subpart H to assure safe use of the product. Labeling includes a Boxed Warning: "Central nervous system depressant with abuse potential. Should not be used with alcohol or other CNS depressants".[1] The restricted distribution program, Xyrem Success Program, is based on the risks of central nervous system depression and abuse/misuse and employs a centralized pharmacy.
- **November 18, 2005**: S-005, Xyrem was approved for the treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy.
- **December 17, 2012**: S-013, labeling was updated to revise the Boxed Warning to: "Central Nervous System (CNS) Depression and Misuse and Abuse". Contraindications were expanded to add, "concomitant use with alcohol".
- **March 10, 2014**: Original issuance of the FDA pediatric WR for Xyrem for the proposed treatment of pediatric patients 7 year to 17 years with cataplexy or EDS with narcolepsy. See entry below (dated April 25, 2017) for an amendment to the WR that includes an interim analysis of the pediatric study. There is not a postmarketing commitment (PMC) or postmarketing requirement (PMR) for the evaluation of Xyrem in pediatric patients with cataplexy and EDS in narcolepsy.
- **April 25, 2017**: Amendment to the Xyrem pediatric WR for patients 7 years to 17 years of age for the treatment of cataplexy or EDS with narcolepsy based on an interim analysis of Study 1

[1] Original NDA 021196 XYREM (sodium oxybate) oral solution for treatment of cataplexy associated with narcolepsy (dated 17Jul2002).

(#13-005) conducted by an independent Data Safety Monitoring Board as a planned analysis after 35 patients completed/discontinued the double-blind segment of the study. The DSMB concluded that there were adequate data to support the efficacy of Xyrem in the treatment of cataplexy in narcolepsy in children and adolescents age 7 years to 17 years of age. The DSMB recommended that the double-blind segment of the study be discontinued; that the open-label (OL) safety segment of that study be continued (currently, ongoing); and that patients continue to be enrolled in the open-label PK segment of the study.[2]

- **January 26, 2017**: S-027, labeling was updated to add "aggression" in Warnings and Precautions (5.6) Other Behavioral or Psychiatric Adverse Reactions.[3] The Xyrem RMP was changed to the Xyrem REMS Program with this labeling supplement (027). The Xyrem REMS Program requires prescribers to be specially certified, to dispense Xyrem only by a specially certified central pharmacy, and only ship Xyrem to patients enrolled in the Xyrem REMS Program with documentation of safe use.
- **May 3, 2018**: submission of the pediatric efficacy supplement (S-030) with the phase 3 pediatric study report in response to the WR, as cited above in this review.

Summary of Applicant's Proposed Labeling Revisions[4]

The applicant's proposed Xyrem labeling updates with pediatric information include the following:

- Section 1 - Indications and Usage: adds the new patient population, 7 years to 17 years of age.
- Section 2.2 - Pediatric Dosing Information: adds pediatric oral solution dosing in tabular format.
- Warnings and Precautions (5.4) - Respiratory Depression and Sleep-Disordered Breathing: adds information on oxygen desaturation reported during polysomnographic evaluation of pediatric patients with narcolepsy.
- Warnings and Precautions (5.5) - Depression and Suicidality: adds information from the pediatric clinical trial in patients with narcolepsy (n=104). One patient experienced suicidal ideation while taking Xyrem. No adverse events of depression were reported in the pediatric study.
- Warnings and Precautions (5.6) - Other Behavioral or Psychiatric Adverse Reactions: adds the findings from pediatric clinical trial in patients with narcolepsy including events of confusion, anxiety, and other neuropsychiatric events, including one event of acute psychosis, reported while taking Xyrem.
- Warnings and Precautions (5.7) - Parasomnias: adds sleepwalking reported in the pediatric clinical trial and in the postmarketing experience with Xyrem.
- Clinical Trials Experience (6.1) - Pediatric Patients (7 years of age and older): adds a summary of the pediatric clinical trial experience including adverse reactions (ARs) that led to patient withdrawal of 5 of 104 patients from the study (specifically, hallucinations, tactile; suicidal ideation; weight decreased; sleep apnea syndrome; and affect lability). The most common ARs (> 5%) are enuresis (18%), nausea (17%), headache (16%), vomiting (16%), weight decreased (12%), decreased appetite (8%), and dizziness (6%).
- Pediatric Use (8.4) - The safety and effectiveness of Xyrem in the treatment of cataplexy and excessive daytime sleepiness in pediatric patients (7 years and older) with narcolepsy have been established in a double-blind, placebo-controlled, randomized-withdrawal study. The applicant also proposes adding detailed pediatric study information, PK information, and new juvenile animal study data to subsection 8.4.
- Pharmacokinetics (12.3) - Pediatric Patients: description of the pharmacokinetics of sodium

[2] NDA 021196 Xyrem (sodium oxybate), Amendment to the pediatric WR, dated
[3] NDA 021196/S-026 XYREM (sodium oxybate) oral solution for treatment of cataplexy associated with narcolepsy (dated April 19, 2017)
[4] NDA 021196/S-030 Xyrem (sodium oxybate) oral solution (dated May 4, 2018)

oxybate, including the population pharmacokinetic model, in pediatric patients (n=29) and adult patients and healthy volunteers (n=145). Body weight appears to be the major intrinsic factor affecting sodium oxybate pharmacokinetics.

- Cataplexy and Excessive Daytime Sleepiness in Pediatric Narcolepsy (14.3) - adds detailed description of the 10-week, double-blind, placebo-controlled, randomized-withdrawal study on a total of 106 pediatric patients.
- Patient Counseling Information (17) - adds language to include patients "and/or caregiver" to address patients with a caregiver (including patients 7 years and older) on the safety risks associated with use of Xyrem.
- Medication Guide - adds "caregivers of pediatric patients (7 years and older)" or "or your child…" to applicable sections of the Medication Guide to address the proposed pediatric patient population.

*Reviewer Comments: DPMH participated in DNP Xyrem labeling meeting on October 2, 2018 in which we provided our recommendations and revisions to the proposed Xyrem labeling. DPMH recommendations for revisions to the relevant labeling sections with pediatric information are detailed later in this review under the section titled, "**DPMH Pediatric Labeling Recommendations**".*

Clinical Study # 13-005
"A Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of Efficacy and Safety of Xyrem with an Open Label Pharmacokinetic Evaluation and Safety Extension in Pediatric Subjects (7 years to 17 years of age) with Narcolepsy with Cataplexy"

The study design (#13-005) was developed with DNP through a Proposed Pediatric Study Request (PPSR) and was conducted in accordance with the amended pediatric WR (dated April 25, 2017). The Pediatric Exclusivity Board met on August 29, 2018 and preliminary conclusions are that the applicant has met the terms of the WR. A final decision on whether to render six months pediatric exclusivity to Jazz Pharmaceuticals, Inc. will be made concurrent with the DNP regulatory action for S-030.

The single phase 2/3 clinical trial (# 13-005) is a 10-week, double-blind, placebo-controlled, randomized-withdrawal study of efficacy and safety of Xyrem with an open-label (OL) pharmacokinetic (PK) evaluation and safety extension with up to 1-year treatment exposure (Part 1) in 106 pediatric patients, 7 years to 17 years of age (mean age 11.9 years). The OL safety extension is the ongoing portion of study #13-005 beyond the interim analysis cut-off date (February 10, 2017) reported in this summary (per S-030). Patients who completed Part 1 either transitioned or re-enrolled in the OL Part 2 of the study in which only safety data will be collected. There was a 2 to 3-week stable dose period followed by a 2-week double-blind treatment period.[5] The study report includes Part 1 (Study #13-005) up to the data cut-off date of February 10, 2017 (completed efficacy and PK assessments; safety data continues to be collected in the ongoing OL part of Study #13-005).

