

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 202090

Name: Sodium Oxybate 500mg/ml

Sponsor: West-Ward Pharmaceuticals International Ltd

Approval Date: January 17, 2017

Indication : Sodium Oxybate Oral Solution is a central nervous system depressant indicated for the treatment of:

- Cataplexy in narcolepsy
- Excessive daytime sleepiness (EDS) in narcolepsy

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
ANDA 202090Orig1s000
CONTENTS**

Reviews / Information Included in this Review
--

Approval Letter	X
Other Action Letter(s)	
Labeling	X
REMS	X
Labeling Review(s)	X
Medical Review(s)	
Chemistry Review(s)	X
Pharm/Tox Review	
Statistical Review(s)	
Clinical Pharm/Bio Review(s)	
Bioequivalence Review(s)	X
Other Review(s)	X
Administrative & Correspondence Documents	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202090

APPROVAL LETTER



ANDA 202090

ANDA APPROVAL

Roxane Laboratories, Inc.
1809 Wilson Road
Columbus, OH 43228
Attention: Sarah A. Smith
Director, Drug Regulatory Affairs and Labeling

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Sodium Oxybate Oral Solution, 500 mg/mL.

Reference is also made to the complete response letter issued by this office on September 19, 2013; to your amendments dated September 30, 2013; April 2, 2014; April 8, May 12, June 6, June 16, July 14, August 22, December 2, 2016; and to the correspondence submitted to your ANDA dated December 28, 2016.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. **Accordingly, the ANDA is approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Sodium Oxybate Oral Solution, 500 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD) Xyrem Oral Solution, 500 mg/mL, of Jazz Pharmaceuticals, Inc. (Jazz).

The RLD upon which you have based your ANDA, Jazz's Xyrem Oral Solution, 500 mg/mL, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
6,780,889 (the '889 patent)	July 4, 2020
7,262,219 (the '219 patent)	July 4, 2020
7,668,730 (the '730 patent)	June 16, 2024
7,765,106 (the '106 patent)	June 16, 2024
7,765,107 (the '107 patent)	June 16, 2024
7,851,506 (the '506 patent)	December 22, 2019
7,895,059 (the '059 patent)	December 17, 2022
8,263,650 (the '650 patent)	December 22, 2019
8,324,275 (the '275 patent)	December 22, 2019
8,457,988 (the '988 patent)	December 17, 2022

8,589,182 (the ‘182 patent)	December 17, 2022
8,731,963 (the ‘963 patent)	December 17, 2022
8,772,306 (the ‘306 patent)	March 15, 2033
8,859,619 (the ‘619 patent)	December 22, 2019
8,952,062 (the ‘062 patent)	December 22, 2019
9,050,302 (the ‘302 patent)	March 15, 2033
9,486,426 (the ‘426 patent)	March 15, 2033

Your ANDA contains paragraph IV certifications to each of the patents¹ under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Sodium Oxybate Oral Solution, 500 mg/mL, under this ANDA. You have notified the Agency that Roxane Laboratories, Inc. (Roxane) complied with the requirements of section 505(j)(2)(B) of the FD&C Act and that litigation was initiated against Roxane for infringement of the ‘889, ‘219, ‘730, ‘106, ‘107, ‘506, ‘059, ‘650, ‘275 patents within the statutory 45-day period in the United States District Court for the District of New Jersey [Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., Civil Action No. 10-6108 (consolidated)], for infringement of the ‘306, ‘619, ‘062, and ‘302 patents [Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals Ireland Limited v. Roxane Laboratories, Inc., Civil Action No. 15-1360 (consolidated)], and for infringement of the ‘963 patent [Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., West-Ward Pharmaceuticals Corp., Eurohealth (USA), Inc., and Hikma Pharmaceuticals PLC, Civil Action No. 16-4971]. Although these litigations remain ongoing, the 30-month period identified in section 505(j)(5)(B)(iii) of the FD&C Act, during which FDA was precluded from approving your ANDA, has expired.

With respect to 180-day generic drug exclusivity, we note that Roxane was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification for Sodium Oxybate Oral Solution, 500 mg/mL. Therefore, with this approval, Roxane is eligible for 180 days of generic drug exclusivity for Sodium Oxybate Oral Solution, 500 mg/mL. It is noted that this ANDA was not tentatively approved within the 30 month² period described in section 505(j)(5)(D)(i)(IV) of the FD&C Act. Nevertheless, the Agency has determined that Roxane has

¹ The Agency notes that the ‘106, ‘107, ‘506, ‘059, ‘650, ‘275, ‘988, ‘182, ‘963, ‘306, ‘619, ‘062, ‘302, and ‘426 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.

² This ANDA for Sodium Oxybate Oral Solution, 500 mg/mL, was submitted on July 8, 2010. For applications submitted between January 9, 2010, and July 9, 2012 containing a paragraph IV certification (or amended to first contain a paragraph IV certification during that period of time), and approved or tentatively approved during the period of time beginning on July 9, 2012, and ending on September 30, 2015, section 1133 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (P.L. 112-144) extends this period to 40 months. For applications submitted between January 9, 2010, and July 9, 2012 (or amended to first contain a paragraph IV certification during that period of time), and approved or tentatively approved during the period of time beginning on October 1, 2015, and ending on September 30, 2016, section 1133 of FDASIA extends this period to 36 months. In addition, if an application was submitted between January 9, 2010, and July 9, 2012 containing a paragraph IV certification (or amended to first contain a paragraph IV certification during that period of time), and FDA has not approved or tentatively approved the application but must consider whether the applicant has forfeited exclusivity because a potentially blocked application is ready for approval, FDA will apply the 36-month period if it makes the forfeiture determination between the period of time beginning on October 1, 2015, and ending on September 30, 2016. For all other applications, the 30-month period set forth in section 505(j)(5)(D)(i)(IV) of the FD&C Act applies.

not forfeited its eligibility for 180-day generic drug exclusivity.³ This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the FD&C Act, will begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the Agency of the date of commercial marketing.

Under section 506A of FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our REMS notification letter dated January 13, 2014. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your REMS, known as the Sodium Oxybate REMS Program, is approved with a waiver of the single, shared system requirement as a separate REMS program from that of the reference listed drug, shared among holders of approved ANDAs for sodium oxybate products with the following condition:

- Your waiver-granted REMS system shall be open to all future sponsors of ANDAs or NDAs for sodium oxybate products.

Your final proposed REMS, submitted on December 2, 2016, and appended to this letter, is approved. The REMS consists of a Medication Guide, ETASU, and an implementation system.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

Additionally, the details for what should be included in your REMS assessments and the dates of the REMS assessments are listed in Appendix 1.

³ ANDA 202090 was received on July 8, 2010. This ANDA was not granted tentative approval within the 40-month period described in section 505(j)(5)(D)(i)(IV) of the FD&C Act. Nevertheless, the Agency has determined that the failure to obtain tentative approval within the 40-month period was caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application was filed.

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:

**ANDA 202090 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY**

We remind you that 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 FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use 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:

ANDA 202090 REMS ASSESSMENT

**NEW SUPPLEMENT FOR ANDA 202090/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR ANDA 202090/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR ANDA 202090/S-000
PRIOR APPROVAL SUPPLEMENT**

PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

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 REVISION FOR ANDA 202090

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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

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 also submit final promotional materials and package insert(s), 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>.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). 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 via publicly available labeling repositories.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs and Drug Master Files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Sincerely yours,

{See appended electronic signature page}

Carol A. Holquist, RPh
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURES: Appendix 1
REMS

Appendix 1

Dates for submission of waiver-granted REMS assessments

Roxane must submit REMS Assessments to FDA six (6) and 12 months following REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Roxane must submit each assessment so that it will be received by the FDA on or before the due date.

REMS Assessment Plan

The REMS Assessment Plan includes, but is not limited to, the following:

1. Program Implementation

- a. Product Launch Date
- b. Date when REMS materials became available to healthcare providers (HCPs) on the website and via the contact center
- c. The dates stakeholders could become specially certified and/or enrolled online, by mail, by fax, by email:
 - i. Prescribers
 - ii. Pharmacies
 - iii. Patients
- d. Date when the Sodium Oxybate REMS Program website went live
- e. Sodium Oxybate REMS Program website utilization
 - i. Number of unique site visits

2. REMS Program Utilization

- a. Prescribers
 - i. Number of specially certified prescribers, status of certification, and method of certification
 - ii. Summary of reasons certification is incomplete for prescribers (e.g. “Prescriber missing information on form”, etc.)
 - iii. Number of specially certified prescribers by specialty
 - iv. Number of specially certified prescribers who were disenrolled during the reporting period and reasons for disenrollment
 - v. Number of patients by current specially certified prescriber
- b. Pharmacies
 - i. Number of specially certified pharmacies, status of certification, and method of certification
 - ii. Summary of reasons certification is incomplete for pharmacies (e.g. “Pharmacy authorized representative changed, no replacement given”, etc.)
 - iii. Number of specially certified pharmacy decertifications during the reporting period and reasons for decertification
- c. Patient Status
 - i. Number, age, and gender of enrolled patients
 - ii. Number of disenrolled patients and reason(s) for disenrollment

- iii. Number of active patients (patients enrolled who received at least one shipment of sodium oxybate during the reporting period)
- iv. Number of duplicate patients detected by the specially certified pharmacies
- v. Number of patients associated with more than one prescriber during their therapy
- vi. Number of patients who have discontinued sodium oxybate after receiving at least one shipment of sodium oxybate
- vii. Number of discontinued patients who were associated with an adverse event, including death

3. Contact Center Report

- a. Number of Contacts
- b. Summary of reason for call (i.e. “Enrollment question”, etc.) by reporter (i.e. pharmacy, prescriber, patient)
- c. Summary of any REMS-related problems identified
- d. Narrative of any corrective actions resulting from issues identified

4. Sodium Oxybate REMS Program Compliance

- a. Prescriptions
 - i. Total number of prescriptions dispensed; stratify by the number of new and the number of refills
 - ii. Number of patients with overlapping prescriptions (more than one active prescription)
 - iii. Number of patients prescribed a daily dose >9 g
 - iv. Number of prescriptions requiring contact with Xyrem REMS program
 - 1. Status of these prescriptions (dispensed, not dispensed); report any delays in shipment of product related to inability to contact Xyrem REMS program
 - v. Number of sodium oxybate prescriptions that were written by non- certified or disenrolled prescribers (reported or detected through audit)
 - 1. Actions taken (e.g. “Provision of sodium oxybate program materials”, “Prescriber certified”, etc.)
 - 2. Outcome of actions taken
- b. Shipments
 - i. Total number of bottles and shipments sent
 - ii. Number of shipments lost in delivery that were unrecovered and the number of corresponding DEA 106 forms and RMRs completed
 - iii. Number of prescriptions dispensed by noncertified pharmacies and actions taken to prevent future occurrences (reported or detected through audit)
 - iv. Number of shipments sent to noncertified pharmacies, source of report, and actions taken to prevent future occurrences
 - v. Number of duplicate patients who were shipped Sodium Oxybate under more than one name or identifier
 - vi. Number of patients who were shipped Sodium Oxybate after being disenrolled
 - vii. Number of initial shipments sent to patients without completion of the Sodium Oxybate REMS Program Patient Counseling Checklist
- c. Early refills
 - i. Number of patients who requested an early refill and reason for the request
 - ii. Number of requests approved
 - iii. Number of requests denied by the prescriber
 - iv. Number of requests denied by the specially certified pharmacies
 - v. Number of patients with multiple requests for early refills

- d. Concomitant medications - Summary table from Sodium Oxybate REMS Program Patient Counseling Checklists of the number of patients taking the following concomitant medications and who subsequently received at least one shipment of Sodium oxybate:
 - i. Sedative hypnotics
 - ii. Alcohol
 - iii. Other potentially interacting agents:
 - iv. Sedating antidepressants, antipsychotics, or anti-epileptics
 - v. General anesthetics
 - vi. Muscle relaxants
 - vii. Opioid analgesics
 - viii. Divalproex sodium or other valproate drug (e.g., valproic acid)
 - ix. Illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB])
 - e. Concomitant diagnoses - Summary table from Sodium oxybate 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 Sodium Oxybate:
 - i. Sleep apnea
 - ii. Asthma, COPD, or other conditions affecting the respiratory system
 - f. Number of notifications by pharmacists to prescribers for the following situations and the outcome of the notification (e.g., dispensed Sodium oxybate, counseled patient, or other actions)
 - i. Patient report of alcohol use
 - ii. Patient report of diagnosis of sleep apnea
 - iii. Patient report of diagnosis of asthma, COPD, or other conditions affecting the respiratory system
 - iv. Suspected abuse, misuse, or diversion
 - v. Alerts regarding potential abuse, misuse, or diversion on the patient profiles
 - g. Risk Management Reports submitted
 - i. Number of patients with an RMR
 - ii. Number of patients with multiple RMRs
 - iii. Number of alerts generated from RMRs
 - iv. Number of RMRs generated from early refill requests
 - v. Number of RMRs generated for other reasons (list reasons)
 - vi. Number of prescriber-related RMRs
 - vii. Early refill requests
 - h. Any other reports of non-compliance with the Sodium oxybate REMS program, source of report, and any corrective actions or resolution.
 - i. A summary report of audits of the specially certified pharmacies conducted during the assessment period including any actions taken to address findings
- 5. Barriers or Delays in Patient Access**
- a. False negatives: i.e., all REMS and safe use requirements were met, but a PDA was not provided by the Sodium Oxybate REMS Program
 - b. Inadvertent disenrollments
 - c. Unintended system interruptions and resolutions
 - d. Total number of PDA rejections, the number of these that were subsequently approved and the duration of time from rejection to approval
- 6. Inappropriate Patient Access**
- a. False positives: e.g., all REMS and safe use requirements were not met, but a PDA was provided by the Sodium Oxybate REMS Program
- 7. Evaluation of Safe Use Procedures**
- a. Provide reasons for prescription rejections/PDA rejected by the Sodium Oxybate REMS Program

- b. Summary and count of RMR events and the corrective actions taken

8. Evaluation of Knowledge/Surveys

- a. An evaluation of knowledge of specially certified prescribers of the risk of respiratory depression, contraindication with sedative hypnotics and alcohol, and the potential for abuse, misuse, and overdose associated with sodium oxybate
- b. An evaluation of knowledge of specially certified pharmacy authorized representatives and pharmacists of the risk of respiratory depression, contraindication with sedative hypnotics and alcohol, and the potential for abuse, misuse, and overdose associated with sodium oxybate
- c. An evaluation of knowledge of patients of the risk of respiratory depression, contraindication with sedative hypnotics and alcohol, and the potential for abuse, misuse, and overdose associated with sodium oxybate

9. Adverse Events

- a. Total aggregate number of the following potential adverse event reports received by the Sodium Oxybate REMS Program and sent to the Sodium Oxybate sponsors during the reporting period, and cumulatively:
 - i. Aggregate number of reports of abuse, misuse, diversion, overdose, accidental exposure, respiratory depression associated with sodium oxybate
 - ii. Aggregate number of potential adverse events associated with dispensed and unused sodium oxybate
 - iii. Aggregate number of potential adverse events associated with a non-certified pharmacy, disenrolled prescriber, disenrolled prescriber, or disenrolled patient
 - iv. Aggregate number of potential adverse events associated with a sodium oxybate medication error
 - v. Aggregate number of potential adverse events associated with use with concurrent sedative hypnotics and alcohol
- b. Total aggregate number of potential adverse event reports in Section III.E.9.a. that were received by the Sodium Oxybate sponsors from all sources during the reporting period
- c. Total aggregate number of potential adverse event reports in Section III.E.9.a. received by the Sodium Oxybate REMS Program and sent to the Sodium Oxybate sponsors that were subsequently reported as an adverse event by a Sodium Oxybate sponsor, during the reporting period and cumulatively
- d. Total aggregate number of potential adverse event reports in Section III.E.9.a. received by the Sodium Oxybate sponsors from all sources that were subsequently reported as an adverse event by a Sodium Oxybate sponsor, during the reporting period and cumulatively

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

- a. Sodium Oxybate REMS Program will report to FDA on the dispensing of the Medication Guide as part of the REMS assessments

11. Surveillance and monitoring

- a. The Sodium Oxybate REMS program 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 Society for Forensic Toxicologists (SOFT) for any information regarding abuse, misuse, or diversion of sodium oxybate. Any relevant information will be included in the REMS assessments



Carol
Holquist

Digitally signed by Carol Holquist
Date: 1/17/2017 02:38:30PM
GUID: 508da712000293e0f6d8acfd3c5e67fe

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 202090

LABELING

NDC 0054-0314-57

One 180 mL Bottle

LOT
EXP

Sodium
Oxybate 
Oral Solution

500 mg/mL

Each mL contains 500 mg sodium oxybate
in purified water, USP.

MUST BE DILUTED BEFORE USE.

For oral administration only.

Use as instructed.

DOSAGE AND ADMINISTRATION: See
accompanying Prescribing Information and
Medication Guide.

WARNING: Keep this and all other
medications out of reach of children.