Efficacy endpoints were assessed using a tiered statistical testing method.

- Primary Endpoint (Tier 1):
  - Change in weekly number of cataplexy attacks from the last 2 weeks of the stable dose period to the 2 weeks of the double-blind treatment period.

[5] NDA 021196 XYREM (sodium oxybate) oral solution, Suppl -030, Module 2.7.3 Summary of Clinical Efficacy, pages 6 to 22.

- Key Secondary Endpoints (Tiers 2 and 3):
  - Clinical Global Impression of Change (CGIC) for cataplexy severity from the end of the stable dose period to the end of the double-blind treatment period.
  - Change in the Epworth Sleepiness Scale for children and Adolescents (ESS [CHAD]) score from the end of the stable dose period to the end of the double-blind treatment period.

The primary efficacy endpoint (change in weekly number of cataplexy attacks) measure, using the Cataplexy Frequency Diary, is similar to the measure used in a prior adult study to establish efficacy. As of February 10, 2017 (data cut-off), 104 patients took the study drug for a median of 332 (170, 357) days in Study #13-005.

Per the applicant, Study #13-005 achieved its primary and secondary efficacy endpoints and demonstrated superiority of sodium oxybate oral solution over placebo in the frequency and severity of cataplexy attacks, EDS, and overall narcolepsy severity. The DNP agrees that the data are adequate to support approval of sodium oxybate oral solution in pediatric patients 7 years to 17 years of age with cataplexy in narcolepsy. During the double-blind treatment period, the median (Q1, Q3) change from baseline (the last 2 weeks of the stable dose period) in the weekly number of cataplexy attacks was 12.71 (3.44, 19.77) for patients randomized to placebo and 0.27 (-1.00, 2.50) for patients randomized to Xyrem. The comparison of the rank change from baseline between treatments was statistically significant ($p<0.0001$) when analyzed by analysis of covariance (ANCOVA) model. These results were consistent with results in previous studies in adult patients.[4]

Safety results demonstrated the treatment emergent adverse events (TEAEs) were most frequently reported in the System Organ Class (SOC) Gastrointestinal disorders: nausea, 22.2% and 6.3%, in patients 7 years to 11 years and 12 years to 17 years of age, respectively; and vomiting, 20.8% and 6.3%, in patients 7 years to 11 years of age and 12 years to 17 years of age, respectively. Nervous system disorders: headache, 10.8% and 19.4%, 7 years to 11 years and 12 years to 17 years of age, respectively, and dizziness, 5.4% and 6%, 7 years to 11 years and 12 years to 17 years of age, respectively. Under the SOC, Renal and urinary disorders: enuresis, 18.9% and 20.9%, patients 7 years to 11 years and 12 years to 17 years of age, respectively. Under the SOC, Psychiatric disorders: nightmares, 8.1% and 1.5%, 7 years to 11 years and 12 years to 17 years of age, respectively. Under the SOC, Investigations: weight decreased, 13.5% and 10.4%, 7 years to 11 years and 12 years to 17 years of age, respectively.

DPMH Pediatric Labeling Recommendations

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric population. Since sodium oxybate will be approved for use in pediatric patients for the treatment of cataplexy or EDS in patients 7 years and older with narcolepsy, the new pediatric information will be included throughout labeling. Information describing the pediatric efficacy study related to the new pediatric indication will be added to Xyrem (sodium oxybate) oral solution labeling. Information will be added to HIGHLIGHTS, the Full Prescribing Information, Section 1 Indications and Usage, Section 2 Dosage and Administration (per the Clinical Pharmacology reviewer), Section 5 Warnings and Precautions, subsections (5.3) Xyrem REMS Program, (5.4) Respiratory Depression and Sleep-Disordered Breathing, (5.5) Depression and Suicidality, (5.6) Other Behavioral or Psychiatric

Adverse Reactions, (5.7) Parasomnias, Section 6.1 Clinical Trial Experience, (b) (4) Section 8.4 Pediatric Use, Section 12.3 Pharmacokinetics (per the Clinical Pharmacology reviewer), Section 14.3 Cataplexy and Excessive Daytime Sleepiness in Pediatric Narcolepsy, Section 17 Patient Counseling Information, and the Medication Guide.

The sponsor's most recent FDA-approved labeling is dated November 16, 2017 (PLR/PLLR format). Our recommendations reflect labeling recommendations provided to the DNP on October 2, 2018. DPMH's recommended information to be added to the labeling is underlined. Information to be deleted has a ~~strikethrough~~. Comments and rationale for DPMH's recommendations to the labeling are in *italics*.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Xyrem is a central nervous system depressant indicated for the treatment of (b) (4)

- (b) (4) cataplexy or excessive daytime sleepiness (EDS) in (b) (4) patients 7 years ~~of age~~ and older with narcolepsy (1)

(b) (4)

Reviewer's Comment:
DPMH agrees with the revised language ("patients 7 years and older"), as written, in the Highlights. The pediatric patients enrolled in Study #13-005 were required to have Type 1 narcolepsy (i.e., narcolepsy with both cataplexy and excessive daytime sleepiness). Note, cataplexy and EDS are considered symptoms of narcolepsy. All patients with narcolepsy have EDS.[6]

(b) (4)

(b) (4)

ADVERSE REACTIONS

Most common adverse reactions in pediatric patients (≥ 5%) were enuresis, nausea, headache, vomiting, weight decreased, decreased appetite, and dizziness (6.2).

Reviewer's Comment:
DPMH agrees with inclusion of these ARs (≥ 5%) based on safety reported in the pediatric clinical trial

[6] https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Narcolepsy-Fact-Sheet.

study report with one caveat. While the rate of enuresis (18%) in pediatric patients is almost double the reported rate of enuresis in adults (7%) during treatment with 9 gm/night, enuresis is not uncommon in pediatric subjects between 4 years and 10 years of age. The reported increased adverse reaction of enuresis may be spurious. Note, that there is no placebo group in this study thus, DNP should ensure that this signal is not driven by pediatric patients less than 10 years of age.

FULL PRESCRIBING INFORMATION

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and (b) (4) ABUSE AND MISUSE

(b) (4)

2 DOSAGE AND ADMINISTRATION

2.2 Pediatric Dosing Information

Xyrem is administered twice nightly. The recommended (b) (4) pediatric (b) (4) specified in Table 2. The dose may be gradually titrated (b) (4)

Note: Table 2 is under revisions from DNP/Clinical Pharmacology and is not in this review.

Reviewer Comments: DPMH defers to the Clinical Pharmacology reviewer in collaboration with DNP on revisions to subsection 2.2 Pediatric Information. As stated previously, the table should be clarified to prevent errors and the instructions should clearly inform prescribers that the total nightly

dose should be administered in two divided doses.

5 WARNINGS AND PRECAUTIONS

5.3 Xyrem REMS Program

(b) (4) Xyrem is available only through a restricted distribution program called the Xyrem REMS Program because of the risks of central nervous system depression and abuse/misuse *[see Warnings and Precautions (5.1, 5.2)]*.

(b) (4) Notable requirements of the (b) (4) Xyrem REMS Program include the following:

- Healthcare Providers who prescribe Xyrem are specially certified
- Xyrem will be dispensed only by the central pharmacy that is specially certified
- Xyrem will be dispensed and shipped only to patients who are enrolled in the Xyrem REMS Program with documentation of safe use.
  Further information is available at www.XYREMREMS.com or 1-866-XYREM88® (1-866-997-3688).