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]

R_x only



WEST-WARD
A HIKMA COMPANY

10006867/01 6

Distr. by: West-Ward Pharmaceuticals Corp.
Eatontown, NJ 07724

N
3 0054-0314-57





(b) (4)

LOT
EXP

NDC 0054-0314-57 One 180 mL Bottle

Sodium Oxybate ^{III} Oral Solution

500 mg/mL

PHARMACIST: Dispense with enclosed Medication Guide. Sodium oxybate oral solution must be dispensed to the patient in the original packaging.

MUST BE DILUTED BEFORE USE.

For oral administration only.

Use as instructed.

WARNING: Keep this and all other medications out of reach of children.

R_x only



Distr. by: **West-Ward Pharmaceuticals Corp.**
Eatontown, NJ 07724

10006868/01

Each mL contains 500 mg sodium oxybate in purified water, USP.

DOSAGE AND ADMINISTRATION:
See accompanying Prescribing Information and Medication Guide.

Each single unit carton contains one 180 mL bottle (500 mg/mL) of Sodium Oxybate Oral Solution, one press-in-bottle-adaptor and one oral dispensing syringe.

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]

Glue

Glue

Glue

Hidden Text Area

Hidden Text Area

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **SODIUM OXYBATE ORAL SOLUTION** safely and effectively. See full prescribing information for **SODIUM OXYBATE ORAL SOLUTION**, **SODIUM OXYBATE oral solution, CIII**
Initial U.S. Approval: 2002

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and MISUSE AND ABUSE

See full prescribing information for complete boxed warning.

- Respiratory depression can occur with sodium oxybate use (5.4).
- Sodium Oxybate Oral Solution is a Schedule III controlled substance and is the sodium salt of gamma hydroxybutyrate (GHB), a Schedule I controlled substance. 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).
- Because of the risks of CNS depression, abuse, and misuse, sodium oxybate is available only through the Sodium Oxybate REMS Program. Prescribers and patients must enroll in the program (5.3).

RECENT MAJOR CHANGES

Boxed Warning, Sodium Oxybate REMS Program 04/2015
Indications and Usage, Sodium Oxybate REMS Program (1) 04/2015
Dosage and Administration, Dose Adjustment with Co-administration of Divalproex Sodium (2.4) 04/2014
Warnings and Precautions, Sodium Oxybate REMS Program required components (5.3) 04/2015

INDICATIONS AND USAGE

Sodium Oxybate Oral Solution is a central nervous system depressant indicated for the treatment of:

- Cataplexy in narcolepsy (1.1).
- Excessive daytime sleepiness (EDS) in narcolepsy (1.2).

Sodium Oxybate Oral Solution may only be dispensed to patients enrolled in the Sodium Oxybate REMS Program (1).

DOSAGE AND ADMINISTRATION

- Initiate dose at 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 (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 dose 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

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION AND MISUSE AND ABUSE

1 INDICATIONS AND USAGE

- 1.1 Cataplexy in Narcolepsy
- 1.2 Excessive Daytime Sleepiness in Narcolepsy

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosing Information
- 2.2 Important Administration Instructions
- 2.3 Dose Modification in Patients with Hepatic Impairment
- 2.4 Dose 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 Sodium Oxybate 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

9 g per night	4.5 g	4.5 g
---------------	-------	-------

- Take each dose while in bed and lie down after dosing (2.2).
- Allow 2 hours after eating before dosing (2.2).
- Prepare both doses prior to bedtime; dilute each dose with approximately 1/4 cup of water in the provided dosing cups (2.2).
- Patients with Hepatic Impairment: Starting dose is 2.25 g per night administered orally in two equal, divided doses of approximately 1.13 g at bedtime and approximately 1.13 g taken 2.5 to 4 hours later (2.3).
- Concomitant use with divalproex sodium: an initial reduction in sodium oxybate dose of at least 20% is recommended (2.4, 7.2).

DOSAGE FORMS AND STRENGTHS

Oral solution, 0.5 g per mL (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- CNS depression: Use caution when considering the concurrent use of sodium oxybate 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 sodium oxybate 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 sodium oxybate: Monitor patients with heart failure, hypertension, or impaired renal function (5.8).

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact West-Ward Pharmaceuticals Corp. at 1-800-962-8364 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 sodium oxybate (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 07/2016

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 Labor and Delivery
- 8.3 Nursing Mothers
- 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 Narcolepsy

14.2 Excessive Daytime Sleepiness in Narcolepsy

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

16.2 Storage

16.3 Handling and Disposal

17 PATIENT COUNSELING INFORMATION

MEDICATION GUIDE - SODIUM OXYBATE (SO-DEE-UM OX-I-BATE) ORAL SOLUTION, CIII

INSTRUCTIONS FOR USE - SODIUM OXYBATE (SO-DEE-UM OX-I-BATE) ORAL SOLUTION, CIII

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

FULL PRESCRIBING INFORMATION

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and MISUSE AND ABUSE

Sodium oxybate is a CNS depressant. In clinical trials at recommended doses obtundation and clinically significant respiratory depression occurred in sodium oxybate-treated patients. Almost all of the patients who received sodium oxybate during clinical trials in narcolepsy were receiving central nervous system stimulants [see *Warnings and Precautions* (5.1)].

Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB). Abuse of 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, abuse, and misuse, sodium oxybate is available only through the Sodium Oxybate REMS Program using certified pharmacies. Prescribers and patients must enroll in the program. For further information call 1-800-XXX-XXXX [see *Warnings and Precautions* (5.3)].

1 INDICATIONS AND USAGE

Limitations of Use

Sodium Oxybate Oral Solution may only be dispensed to patients enrolled in the Sodium Oxybate REMS Program [see *Warnings and Precautions* (5.3)].

1.1 Cataplexy in Narcolepsy

Sodium Oxybate Oral Solution is indicated for the treatment of cataplexy in narcolepsy.

1.2 Excessive Daytime Sleepiness in Narcolepsy

Sodium Oxybate Oral Solution is indicated for the treatment of excessive daytime sleepiness (EDS) in narcolepsy.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe sodium oxybate must enroll in the Sodium Oxybate REMS Program and must comply with the requirements to ensure safe use of sodium oxybate [see *Warnings and Precautions* (5.3)].

2.1 Dosing Information

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 (see Table 1). Increase the dose 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 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: Sodium Oxybate 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 Important Administration Instructions

Take the first dose of sodium oxybate at least 2 hours after eating because food significantly reduces the bioavailability of sodium oxybate.

Prepare both doses of sodium oxybate prior to bedtime. Prior to ingestion, each dose of sodium oxybate should be diluted with approximately ¼ cup (approximately 60 mL) of water in the empty dosing cups provided with your prescription. Patients should take both doses of sodium oxybate while in bed and lie down immediately after dosing as sodium oxybate may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking sodium oxybate, 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.

2.3 Dose Modification in Patients with Hepatic Impairment

The recommended starting dose in patients with hepatic impairment is 2.25 g per night administered orally in two equal, divided doses: approximately 1.13 g at bedtime and approximately 1.13 g taken 2.5 to 4 hours later [see *Use in Specific Populations* (8.6); *Clinical Pharmacology* (12.3)].

2.4 Dose Adjustment with Co-Administration of Divalproex Sodium

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

3 DOSAGE FORMS AND STRENGTHS

Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution, in a concentration of 0.5 g per mL.

4 CONTRAINDICATIONS

Sodium Oxybate Oral Solution is contraindicated in patients being treated with sedative hypnotic agents.

Patients should not drink alcohol when using Sodium Oxybate Oral Solution.

Sodium Oxybate Oral Solution is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency. 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

Sodium oxybate is a central nervous system (CNS) depressant. Alcohol and sedative hypnotics are contraindicated in patients who are using sodium oxybate. The concurrent use of sodium oxybate 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 sodium oxybate is required, dose reduction or discontinuation of one or more CNS depressants (including sodium oxybate) should be considered. In addition, if short-term use of an opioid (e.g. post- or perioperative) is required, interruption of treatment with sodium oxybate should be considered.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that sodium oxybate 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 the second nightly dose of sodium oxybate. Patients should be queried about CNS depression-related events upon initiation of sodium oxybate therapy and periodically thereafter [*see Warnings and Precautions (5.3)*].

5.2 Abuse and Misuse

Sodium Oxybate Oral Solution is a Schedule III controlled substance. The active ingredient of Sodium Oxybate Oral Solution, 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 amnesic features of sodium oxybate, 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 Warnings and Precautions (5.3)*; *Drug Abuse and Dependence (9.2)*].

5.3 Sodium Oxybate REMS Program

Because of the risks of central nervous system depression and abuse/misuse, sodium oxybate is available only through the Sodium Oxybate REMS Program.

Required components of the Sodium Oxybate REMS Program are:

- Use of certified pharmacies.
- Healthcare providers who prescribe sodium oxybate must complete the enrollment forms and comply with the requirements.
- Pharmacists, wholesalers and distributors must complete the enrollment forms and comply with the requirements.
- To receive Sodium Oxybate Oral Solution, patients must understand the risks and benefits of sodium oxybate.

Further information is available by calling 1-800-XXX-XXXX.

5.4 Respiratory Depression and Sleep-Disordered Breathing

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

In a study assessing the respiratory-depressant effects of sodium oxybate 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 a study assessing the effects of sodium oxybate 9 g per night in 50 patients with obstructive sleep apnea, sodium oxybate 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 sodium oxybate, and clinically significant oxygen desaturation ($\leq 55\%$) was measured in three patients (6%) after sodium oxybate administration, with one patient withdrawing from the study and two continuing after single brief instances of desaturation. Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with sodium oxybate administration.

In 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 polysomnographic (PSG) measures in 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 clinical trials in patients with narcolepsy (n=781), there were two suicides and two attempted suicides in sodium oxybate-treated patients, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used sodium oxybate in conjunction with other drugs. Sodium oxybate was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 sodium oxybate-treated patients, with four patients (<1%) discontinuing because of depression. In most cases, no change in sodium oxybate treatment was required.

In a controlled trial, with patients randomized to fixed doses of 3 g, 6 g, or 9 g per night sodium oxybate or placebo, there was a single event of depression at the 3 g per night dose. In another 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.

The emergence of depression in patients treated with sodium oxybate 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 sodium oxybate.

5.6 Other Behavioral or Psychiatric Adverse Reactions

During clinical trials in narcolepsy, 3% of 781 patients treated with sodium oxybate 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 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 clinical trials in narcolepsy, confusion resolved either soon after termination of dosing or with continued treatment. However, patients treated with sodium oxybate who become confused should be evaluated fully, and appropriate intervention considered on an individual basis.

Anxiety occurred in 5.8% of the 874 patients receiving sodium oxybate in clinical trials in another population. The emergence of or increase in anxiety in patients taking sodium oxybate should be carefully monitored.

Other neuropsychiatric reactions reported in sodium oxybate clinical trials included hallucinations, paranoia, psychosis, and agitation. The emergence of thought disorders and/or behavior abnormalities requires careful and immediate evaluation.

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 sodium oxybate in 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 sodium oxybate 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 sodium oxybate in patients with narcolepsy.

Parasomnias including sleepwalking have been reported in postmarketing experience with sodium oxybate. Therefore, episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

5.8 Use in Patients Sensitive to High Sodium Intake

Sodium oxybate 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 sodium oxybate. Table 2 provides the approximate sodium content per sodium oxybate oral solution dose.

Table 2: Approximate Sodium Content per Total Nightly Dose of Sodium Oxybate (g = grams)

Sodium Oxybate 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 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.

Sodium oxybate 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 sodium oxybate, and 213 with placebo). A total of 781 patients with narcolepsy were treated with sodium oxybate in controlled and uncontrolled clinical trials.

Section 6.1 and Table 3 presents adverse reactions from three pooled, controlled trials (N1, N3, N4,) in patients with narcolepsy.

Adverse Reactions Leading to Treatment Discontinuation

Of the 398 sodium oxybate-treated 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.

Commonly Observed Adverse Reactions in Controlled Clinical Trials

The most common adverse reactions (incidence $\geq 5\%$ and twice the rate seen with placebo) in sodium oxybate-treated patients were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.

Adverse Reactions Occurring at an Incidence of 2% or Greater

Table 3 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 sodium oxybate 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 3: Adverse Reactions Occurring in $\geq 2\%$ of Patients and More Frequently with Sodium Oxybate than Placebo in Three Controlled Trials (N1, N3, N4) by Body System and Dose at Onset

System Organ Class/MedDRA Preferred Term	Placebo (n=213) %	Sodium Oxybate 4.5 g (n=185) %	Sodium Oxybate 6 g (n=258) %	Sodium Oxybate 9 g (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 sodium oxybate.

6.2 Postmarketing Experience

The following additional adverse reactions that have a likely causal relationship to sodium oxybate exposure have been identified during postmarketing use of sodium oxybate. These adverse reactions include: arthralgia, decreased appetite, fall, fluid retention, hangover, headache, hypersensitivity, hypertension, memory impairment, panic attack, vision blurred, and weight decreased. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency.

7 DRUG INTERACTIONS

7.1 Alcohol, Sedative Hypnotics, and CNS Depressants

Sodium oxybate should not be used in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of sodium oxybate.

7.2 Divalproex Sodium

Concomitant use of sodium oxybate with divalproex sodium resulted in a 25% mean increase in systemic exposure to sodium oxybate (AUC ratio range of 0.8 to 1.7) and in a greater impairment on some tests of attention and working memory. An initial sodium oxybate dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking sodium oxybate [see *Dosage and Administration* (2.4); *Clinical Pharmacology* (12.3)]. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of sodium oxybate and divalproex sodium is warranted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Sodium oxybate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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/m²) 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 postnatal developmental toxicity in rats is less than the MRHD on a mg/m² basis.

8.2 Labor and Delivery

Sodium oxybate 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, but umbilical vein levels of sodium oxybate were no more than 25% of the maternal concentration. No sodium oxybate was detected in the infant's blood 30 minutes after delivery. Elimination curves of sodium oxybate between a 2-day-old infant and a 15-year-old patient were similar. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

8.3 Nursing Mothers

It is not known whether sodium oxybate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sodium oxybate is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of sodium oxybate 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

The starting dose of sodium oxybate should be reduced by one-half in patients with liver impairment [*see Dosage and Administration (2.3); Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Sodium Oxybate Oral Solution is a Schedule III controlled substance under the Federal Controlled Substances Act. Non-medical use of sodium oxybate could lead to penalties assessed under the higher Schedule I controls.

9.2 Abuse

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 amnesic features of sodium oxybate, 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 sodium oxybate according to state and federal regulations. It is safe to dispose of sodium oxybate 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 therapeutic dose 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 sodium oxybate have not been systematically evaluated in controlled clinical trials. In the clinical trial experience with sodium oxybate in narcolepsy/cataplexy patients at therapeutic 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 sodium oxybate 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 sodium oxybate 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 sodium oxybate in the treatment of alcohol withdrawal have not been established.

10 OVERDOSAGE

10.1 Human Experience

Information regarding overdose with sodium oxybate 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 clinical trials two cases of overdose with sodium oxybate 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 sodium oxybate and numerous other drugs.

10.2 Signs and Symptoms

Information about signs and symptoms associated with overdosage with sodium oxybate derives from reports of its illicit use. 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

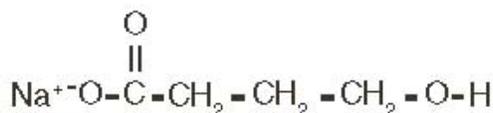
General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation 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 sodium oxybate 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 Sodium Oxybate Oral Solution. 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 Sodium Oxybate Oral Solution contains 0.5 g of sodium oxybate in purified water, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sodium oxybate is a CNS depressant. The mechanism of action of sodium oxybate in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of gamma hydroxybutyrate, an endogenous compound and metabolite of the neurotransmitter GABA. It is hypothesized that the therapeutic effects of sodium oxybate 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 sodium oxybate are nonlinear and are similar following single or repeat dosing.

Absorption

Following oral administration, sodium oxybate 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, the plasma levels of sodium oxybate 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. Administration of sodium oxybate 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} by a mean of 59% and of systemic exposure (AUC) by 37%.

Distribution

Sodium oxybate is a hydrophilic compound with an apparent volume of distribution averaging 190 mL/kg to 384 mL/kg. At sodium oxybate concentrations ranging from 3 mcg/mL to 300 mcg/mL, less than 1% is bound to plasma proteins.

Metabolism

Animal studies indicate that metabolism is the major elimination pathway for sodium oxybate, 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 sodium oxybate 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.

Elimination

The clearance of sodium oxybate 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. Sodium oxybate has an elimination half-life of 0.5 to 1 hour.

Specific Populations

Geriatric

There is limited experience with sodium oxybate in the elderly. Results from a pharmacokinetic study (n=20) in another studied population indicate that the pharmacokinetic characteristics of sodium oxybate are consistent among younger (age 48 to 64 years) and older (age 65 to 75 years) adults.

Pediatric

The pharmacokinetics of sodium oxybate in patients younger than 18 years of age have not been studied.