Reviewer's Comments:
DPMH recommended (b) (4)

5.4 Respiratory Depression and Sleep-Disordered Breathing

Xyrem may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported *[see Overdosage (10)]*.

…. During polysomnographic evaluation (PSG) (b) (4) central sleep apnea and (b) (4) oxygen desaturation were observed in pediatric patients (b) (4) with (b) (4) Xyrem. Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with Xyrem administration in adult and pediatric patients.

Reviewer Comments: DPMH recommends adding risk information from polysomnographic evaluation results during the pediatric clinical trial with edits that do not minimize the risk. (b) (4) (b) (4)

5.5 Depression and Suicidality

…. In the pediatric clinical trial in patients with narcolepsy (n=104), one patient experienced suicidal ideation while taking Xyrem. (b) (4)

Reviewer Comments: DPMH recommends adding the risk of suicidal ideation experienced by one patient in the pediatric clinical trial in patients with narcolepsy. (b) (4)

5.6 (b) (4)

…. In the pediatric clinical trial in patients with narcolepsy, (b) (4) neuropsychiatric (b) (4) reactions (b) (4) including (b) (4) acute psychosis, were reported while taking Xyrem.

The emergence or increase in the occurrence of behavioral or psychiatric (b) (4) ~~events~~ in adult and pediatric patients taking Xyrem should be carefully monitored.

Reviewer Comments: DPMH recommends including the risks of confusion, anxiety, as well as acute psychosis reported in the pediatric clinical trial along with the recommendation to closely monitor these adverse reactions.

5.7 Parasomnias

… Parasomnias, including sleepwalking, also have been reported in the pediatric clinical trial and in postmarketing experience with Xyrem. Therefore, episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

Reviewer Comment: DPMH agrees with inclusion of the risk of sleepwalking in Warnings and Precautions (5.7) as reported in the pediatric clinical trial.

6.1 Clinical Trials Experience

Pediatric Patients (7 Years of Age and Older)

In the pediatric clinical trial (Trial N5), 104 patients (b) (4) 7 to 17 years (37 patients ages 7 to 11 years) with narcolepsy received Xyrem up to 377 days (median exposure 332 days) (b) (4)

Adverse (b) (4) *Reactions Leading to Treatment Discontinuation*

In the pediatric clinical trial, 5 of 104 patients reported adverse (b) (4) reactions that led to withdrawal from the study (hallucination, tactile; suicidal ideation; weight decreased; sleep apnea syndrome and affect lability).

Adverse Reactions in the Pediatric Clinical Trial

(b) (4) (b) (4) The most common adverse reactions (>5%) were enuresis (18%), nausea (17%), headache (16%), vomiting (16%), weight decreased (12%), decreased appetite (8%), and dizziness (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)]

Reviewer Comments: DPMH agrees with inclusion of the ARs reported in the pediatric clinical trial and the Warnings and Precautions sections that are cross-referenced. As state earlier in this review,

enuresis is a known adverse reaction associated with Xyrem treatment in adult patients. It is more challenging to tease out enuresis in pediatric patients particularly between 7 years and 10 years of age. (b) (4)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

(b) (4) The safety and effectiveness of Xyrem in the treatment of cataplexy and excessive daytime sleepiness in pediatric patients (7 years and older (b) (4) with narcolepsy have been established in a double-blind, placebo-controlled, randomized-withdrawal study (b) (4) *[see Adverse Reactions (6.1) and Clinical Studies (14.3)].*

S (b) (4) afety and effectiveness of Xyrem in pediatric patients less than 7 years old have not been established. (b) (4)

(b) (4) In the pediatric clinical trial with Xyrem administration in patients with narcolepsy, serious adverse reactions of central sleep apnea and oxygen desaturation documented by polysomnography evaluation; suicidal ideation in one patient; confusion, anxiety including one episode of acute psychosis; and parasomnias, including sleepwalking, have been reported [*see Warnings and Precautions (5.4), (5.5), (5.6), and (5.7); Clinical Trials Experience (6.1)].*

(b) (4)

Reviewer's Comments:

(b) (4)

[7] Katz RK and DeMaso DR. Chapter 21.3 Enuresis (Bed-Wetting) and Katz, Nelson Textbook of Pediatrics, 19th Ed, 2011, pp 71 to 73

(b) (4)

. DPMH defers to the Pharmacology Toxicology reviewer on the specific description of juvenile animal study data that supports use of sodium oxybate in pediatric patients 7 years and older. The relationship to the maximum recommended human dose (MRHD) is important on informing prescribers who may consider prescribing Xyrem for pediatric patients with cataplexy and EDS in narcolepsy.

12. 3 Pharmacokinetics

Pediatric Patients

(b) (4)

he pharmacokinetics of sodium oxybate were evaluated in pediatric patients ages 7 to 17 years (n=29). (b) (4)

The pharmacokinetic characteristics of sodium oxybate (b) (4) were shown to be similar in adults and pediatric patients. (b) (4) Body weight was found to be~~is~~ the major intrinsic factor affecting oxybate pharmacokinetics. (b) (4)

Reviewer's Comment: DPMH defers to the Clinical Pharmacology reviewer on revisions to subsection 12.3 Pharmacokinetics, Pediatric Patients. DPMH recommends removing the last sentence as it implies that it is acceptable to (b) (4)

14 CLINICAL STUDIES

The efficacy of Xyrem for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years and older with narcolepsy has been established in the following adequate and well-controlled trials:

- Cataplexy in adult narcolepsy in Trials N1 and N2 [see Clinical Studies (14.1)]
- Excessive Daytime Sleepiness (EDS) in adult narcolepsy in Trials N3 and N4 [see Clinical Studies (14.2)]
- Cataplexy and EDS in pediatric narcolepsy in Trial N5 [see Clinical Studies (14.3)]

Reviewer Comment: DPMH agrees with the addition of the pediatric trial (Trial N5) cited in the new subsection 14.3 Cataplexy and EDS in pediatric narcolepsy.

14.3 Cataplexy and Excessive Daytime Sleepiness in Pediatric Narcolepsy

(b) (4)

The effectiveness of Xyrem in the treatment of pediatric cataplexy and excessive daytime sleepiness ~~in pediatric patients 7 years of age and older with narcolepsy~~ was established in a (b) (4) double-blind, placebo-controlled, randomized-withdrawal study (Trial N5) (NCT02221869) (b) (4) ~~The study enrolled~~ 106 pediatric patients, (b) (4) (median age: 12 years; range: 7 to 16 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

[8] www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm341394.pdf

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. (b) (4)

Patients entered the study either on a stable dose of Xyrem or were Xyrem-naïve. 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 the Xyrem dose had been optimized, these patients entered the 2-week stable-dose period; patients on a stable dose of Xyrem at study entry remained on this dose for 3 weeks, prior to randomization. Efficacy was established at doses ranging from 3 g to 9 g of Xyrem per night.

(b) (4)

The primary efficacy measure was the change in frequency of cataplexy attacks evaluated with the Clinical Global Impression of Change (CGIC) for cataplexy severity [see Clinical Studies (14.2) for description of scale]. 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 adult clinical.

Pediatric patients on stable doses of Xyrem who were withdrawn from Xyrem treatment and 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 9).

Reviewer Comment:
DPMH recommends shortening the clinical study description for Xyrem in the treatment of pediatric patients with cataplexy or EDS with narcolepsy and inserting the statistically significant endpoint results employing the Clinical Global Impression of Change (CGIC) frequency of cataplexy events and improvement in the Epworth Sleepiness scores for children and adolescents.

Section 17. Patient Counseling Information

Xyrem REMS Program
(b) (4) Xyrem is available only through a restricted (b) (4) program called the Xyrem REMS Program *[see Warnings and Precautions (5.3)]*. Inform the patient and/or caregiver of the following notable requirements:

- Xyrem is dispensed only by the central pharmacy
- Xyrem will be dispensed and shipped only to patients enrolled in the Xyrem REMS Program (b) (4)

(b) (4)

Reviewer Comments:
DPMH agrees with the addition of "and/or caregivers" throughout each sub-header in Section 17 Patient Counseling Information to address the new patient population, pediatric patients, 7 years to 17 years of age, who may be prescribed Xyrem, should this efficacy supplement be approved by FDA. The sub-header "Xyrem REMS Program" was included in this review as an example. (b) (4)

Medication Guide
Xyrem® (ZIE-rem)
(sodium oxybate)
Oral solution CIII

(b) (4)

Read this Medication Guide carefully before you start or your child starts taking Xyrem 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 (b) (4) treatment.

Note: Each section in the Medication Guide includes the insertion of "or your child" to address the proposed new patient population. Each section of the Medication Guide is not presented in this review.

What is Xyrem?
Xyrem is a prescription medicine used to treat the following symptoms in people (b) (4) :

- (b) (4) weak or paralyzed muscles (b) (4) (cataplexy)
- Excessive daytime sleepiness (EDS) (b) (4)

It is not known if Xyrem is safe and effective in children less than 7 years of age.

Xyrem can cause serious side effects, including:
….. The most common side effects of Xyrem include:

- nausea
- dizziness
- vomiting

- bedwetting
- (b) (4)

In pediatric patients, headache, decreased appetite, and weight decrease were also common.

Reviewer Comments:
DPMH recommends inserting "bedwetting" at the beginning of this sentence. Enuresis is reported in 18% of pediatric patients who participated in the pediatric clinical trial with Xyrem in narcolepsy followed by nausea, headache, vomiting, weight decreased, decreased appetite, and dizziness in this order (see HIGHLIGHTS, Adverse Reactions). DPMH defers to the Patient Labeling reviewer for consideration of rewording/re-ordering adverse reactions as reported in pediatric patients are similar to ARs reported in adult patients. (b) (4)
(b) (4)

DPMH Actions and Labeling Recommendations

DPMH reviewed the sponsor's proposed labeling and participated in the internal DNP meetings on June 1 and October 2, 2018. Labeling recommendations were provided in track changes for DNP consideration to the XYREM labeling to conform to the *Guidance for Industry and Review Staff* on Pediatric Labeling.[8] DPMH's input will be reflected in the final labeling and the approval letter. Final labeling, which will be negotiated with the applicant, may differ from recommendations in this DPMH labeling review.

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/s/

CAROLYN L YANCEY
10/26/2018
DPMH Review - sNDA 021196 XYREM Cataplexy or EDS in Narcolepsy, pediatric patients 7 years and older

HARI C SACHS
10/26/2018
I agree with these recommendations.

JOHN J ALEXANDER
10/26/2018

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/s/

CHRISTINE J BRADSHAW
10/23/2018

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:	October 22, 2018
To:	William Dunn, MD Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Christine Bradshaw, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	XYREM (sodium oxybate)
Dosage Form and Route:	oral solution, CIII
Application Type/Number:	NDA 21196
Supplement Number:	S-30
Applicant:	Jazz Pharmaceuticals

1 INTRODUCTION

On April 27, 2018, Jazz Pharmaceuticals submitted for the Agency's review a Pediatric Efficacy Supplement for XYREM (sodium oxybate), oral solution, CIII. The Applicant is seeking FDA approval for the use of XYREM (sodium oxybate), oral solution, CIII in pediatric patients based on a phase 3 clinical trial 13-005 entitled *"A Double-Blind, Placebo-Contolled, Randomized-Withdrawal, Multicenter Study of the Efficacy and Safety of Xyrem with an Open-Label Pharmacokinetic Evaluation and Safety Extension in Pediatric Subjects with Narcolepsy with Cataplexy"*. XYREM (sodium oxybate), oral solution, CIII is approved for the treatment of cataplexy and excessive daytime sleepiness (EDS) in patients with narcolepsy.

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 Products (DNP) on October 9, 2018, for DMPP and OPDP to review the Applicant's proposed MG and IFU for XYREM (sodium oxybate), oral solution, CIII.

2 MATERIAL REVIEWED

- Draft XYREM (sodium oxybate), oral solution, CIII received on April 27, 2018, and received by DMPP and OPDP on October 9, 2018.
- Draft XYREM (sodium oxybate), oral solution, CIII Prescribing Information (PI) received on April 27, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 9, 2018.

3 REVIEW METHODS

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. We reformatted the MG and IFU documents using the Arial font, size 10.

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)

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.

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/s/

SHARON W WILLIAMS
10/22/2018

CHRISTINE J BRADSHAW
10/22/2018

LASHAWN M GRIFFITHS
10/22/2018

Clinical Inspection Summary

Date	October 12, 2018
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Ranjit Mani, M.D., Clinical Team Leader\Reviewer Vandna Kishore, Regulatory Project Manager
NDA#	21196/S-030
Applicant	Jazz Pharmaceuticals, Inc.
Drug	Xyrem (sodium oxybate oral solution)
NME	No
Review Priority	Priority
Proposed Indication	Treatment of cataplexy (b) (4) excessive daytime sleepiness (EDS) in (b) (4) patients (b) (4)
Consultation Request Date	May 24, 2018
Summary Goal Date	October 19, 2018
Action Goal Date	October 27, 2018
PDUFA Date	October 27, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of (b) (4) were inspected in support of this NDA. Based on the results of these inspections, the study (Protocol 13-005) appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final classification of the inspections of both (b) (4) was No Action Indicated (NAI).

II. BACKGROUND

The Applicant submitted this NDA to support the use of Xyrem (sodium oxybate oral solution) for the treatment of cataplexy (b) (4) excessive daytime sleepiness in pediatric patients (b) (4)

Clinical inspections were requested for the following protocol in support of this application:

Protocol 13-005, "A Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Efficacy and Safety of Xyrem with an Open- Label Pharmacokinetic Evaluation and Safety Extension in Pediatric Subjects with Narcolepsy with Cataplexy"

This protocol, randomizing 63 subjects, was conducted globally at 30 centers: United States (25), Italy (1), France (2), the Netherlands (1), and Finland (1).

The primary objectives of this study were to evaluate the efficacy and safety of Xyrem oral solution in the treatment of cataplexy in pediatric subjects with narcolepsy. Secondary objectives included the evaluation of the efficacy of Xyrem in the treatment of excessive daytime sleepiness (EDS) with narcolepsy and the characterization of the pharmacokinetics of Xyrem in pediatric subjects.

The primary efficacy endpoint was the change in the weekly number of cataplexy attacks from the last 2 weeks of the Stable-Dose Period to the 2 weeks of the Double-blind Treatment Period.

Rationale for Site Selection

The clinical sites of (b) (4) were selected for inspection because of their relatively large enrollment and lack of previous inspections.

III. RESULTS (by site):

Site # Name of CI/ Address	**Protocol #/ # of Subjects (enrolled)**	**Inspection Dates**	**Classification**
(b) (4)	13-005 Subjects: 12	13-17 Aug 2018	NAI
	13-005 Subjects: 25	17-20 Sep 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

1. (b) (4)

At this site for Protocol 13-005, 12 subjects were screened, and 11 subjects were enrolled in the study. The informed consent forms for all 12 screened subjects were reviewed; consent and parental assent were obtained appropriately from these subjects prior to any study-related activities. The study records of all 12 screened subjects were compared to the data listings.