Gender

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

Race

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

Renal Impairment

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

Hepatic Impairment

The pharmacokinetics of sodium oxybate 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 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 sodium oxybate should be reduced by one-half in patients with liver impairment [see *Dosage and Administration* (2.3); *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 therapeutic doses.

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

- Divalproex sodium: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with divalproex sodium (valproic acid, 1250 mg per day) increased mean systemic exposure to sodium oxybate 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); *Dosage and Administration* (2.4)].
- Diclofenac: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with diclofenac (50 mg/dose twice per day) showed no significant differences in systemic exposure to sodium oxybate. Co-administration did not appear to affect the pharmacokinetics of diclofenac.
- Ibuprofen: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with ibuprofen (800 mg/dose four times per day also dosed four hours apart) resulted in comparable systemic exposure to sodium oxybate as shown by plasma C_{max} and AUC values. Co-administration did not affect the pharmacokinetics of ibuprofen.

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. Also, there were no pharmacokinetic interactions with the alcohol dehydrogenase inhibitor fomepizole. However, pharmacodynamic interactions with these drugs cannot be ruled out. Alteration of gastric pH with omeprazole produced no significant change in the oxybate kinetics. In addition, drug interaction studies in healthy adults demonstrated no pharmacokinetic or clinically significant pharmacodynamic interactions between sodium oxybate and the SNRI 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 recommend 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/m² basis.

14 CLINICAL STUDIES

14.1 Cataplexy in Narcolepsy

The effectiveness of sodium oxybate 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 4). 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 sodium oxybate independent of stimulant use. In each trial, the treatment period was 4 weeks and the total nightly sodium oxybate 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, sodium oxybate 3 g per night, sodium oxybate 6 g per night, or sodium oxybate 9 g per night.

Trial N2 was a randomized withdrawal trial with 55 narcoleptic patients who had been taking open-label sodium oxybate 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 sodium oxybate 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 4: 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	-
Sodium oxybate 6 g per night (n=31)	23.0	-10	0.0451
Sodium oxybate 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	-
Sodium oxybate (n=26)	1.9	0	<0.001

In Trial N1, both the 6 g and 9 g per night sodium oxybate 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 sodium oxybate therapy experienced a significant increase in cataplexy attacks ($p < 0.001$), providing evidence of long-term efficacy of sodium oxybate. 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 Narcolepsy

The effectiveness of sodium oxybate 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 5 to 7). 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, sodium oxybate 4.5 g per night, sodium oxybate 6 g per night, or sodium oxybate 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 sodium oxybate compared to the placebo group.

Table 5: Change From Baseline in Daytime Sleepiness Score (Epworth Sleepiness Scale) at Week 8 in Trial N3 (Range 0 to 24)

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

Table 6: 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 (n=59)	22%	-
Sodium oxybate 6 g per night (n=58)	52%	<0.001
Sodium oxybate 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, sodium oxybate, modafinil, or sodium oxybate plus modafinil. Sodium oxybate 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 sodium oxybate plus modafinil treatment groups at the patient's prior dose. Trial N4 was not designed to compare the effects of sodium oxybate to modafinil because patients receiving modafinil were not titrated to a maximal dose. Patients randomized to placebo or to sodium oxybate 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 sodium oxybate and sodium oxybate plus modafinil groups compared to the placebo group.

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

Table 7: 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	-
Sodium oxybate (modafinil withdrawn) (n=50)	11.3	12.0	0.6	<0.001
Sodium oxybate plus modafinil (n=54)	10.4	13.2	2.7	<0.001

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution. It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert. Two 75 mL dosing cups with child-resistant caps are included with each Sodium Oxybate Oral Solution shipment. Each white oblong HDPE bottle contains 180 mL of Sodium Oxybate Oral Solution at a concentration of 500 mg/mL and is sealed with a child resistant cap.

NDC 0054-0314-57: Each tamper evident single unit carton contains one 180 mL bottle (500 mg/mL) of Sodium Oxybate Oral Solution, one press-in-bottle adaptor and one oral dispensing syringe

16.2 Storage

Keep out of reach of children.

Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.

Solutions prepared following dilution should be consumed within 24 hours.

16.3 Handling and Disposal

Sodium Oxybate Oral Solution is a Schedule III drug under the Controlled Substances Act. Sodium oxybate should be handled according to state and federal regulations. It is safe to dispose of sodium oxybate down the sanitary sewer.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Sodium Oxybate REMS Program

- Inform patients that sodium oxybate is available only through the Sodium Oxybate REMS Program.
- The contents of the sodium oxybate Medication Guide and educational materials are reviewed with every patient before initiating treatment with sodium oxybate.
- Patients must read and understand the materials in the Sodium Oxybate REMS Program prior to initiating treatment. Inform the patient that they should be seen by the prescriber frequently to review dose titration, symptom response, and adverse reactions; a follow-up of every three months is recommended.
- Discuss safe and proper use of sodium oxybate and dosing information with patients prior to the initiation of treatment. Instruct patients to store sodium oxybate bottles and sodium oxybate doses in a secure place, out of the reach of children and pets.

Alcohol or Sedative Hypnotics

Advise patients not to drink alcohol or take other sedative hypnotics if they are taking sodium oxybate.

Sedation

Inform patients that after taking sodium oxybate they are likely to fall asleep quickly (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 to remain in bed following ingestion of their first and second doses. Instruct patients not to take their second dose until 2.5 to 4 hours after the first dose.

Food Effects on Sodium Oxybate

Inform patients to take the first dose at least 2 hours after eating.

Respiratory Depression

Inform patients that sodium oxybate can be associated with respiratory depression.

Operating Hazardous Machinery

Inform patients that until they are reasonably certain that sodium oxybate does not affect them adversely (e.g., impair judgment, thinking, or motor skills) they should not operate hazardous machinery, including automobiles or airplanes.

Suicidality

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

Sodium Intake

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

Medication Guide - Sodium Oxybate (soe' dee um ox' i bate) Oral Solution, CIII

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

What is the most important information I should know about sodium oxybate?

Sodium oxybate can cause serious side effects including slow breathing or changes in your alertness. Do not drink alcohol or take medicines intended to make you fall asleep while you are taking sodium oxybate because they can make these side effects worse. Call your doctor right away if you have any of these serious side effects.

- The active ingredient of Sodium Oxybate Oral Solution is a form of gamma-hydroxybutyrate (GHB). GHB is a chemical that has been abused and misused. Abuse and misuse of sodium oxybate can cause serious medical problems, including:
 - seizures
 - trouble breathing
 - changes in alertness
 - coma
 - death
- Do not drive a car, use heavy machinery, fly an airplane, or do anything that is dangerous or that requires you to be fully awake for at least 6 hours after you take sodium oxybate. You should not do those activities until you know how sodium oxybate affects you.
- Sodium oxybate is available only by prescription and filled through the Sodium Oxybate REMS Program. Before you receive sodium oxybate, your doctor or pharmacist will make sure that you understand how to use sodium oxybate safely and effectively. If you have any questions about sodium oxybate, ask your doctor or call the Sodium Oxybate REMS Program at 1-800-XXX-XXXX.

What is sodium oxybate?

Sodium oxybate is a prescription medicine used to treat the following symptoms in people who fall asleep frequently during the day, often at unexpected times (narcolepsy):

- suddenly weak or paralyzed muscles when they feel strong emotions (cataplexy)
- excessive daytime sleepiness (EDS) in people who have narcolepsy

It is not known if sodium oxybate is safe and effective in children.

Sodium Oxybate Oral Solution is a controlled substance (CIII) because it contains sodium oxybate that can be a target for people who abuse prescription medicines or street drugs. Keep your sodium oxybate in a safe place to protect it from theft. Never give your sodium oxybate to anyone else because it may cause death or harm them. Selling or giving away this medicine is against the law.

Who should not take sodium oxybate?

Do not take sodium oxybate if you:

- take other sleep medicines or sedatives (medicines that cause sleepiness)
- drink alcohol
- have a rare problem called succinic semialdehyde dehydrogenase deficiency

Before you take sodium oxybate, tell your doctor if you:

- have short periods of not breathing while you sleep (sleep apnea).
- snore, have trouble breathing, or have lung problems. You may have a higher chance of having serious breathing problems when you take sodium oxybate.
- have or had depression or have tried to harm yourself. You should be watched carefully for new symptoms of depression.
- have liver problems.
- are on a salt-restricted diet. Sodium oxybate contains a lot of sodium (salt) and may not be right for you.
- have high blood pressure.
- have heart failure.
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if sodium oxybate can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if sodium oxybate passes into your breast milk. You and your doctor should decide if you will take sodium oxybate or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially, tell your doctor if you take other medicines to help you sleep (sedatives). Do not take medicines that make you sleepy with sodium oxybate.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take sodium oxybate?

- Read the **Instructions for Use** at the end of this Medication Guide for detailed instructions on how to take sodium oxybate.
- Take sodium oxybate exactly as your doctor tells you to take it.
- Never change your sodium oxybate dose without talking to your doctor.
- Sodium oxybate can cause sleep very quickly. You 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 to fall asleep might be different from night to night.
- Take your first sodium oxybate dose at bedtime while you are in bed. Take your second sodium oxybate dose 2.5 to 4 hours after you take your first sodium oxybate dose. You may want to set an alarm clock to make sure you wake up to take your second sodium oxybate dose. You should remain in bed after taking the first and second doses of sodium oxybate.
- If you miss your second sodium oxybate dose, skip that dose and do not take sodium oxybate again until the next night. Never take 2 sodium oxybate doses at 1 time.
- Wait at least 2 hours after eating before you take sodium oxybate.
- You should see your doctor every 3 months for a check-up while taking sodium oxybate. Your doctor should check to see if sodium oxybate is helping to lessen your symptoms and if you feel any side effects while you take sodium oxybate.

- If you take too much sodium oxybate, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of sodium oxybate?

Sodium oxybate can cause serious side effects, including:

- See “**What is the most important information I should know about sodium oxybate?**”
- **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 sodium oxybate.
- **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 symptoms of mental health problems.

- **Sleepwalking.** Sleepwalking can cause injuries. Call your doctor if you start sleepwalking. Your doctor should check you.

The most common side effects of sodium oxybate include:

- nausea
- dizziness
- vomiting
- bedwetting
- diarrhea

Your side effects may increase when you take higher doses of sodium oxybate. Sodium oxybate can cause physical dependence and craving for the medicine when it is not taken as directed.

These are not all the possible side effects of sodium oxybate. 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 sodium oxybate?

- **Always store sodium oxybate in the original bottle or in the dosing cups with child-resistant caps provided with your prescription.**
- **Keep sodium oxybate in a safe place out of the reach of children and pets.**
- **Get emergency medical help right away if a child drinks your sodium oxybate.**
- Store sodium oxybate between 68°F to 77°F (20°C to 24°C). When you have finished using a sodium oxybate bottle:
 - empty any unused sodium oxybate down the sink drain
 - cross out the label on the sodium oxybate bottle with a marker
 - place the empty sodium oxybate bottle in the trash

General information about the safe and effective use of sodium oxybate

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

This Medication Guide summarizes the most important information about sodium oxybate. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about sodium oxybate that is written for health professionals.

For more information, call the Sodium Oxybate REMS Program at 1-800-XXX-XXXX.

What are the ingredients in Sodium Oxybate Oral Solution?

Active Ingredients: sodium oxybate

Inactive Ingredients: purified water, USP

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

Instructions for Use - Sodium Oxybate (soe' dee um ox' i bate) Oral Solution, CIII

Read these Instructions for Use carefully before you start taking sodium oxybate and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

Note:

- **You will need to split your prescribed sodium oxybate dose into 2 separate dosing cups for mixing (provided with your prescription).**
- **You will need to mix sodium oxybate with water before you take your dose.**
- **Take your dose within 24 hours after mixing sodium oxybate with water. If you do not take your dose within this time, you will need to throw the mixture away.**

Supplies you will need for mixing and taking sodium oxybate: See Figure A.

- bottle of your sodium oxybate medicine
- press-in-bottle adaptor with straw attached
- syringe for drawing up your sodium oxybate dose
- a measuring cup containing about 1/4 cup of water (not provided with your sodium oxybate prescription)
- 2 **empty** dosing cups with child-resistant caps
- alarm clock by your bedside (not provided with your sodium oxybate prescription)



Figure A

Step 1. Take the sodium oxybate bottle, press-in-bottle adaptor, and syringe out of the box.

Step 2. Remove the bottle cap from the sodium oxybate bottle by pushing down while turning the cap counterclockwise (to the left). See Figure B.

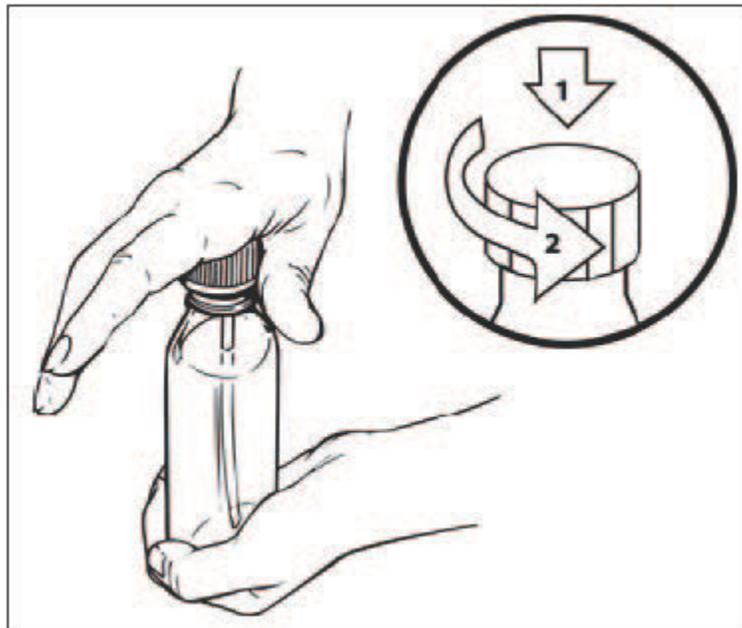


Figure B

Step 3.

- The press-in-bottle adaptor may already be put in place by the pharmacy. If it is not already in place, you will have to do it yourself. After removing the cap from the sodium oxybate bottle, set the bottle upright on a tabletop.
- While holding the sodium oxybate bottle in its upright position, insert the press-in-bottle adaptor into the neck of the sodium oxybate bottle. See Figure C.



Figure C

- Tilt the straw toward the edge of the bottom of the bottle to be sure you can draw out your dose of the medicine. You only need to do this the first time you open the bottle. See Figure D.



Figure D

- After you draw out your dose of the medicine, leave the adaptor in the bottle for all your future uses. See Figure E.

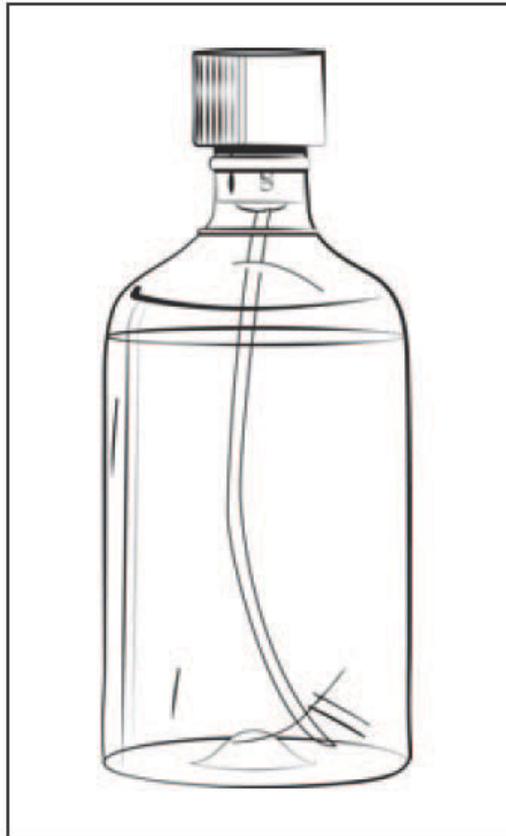


Figure E

Step 4.

- Take the syringe out of the plastic wrapper. Use only the syringe provided with your sodium oxybate prescription.
- While holding the sodium oxybate bottle upright on the tabletop, insert the tip of the syringe into the opening on top of the sodium oxybate bottle and press down firmly. See Figure F.

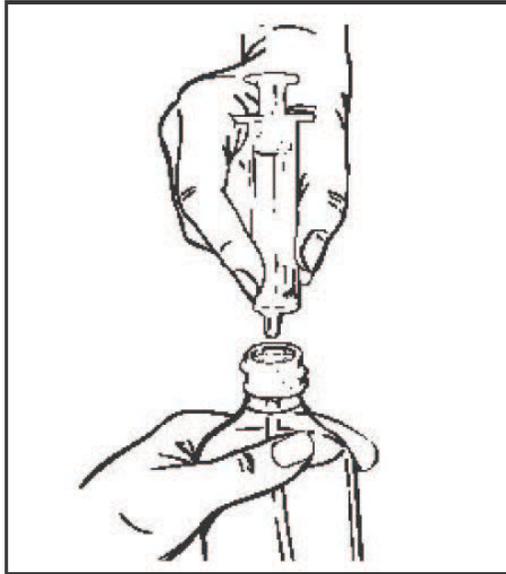


Figure F

Step 5.

- Hold the bottle and syringe down with one hand, and draw up one-half (1/2) of your total prescribed nightly dose with the other hand by pulling up on the plunger. For example, if your total nightly dose of sodium oxybate is 4.5 grams a night, you will need to draw up 2 separate doses of 2.25 grams each, one for each dosing cup. See Figure G.

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

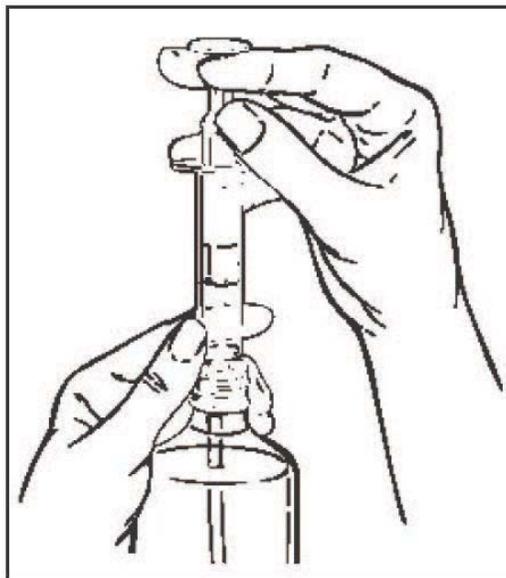


Figure G

Step 6.

- After you draw up each separate sodium oxybate dose, remove the syringe from the opening of the sodium oxybate bottle. Put the tip into 1 of the **empty** dosing cups with child-resistant caps.
- **Make sure the dosing cup is empty and does not contain any medicine from your previous night's dose.**

- Empty each separate sodium oxybate dose into 1 of the **empty** dosing cups by pushing down on the plunger. (See Figure H).
- Using a measuring cup, pour about 1/4 cup of water into **each** dosing cup. **Be careful to add only water to each dosing cup and not more sodium oxybate. All shipped bottles of sodium oxybate contain the concentrated medicine. Water for mixing the medicine is not provided in the shipment.**

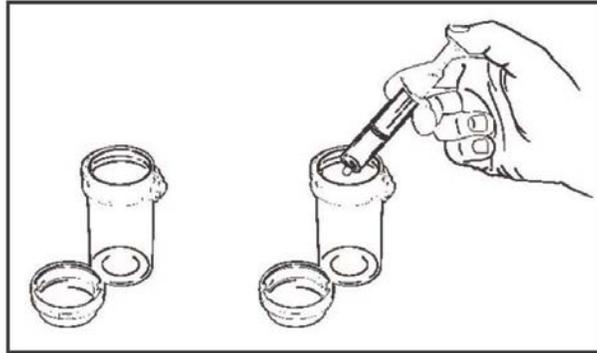


Figure H

Step 7.

- Place the child-resistant caps provided on the filled dosing cups and turn each cap clockwise (to the right) until it clicks and locks into its child-resistant position. See Figure I.

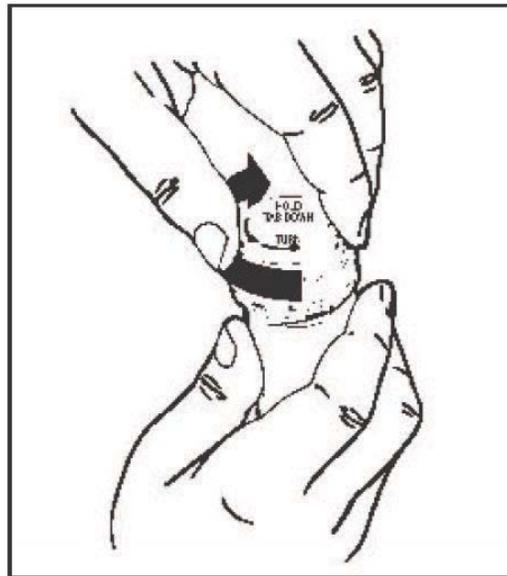


Figure I

- Put the cap back on the sodium oxybate bottle and store it in a safe and secure place. Store in a locked place if needed. Keep sodium oxybate out of the reach of children and pets.
- Rinse the syringe out with water and squirt the liquid into the sink drain.

Step 8.

- At bedtime, and before you take your first sodium oxybate dose, put your second sodium oxybate dose in a safe place near your bed.
- You may want to set an alarm clock to make sure you wake up to take the second dose.

- When it is time to take your first sodium oxybate dose, remove the cap from the dosing cup by pressing down on the child-resistant locking tab and turning the cap counterclockwise (to the left).
- Drink all of your first sodium oxybate dose at bedtime. Put the cap back on the first dosing cup before lying down to sleep.
- You 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 to fall asleep might be different from night to night.

Step 9.

- When you wake up 2.5 to 4 hours later, take the cap off the second dosing cup.
- If you wake up before the alarm and it has been at least 2.5 hours since your first sodium oxybate dose, turn off your alarm and take your second sodium oxybate dose.
- While sitting in bed, drink all of the second sodium oxybate dose and put the cap back on the second dosing cup before lying down to continue sleeping.

These Instructions for Use have been approved by the U.S. Food and Drug Administration.

Distr. By:

West-Ward Pharmaceuticals Corp.

Eatontown, NJ 07724

10006869/01

Revised July 2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

ANDA202090

REMS

Initial REMS approval: 01/2017

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Shared System REMS Program for Sodium Oxybate Oral Solution

I. GOAL:

The goal of the Sodium Oxybate REMS Program is to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of sodium oxybate by:

A. Informing prescribers, pharmacists, and patients of:

1. The risk of significant CNS and respiratory depression associated with sodium oxybate
2. The contraindication of use of sodium oxybate with sedative hypnotics and alcohol
3. The potential for abuse, misuse, and overdose associated with sodium oxybate
4. The safe use, handling, and storage of sodium oxybate

B. Ensuring that pharmacy controls exist prior to filling prescriptions for sodium oxybate that:

1. Screen for concomitant use of sedative hypnotics and other potentially interacting agents
2. Monitor for inappropriate prescribing, misuse, abuse, and diversion of sodium oxybate
3. Notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each sodium oxybate prescription in accordance with 21 CFR 208.24

The sodium oxybate Medication Guides are part of the REMS and are available on the Sodium Oxybate REMS Program website

B. Elements to Assure Safe Use

1. Healthcare Providers who prescribe sodium oxybate products are specially certified

- a. Sodium Oxybate sponsors will ensure that healthcare providers who prescribe sodium oxybate are specially certified in the Sodium Oxybate REMS Program.
- b. To become specially certified to prescribe sodium oxybate, each prescriber must complete and submit to the Sodium Oxybate REMS Program the *Sodium Oxybate REMS Program Prescriber Enrollment Form*, which includes the prescriber agreeing to:
 - i. Review the Prescribing Information (PI) and the *Sodium Oxybate REMS Program Prescriber Brochure*
 - ii. Screen each patient for whom sodium oxybate is prescribed for:
 - 1) History of alcohol or substance abuse
 - 2) History of sleep-related breathing disorders
 - 3) History of compromised respiratory function
 - 4) Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
 - 5) History of depression or suicidality
 - iii. Counsel each patient prior to initiating therapy regarding the serious risks and safe use, handling, and storage of sodium oxybate

- iv. Enroll each patient in the Sodium Oxybate REMS Program by completing and submitting the *Sodium Oxybate REMS Program Patient Enrollment Form* to the Sodium Oxybate REMS Program
 - v. Evaluate each patient within the first 3 months of starting sodium oxybate therapy, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while on sodium oxybate therapy:
 - 1) Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
 - 2) Serious adverse events
 - 3) Signs of abuse and misuse, including:
 - a) An increase in dose or frequency of dosing
 - b) Reports of lost, stolen, or spilled medication
 - c) Drug-seeking behavior
 - vi. Report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, death, and any cases of abuse, misuse, or diversion by calling the Sodium Oxybate REMS Program
- b. The prescriber will complete the *Sodium Oxybate REMS Program Prescription Form* for each new prescription and submit the form to one of the specially certified pharmacies. By completing and signing this form, the prescriber acknowledges:
- i. Having an understanding of:
 - 1) The approved indications of sodium oxybate:
 - a) Treatment of cataplexy in narcolepsy
 - b) Treatment of excessive daytime sleepiness in narcolepsy
 - 2) The serious risks associated with sodium oxybate
 - 3) The Prescribing Information (PI) and the *Sodium Oxybate REMS Program Prescriber Brochure*

- ii. Having screened the patient for the following:
 - 1) History of alcohol or substance abuse
 - 2) History of sleep-related breathing disorders
 - 3) History of compromised respiratory function
 - 4) Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
 - 5) History of depression or suicidality
 - iii. Having counseled the patient on:
 - 1) The serious risks associated with sodium oxybate
 - 2) Contraindications (alcohol and sedative hypnotics) and implications of concomitant use of sodium oxybate with other potentially interacting agents
 - 3) Preparation and dosing instructions for sodium oxybate
 - 4) Risk of abuse and misuse associated with sodium oxybate
 - 5) Risk of operating hazardous machinery, including automobiles or airplanes, for the first 6 hours after taking a dose of sodium oxybate
 - 6) Safe use, handling, and storage of sodium oxybate
 - iv. That sodium oxybate is medically appropriate for the patient
 - v. Having listed all known prescription and nonprescription medications and doses on the *Sodium Oxybate REMS Program Prescription Form*
- c. Sodium Oxybate sponsors will:
- i. Ensure that the *Sodium Oxybate REMS Program Prescriber Enrollment Form* can be completed via fax, mail, or the Sodium Oxybate REMS Program website (www.SodiumOxybateREMSProgram.com)
 - ii. Ensure that the *Sodium Oxybate REMS Program Patient Enrollment Form* can be completed via fax, mail, or the Sodium Oxybate REMS Program website (www.SodiumOxybateREMSProgram.com)

- iii. Ensure that the *Sodium Oxybate REMS Program Prescription Form* can be completed via fax
 - iv. Ensure that materials appended to the Sodium Oxybate REMS document will be made available through the Sodium Oxybate REMS Program website (www.SodiumOxybateREMSProgram.com) or by calling the Sodium Oxybate REMS Program at 855-705-2424
 - v. Ensure that a prescriber is specially certified in the Sodium Oxybate REMS Program only after verification that the *Sodium Oxybate REMS Program Prescriber Enrollment Form* is complete and all certification requirements are met
 - vi. Ensure that prescribers are notified when they are successfully specially certified in the Sodium Oxybate REMS Program and are eligible to prescribe sodium oxybate
 - vii. Ensure that secure, validated, separate, and distinct Sodium Oxybate REMS Program databases (patient database, specially certified prescriber database, specially certified pharmacy database and disenrolled prescriber database) are maintained and will only be queried independently through electronic telecommunication verification (see [Section II.C.1.d.](#))
 - viii. Ensure that specially certified prescribers continue to meet the requirements of the Sodium Oxybate REMS Program and can disenroll noncompliant prescribers if the requirements are not met
- d. The following are part of the Sodium Oxybate REMS Program and are appended:
- i. *Sodium Oxybate REMS Program Prescriber Enrollment Form*
 - ii. *Sodium Oxybate REMS Program Prescriber Brochure*
 - iii. *Sodium Oxybate REMS Program Patient Enrollment Form*
 - iv. *Sodium Oxybate REMS Program Prescription Form*
 - v. *Sodium Oxybate REMS Program Patient Quick Start Guide*
 - vi. Sodium Oxybate REMS Program website (www.SodiumOxybateREMSProgram.com)

2. Sodium oxybate will be dispensed only by pharmacies that are specially certified

- a. The Sodium Oxybate REMS Program will certify pharmacies that dispense sodium oxybate. Sodium oxybate will not be stocked in retail pharmacy outlets. To become specially certified in the Sodium Oxybate REMS Program, pharmacies must agree to:
- i. Designate an authorized representative to complete and submit the *Sodium Oxybate REMS Pharmacy Enrollment Form* on behalf of the pharmacy
 - ii. Ensure that the authorized representative oversees implementation and compliance with the Sodium Oxybate REMS Program by the following:
 - 1) Ensure that all pharmacy staff involved in the Sodium Oxybate REMS Program complete the *Sodium Oxybate REMS Program Certified Pharmacy Training Program Module A*
 - 2) Ensure that all pharmacists who dispense sodium oxybate complete the *Sodium Oxybate REMS Program Certified Pharmacy Training Program Modules A and B*
 - iii. Dispense sodium oxybate only to patients enrolled in the Sodium Oxybate REMS Program pursuant to a valid prescription written by a prescriber specially certified in the Sodium Oxybate REMS Program (see [Section II.B.1.a.](#))
 - iv. Dispense only after obtaining a Pre-Dispense Authorization (PDA) for each sodium oxybate prescription by requesting that the Sodium Oxybate REMS Program access the secure, validated, separate, and distinct Sodium Oxybate REMS Program databases (patient database, specially certified prescriber database, specially certified pharmacy database, and disenrolled prescriber database) that will only be queried independently through electronic telecommunication verification to verify the following:
 - 1) Pharmacy is specially certified
 - 2) Prescriber is specially certified
 - 3) Patient is enrolled
 - 4) Patient has no other known active, overlapping prescriptions for sodium oxybate

- v. Recertify in the Sodium Oxybate REMS Program if the pharmacy designates a new authorized representative
 - vi. Provide 24-7 toll-free access to a pharmacist at a Sodium Oxybate REMS Program specially certified pharmacy
 - vii. Ship sodium oxybate directly to each patient or a patient-authorized adult designee, and track and verify receipt of each shipment of sodium oxybate
 - viii. Limit the first shipment for each patient to a one-month supply of sodium oxybate, and subsequent shipments to no more than a three-month supply of sodium oxybate
 - ix. 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 the Sodium Oxybate REMS Program for documentation
- b. Prior to dispensing sodium oxybate, the specially certified pharmacies will:
- i. With every sodium oxybate prescription, ensure that a pharmacist completes the *Sodium Oxybate REMS Program Patient Counseling Checklist* and submits the checklist to the Sodium Oxybate REMS Program
 - ii. Validate each Sodium Oxybate REMS Program prescription by:
 - 1) Verifying that the prescriber is specially certified, the patient is enrolled and the patient has no other active sodium oxybate prescription by entering all prescriptions in the pharmacy management system, including cash payments by obtaining a pre-dispense authorization (PDA) via electronic telecommunication verification
 - 2) Review patient information obtained from the Sodium Oxybate REMS Program website (www.SodiumOxybateREMSProgram.com) and the *Sodium Oxybate REMS Program Prescription Form*, 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 sodium oxybate
 - b) Alerts and *Sodium Oxybate REMS Program Risk Management*

Report (RMR) Forms regarding potential abuse, misuse, or diversion

- 3) 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
 - 4) Contacting the Xyrem REMS Program by phone to:
 - a) Verify that the patient has no other active prescriptions for sodium oxybate that overlap with the current prescription
 - b) Verify that the patient/prescriber has not been disenrolled in the Xyrem REMS Program for suspected abuse, misuse, or diversion
 - c) Report each prescription filled for sodium oxybate
 - 5) Documenting that the call to the Xyrem REMS Program was completed using the *Sodium Oxybate REMS Program Prescription Form*
- c. Sodium Oxybate REMS Program specially certified pharmacies will ship sodium oxybate directly to each patient using an overnight service. In addition, each Sodium Oxybate REMS Program specially 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 sodium oxybate Medication Guide is included with each shipment, and a copy of the *Sodium Oxybate REMS Program Patient Quick Start Guide* is provided to a new patient who has not already received it from the prescriber
 - iv. Receipt of each shipment is confirmed and shipment and receipt dates are provided to the Sodium Oxybate REMS Program to be maintained in the patient database

- d. The Sodium Oxybate REMS Program specially certified pharmacies will monitor and report to the Sodium Oxybate REMS Program all instances of patient or prescriber behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion of sodium oxybate
 - i. Pharmacies will document these events, including all requests for early refills by completing and submitting a *Sodium Oxybate REMS Program RMR Form* to the Sodium Oxybate REMS Program
 - 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 obtained from the Sodium Oxybate REMS Program website (www.SodiumOxybateREMSProgram.com), and ensure the request or concern has been discussed with the prescriber prior to shipping sodium oxybate
 - iii. All reports of lost, stolen, destroyed, or spilled drug will be documented in the Sodium Oxybate REMS Program patient database when a specially certified pharmacy completes and submits a *Sodium Oxybate REMS Program RMR Form* to the Sodium Oxybate REMS Program
 - iv. Repeated reports of lost, stolen, destroyed, or spilled drug may be documented as an alert to the patient profile stored in the Sodium Oxybate REMS Program patient database
 - v. Pharmacies and/or prescribers that are specially certified in the Sodium Oxybate REMS Program may direct that a patient be disenrolled from the Sodium Oxybate REMS Program after reviewing or receiving reports of incidents suggestive of abuse, misuse, or diversion by completing and submitting an *Sodium Oxybate REMS Program RMR Form* to the Sodium Oxybate REMS Program
 - vi. Pharmacies may recommend that a prescriber be disenrolled by submitting a *Sodium Oxybate REMS Program RMR Form* to the Sodium Oxybate REMS Program. Sodium Oxybate sponsors will review the information and determine if the prescriber should be disenrolled
- e. Sodium Oxybate Sponsors will:
 - i. Ensure that the *Sodium Oxybate REMS Program Pharmacy Enrollment Form* can be completed via fax, or online at www.SodiumOxybateREMSProgram.com