Other records reviewed included staff qualifications and training, IRB correspondence and approvals, inclusion/exclusion criteria, primary and secondary efficacy endpoints, concomitant medications, protocol deviations, and drug accountability records. There was no evidence of under-reporting of adverse events.

Primary efficacy endpoint data were verified for Subjects (b) (6) The data for Subject (b) (6) were discrepant for the following time points:

Date	# of cataplectic episodes (source)	# of cataplectic episodes (line listings)
03 Apr 15	20	No data
04 Apr 15	24	20
05 Apr 15	25	25
06 Apr 15	No data	20

Reviewers Comment: The data discrepancy noted above for Subject (b) (6) would result in four additional cataplectic episodes over the same evaluation period based on source data as compared to the line listings (177 episodes compared to 173 episodes), a difference of approximately 2%. In terms of the change of the average number of episodes per week, this difference would result in a change of -0.4 episodes per week. This difference would appear insignificant given the occurrence of more than 70 episodes per week, whether based on source data or the line listings.

2. (b) (4)

At this site for Protocol 13-005, 27 subjects were screened, and 25 subjects were enrolled in the study. Of these 25 subjects, seven subjects went directly into the open-label portion of the study because of the sponsor's closure of the site's randomization status. Informed consent for all 18 randomized subjects was obtained appropriately prior to any study-related activities. The study records of all 18 randomized subjects were compared to the data listings.

Other records reviewed included Ethics Committee and monitoring correspondence, training records/documentation, source records including, but not limited to, screening visit worksheets, progress notes, laboratory results, EKGs, and polysomnography reports; inclusion/exclusion criteria, diaries and questionnaires, primary and secondary efficacy endpoints, protocol deviations, concomitant medications, and test article accountability and storage records. The primary endpoint was verifiable, and there was no evidence of under-reporting of adverse events.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H
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cc:
Central Doc. Rm.\NDA 21196-S030
DNP\Division Director\Billy Dunn
DNP\Team Leader\Reviewer\Ranjit Mani
DNP\Project Manager\Vandna Kishore
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Phillip Kronstein
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Yolanda Patague
OSI\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
10/16/2018

PHILLIP D KRONSTEIN
10/16/2018

KASSA AYALEW
10/16/2018

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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: September 25, 2018
To: Billy Dunn, M.D, Director
Division of Neurology Products (DNP)

Through: Dominic Chiapperino, Ph.D., Director
Martin Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff (CDER/OCD/CSS)

From: Alan Trachtenberg, M.D., M.P.H., Medical Officer
Controlled Substance Staff (CDER/OCD/CSS)

Subject: **sNDA: 21196/S-030**
Trade name: Sodium Oxybate (Xyrem); A.K.A. gamma-hydroxybutyrate (GHB).
Indication: Cataplexy and excessive daytime sleepiness (b) (4)
Dosage: (b) (4) 4.5-9.0 g at bedtime
Sponsor: Jazz Pharmaceuticals

Material Reviewed: sNDA 21196/S-030, Submission of Pediatric Study Reports, which includes:

- Study 13-005, investigating pediatric efficacy, safety, and PK
- Study 13-008 (flavor study for blinding purposes)
- Study 13-002 (BE study, flavored versus unflavored oral solutions)
- Cumulative U.S. Postmarketing Safety Report of Xyrem in Pediatric Use from Product Launch in 2002 through October 12, 2017
- Revised product labeling and REMS

I. Background

This memorandum is in response to a consult request dated May 3, 2018, from the Division of Neurology Products (DNP), pertaining to an approved Schedule III drug, Xyrem (NDA 021196), sodium oxybate, which is an orphan designated drug for the treatment of cataplexy and excessive daytime sleepiness (EDS) in patients with narcolepsy. Xyrem is taken at night in divided doses at a recommended dose of 6 to 9 g/night (with an initiation dose of 4.5 g/night).

Sodium oxybate, marketed as Xyrem oral solution (with one approved generic), is the only FDA-approved form of gamma hydroxybutyrate (GHB). GHB is a sedative drug scheduled under C-I of the Controlled Substances Act (CSA), except when formulated as an FDA-approved drug, in which case it is controlled under C-III of the CSA. GHB has a historical public reputation as a "date rape drug," in which it is administered surreptitiously with the intention of rendering a victim unable to resist the predatory intentions of the perpetrator. It gained initial notoriety when it was easily available as a dietary supplement, until such marketing was made illegal in 1990 due to safety concerns.

Xyrem was originally approved by the Agency on July 17, 2002, for the treatment of cataplexy in narcolepsy, under NDA 21196. A supplemental NDA (an efficacy supplement; S-005), proposing an expansion of the originally approved claim, was approved on November 18, 2005; the approved expanded indication was "The treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy." The drug was originally approved for marketing under a restricted distribution program. A Risk Evaluation and Mitigation Strategy (REMS) was approved by the Agency on February 27, 2015. A pediatric Written Request (WR) was issued to the Sponsor on March 10, 2014 and amended on April 25, 2017. Most recently, a Type B pre-submission meeting was held between DNP and the Sponsor, on September 6, 2017, regarding IND 49641, to discuss the main Study 13-005, to substantiate the current sNDA for Xyrem to support a new pediatric indication. Xyrem is a controlled substance available only through the Xyrem REMS Program, which has Elements to Assure Safe Use.

The pediatric supplemental New Drug Application (sNDA) now under review was submitted to support an expansion of labeling to include the pediatric use of Xyrem for the treatment of cataplexy and EDS in narcolepsy. The Xyrem pediatric clinical program consisted of a single Phase 2/3 study (Study 13-005) intended to support the safety and efficacy of Xyrem in pediatric patients, ages 7 to 17 years, with narcolepsy along with

cataplexy. The submitted study was developed in collaboration with FDA through a Proposed Pediatric Study Request (PPSR).

Study 13-005 was a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of Xyrem with an open-label pharmacokinetic (PK) evaluation and safety extension with up to 1 year treatment exposure (Part 1). Subjects who completed Part 1 were allowed to either transition or re-enroll in the open-label Part 2 of the study, in which only safety data were collected, based on a commitment from the Sponsor to the subjects who were benefiting from Xyrem to provide continuity while this sNDA was under review.

Narcolepsy is a life-long neurologic disease with no known cure. The onset of narcolepsy has been reported in children as young as 3 years old and up to 50% of patients may become symptomatic prior to the age of 15 years (Challamel 1994; Yoss and Daly 1960). Management of narcolepsy includes pharmacological and non-pharmacological approaches in pediatric patients. Although up to 50% of adult patients with narcolepsy develop symptoms before age 15 years, no treatments are approved for pediatric narcolepsy or cataplexy (Dauvilliers 2001; Okun 2002; Yoss and Daly 1960). However, treatments used for adults are often used off label for pediatric narcolepsy (Mignot 2012). Some stimulants, such as dextroamphetamine, provide dosing information for pediatric patients with narcolepsy, but clinical studies demonstrating safety and efficacy in pediatric patients have not been conducted (Dexedrine Spansules® US PI 2010).

II. Conclusions

1. Sodium oxybate, when formulated in a drug product that is approved by FDA (under an NDA or ANDA), is controlled under Schedule III of the CSA. Otherwise, sodium oxybate (also known as GHB) is controlled under Schedule I.
2. If the current pediatric supplement is approved, there would be no recommended change in the drug product's current placement within Schedule III of the CSA.
3. The Sponsor's proposed revised Xyrem labeling to reflect Study 13-005 is acceptable from CSS perspective.
4. From CSS perspective this pediatric supplement is approvable.

III. Recommendations

1. From the CSS point of view, the current sNDA can be approved.
2. The proposed changes to Xyrem labeling do not involve changes to section 9 Drug Abuse and Dependence or any other sections which address abuse or dependence.