- ii. Ensure the pharmacy is specially certified in the Sodium Oxybate REMS Program only after verification that the *Sodium Oxybate REMS Program Pharmacy Enrollment Form* is complete and all certification requirements are met
 - iii. Ensure that pharmacies are notified when they are successfully specially certified in the Sodium Oxybate REMS Program
 - iv. Ensure that the secure, validated, separate, and distinct Sodium Oxybate REMS Program databases (patient database, specially certified prescriber database, specially certified pharmacy database, and disenrolled prescriber database) are maintained and will only be queried independently through electronic telecommunication verification (see Section II.C.1.d)
 - v. Ensure that specially certified pharmacies continue to meet the requirements of the Sodium Oxybate REMS Program. Non-compliant pharmacies can be disenrolled if the requirements are not met
- f. The following materials are part of the REMS and are appended:
- i. *Sodium Oxybate REMS Program Certified Pharmacy Training Program*
 - ii. *Sodium Oxybate REMS Program Pharmacy Enrollment Form*
 - iii. *Sodium Oxybate REMS Program Patient Counseling Checklist*
 - iv. *Sodium Oxybate REMS Program Risk Management Report Form*

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

- a. Sodium Oxybate sponsors will ensure that sodium oxybate is dispensed only by pharmacies that are specially certified in the Sodium Oxybate REMS Program, by direct shipment, to patients or patient-authorized adult designees enrolled in the Sodium Oxybate REMS Program
- b. Sodium Oxybate sponsors will ensure that patients are enrolled in the Sodium Oxybate REMS Program only if a prescriber specially certified in the Sodium Oxybate REMS Program completes the *Sodium Oxybate REMS Program Patient Enrollment Form* and submits the form to the Sodium Oxybate REMS Program

- c. Sodium Oxybate sponsors will ensure that sodium oxybate is dispensed and shipped only to patients who have signed the *Sodium Oxybate REMS Program Patient Enrollment Form* and acknowledged that:
 - i. He/she has been counseled on the serious risks and safe use of sodium oxybate
 - ii. He/she has asked the prescriber any questions they may have about sodium oxybate
- d. Following enrollment, the patient remains in the Sodium Oxybate REMS Program unless they are disenrolled by the Sodium Oxybate REMS Program at the direction of a specially certified prescriber and/or pharmacy. Specially certified pharmacies and/or prescribers can direct that a patient is disenrolled if the pharmacy and/or prescriber suspect abuse, misuse, or diversion. Reasons for disenrollment include multiple suspicious early refill requests or other information that indicates possible abuse, misuse, or diversion
- e. Following disenrollment, the Sodium Oxybate REMS Program will contact the Xyrem REMS Program to report instances of patient/prescriber disenrollment in Sodium Oxybate REMS Program due to suspected abuse, misuse, or diversion and document that the call was completed in the appropriate database.
- f. A disenrolled patient may be re-enrolled in the Sodium Oxybate REMS Program. In order to re-enroll a patient who had been previously disenrolled for suspicions of abuse, misuse, or diversion, one of the specially certified pharmacies must consult with the specially certified prescriber seeking to re-enroll the patient and will communicate all relevant patient history to the specially certified prescriber, and both the specially certified pharmacy and the requesting specially certified prescriber must agree to re-enroll the patient
- g. A patient may change prescribers if the new prescriber is also specially certified in the Sodium Oxybate REMS Program, and the new prescription does not overlap with another active prescription for sodium oxybate

C. Implementation System

1. The Implementation System for the Sodium Oxybate REMS Program includes the following:

- a. Sodium Oxybate sponsors will ensure that sodium oxybate is distributed only by wholesalers/distributors that have registered with the Sodium Oxybate REMS Program. Registered wholesalers/distributors will only sell/distribute to

pharmacies specially certified in the Sodium Oxybate REMS Program

- b. Sodium Oxybate sponsors will ensure that sodium oxybate is dispensed only by pharmacies that are specially certified in the Sodium Oxybate REMS Program. Sodium oxybate will not be stocked in retail pharmacy outlets
- c. Sodium oxybate will be shipped only to patients enrolled in the Sodium Oxybate REMS Program pursuant to a valid prescription written by a prescriber specially certified in the Sodium Oxybate REMS Program that does not overlap with another active prescription for sodium oxybate
- d. Sodium Oxybate sponsors will ensure that the secure, validated, separate, and distinct Sodium Oxybate REMS Program databases (patient database, specially certified prescriber database, specially certified pharmacy database, and disenrolled prescriber database) are maintained and will only be queried independently through electronic telecommunication verification.
- e. Completed data forms, prescription and distribution data, as well as information related to dosing, concomitant medications, and behavior that raises suspicion of abuse, misuse, or diversion, including complete RMR histories, will be contained only in the appropriate database. The Sodium Oxybate REMS Program will utilize the secure, validated, separate, and distinct databases that will only be queried independently through electronic telecommunication verification, listed below:
 - i. Enrolled patient database
 - ii. Specially certified prescriber database
 - iii. Disenrolled prescriber database
 - iv. Specially certified pharmacy database
 - v. Wholesaler/Distributor database
- f. Sodium Oxybate sponsors will ensure that a sodium oxybate Medication Guide is included with each shipment of sodium oxybate
- g. Sodium Oxybate sponsors will monitor the Sodium Oxybate REMS Program databases for timely reporting to specially certified prescribers and pharmacies of any behavior by enrolled patients or specially certified prescribers in the Sodium Oxybate REMS Program that raises suspicion of abuse, misuse, or diversion

- h. Sodium Oxybate sponsors will monitor the Sodium Oxybate REMS Program databases to ensure compliance with the Sodium Oxybate REMS Program and to evaluate the implementation of the Sodium Oxybate REMS Program. Sodium Oxybate sponsors will ensure that appropriate corrective actions are implemented to address compliance concerns
- i. Sodium Oxybate sponsors must audit the wholesalers/distributors within 90 calendar days after the wholesaler/distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Sodium Oxybate REMS Program. Corrective action must be instituted by Sodium Oxybate sponsors if noncompliance is identified
- j. Sodium Oxybate sponsors will audit all specially certified pharmacies after approval of the Sodium Oxybate REMS Program to ensure that each pharmacy implements the Sodium Oxybate REMS Program as directed within 90 calendar days after the pharmacy places its first order of sodium oxybate. Thereafter, Sodium Oxybate sponsors will audit at least 50% of the Sodium Oxybate REMS Program specially certified pharmacy dispensing locations at least annually, identify all issues of noncompliance, and institute appropriate corrective actions, potentially including pharmacy decertification.
- k. The Sodium Oxybate sponsors will monitor the Sodium Oxybate REMS Program for timely reporting of all potential adverse events
- l. Sodium Oxybate sponsors 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

**SODIUM OXYBATE REMS PROGRAM
PRESCRIBER ENROLLMENT FORM**
Sodium oxybate oral solution 500 mg/mL

Sodium Oxybate
REMS Program

Complete this form through www.SodiumOxybateREMSProgram.com.
OR fax the completed form to the Sodium Oxybate REMS Program at 800-353-0987 (toll free).
OR mail to: Sodium Oxybate REMS Program, PO Box XXXXX, City, ST XXXXX-XXXX.
For further information, please call the Sodium Oxybate REMS Program at 855-705-2424.

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 SODIUM OXYBATE

- I understand that sodium oxybate is approved for the treatment of:
- Cataplexy in narcolepsy
 - Excessive daytime sleepiness (EDS) in narcolepsy
- I have read the Prescribing Information (PI) and the *Sodium Oxybate REMS Program Prescriber Brochure* and understand that:
- Sodium oxybate 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 sodium oxybate
 - Concurrent use of sodium oxybate 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 sodium oxybate use

I agree to:

- Enroll each patient in the Sodium Oxybate 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 prior to initiating therapy on the serious risks and safe use, handling, and storage of sodium oxybate
- Evaluate patients within the first 3 months of starting sodium oxybate. It is recommended that patients be re-evaluated every 3 months thereafter while taking sodium oxybate
- Report all potential adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death, and any cases of suspected abuse, misuse, or diversion to the Sodium Oxybate REMS Program

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.:		
FACILITY/PRACTICE NAME:			NPI No.:
*STREET ADDRESS:			
*CITY:	*STATE:	*ZIP CODE:	
*PHONE:	*FAX:	EMAIL:	
*PREFERRED METHOD OF CONTACT: <input type="checkbox"/> EMAIL <input type="checkbox"/> FAX			
OFFICE CONTACT:		OFFICE CONTACT PHONE:	

STEP 3: PRESCRIBER SIGNATURE IS REQUIRED BELOW FOR ENROLLMENT IN THE SODIUM OXYBATE REMS PROGRAM

By signing below, I acknowledge the above attestations, and I understand that my personally identifiable information provided above will be shared with the Sodium Oxybate REMS Program, its agents, contractors, and affiliates and entered into a prescriber database for the Sodium Oxybate REMS Program. I agree that I may be contacted in the future by mail, email, fax, and/or telephone concerning sodium oxybate, the Sodium Oxybate REMS Program, and other sodium oxybate programs and services.

*Prescriber Signature: _____ *Date: _____

Report adverse events by contacting the Sodium Oxybate REMS Program at 855-705-2424.

Sodium Oxybate REMS
Program Prescriber Brochure

Dear Prescriber,

Welcome to the Sodium Oxybate 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 Sodium Oxybate REMS Program that includes important prescribing information, educational and counseling requirements, and materials necessary for program certification and prescribing sodium oxybate oral solution, including:

- *Sodium Oxybate REMS Program Prescriber Enrollment Form* – a one-time certification is required for all prescribers of sodium oxybate.
- *Sodium Oxybate REMS Program Patient Enrollment Form* – a one-time patient enrollment in the Sodium Oxybate REMS Program is required for each new patient for whom sodium oxybate will be prescribed.
- *Sodium Oxybate REMS Program Prescription Form* – required for prescribing sodium oxybate. This form must be used for new prescriptions and may also be used for refills and renewals of sodium oxybate prescriptions.
- *Sodium Oxybate REMS Program Patient Quick Start Guide* – answers important questions for patients about how to get sodium oxybate, how to use sodium oxybate properly, and how to store it safely. It also gives important information about the risks associated with sodium oxybate.

The *Sodium Oxybate REMS Program Prescriber Enrollment Form* and *Sodium Oxybate REMS Program Patient Enrollment Form* must be completed in full and sent to the Sodium Oxybate REMS Program. The *Sodium Oxybate REMS Program Prescription Form* must be completed in full and sent to one of the certified pharmacies. For your convenience, the *Sodium Oxybate REMS Program Prescriber Enrollment Form* and the *Sodium Oxybate REMS Program Patient Enrollment Form* are available online at www.SodiumOxybateREMSProgram.com and all three forms can be requested by calling the Sodium Oxybate REMS Program toll-free at 855-705-2424. A certified pharmacy in the Sodium Oxybate REMS Program is responsible for processing prescriptions for sodium oxybate.

Continue reading this brochure to learn more about the Sodium Oxybate REMS Program and your responsibilities as a prescriber of sodium oxybate. Please review the Prescribing Information (PI) for sodium oxybate.

Sodium oxybate may be dispensed only to patients enrolled in the Sodium Oxybate REMS Program.

Sodium oxybate is approved for:

- **Treatment of cataplexy in narcolepsy**
- **Treatment of excessive daytime sleepiness (EDS) in narcolepsy**

If you require any additional assistance or information, please call the Sodium Oxybate REMS Program at 855-705-2424 or visit www.SodiumOxybateREMSProgram.com.

Sincerely,

Sodium Oxybate sponsors

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

CNS Depression

- Sodium oxybate is a CNS depressant. Concurrent use of sodium oxybate 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 sodium oxybate is required, dose reduction or discontinuation of one or more CNS depressants (including sodium oxybate) should be considered.
 - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with sodium oxybate 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 sodium oxybate use.

Healthcare providers should caution patients about operating hazardous machinery for the first 6 hours after taking a dose of sodium oxybate.

Abuse and Misuse

- Sodium oxybate is a Schedule III controlled substance.
- 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 amnesic features of sodium oxybate, 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 sodium oxybate (e.g. increase in size or frequency of dosing; reports of lost, stolen, or spilled medication; drug-seeking behavior; feigned cataplexy).

Sodium Oxybate REMS Program

- Sodium oxybate is to be prescribed only to patients enrolled in the Sodium Oxybate REMS Program. Sodium oxybate is available only through a restricted distribution program called the Sodium Oxybate REMS Program. Required components of the Sodium Oxybate REMS Program are:
 - Healthcare providers who prescribe sodium oxybate must be certified. To be certified, prescribers must complete the *Sodium Oxybate REMS Program Prescriber Enrollment Form* and comply with the Sodium Oxybate REMS Program requirements.
 - Sodium oxybate will be dispensed only by pharmacies that are certified.
 - Sodium oxybate will be shipped only to enrolled patients with documentation of safe use conditions. To be enrolled, patients must sign the *Sodium Oxybate REMS Program Patient Enrollment Form* and acknowledge that they have been counseled on the serious risks and safe use of sodium oxybate.

Further information is available at www.SodiumOxybateREMSProgram.com or 855-705-2424.

Depression, Suicidality, and Other Behavioral/Neuropsychiatric Adverse Events

- The emergence of depression in patients treated with sodium oxybate 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 sodium oxybate. Sodium oxybate can cause the emergence of neuropsychiatric adverse events (psychosis, paranoia, hallucination, and agitation), loss of consciousness, 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 sodium oxybate.

Use in Patients Sensitive to High Sodium Intake

- Sodium oxybate 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, the most common adverse reactions (incidence 25% and twice the rate seen with placebo) in sodium oxybate -treated patients were nausea (20%), dizziness (15%), vomiting (11%), somnolence (8%), enuresis (7%), and tremor (5%).
- Of the 398 sodium oxybate treated 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.
- Please see PI for sodium oxybate.

TABLE OF CONTENTS

Prescribing Sodium Oxybate - A Brief Guide.....	6
Responsibilities of the Sodium Oxybate REMS Program Certified Pharmacies	9
Guidelines for Dosing and Titrating Sodium Oxybate.....	10
Additional Information about Sodium Oxybate	11
Use in Specific Populations	12
Patient Counseling Information.....	13

Prescribing Information and a Medication Guide are also included.

PRESCRIBING SODIUM OXYBATE – A BRIEF GUIDE

The procedure for writing and dispensing prescriptions for sodium oxybate is outlined below.

PRESCRIBERS OF SODIUM OXYBATE

Prescribing sodium oxybate requires a one-time certification.

- If you are prescribing sodium oxybate for the first time, complete the *Sodium Oxybate REMS Program Prescriber Enrollment Form*, found either in this *Sodium Oxybate REMS Program Prescriber Brochure* or online at www.SodiumOxybateREMSProgram.com. If you choose not to complete the *Sodium Oxybate REMS Program Prescriber Enrollment Form* online, please fax it to the Sodium Oxybate REMS Program at 800-353-0987 or mail to Sodium Oxybate REMS Program, PO Box XXXXX, City, ST XXXXX-XXXX.
- On the *Sodium Oxybate REMS Program Prescriber Enrollment Form*, please confirm that:
 - You understand that sodium oxybate is approved for:
 - Treatment of cataplexy in patients with narcolepsy
 - Treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy
 - You have read and understand the PI and this *Sodium Oxybate REMS Program Prescriber Brochure*
 - 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
 - You agree to counsel your patients on:
 - The serious risks associated with sodium oxybate
 - Contraindications (alcohol and sedative hypnotics)
 - Risks of concomitant use of sodium oxybate with alcohol and/or other CNS depressants
 - Risk of operating hazardous machinery, including automobiles or airplanes, for the first 6 hours after taking a dose of sodium oxybate
 - Preparation and dosing instructions for sodium oxybate
 - Risk of abuse and misuse associated with use of sodium oxybate
 - Safe use, handling, and storage of sodium oxybate
 - You will enroll each patient in the Sodium Oxybate REMS Program by completing the one-time *Sodium Oxybate REMS Program Patient Enrollment Form* and submitting the form to the Sodium Oxybate REMS Program
 - You will evaluate each patient within the first 3 months of starting sodium oxybate, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while on sodium oxybate therapy:
 - Patient's concomitant medications
 - 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
 - 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 the Sodium Oxybate REMS Program

PRESCRIBING SODIUM OXYBATE A BRIEF GUIDE (CONT'D)

- On the *Sodium Oxybate REMS Program Patient Enrollment Form*:
 - Verify that you have provided counseling to each patient about the serious risks associated with the use of sodium oxybate and the safe use conditions as described in the *Sodium Oxybate REMS Program Patient Quick Start Guide*
 - Obtain mandatory patient signature acknowledging that he/she has been counseled on the serious risks and safe use conditions of sodium oxybate and has had the opportunity to ask you any questions he/she may have about sodium oxybate, and the patient grants you the authority to release personal information to the Sodium Oxybate REMS Program, other Sodium Oxybate REMS Programs and its business partners and agents, including the certified pharmacy that will fill the prescription
 - Fax the completed *Sodium Oxybate REMS Program Patient Enrollment Form* to the Sodium Oxybate REMS Program at 855-705-2424, complete online at www.SodiumOxybateREMSProgram.com, or mail to Sodium Oxybate REMS Program, PO Box XXXXX, City, ST XXXXX-XXXX

PRESCRIBING REQUIREMENTS

- Write prescriptions for both new and existing patients using the *Sodium Oxybate REMS Program Prescription Form*. If the patient has a lapse in therapy for 6 months or more, a new prescription will be required.
 - 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 patient regarding:
 - The serious risks associated with sodium oxybate
 - 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 operating hazardous machinery, including automobiles or airplanes, for the first 6 hours after taking a dose of sodium oxybate
 - Preparation and dosing instructions for sodium oxybate
 - The risk of abuse and misuse associated with sodium oxybate
 - Safe use, handling, and storage of sodium oxybate (refer to pages 13 & 14 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. This can be done by completing the Medications field on the *Sodium Oxybate REMS Program Prescription Form* or by faxing a separate page from the patient's medical history

NOTE: Prior to dispensing each sodium oxybate prescription (including refills), the certified pharmacy responsible to dispense sodium oxybate to the patient will complete a Drug Utilization Review (DUR) and, during the patient counseling process, will ask the patient about the use of other medicines. If the patient's certified pharmacy 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 patient's certified pharmacy will contact and inform the prescriber of the concomitant medication use prior to dispensing sodium oxybate. The patient's certified pharmacy may also contact the prescriber about other concomitant medications of concern.