IV. Discussion

Clinical Studies

Study13-008 was a Phase 1, double-blind, randomized, crossover Taste Testing Study, to compare the taste of Xyrem and Xyrem placebo, both prepared with the same flavored diluent solutions (in two flavors), for evaluation of sameness in taste to ensure adequate blinding in subsequent placebo controlled trials. Xyrem and placebo were tasted only, with no swallowing or consumption, and then expectorated. Treatments A and B were 4.5 g Xyrem or placebo prepared with 60 mL of one flavored diluent (Diluent 1), and Treatments C and D were Xyrem or placebo prepared with 60 mL of another flavored diluent (Diluent 2). Duration of treatment was 4 days for each subject. Subjects were 26 male and 27 female healthy adults, 19 to 50 years old, with a mean age of 28.2 years. Subjects were entered into the study to taste Xyrem and Xyrem placebo prepared with the same flavored diluent solution in pair-wise combinations. One flavor of diluent solution was used for all subjects on Day 1 and a different flavor of diluent solution was used for all subjects on Day 2. Subjects were instructed to spit out the liquids after tasting and not to swallow the liquids. On Day 1 and Day 2, two liquids were compared in duplicate for each subject.

Each subject was asked to taste the first liquid of the pair and then remember that taste and compare that liquid for sameness to the second liquid. An hour later, the subject tasted the second liquid and rated it by answering "Yes" or "No" to the question: "Does liquid Y taste the same as liquid X?" There were 4 period crossovers within each day. An hour following the taste test of the first pair of liquids (Replicate 1, Period 1), the second pair of liquids was tested (Replicate 1, Period 2). In the afternoon of each day, subjects tested two more pairs of liquids (Replicate 2, during Periods 3 and 4). After each taste test, subjects were evaluated for alertness and dizziness and then allowed to ambulate. Subjects who swallowed study drug were excluded from further tasting in the study and were asked to remain at the study center for close observation for a minimum of 8 hours prior to release.

There were no serious abuse-related or other AEs attributed to the treatments. A total of 9 TEAEs were reported by 6 (11.3%) of the 53 subjects, with headache being the most

frequently reported, in 4 (7.5%) of the subjects. Other TEAEs included single events of dizziness, nausea, and pain in an extremity, each occurring in one subject, and oropharyngeal pain and rhinorrhea, both occurring in the same subject. None were considered related to treatment, and most (7/9) TEAEs were judged to be of mild severity. Two TEAEs, nausea and pain in an extremity, were considered to be of moderate severity; none were considered to be serious. All but one of the AEs were reported as resolved at the end of the study, the exception being one subject who discontinued early because of a TEAE of oropharyngeal pain. This resolved by 10 days of follow-up after her early discontinuation from the study.

Study 13-002 was a Phase 1 bioavailability, bioequivalence, open-label, PK, randomized single-dose crossover trial with the control being unflavored Xyrem, to evaluate the PK of Xyrem prepared with a flavored diluent solution to assess its relative bioavailability and bioequivalence when compared with Xyrem prepared with water. Treatment A was one 4.5 g oral dose of Xyrem prepared with 60 mL of diluent flavored with a commercially available drink mix sweetened with sucralose. Treatment B was one 4.5 g oral dose of Xyrem prepared with 60 mL of water. Thirteen male and 21 female subjects received a single dose of each treatment in randomized crossover fashion over a 4 day stay in clinic. Subjects were healthy adults aged 18 to 50 years old with a mean age of 25.7 years.

Subjects were randomized to one of the above treatments on Day 1 and then crossed over to the other treatment on Day 3, after a 1-day washout. Subjects received study drug in the morning following a 10-hour fast and continued fasting for 4 hours after dosing. After swallowing the first treatment, subjects drank 180 mL of water, but no more during the period from 1 hour before to 1 hour after each dose. On Days 1 and 3, subjects rested in bed for 4 hours prior to taking the first dose of study drug. Subjects were monitored for any signs of dizziness, unstable gait, or any other impairment while getting out of bed. No intense physical exercise was allowed during the study. Subjects received a standard low-fat lunch about 4 hours after dosing (after a 4-hour postdose PK sampling), and a standard dinner about 8 hours after dosing. No food was allowed between meals. After the last plasma PK sample was collected at 8 hours postdose, subjects were free to eat and drink ad lib. Sodium oxybate concentrations were assayed in blood samples collected predose and at 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, and 8 hours following administration. Safety was assessed at specified time points and throughout the study. Adverse events were classified into a standardized terminology using the Medical Dictionary for Regulatory Activities (MedDRA, Version 16.1).
A total of 34 subjects were randomized to treatment sequence and 32 subjects completed the study. Two subjects discontinued early: one discontinued for an AE of mild anxiety and one withdrew to address urgent family issues. The Sponsor reported no major

protocol deviations. A total of 317 AEs were reported by 34 (100%) of the 34 subjects treated. Overall, the safety profile was similar in both flavored and unflavored groups. Most AEs (274/317 events) were reportedly of mild severity and 43 moderate. None were judged to be serious . Most AEs (308/317 events) were judged to be related to the study drug. The sponsor's Table of TEAE (Table 9) is shown below. Notably, all subjects reported somnolence, and 10 (30%) reported euphoric mood with Xyrem.

Sponsor's Table 9: Number (%) of Subjects with Treatment-Emergent Adverse Events (Reported in ≥2 Subjects in Any Treatment Group or Overall) (Safety Population)

Preferred Term	Treatment A Xyrem prepared with flavored diluent (n=33)	Treatment B Xyrem prepared with water (n=33)	All Subjects (n=34)
Any adverse event	33 (100.0)	32 (97.0)	34 (100.0)
Somnolence	33 (100.0)	31 (93.9)	34 (100.0)
Dizziness	12 (36.4)	14 (42.4)	21 (61.8)
Nausea	14 (42.4)	11 (33.3)	20 (58.8)
Snoring	13 (39.4)	10 (30.3)	16 (47.1)
Vomiting	9 (27.3)	9 (27.3)	14 (41.2)
Headache	8 (24.2)	8 (24.2)	14 (41.2)
Euphoric mood	5 (15.2)	9 (27.3)	10 (29.4)
Emotional disorder	2 (6.1)	4 (12.1)	6 (17.6)
Feeling of relaxation	4 (12.1)	1 (3.0)	5 (14.7)
Crying	3 (9.1)	2 (6.1)	4 (11.8)
Paresthesia	0 (0.0)	4 (12.1)	4 (11.8)
Hypoesthesia	1 (3.0)	3 (9.1)	3 (8.8)
Feeling abnormal	1 (3.0)	2 (6.1)	3 (8.8)
Nystagmus	0 (0.0)	3 (9.1)	3 (8.8)
Sensation of heaviness	1 (3.0)	2 (6.1)	3 (8.8)
Myoclonus	2 (6.1)	2 (6.1)	2 (5.9)
Throat tightness	2 (6.1)	1 (3.0)	2 (5.9)
Akathisia	1 (3.0)	1 (3.0)	2 (5.9)
Anxiety	2 (6.1)	0 (0.0)	2 (5.9)
Chest discomfort	1 (3.0)	1 (3.0)	2 (5.9)
Diplopia	2 (6.1)	0 (0.0)	2 (5.9)
Fatigue	1 (3.0)	1 (3.0)	2 (5.9)
Feeling drunk	0 (0.0)	2 (6.1)	2 (5.9)
Hunger	1 (3.0)	1 (3.0)	2 (5.9)
Hyperhidrosis	0 (0.0)	2 (6.1)	2 (5.9)
Hypertonia	0 (0.0)	2 (6.1)	2 (5.9)
Hypoesthesia oral	2 (6.1)	0 (0.0)	2 (5.9)

Study 13-005 was a Phase 2/3 study of efficacy, safety, and PK. This was a double-blind, placebo-controlled, randomized withdrawal, open-label study with PK evaluation and a safety extension. The study was intended to evaluate the efficacy of Xyrem oral solution in the treatment of cataplexy in pediatric subjects with narcolepsy and to evaluate safety for up to 1 additional year. Xyrem naïve subjects were titrated to individual effective and tolerable doses with the total nightly dose no higher than 9 g/night. Subjects on Xyrem at study entry were continued on their stable dose and regimen of Xyrem they were receiving prior to study entry. The duration of treatment went up to 1 year in Part 1 of the study. Sixty three male and 43 female pediatric subjects with narcolepsy, aged 7 to 16 (mean=11.9) years, were initially randomized to either active Xyrem treatment continuation at the stable dose taken and regimen used in the prior 2 weeks; or (in double-blind fashion), Xyrem placebo, initiated as a double-blind treatment at an apparent volume and regimen identical to what had been finalized during the titration phase.

Subjects entering the 2 week double-blind treatment period prior to Study Amendment 4 were randomized 1:1 to receive one of these 2 treatment conditions, creating a randomized-withdrawal to evaluate the safety and efficacy of continuing stable Xyrem treatment in the pediatric population. Subjects who were Xyrem naïve entered an open-label Dose Titration Period of up to 10 weeks. Once the Xyrem dose had been optimized per the Investigator's judgment, these subjects entered the open-label Stable Dose Period on that dose.

For subjects who were on Xyrem at study entry, they were retained on their stable dose and regimen (i.e., 2 equally divided doses or 2 unequally divided doses of Xyrem) and entered the Stable Dose Period for 3 weeks. This was followed by the Double-Blind Treatment Period if the dose and regimen of Xyrem remained unchanged during the Stable Dose Period with no clinically significant worsening in narcolepsy symptoms or clinically significant AEs judged by Investigators to be due to Xyrem treatment. These not previously naïve subjects entering the Double-blind Treatment Period prior to implementation of Amendment 4 were likewise randomized 1:1 to receive one of the 2 treatments during the 2-week double-blind treatment period, randomized to either Xyrem withdrawal or continuation on the Xyrem dose taken in the prior 2 weeks.

However, a preplanned interim analysis demonstrated positive efficacy results on the primary efficacy endpoint and the protocol was amended to replace the placebo treatment in the double-blind treatment period with open-label Xyrem treatment. After Amendment 4 became effective, all subjects entering what would have been the double-blind

treatment period instead received open-label Xyrem treatment. Subjects who completed the entire double-blind treatment period were continued into the open-label safety period for up to 1 year.

Additionally, a subset of subjects on a stable dose of Xyrem were invited to participate in an open-label PK evaluation. These subjects were stratified to two age groups, 7 to 11 years old and 12 to 17 years old. Subjects participating in the PK evaluation had blood samples taken at T=0 (predose), 0.75, 1.5, 2.5, and 4 hours after the first dose and before the 2nd dose; and at 4.75 and 8 hours for PK evaluation of peak and residual exposure in relation to the 2 doses. An N of 100 subjects age 7-17 years old were planned, with 63 subjects randomized in the Efficacy population and a total of 106 subjects in the Safety population.

For subjects entering the study Xyrem naïve, Xyrem therapy was initiated based on the subjects' weight as indicated in the table below. Xyrem doses were administered in two equally divided doses. Subjects were titrated to a point of maximum clinical benefit in cataplexy and EDS while maintaining tolerability. Dose adjustment during the open-label Dose Titration Period occurred based on the subject's weight to a dose level targeted to be no higher than the maximum dose described in the Table below in up to 10 weeks. The drug titration rate was ≤ 1 g/night/week for subjects < 45 kg, and ≤ 1.5 g/night/week for subjects ≥ 45 kg. Once the Investigator judged the Xyrem dose was optimized, the subject entered the 2-week open-label Stable Dose Period on that dose.

Xyrem Dose Initiation and Titration for Xyrem Naïve Subjects in Study 13-005

Subject weight	Initiation dose *	Titration regimen	Maximum total nightly dose
< 30 kg	≤ 2 g/night	≤ 1 g/night/week	6 g/night
≥ 30 kg – < 45 kg	≤ 3 g/night	≤ 1 g/night/week	7.5 g/night
≥ 45 kg	≤ 4.5 g/night	≤ 1.5 g/night/week	9 g/night

* Taken in two equally divided doses at bedtime and 2.5 to 4 hours later. For children who slept more than 8 hours per night, Xyrem could be given after bedtime, while the child was in bed, in two equally divided doses 2.5 to 4 hours apart.

Flavorant: A flavorant that could be added to the water used as diluent was provided upon request for use in study drug preparation.

AEs in the Study 13-005 Safety population were coded using MedDRA Version 17, and summarized by system organ classes (SOC) and preferred terms (PT). TEAEs were summarized overall for each period and across all periods while on Xyrem, as appropriate. Prespecified AEs

of special interest included Confusion, Somnolence (and more pronounced levels of depressed consciousness), Respiratory depression, Depressed mood and suicidality, Anxiety, Sleepwalking and other parasomnias, Abuse and misuse of study drug, and Weight loss. Across all treatment periods, a total of 74/104 subjects (71.2%) reported TEAEs while on Xyrem, the majority of which were non-serious and mild or moderate in severity. TEAEs were reported by a total of 75.7% of subjects 7 to 11 years of age and 68.7% of subjects 12 to 17 years of age. No event of abuse or misuse was reported; however, 2 patients, ages 9 and 11, yielded unexplained accounting discrepancies, without further definition, and were terminated early from the study because of treatment non-compliance.

Postmarketing Data on abuse or addiction

The Sponsor provided postmarketing data in eCTD section 5.3.6., in report titled, Cumulative US Postmarketing Safety Report of Xyrem in Pediatric Use from Product Launch in 2002 through 12 October 2017. This document reports on cases of abuse, misuse, overdose, and diversion since the first US launch of Xyrem in September 2002 through October 12, 2017, there were 2,874 pediatric patients who initiated Xyrem treatment. This number included 422 children ages 0 - 12 years old, which included a subset of 44 young children aged 0 - 7 years old. There were 2,452 adolescent patients aged 12 - 18 years old. Cumulative exposure totaled 2,797 patient-years, of which there were 488 patient-years for children, and 2,309 patient-years for adolescents. The Sponsor reports postmarketing data in their ARGUS Safety Database suggesting that there are similar safety profiles between pediatric and adult patients. The Sponsor could not identify any new safety signals in their analysis of postmarketing safety data over this 15-year period reviewed.

There were 97 cases with abuse signals over this 15 year period. The most frequent abuse-related AE mentioned was an intentional product misuse issue. These were reported in similar frequencies in both children and adolescents. In 12 of the 31 intentional product misuse cases, a patient was taking Xyrem at a slightly higher dose (generally less than 1 g higher than prescribed, and nightly dose never greater than 9 g) than prescribed, or was following medical directions to slightly increase the dose over the prescribed amount without a formal change to the prescription. In 14 cases, the dose being taken was slightly lower than the amount prescribed. Other cases involved minor dose adjustments, such as one patient taking Zofran, and a case of alcohol use within 12 hours of taking Xyrem.

Of the 12 (0.3%) cases of intentional product misuse, none were categorized as serious. These cases, as with those counted as intentional product misuse, generally involved dose adjustments up or down. There were 3 cases of using a parent's or sibling's Xyrem (3 cases, counted as drug diversion; and one case of diluting Xyrem with Kool-Aid).