PRESCRIBING SODIUM OXYBATE A BRIEF GUIDE (CONT'D)

- Verify that you have informed the patient that his or her certified pharmacy will send him/her a copy of the sodium oxybate Medication Guide with each prescription fill and a *Sodium Oxybate REMS Program Patient Quick Start Guide* prior to his/her first prescription fill, if you haven't provided one previously. These materials are available through the Sodium Oxybate REMS Program at www.SodiumOxybateREMSProgram.com
- Access www.SodiumOxybateREMSProgram.com to look up the certified pharmacies
- Fax the completed *Sodium Oxybate REMS Program Prescription Form* and all renewal/refill prescriptions to one of the certified pharmacies

Patient Evaluation

- Evaluate each patient within the first 3 months of starting sodium oxybate therapy, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while they are taking sodium oxybate.
 - 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

Refill Prescriptions

- One of the certified pharmacies will send you a *Sodium Oxybate REMS Program Prescription Form* in advance of a patient's prescription expiring or running out of refills. Prescription refills and renewals may also be conveyed by phone or fax to the patient's certified pharmacy, and must be documented in the Sodium Oxybate REMS Program.
 - Fill out the form completely and clearly to ensure timely fulfillment of your patient's prescription
 - Access www.SodiumOxybateREMSProgram.com to look up the certified pharmacies
 - Fax the completed *Sodium Oxybate REMS Program Prescription Form* and all subsequent prescriptions to one of the certified pharmacies

RESPONSIBILITIES OF THE SODIUM OXYBATE REMS PROGRAM CERTIFIED PHARMACIES

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

- Provide you with confirmation of each new *Sodium Oxybate REMS Program Prescription Form* received from your office
- Contact the patient's insurance provider to verify sodium oxybate prescription benefits
- Prior to the first shipment, contact the patient to:
 - Confirm whether he or she has received a copy of the *Sodium Oxybate REMS Program Patient Quick Start Guide*. The patient's certified pharmacy will send a copy of the *Sodium Oxybate REMS Program Patient Quick Start Guide* to any patient not previously receiving one from his or her prescriber
 - Counsel the patient using the *Sodium Oxybate REMS Program Patient Counseling Checklist* on expectations from sodium oxybate therapy and how to prepare and take sodium oxybate doses safely and effectively
 - Review important sodium oxybate safety information and precautions for sodium oxybate use
 - Review sodium oxybate safe handling and storage procedures
 - Review the adverse events associated with sodium oxybate
 - Review the patient's use of concomitant medications
 - You will be notified of any potential for drug interactions based on patient counseling
 - Ask if the patient has any questions about sodium oxybate and answer the questions and/or refer the patient back to the prescriber, as appropriate
- Provide 24/7 toll-free telephone access to pharmacist support for prescribers, office staff, and patients by answering questions about safety, dosing, and patient care
- Dispense and ship sodium oxybate by overnight service to the patient or his or 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 Sodium Oxybate REMS Program are available online at www.SodiumOxybateREMSProgram.com.

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

GUIDELINES FOR DOSING AND TITRATING SODIUM OXYBATE

DOSING SODIUM OXYBATE

Sodium oxybate is a liquid medication taken orally at bedtime. Due to its short half-life, sodium oxybate is taken in 2 equal doses at night, with the first dose taken at bedtime and the second dose taken 2.5 to 4 hours later.

- **The recommended starting dose is 4.5 g/night divided into 2 equal doses of 2.25 g each**
- The effective dose range is 6 g to 9 g/night
- Doses higher than 9 g/night have not been studied and should not ordinarily be administered
- The dose of sodium oxybate should be titrated to effect
 - Sodium oxybate should be titrated in increments of 1.5 g/night at weekly intervals
- An initial sodium oxybate dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking sodium oxybate. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting sodium oxybate dose when introducing sodium oxybate. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of sodium oxybate 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

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

DOSING AND TITRATION			
	1 st Dose	2 nd Dose	Total Nightly Dose
Recommended Starting Dose	2.25 g	2.25 g	4.5 g
	3 g	3 g	6 g
	3.75 g	3.75 g	7.5 g
Maximum Dose	4.5 g	4.5 g	9 g
			Effective Dosing Range

Please see PI for sodium oxybate for additional guidelines for dosing and titration.

PATIENT DOSING INFORMATION:

- Inform patients that all bottles contain concentrated medication ONLY and that water for dilution is not contained in the box. Advise patients to keep sodium oxybate 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 sodium oxybate should be diluted with about 1/4 cup of water
 - Patients should be instructed to store sodium oxybate bottles and prepared nightly doses in a secure place out of the reach of children and pets
- Food significantly reduces the bioavailability of sodium oxybate; therefore, **doses should be taken at least 2 hours after eating**
- Both doses should be taken while in bed
- The first dose should be taken at bedtime and the second dose 2.5 to 4 hours later

ADDITIONAL INFORMATION ABOUT SODIUM OXYBATE

Sodium oxybate has been placed in a bifurcated federal schedule. Sodium oxybate is a Schedule III controlled substance when used for legitimate medical purposes, as prescribed. The active ingredient, 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 sodium oxybate to any persons other than the patient for whom it was prescribed. If you have any questions regarding this, please call the Sodium Oxybate REMS Program toll-free at 855-705-2424.

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 sodium oxybate

It is important you know that the Sodium Oxybate REMS Program maintains records about who is prescribing sodium oxybate. 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 sodium oxybate dosage regimen

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

For your convenience, materials and information regarding the Sodium Oxybate REMS Program are available online at www.SodiumOxybateREMSProgram.com

USE IN SPECIFIC POPULATIONS

PREGNANCY

Teratogenic Effects: Pregnancy Category C.

Nonteratogenic Effects: Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Sodium oxybate 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, but umbilical vein levels of sodium oxybate were no more than 25% of the maternal concentration. No sodium oxybate was detected in the infant's blood 30 minutes after delivery. Elimination curves of sodium oxybate between a 2-day-old infant and a 15-year-old patient were similar. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

NURSING MOTHERS

It is not known whether sodium oxybate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sodium oxybate is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients 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 Sodium Oxybate REMS Program is here to support you, your staff, and your patients.

For assistance, call 855-705-2424 (toll-free).

PATIENT COUNSELING INFORMATION

Prior to initiating therapy, counsel each patient regarding the serious risks and safe use, handling and storage of sodium oxybate using the *Sodium Oxybate REMS Program Patient Quick Start Guide* and encourage all patients to read the sodium oxybate Medication Guide.

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

As a component of the Sodium Oxybate REMS Program, the contents of the sodium oxybate Medication Guide are reviewed with every patient by a Sodium Oxybate REMS Program certified pharmacy before initiating treatment with sodium oxybate.

To ensure safe and effective use of sodium oxybate, you should provide your patient with the following guidance:

ALCOHOL OR SEDATIVE HYPNOTICS

Advise patients not to drink alcohol or take other sedative hypnotics if they are taking sodium oxybate.

SEDATION

Inform patients that after taking sodium oxybate they are likely to fall asleep quickly (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 to remain in bed following ingestion of their first dose, and not to take their second dose until 2.5 to 4 hours later.

FOOD EFFECTS ON SODIUM OXYBATE

Food significantly decreases the bioavailability of sodium oxybate. Inform patients to take the first dose at least 2 hours after eating.

RESPIRATORY DEPRESSION

Inform patients that sodium oxybate can be associated with respiratory depression even at recommended doses and with concurrent use of sodium oxybate with other CNS depressants.

OPERATING HAZARDOUS MACHINERY

Inform patients that until they are reasonably certain that sodium oxybate does not affect them adversely (e.g., impair judgment, thinking, or motor skills) they should not operate hazardous machinery, including automobiles or airplanes.

SUICIDALITY

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

SODIUM INTAKE

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

SAFE USE, HANDLING, STORAGE, AND DISPOSAL

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

**SODIUM OXYBATE REMS PROGRAM
PATIENT ENROLLMENT FORM**
Sodium oxybate oral solution 500 mg/mL

Sodium Oxybate
REMS Program

Complete this form through www.SodiumOxybateREMSProgram.com,
OR fax completed form to the Sodium Oxybate REMS Program at 800-353-0987 (toll free),
OR mail to: Sodium Oxybate REMS Program, PO Box XXXXX, City, ST XXXXX-XXXX.
For more information, please call the Sodium Oxybate REMS Program at 855-705-2424.

Please Print (*denotes required field)

Patient Information			
*FIRST NAME:	M.I.:	*LAST NAME:	*PRIMARY PHONE:
*DATE OF BIRTH (MM/DD/YYYY):	*GENDER:	<input type="checkbox"/> M <input type="checkbox"/> F	CELL PHONE:
*ADDRESS:			WORK PHONE:
*CITY:	*STATE:	*ZIP CODE:	EMAIL:
*MEDICATIONS: (list all known current prescription and non-prescription medications and dosages or submit as a separate page) <input type="checkbox"/> Check box if separate page attached			
Insurance Information			
Does Patient Have Prescription Coverage? <input type="checkbox"/> Yes (Please provide photocopy of both sides of insurance identification Card with this form) <input type="checkbox"/> No			
POLICY HOLDER'S NAME:		POLICY HOLDER'S DATE OF BIRTH:	
INSURANCE COMPANY NAME:		RELATIONSHIP TO PATIENT:	
INSURANCE PHONE:	RxID No:	RxGrp No:	
RxBIN No:	RxPCN No:		
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: 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 sodium oxybate
- I have asked my doctor/prescriber any questions I have about sodium oxybate
- I understand that my personally identifiable information provided above will be shared with the Sodium Oxybate REMS Program, its agents, contractors, and affiliates, and entered into a patient database for the Sodium Oxybate REMS Program
- I understand that my personally identifiable information provided above will be shared with other sodium oxybate REMS programs, its agents, contractors, and affiliates

*Patient/Guardian Signature: _____ *Date: _____

*Printed Guardian Name (if applicable): _____

PRESCRIBER: FORM MUST BE SIGNED BEFORE ENROLLMENT CAN BE PROCESSED

By signing below, I acknowledge that:

- I have counseled the patient about the serious risks associated with the use of sodium oxybate and the safe use conditions as described in the *Sodium Oxybate REMS Program Patient Quick Start Guide*
 I have provided the patient with the *Sodium Oxybate REMS Program Patient Quick Start Guide* (optional)

*Prescriber Signature: _____ *Date: _____

**SODIUM OXYBATE REMS PROGRAM
PRESCRIPTION FORM**

Sodium oxybate oral solution 500 mg/mL

Sodium Oxybate
REMS Program

Fax the completed *Sodium Oxybate REMS Program Prescription Form* to one of the certified pharmacies for the patient.
You can look up certified pharmacies on www.SodiumOxybateREMSProgram.com,
or call the Sodium Oxybate REMS Program at 855-705-2424.
For more information, please call the Sodium Oxybate REMS Program at 855-705-2424.

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. (opt):	*LAST NAME	*PRIMARY PHONE:
*DATE OF BIRTH (MM/DD/YYYY):	GENDER: <input type="checkbox"/> M <input type="checkbox"/> F	CELL PHONE:	
*ADDRESS:			WORK PHONE:
*CITY:	*STATE:	*ZIP CODE:	EMAIL:
*MEDICATIONS: (list all known current prescription and non-prescription medications and dosages or submit as a separate page) <input type="checkbox"/> Check box if separate page attached			

Please complete either the fixed dosing or titrated dosing section.

Fixed Sodium Oxybate Dosing

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

Titrated Sodium Oxybate Dosing (First dose is at bedtime; second dose is taken 2.5 to 4 hours later)

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

Dispensing Instructions

Total Quantity: 1 2 3 month(s) supply (circle one) (initial prescription fill cannot exceed 1 month of therapy; refills cannot exceed 3 months).	Refills: 0 1 2 3 4 5 (circle one)
Directions: Take first dose p.o., diluted in ¼ cup of water at bedtime. Take second dose p.o., diluted in ¼ cup of water 2.5 to 4 hours later. Note: Prepare both doses at the same time prior to bedtime. The sodium oxybate shipment does not include water for dilution.	
Special Instructions:	

Prescriber Verification – My signature below signifies that: I understand the statements and agree to the Sodium Oxybate REMS Program requirements which are found on the back of this form; sodium oxybate is medically appropriate for this patient; and, I have informed the patient that the Sodium Oxybate REMS Program will send him or her a copy of the sodium oxybate Medication Guide with each prescription fill and a *Sodium Oxybate REMS Program Patient Quick Start Guide* prior to his or her first prescription fill, if I have not previously provided one.

*Prescriber Signature: _____ *Date: _____

Supervising Physician Signature: _____ Date: _____

(if required by state law for prescriptions written by NPs or PAs)

Note: This form may not satisfy all legal requirements for prescribing sodium oxybate in your state. Please submit all prescriptions in accordance with applicable state laws.

Prescriber: Signature verification is required on the **front** page of this *Sodium Oxybate REMS Program Prescription Form* as acknowledgment that you have an understanding of and/or agree to the following:

I understand that sodium oxybate is approved for:

- Treatment of cataplexy in narcolepsy
- Treatment of excessive daytime sleepiness (EDS) in narcolepsy

I understand that:

- Sodium oxybate 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 sodium oxybate
- Concurrent use of sodium oxybate 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 sodium oxybate is required, dose reduction or discontinuation of one or more CNS depressants (including sodium oxybate) should be considered
 - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with sodium oxybate 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 sodium oxybate use
- Sodium oxybate is a Schedule III controlled substance with potential for abuse and misuse
- Safe use, handling and storage by patients is important in order to prevent abuse/misuse and accidental exposure to family/friends including children
- Sodium oxybate is to be prescribed only to patients enrolled in the Sodium Oxybate REMS Program

I have read and understand the Prescribing Information (PI) and *Sodium Oxybate 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 on:

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

Pharmacy Use Only – My signature below signifies that: I have contacted the Xyrem REMS Program to:

- Verify that the patient has no other active prescriptions for sodium oxybate that overlap with the current prescription
- Verify the patient/prescriber has not been disenrolled in the Xyrem REMS Program for suspected abuse, misuse, or diversion
- Report this prescription filled for sodium oxybate

*Pharmacist Name (please print): _____ *Phone: _____

*Pharmacist Signature: _____ *Date: _____

Read this **Quick Start Guide** and the sodium oxybate Medication Guide carefully before you start taking sodium oxybate.

YOUR DOCTOR HAS PRESCRIBED
SODIUM OXYBATE ORAL SOLUTION

Frequently asked questions about the safe use and handling of sodium oxybate

SODIUM OXYBATE REMS PROGRAM
Sodium oxybate oral solution
For Patients

Dear Patient,

Welcome to the Sodium Oxybate REMS Program. You are receiving these materials because your healthcare provider has prescribed sodium oxybate oral solution for you. Sodium oxybate is a medicine used to treat excessive daytime sleepiness and/or cataplexy in patients with narcolepsy.

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

After your healthcare provider sends your enrollment form to the Sodium Oxybate REMS Program and first prescription for sodium oxybate to your certified pharmacy, you will receive a call from your certified pharmacy of the Sodium Oxybate REMS Program to tell you how the Sodium Oxybate REMS Program helps you get started with taking sodium oxybate and to answer any questions you may have about sodium oxybate.