There were 4 cases of drug abuse in which a parent reported that the child might be using illicit drugs, and one nonfatal suicide attempt. There was one case of Xyrem reported being stolen, one

patient concurrently using marijuana, and one patient was hospitalized with intentional abuse of Xyrem. Intentional overdose is discussed below as a serious AE (SAE). Drug diversion was reported in 13 cases, 11 of these in adolescent patients. These included one case in which a bottle of Xyrem was stolen from a patient, 10 cases in which Xyrem was shared with family members who were Xyrem patients and one case in which a non-patient abused Xyrem and had a nonfatal overdose. There was one case of Xyrem delivered to the wrong address and one case in which a patient was left at the door of the ER with a bottle of Xyrem that had no identifying information. This patient required assisted ventilation. With the exception of this one serious case, all outcomes were reported as unknown/not applicable. None of the cases were fatal.

Table 1. Reported AEs across the Drug Abuse, Dependence, and Drug Withdrawal SMQs by Age Group

	Counts (% of cases) by Age Group		
Drug Abuse, Dependence and Drug Withdrawal SMQs	**Children (0-<12 y) n = 723**	**Adolescent (12-<18 y) n = 2,948**	**Pediatric (0-<18 y) n= 3,671**
Total	**22 (3.0%)**	**75 (2.5%)**	**97 (2.6%)**
Intentional product use issue	8 (1.1%)	23 (0.8%)	31 (0.8%)
Accidental overdose	5 (0.7%)	9 (0.3%)	14 (0.4%)
Drug diversion	2 (0.3%)	11 (0.4%)	13 (0.4%)
Intentional product misuse	5 (0.7%)	7 (0.2%)	12 (0.3%)
Intentional overdose	0 (0.0%)	6 (0.2%)	6 (0.2%)
Overdose	2 (0.3%)	3 (0.1%)	5 (0.1%)
Drug tolerance	0 (0.0%)	4 (0.1%)	4 (0.1%)
Drug abuse	0 (0.0%)	4 (0.1%)	4 (0.1%)
Prescribed overdose	0 (0.0%)	3 (0.1%)	3 (0.1%)
Rebound effect	0 (0.0%)	3 (0.1%)	3 (0.1%)
Toxicity to various agents	1 (0.1%)	1 (0.0%)	2 (0.1%)
Withdrawal syndrome	0 (0.0%)	2 (0.1%)	2 (0.1%)
Disturbance in social behaviour	0 (0.0%)	1 (0.0%)	1 (0.0%)
Substance use	0 (0.0%)	1 (0.0%)	1 (0.0%)
Drug withdrawal syndrome	0 (0.0%)	1 (0.0%)	1 (0.0%)
Drug withdrawal syndrome neonatal	1 (0.1%)	0 (0.0%)	1 (0.0%)

Of these 97 cases, 17 were categorized as serious and are shown in Table 2, below. Nine were associated with depression or suicide/self-injury, 3 were associated with acute central respiratory depression and/or respiratory failure, 2 were associated with psychotic disorders, and 6 involved medication errors.

There were 2 cases of serious drug withdrawal. In one case the patient reported withdrawal symptoms when she stopped Xyrem. The other case involved withdrawal in a newborn whose mother had been given Xyrem for insomnia, along with fluoxetine. The baby was born with irritability, being difficult to console, a high-pitched cry, increased muscle tone, and a wide nasal bridge (suggesting a potential congenital issue). There were 6 cases of intentional overdose, 4 of

which were categorized as serious. These included one case that involved an overdose of Depakote and Paxil rather than Xyrem, which was a nonfatal suicide attempt, one case involving a nonfatal suicide attempt by a patient with pre-existing depression, one case where an entire bottle of Xyrem was ingested as a suicide attempt, and one case where more Xyrem was taken than prescribed as a suicide attempt. Three of these patients were hospitalized. The case with pre-existing depression had an outcome of not recovered/not resolved, but the physician resumed Xyrem prescriptions after a few months. The patient who swallowed a bottle of Xyrem had a nonfatal outcome. Twelve of these patients were taking concomitant medications, including sedative hypnotics, and sedating antipsychotics or antiepileptics (9 cases, 53%), stimulants (4 cases, 23%), and sedating antidepressants (2 cases, 12%). One serious case involved a suicide attempt, and 3 cases involved patients with anxiety or depression. One case involved a patient with a history of head trauma and abnormal thinking. There were no new risk factors identified among concomitant medications, AEs, or reported history. Outcomes for the 17 serious cases included 8 (47%) with drug abuse, misuse or overdose that were recovered or resolved (one with sequelae), whether Xyrem was continued or stopped; 4 (23%) cases were not recovered or resolved, and 5 (30%) cases had unknown outcomes.

Table 2. Reported SAEs across Drug Abuse, Dependence, and Drug Withdrawal SMQs by Age Group

	Counts (% of cases) by Age Group		
Drug Abuse, Dependence and Drug Withdrawal SMQs	**Children (0-<12 y) n = 723**	**Adolescent (12-<18 y) n = 2,948**	**Pediatric (0-<18 y) n= 3,671**
Total	**4 (0.6%)**	**13 (0.4%)**	**17 (0.5%)**
Accidental overdose	2 (0.3%)	2 (0.1%)	4 (0.1%)
Drug abuse	0 (0.0%)	4 (0.1%)	4 (0.1%)
Intentional overdose	0 (0.0%)	4 (0.1%)	4 (0.1%)
Overdose	1 (0.1%)	1 (0.0%)	2 (0.1%)
Toxicity to various agents	1 (0.1%)	1 (0.0%)	2 (0.1%)
Drug diversion	0 (0.0%)	1 (0.0%)	1 (0.0%)
Drug withdrawal syndrome	0 (0.0%)	1 (0.0%)	1 (0.0%)
Drug withdrawal syndrome neonatal	1 (0.1%)	0 (0.0%)	1 (0.0%)

The Sponsor maintains that these data from 15 years of use, together with their controlled clinical data in the pediatric population, indicates that the overall safety profile for pediatric patients is similar to that in adults. They can identify no new safety signals or any greater suggestions of abuse and claim that their data provide strong support for the safety of Xyrem in pediatric patients. We agree that these postmarket data do not identify any unexpected or higher than expected signal.

Labeling

There are no labelling changes proposed by the Sponsor in sections 9.1 or 9.3, and only a non-significant change in 9.2 (a comma was added). The Sponsor also proposes to leave Section 5.2, Abuse and Misuse, completely unchanged. This supplement to provide for pediatric use does not require labeling changes to abuse or dependence related sections, and none are proposed by the Sponsor nor by CSS. DRISK has proposed (b) (4) as an element of the REMS, (b) (4) (b) (4)

Xyrem REMS

Distribution will remain controlled by the existing closed system as under the current REMS. There are no new aspects of the REMS specifically relevant to abuse of the product. However, some language has been added specifically for pediatric patients and their caregivers regarding misuse or diversion: The child is exhorted in the new REMS **Brochure For Pediatric Patients And Their Caregivers** to:

> "*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 one of your XYREM cups at a time*
> – *Only drink XYREM from your XYREM cup*."

The new REMS brochure also reminds caregivers that:

• "*If your child's XYREM is lost or stolen, report the incident right away to the local police and to the Certified Pharmacy" and to:*
• *"Give XYREM only as your child's healthcare provider tells you. Remember that* ***use of your child's XYREM by others is illegal.****"*

These precautions seem adequate and appropriate.

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/

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09/25/2018

MARTIN S RUSINOWITZ
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