You will also speak with appropriate staff at a certified pharmacy, who will go over your insurance information with you. Before you can receive your first shipment of sodium oxybate, a pharmacist at a certified pharmacy must confirm whether you have read and understood this *Quick Start Guide*, ask you about your medical history and other medications you may be taking, and give you advice on how to prepare and take your sodium oxybate and how to store it safely. **You must take this call before you can get your sodium oxybate.**

Please call your healthcare provider if you have questions about sodium oxybate, or you can contact the Sodium Oxybate REMS Program toll free at 855-705-2424. You can reach your certified pharmacy through this number 24 hours a day, 7 days a week with any questions.

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

Sincerely,

Sodium Oxybate sponsors

SODIUM OXYBATE REMS PROGRAM
Sodium oxybate oral solution
For Patients

**WARNING: Sodium oxybate can cause
serious side effects.**

Do not drink alcohol or take other medicines that make you sleepy.

Sodium oxybate 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 sodium oxybate includes the following:

- When taking sodium oxybate, 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
- Sodium oxybate 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 sodium oxybate
- Abuse of sodium oxybate 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)

(continued on next page)

- 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 sodium oxybate while in bed. Take the first dose at bedtime and the second 2 ½ to 4 hours later. You may need to set an alarm to awaken for the second dose
- Do not drive a car, use heavy machinery, fly an airplane, or do anything that is dangerous or that requires you to be alert for the first 6 hours after taking sodium oxybate. When you first start taking sodium oxybate, be careful until you know how sodium oxybate affects you
- Keep sodium oxybate out of the reach of children and pets. Get emergency medical help right away if a child drinks your sodium oxybate
- Report all side effects to your healthcare provider

Any questions? Please call the Sodium Oxybate REMS Program at 855-705-2424.

SODIUM OXYBATE REMS PROGRAM
Sodium oxybate oral solution
For Patients

Please see the Medication Guide for more detailed information about sodium oxybate.

What will you find in this booklet?

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

What is the Sodium Oxybate REMS Program?

Because of the serious risks associated with sodium oxybate, the FDA has required a special program called REMS for sodium oxybate. Enrollment in the Sodium Oxybate REMS Program by prescribers, pharmacies, and patients is required by the FDA to ensure the benefits of sodium oxybate outweigh the risks associated with sodium oxybate. You are enrolled in the program when your healthcare provider sends the enrollment form you signed in his or her office to the Sodium Oxybate REMS Program. At that time, your healthcare provider also sent your prescription for sodium oxybate to a certified pharmacy.

Certified pharmacy staff will review important information about sodium oxybate with you. They will also answer any questions you may have about sodium oxybate.

TABLE OF CONTENTS

ENROLLING IN THE SODIUM OXYBATE REMS PROGRAM

What am I required to do in this program?	10
Do I have to enroll in this program?	10

FILLING YOUR SODIUM OXYBATE PRESCRIPTION

How is my prescription filled?	10
What does a certified pharmacy do?	11
What will I get with my sodium oxybate prescription?	12
How do I get my sodium oxybate refills?	12
Can my local pharmacy provide sodium oxybate?	12

Any questions? Please call the Sodium Oxybate REMS Program at 855-705-2424.

SODIUM OXYBATE REMS PROGRAM
Sodium oxybate oral solution
For Patients

Please see the Medication Guide for more detailed information about sodium oxybate.

TABLE OF CONTENTS (cont'd)

INSURANCE COVERAGE

Will insurance pay for my sodium oxybate?	13
What is the pharmacy's role with my insurance?	13

HOW DO I TAKE MY SODIUM OXYBATE

How do I prepare my doses?	14
How do I take my doses?	16
What should I do if I miss a sodium oxybate dose?	17
How soon will I see a change in my symptoms?	17
What are the side effects of sodium oxybate?	18
Are there any precautions I should take while on sodium oxybate?	19
How often should my healthcare provider check my progress with sodium oxybate?	20

STORAGE AND SAFETY TIPS AT HOME

How do I store sodium oxybate?..... 21
How do I properly dispose of sodium oxybate?..... 21
What if I have concerns about having sodium oxybate in my home?..... 22

GETTING MORE INFORMATION

Where can I get more information about sodium oxybate?..... 23

Any questions? Please call the Sodium Oxybate REMS Program at 855-705-2424.

SODIUM OXYBATE REMS PROGRAM
Sodium oxybate oral solution
For Patients

Please see the Medication Guide for more detailed information about sodium oxybate.

ENROLLING IN THE SODIUM OXYBATE REMS PROGRAM

What am I required to do in this program?

As a patient, your responsibility is to discuss the safe use of sodium oxybate with your healthcare provider and to read this *Sodium Oxybate REMS Program Patient Quick Start Guide* before receiving your first sodium oxybate prescription. 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.

You must also read the sodium oxybate Medication Guide that you will receive with each prescription from your certified pharmacy.

Do I have to enroll in this program?

You will be required to sign an enrollment form at your healthcare provider's office in order to receive sodium oxybate. You must verify that you have been counseled by your healthcare provider on the serious risks and safe use of sodium oxybate and that you were able to ask your healthcare provider any questions you have about sodium oxybate.

FILLING YOUR SODIUM OXYBATE PRESCRIPTION

How is my prescription filled?

All sodium oxybate prescriptions are filled only by pharmacies certified in the Sodium Oxybate REMS Program.

What does a certified pharmacy do?

Your healthcare provider sends your sodium oxybate prescription directly to a certified pharmacy.

After your healthcare provider sends in your first prescription of sodium oxybate, you will receive a call from your certified pharmacy to tell you how the Sodium Oxybate REMS Program helps you get started with taking sodium oxybate and to answer any questions you may have about sodium oxybate. A staff member from your 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 that might increase your risk of serious side effects. Your certified pharmacy will go over the information about how to use sodium oxybate safely and provide a copy of the Medication Guide with each sodium oxybate shipment.

Your certified pharmacy will always ask you where and when you would like your sodium oxybate delivered and who will sign for the shipment. Sodium oxybate will be shipped by an overnight service. When the courier arrives, you or an adult you name must sign for your sodium oxybate.

Any questions? Please call the Sodium Oxybate REMS Program at 855-705-2424.

SODIUM OXYBATE REMS PROGRAM
Sodium oxybate oral solution
For Patients

Please see the Medication Guide for more detailed information about sodium oxybate.

FILLING YOUR SODIUM OXYBATE PRESCRIPTION (cont'd)

What will I get with my sodium oxybate prescription?

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

How do I get my sodium oxybate refills?

Your certified pharmacy will contact you when it is close to your refill time. You may also call your certified pharmacy to schedule your refills.

Can my local pharmacy provide sodium oxybate?

No. You can get your sodium oxybate only from a Sodium Oxybate REMS Program certified pharmacy. You may be able to have your sodium oxybate shipped to your place of work or to a local overnight carrier hub for pickup. Saturday deliveries may also be an option for you. Your certified pharmacy will work with you on the best options available.

INSURANCE COVERAGE

Will insurance pay for my sodium oxybate?

In most cases, YES. A staff member from your certified pharmacy will call and work with your insurance company to help you get coverage for sodium oxybate.

What is the pharmacy's role with my insurance?

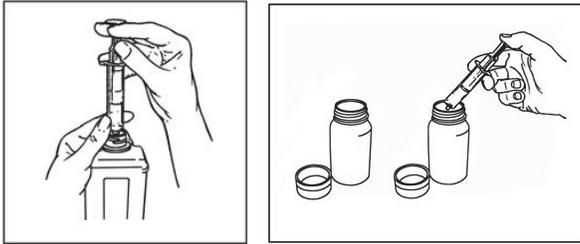
An experienced staff member will:

- Go over your prescription benefits and coverage
- Tell you what your co-pay is, if applicable
- Work with your healthcare provider on prior authorizations, if required by your insurance company

Your certified pharmacy's attempt to get coverage from a third-party payer does not guarantee that you will get coverage.

HOW DO I TAKE MY SODIUM OXYBATE?

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



*For illustration purposes only. Your product may look different.

How do I prepare my doses?

Before going to bed, draw up each of your sodium oxybate doses with the syringe that comes in your shipment. Add each sodium oxybate dose into 1 of the 2 empty pharmacy containers by pushing down on the plunger. Be sure each pharmacy container is empty before adding sodium oxybate into it.

HOW DO I TAKE MY SODIUM OXYBATE? (cont'd)

How do I prepare my doses? (cont'd)

Any questions? Please call the Sodium Oxybate REMS Program at 855-705-2424.

SODIUM OXYBATE REMS PROGRAM
Sodium oxybate oral solution
For Patients

Please see the Medication Guide for more detailed information about sodium oxybate.

Add about $\frac{1}{4}$ cup of water to each dose of sodium oxybate. Then place the child-resistant caps onto the pharmacy containers and turn each cap clockwise (to the right) until it clicks and locks in its child-resistant position.

Then put the 2 prepared doses in a safe place by your bed, out of the reach of children and pets.

Place the cap back on the sodium oxybate bottle and store it in a safe and secure place (locked up if needed), out of the reach of children and pets.

Sodium oxybate should always be stored in the bottle provided. Rinse out the syringe and pharmacy containers with water after each use.

How do I take my doses?

Food will lower the amount of sodium oxybate that passes into your body. You should allow at least 2 hours after a meal before taking your first dose of sodium oxybate.

Sodium oxybate 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 2 ½ 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.

Any questions? Please call the Sodium Oxybate REMS Program at 855-705-2424.

SODIUM OXYBATE REMS PROGRAM
Sodium oxybate oral solution
For Patients

Please see the Medication Guide for more detailed information about sodium oxybate.

HOW DO I TAKE MY SODIUM OXYBATE? (cont'd)

What should I do if I miss a sodium oxybate dose?

- It is very important to take both doses of sodium oxybate each night, as prescribed. If you miss the second dose, skip that dose
 - Do not take sodium oxybate again until the next night
 - Never take both sodium oxybate doses at once
- Any unused sodium oxybate 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 sodium oxybate, 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 sodium oxybate.

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

What are the side effects of sodium oxybate?

Sodium oxybate 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 sodium oxybate are nausea, dizziness, throwing up, bedwetting, and diarrhea. Side effects may increase with higher doses.

These are not the only possible side effects with sodium oxybate. If you are worried about any possible side effects with sodium oxybate, talk with your healthcare provider or the pharmacist at one of the certified pharmacies. You should report all side effects by contacting your healthcare provider, the Sodium Oxybate REMS Program at 855-705-2424, or the FDA at 1-800-FDA-1088.

**Any questions? Please call the
Sodium Oxybate REMS
Program at 855-705-2424.**

SODIUM OXYBATE REMS PROGRAM
Sodium oxybate oral solution
For Patients

Please see the Medication Guide for more detailed information about sodium oxybate.

HOW DO I TAKE MY SODIUM OXYBATE? (cont'd)

Are there any precautions I should take while on sodium oxybate?

- While taking sodium oxybate, 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 sodium oxybate. When you first start taking sodium oxybate, be careful until you know how it will affect you
- Before starting sodium oxybate, tell your healthcare provider if you are pregnant, or plan to become pregnant, or if you are breastfeeding. It is not known whether sodium oxybate can pass through your breast milk
- Keep your sodium oxybate in a safe place, out of the reach of children
- Take sodium oxybate 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 sodium oxybate before you start or change any medications.

How often should my healthcare provider check my progress with sodium oxybate?

When you first start taking sodium oxybate, 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 sodium oxybate.

Any questions? Please call the Sodium Oxybate REMS Program at 855-705-2424.

SODIUM OXYBATE REMS PROGRAM
Sodium oxybate oral solution
For Patients

Please see the Medication Guide for more detailed information about sodium oxybate.

STORAGE AND SAFETY TIPS AT HOME

How do I store sodium oxybate?

- Always store sodium oxybate in its original bottle
- Store sodium oxybate at room temperature. Do not refrigerate sodium oxybate
- Keep sodium oxybate 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 sodium oxybate

How do I properly dispose of sodium oxybate?

When you have finished a bottle, pour any unused sodium oxybate down the sink or toilet drain. Mark out over the prescription label with a marker to protect your confidentiality before putting the empty bottle in the trash.

If you misplace, lose, or damage your sodium oxybate dosing syringe, contact your 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 sodium oxybate in my home?

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

Any questions? Please call the Sodium Oxybate REMS Program at 855-705-2424.

SODIUM OXYBATE REMS PROGRAM
Sodium oxybate oral solution
For Patients

Please see the Medication Guide for more detailed information about sodium oxybate.

Where can I get more information about sodium oxybate?

For more information about sodium oxybate, contact the Sodium Oxybate REMS Program

- **Phone:** 855-705-2424
- **Fax:** 800-353-0987 (toll free)
- **Outside the US:** +1-855-705-2424
- **Website:** www.SodiumOxybateREMSProgram.com

----- **Keep this booklet as a helpful reminder** -----

If you have questions or need information,
contact the Sodium Oxybate REMS Program

**Any questions? Please call the
Sodium Oxybate REMS
Program at 855-705-2424.**

SODIUM OXYBATE REMS PROGRAM
Sodium oxybate oral solution
For Patients

Please see the Medication Guide for more
detailed information about sodium oxybate.

SODIUM OXYBATE REMS PROGRAM PHARMACY ENROLLMENT FORM

Sodium oxybate oral solution 500 mg/mL

Sodium Oxybate
REMS Program

For immediate enrollment, please go to www.SodiumOxybateREMSprogram.com.

To submit this form via fax, please complete all required fields below and fax to 800-353-0987. You will receive a confirmation via the contact preference you list below.

Pharmacies must be specially certified in the Sodium Oxybate REMS Program to dispense sodium oxybate. Sodium oxybate will not be stocked in retail pharmacy outlets. To become certified, every pharmacy must designate an authorized representative to:

1. Complete certification using this *Sodium Oxybate REMS Pharmacy Enrollment Form* and submit the completed form to the Sodium Oxybate REMS Program.
2. Provide relevant training to the pharmacy staff and pharmacists in each pharmacy and maintain a record of the training.
3. Ensure the pharmacy enables its Pharmacy Management System (PMS) to support electronic communication with the Sodium Oxybate REMS Program system using established telecommunication standards.

Authorized Representative Responsibilities

By signing this form, I attest that my pharmacy has put processes and procedures in place to:

1. Dispense sodium oxybate only to patients enrolled in the Sodium Oxybate REMS Program pursuant to a valid prescription written by a prescriber certified in the Sodium Oxybate REMS Program.
2. Ensure that all pharmacy staff involved in the Sodium Oxybate REMS Program complete the *Sodium Oxybate REMS Program Certified Pharmacy Training Program* and maintain a record of the training.
3. Ensure that all pharmacists that dispense sodium oxybate complete the pharmacist training in the *Sodium Oxybate REMS Program Certified Pharmacy Training Program* and maintain a record of the training.
4. Obtain a Pre-Dispense Authorization (PDA) for each sodium oxybate prescription by entering all prescriptions in the pharmacy management system, including cash payments.
5. Provide 24-7 toll-free access to a pharmacist at a Sodium Oxybate REMS Program specially certified pharmacy.
6. Recertify in the Sodium Oxybate REMS Program if the pharmacy designates a new authorized representative.
7. Ship sodium oxybate directly to each patient or a patient-authorized adult designee using an overnight service, track and verify receipt of each shipment of sodium oxybate, and provide shipment and receipt dates to the Sodium Oxybate REMS program for documentation.
8. Limit the first shipment for each patient to a one-month supply of sodium oxybate, and subsequent shipments to no more than a three-month supply of sodium oxybate.
9. Include a sodium oxybate Medication Guide with each shipment and provide a copy of the *Sodium Oxybate REMS Program Patient Quick Start Guide* to each new patient.
10. Document and report all potential serious adverse events reported by all sources, including any CNS depression, respiratory depression, loss of consciousness, coma, and death, and any instances of patient or prescriber behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion to the Sodium Oxybate REMS Program.
11. Report all potential adverse events related to suspected abuse, misuse, or diversion, by completing and submitting the *Sodium Oxybate REMS Program Risk Management Report (RMR)* to the Sodium Oxybate REMS Program.
12. Maintain documentation that all processes and procedures are in place and are being followed for the Sodium Oxybate REMS Program and provide upon request to the Sodium Oxybate Sponsors, FDA, or a third party acting on behalf of the Sodium Oxybate Sponsors or FDA.
13. Comply with audits by the Sodium Oxybate Sponsors, FDA, or a third party acting on behalf of the Sodium Oxybate Sponsors or FDA to ensure that all processes and procedures are in place and are being followed for the Sodium Oxybate REMS Program.
14. Prohibit the sale, loan, or transfer of any sodium oxybate inventory to any other pharmacy institution, distributor, or prescriber.

Prior to dispensing sodium oxybate, my pharmacy will:

15. Complete the *Sodium Oxybate REMS Program Patient Counseling Checklist* and its requirements each time sodium oxybate is dispensed and submit the completed checklist to the Sodium Oxybate REMS Program.
16. Validate each sodium oxybate prescription by:
 - a. Verifying that the prescriber is certified, the patient is enrolled and the patient has no other active sodium oxybate prescription by entering all prescriptions in the pharmacy management system, including cash payments by obtaining a PDA via electronic telecommunication verification.
 - 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, totally quantity (days' supply), and concomitant medications.
 - c. Contacting the Xyrem REMS Program by phone to verify that the patient has no other active prescriptions for sodium oxybate, the patient/prescriber has not been disenrolled in the Xyrem REMS program for suspected abuse, misuse, or diversion, and to report all prescriptions filled for sodium oxybate.
 - d. Documenting that the call to the Xyrem REMS Program was completed using the *Sodium Oxybate REMS Program Prescription Form*.
17. Review the relevant patient information obtained from the Sodium Oxybate REMS Program website (www.SodiumOxybateREMSProgram.com) and the *Sodium Oxybate REMS Program Prescription Form*, 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 sodium oxybate.
 - b. Alerts and *Sodium Oxybate REMS Program RMR* regarding potential abuse, misuse, or diversion.

Pharmacy Information (All fields required)			
Pharmacy Name:			
Address:		City:	State: Zip Code:
NCPDP:	NPI:	DEA:	
Authorized Representative Information (All fields required)			
First Name:		Last Name:	
Phone:	Fax:	Email:	
Preferred Contact Method: <input type="checkbox"/> Phone <input type="checkbox"/> Fax <input type="checkbox"/> Email			
By signing below, I acknowledge that I will comply with the Authorized Representative Responsibilities outlined on this form.			
Authorized Representative Signature:			Date:
Next Steps			
<ol style="list-style-type: none"> 1. After completing and signing this form, please fax to 800-353-0987. 2. Once this form is processed, you will receive instructions on submitting test transaction to the Sodium Oxybate REMS Program to ensure that your pharmacy management system has been successfully configured/updated to communicate with the Sodium Oxybate REMS Program. 3. After successful completion of the test transactions, you will receive a pharmacy certification confirmation. Upon receipt, your pharmacy is certified and your pharmacy staff is now eligible to complete their training. 			

Sodium Oxybate REMS Program

Certified Pharmacy Training Modules A and B

All Sodium Oxybate REMS Program Certified Pharmacy staff and pharmacists must complete **Module A** and the Module A Knowledge Assessment. Pharmacists must also complete **Module B** and the Module B Knowledge Assessment.

Dear Sodium Oxybate REMS Program Certified Pharmacy Staff,

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

The Sodium Oxybate REMS Program

The FDA has determined that a REMS is necessary to ensure that the benefits of sodium oxybate oral solution outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of sodium oxybate by:

1. Informing prescribers, pharmacists, and patients of:
 - The risk of significant central nervous system (CNS) and respiratory depression associated with sodium oxybate
 - The contraindication of use of sodium oxybate with sedative hypnotics and alcohol
 - The potential for abuse, misuse, and overdose associated with sodium oxybate
 - The safe use, handling, and storage of sodium oxybate

2. Ensuring that pharmacy controls exist prior to filling prescriptions for sodium oxybate that:
 - Screen for concomitant use of sedative hypnotics and other potential interacting agents
 - Monitor for inappropriate prescribing, misuse, abuse, and diversion of sodium oxybate
 - 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 Sodium Oxybate REMS Program that includes important information about sodium oxybate and the responsibilities of certified pharmacy staff involved in the dispensing of sodium oxybate.

Sodium oxybate is approved for:

- Treatment of cataplexy in narcolepsy
- Treatment of excessive daytime sleepiness (EDS) in narcolepsy

Sodium oxybate may be prescribed only by prescribers certified in the Sodium Oxybate REMS Program and dispensed only to patients enrolled in the Sodium Oxybate REMS Program and dispensed by pharmacies certified in the Sodium Oxybate REMS Program.

Sincerely,

Sodium Oxybate sponsors

Table of Contents

MODULE A: SODIUM OXYBATE REMS PROGRAM	5
Indications and Usage.....	5
How Supplied	5
Controlled Substance Scheduling.....	5
Boxed Warning.....	6
Contraindications	6
Warnings and Precautions.....	6
Sodium Oxybate REMS Program Requirements.....	7
Overview of Certified Pharmacy Responsibilities	7
Prescription Processing	8
Shipping	9
Monitoring for Inappropriate Prescribing, Abuse, Misuse, and Diversion.....	9
MODULE B: SODIUM OXYBATE REMS PROGRAM TRAINING FOR PHARMACISTS	12
Sodium Oxybate REMS Program Requirements.....	12
Certified Pharmacy Responsibilities	12
Patient Counseling and Screening.....	13
Clinical Usage Clarifications	14
Prescription Refills	14
Monitoring and Assessing for Signs of Abuse, Misuse, and Diversion.....	15
Shipping Procedures.....	15
Inventory Control.....	16

Sodium Oxybate REMS Program

Certified Pharmacy Training Module A

Training for Pharmacy Staff Involved in the Sodium Oxybate REMS Program

All pharmacy staff within a Sodium Oxybate REMS Program certified pharmacy must complete training on **Module A** and successfully complete the Module A Knowledge Assessment. Training must be completed annually.

MODULE A: SODIUM OXYBATE REMS PROGRAM

Important Safety Information

Indications and Usage

Sodium oxybate oral solution is a central nervous system (CNS) depressant that is indicated for the following:

- Treatment of cataplexy in narcolepsy
- Treatment of excessive daytime sleepiness (EDS) in narcolepsy

Sodium oxybate may be prescribed only by prescribers certified in the Sodium Oxybate REMS Program and dispensed only to patients enrolled in the Sodium Oxybate REMS Program.

How Supplied

Sodium oxybate is shipped from a Sodium Oxybate 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 sodium oxybate
- A press-in-bottle adaptor (PIBA) inserted into the bottle at the certified pharmacies
- A sodium oxybate-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 (sodium oxybate dose mixed with water)
- A sodium oxybate Medication Guide

Controlled Substance Scheduling

The active ingredient in sodium oxybate 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 sodium oxybate, and used as prescribed for therapeutic purposes are Schedule III drugs

The active ingredient of sodium oxybate 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 sodium oxybate to any persons other than the patient for whom it was prescribed.

Boxed Warning

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and MISUSE AND ABUSE

Sodium oxybate is a CNS depressant. In clinical trials at recommended doses obtundation and clinically significant respiratory depression occurred in sodium oxybate-treated patients. Almost all of the patients who received sodium oxybate during clinical trials in narcolepsy were receiving central nervous system stimulants.

Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB). Abuse of 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, abuse and misuse, sodium oxybate is available only through a restricted distribution program called the Sodium Oxybate REMS Program, using certified pharmacies. Prescribers must certify and patients must enroll in the Sodium Oxybate REMS Program. For further information go to www.SodiumOxybateREMSProgram.com or call 855-705-2424.

Contraindications

- Sodium oxybate is contraindicated in:
 - Patients who take sedative hypnotic agents.
 - Patients who drink alcohol while using sodium oxybate.
 - Patients with succinic semi aldehyde dehydrogenase deficiency, a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.

Warnings and Precautions

CNS Depression

- Sodium oxybate is a CNS depressant.
- Concurrent use of sodium oxybate 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 sodium oxybate is required, dose reduction or discontinuation of one or more CNS depressants (including sodium oxybate) should be considered.
 - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with sodium oxybate 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 sodium oxybate use.
- Healthcare providers should caution patients about operating hazardous machinery for the first 6 hours after taking a dose of sodium oxybate.

Abuse, Misuse, and Diversion

- 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 amnesic features of sodium oxybate, 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 Prescribing Information for sodium oxybate.

Sodium Oxybate REMS Program Requirements

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

Required components of this program include:

- Use of a certified pharmacy.
- Healthcare Providers who prescribe sodium oxybate must have completed the *Sodium Oxybate REMS Program Prescriber Enrollment Form* and must comply with the requirements of the Sodium Oxybate REMS Program.
- To receive sodium oxybate, patients must be enrolled in the Sodium Oxybate REMS Program and be counseled on the serious risks and safe use of sodium oxybate treatment. Patients are enrolled by certified prescribers who must fill out and submit the *Sodium Oxybate REMS Program Patient Enrollment Form*. Prescribers must also complete and submit the *Sodium Oxybate REMS Program Prescription Form* to one of the certified pharmacies for all new sodium oxybate prescriptions and for sodium oxybate prescriptions for patients restarting sodium oxybate treatment after not receiving sodium oxybate for 6 months or more.
- Further information is available at www.SodiumOxybateREMSProgram.com.

Overview of Certified Pharmacy Responsibilities

Enrollment Verification

- The *Sodium Oxybate REMS Program Prescriber Enrollment Form* and the *Sodium Oxybate REMS Program Patient Enrollment Form* are sent to the Sodium Oxybate REMS Program by the prescriber.
- Information from the enrollment forms is maintained in the appropriate Sodium Oxybate REMS Program database by the Sodium Oxybate REMS Program.
- No duplicate patients may be enrolled.
- Patients must confirm that they have been counseled on the serious risks and safe use of sodium oxybate; their certified pharmacy will provide counseling with every sodium oxybate prescription dispensed.
- The Sodium Oxybate REMS Program will notify the prescriber of successful certification in the Sodium Oxybate REMS Program, and that he or she is eligible to prescribe sodium oxybate.
 - If there is a delay in shipping while a question about the prescriber's credentials is being resolved, the patient will be notified by their certified pharmacy.
 - If the prescription cannot be filled because a question about the prescriber's credentials could not be resolved, the patient will be notified by their certified pharmacy.
 - The prescriber will be notified by the Sodium Oxybate REMS Program that he/she cannot be certified due to credential verification failure.
- The Sodium Oxybate REMS Program will notify the prescriber of successful patient enrollment in the Sodium Oxybate REMS Program.
- Enrollment status is maintained in the Sodium Oxybate REMS Program.
 - The Sodium Oxybate REMS Program will confirm that the prescriber's DEA and state license 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 state licensures or for non-compliance with the Sodium Oxybate REMS Program.
 - Following enrollment, the patient remains in the Sodium Oxybate REMS Program unless their certified pharmacy, and/or certified prescriber determine that the patient should be disenrolled.
- A certified prescriber and/or a certified pharmacy can direct that a patient be disenrolled from the Sodium Oxybate REMS Program.
 - A patient may be disenrolled from the program for non-compliance with the Sodium Oxybate REMS Program, including for multiple suspicious early refill requests, or other information that indicates abuse, misuse, or diversion.
 - The Sodium Oxybate REMS Program will contact a prescriber if an enrollment form is received for a patient previously disenrolled from the program, or for suspicions of abuse, misuse, or diversion, and will provide the prescriber with all relevant patient history.

Prescription Processing

- A certified pharmacy must validate all prescriptions prior to dispensing sodium oxybate. This includes obtaining a Pre-Dispense Authorization (PDA) from the Sodium Oxybate REMS Program for each prescription upon receipt of a *Sodium Oxybate REMS Program Prescription Form*. The issuance of PDA informs the pharmacy that the prescriber is certified and patient is enrolled in the Sodium Oxybate REMS Program and the patient has no other active sodium oxybate prescriptions.
 - The certified pharmacy will process all sodium oxybate prescriptions, including cash payments, through the pharmacy management system (PMS) and obtain a PDA via electronic telecommunication verification to verify the prescriber is certified, the patient is enrolled in the Sodium Oxybate REMS Program and the patient has no other active sodium oxybate prescriptions.
 - To verify the safe use conditions electronically through the PMS, the following prescription information, at a minimum, is required to be submitted upon processing every sodium oxybate prescriptions:
 - Patient First Name
 - Patient Last Name
 - Patient Date of Birth
 - Patient Zip Code
 - Prescriber Identifier on prescription (NPI or DEA)
 - Date of Fill
 - Days' Supply
 - Quantity
 - Product/NDC
 - If all safe use conditions are met, a PDA will be generated by the Sodium Oxybate REMS Program. The PDA will be maintained in the Sodium Oxybate REMS Program patient database, and does not need to be recorded by the pharmacy. The pharmacy is authorized to dispense sodium oxybate upon receiving a PDA.
 - If the safe use conditions are not met, a PDA will not be issued and the pharmacy will be notified of the reason why:
 - Pharmacy is not certified
 - Prescriber is not certified
 - Patient is not enrolled
 - Patient has a known active, overlapping prescription for sodium oxybate
- Before ordering sodium oxybate from your distributor/wholesaler, you must obtain a PDA from the Sodium Oxybate REMS Program. Distributors/wholesalers are required to verify with the Sodium Oxybate REMS Program that you have a PDA before sending sodium oxybate to your pharmacy. Each bottle of Sodium Oxybate is to be ordered on a per-patient basis only.
- Before a prescription for sodium oxybate can be shipped to a patient, the pharmacy must:
 - Verify that the *Sodium Oxybate REMS Program Prescription Form* is complete and signed by the prescriber.
 - Verify the *Sodium Oxybate REMS Program Prescription Form* was received from the prescriber's office.
 - Verify the prescription is dated according to state controlled prescription regulations.
 - Verify the prescription is for only a one-month supply on a patient's first sodium oxybate fill and no more than a 3-month supply on subsequent fills.
 - Verify there are no discrepancies or concerns with the dosing and titration.
 - If there are discrepancies or concerns, the certified pharmacy must contact the prescriber to revise and resubmit the *Sodium Oxybate REMS Program Prescription Form*.
 - Review the patient information contained in the Sodium Oxybate REMS Program patient database using the secure web viewing portal and the *Sodium Oxybate REMS Program Prescription Form* including:
 - 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 sodium oxybate.
 - 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 and document the call and the prescriber's treatment rationale on the *Sodium Oxybate Patient Counseling Checklist*.
 - Alerts and Sodium Oxybate REMS Program RMRs regarding potential abuse, misuse, or diversion.
 - Contact the Xyrem REMS Program by phone to:
 - Verify that the patient has no other active prescriptions for sodium oxybate that overlap with the current prescription.
 - Verify that the patient/prescriber has not been disenrolled in the Xyrem REMS Program for suspected abuse, misuse, or diversion.
 - Report all prescriptions filled for sodium oxybate.
 - Document that the call to the Xyrem REMS Program was completed using the *Sodium Oxybate REMS Program Prescription Form*.
- If a certified pharmacy receives overlapping prescriptions for sodium oxybate for a patient, the certified pharmacy responsible for dispensing the current prescription will notify and consult each prescriber.

- Prescriptions are considered overlapping when more than one prescription for sodium oxybate is received for a patient from multiple prescribers within an overlapping timeframe.
 - If a certified pharmacy suspects abuse, misuse, or diversion, the prescription should not be filled, the certified pharmacy must complete and submit a *Sodium Oxybate REMS Program RMR* to the Sodium Oxybate REMS Program, and the prescriber will be notified.
 - 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.
 - A certified pharmacy responsible for dispensing sodium oxybate to a patient must ensure that under these situations a patient does not receive multiple overlapping shipments of sodium oxybate.
- Once a PDA is obtained from the Sodium Oxybate REMS Program, review of the patient information in the patient database using the secure web viewing portal has been performed, and the Xyrem REMS Program has been contacted, the certified pharmacy will contact the patient to schedule shipment and complete the required counseling.
 - For a new patient, the certified pharmacy provides the *Sodium Oxybate REMS Program Patient Quick Start Guide*.
 - A pharmacist must counsel the patient by completing the *Sodium Oxybate REMS Program Patient Counseling Checklist* prior to every dispense of sodium oxybate.
 - The certified pharmacy must submit the *Sodium Oxybate REMS Program Patient Counseling Checklist* to the Sodium Oxybate REMS Program online at www.SodiumOxybateREMSProgram.com or complete a print version and fax to the Sodium Oxybate REMS Program at 800-353-0987.

Shipping

All sodium oxybate is shipped to patients (or their adult designee) by an overnight service with receipt signature required. Certified pharmacies must provide confirmation of receipt of each prescription of sodium oxybate to the Sodium Oxybate REMS Program by accessing the Sodium Oxybate REMS Program website (www.SodiumOxybateREMSProgram.com), or calling the Sodium Oxybate REMS Program (855-705-2424).

- The patient may request an alternate shipping address, which is subject to approval by a pharmacist.
- See [How Supplied](#) for details of the contents of each sodium oxybate 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

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

- Document early refill requests and instances of patient and prescriber behavior that suggest potential abuse, misuse, or diversion by completing and submitting a *Sodium Oxybate REMS Program RMR* to the Sodium Oxybate REMS Program online at www.SodiumOxybateREMSProgram.com or complete a print version and fax to the Sodium Oxybate REMS Program at 800-353-0987. This information is maintained in the prescriber and/or patient databases in the Sodium Oxybate REMS Program.
 - Direct the Sodium Oxybate REMS Program to disenroll a patient that has demonstrated behavior that suggests potential abuse, misuse, or diversion by completing and submitting a *Sodium Oxybate REMS Program RMR* to the Sodium Oxybate REMS Program. The Sodium Oxybate REMS Program will notify the Xyrem REMS Program that the patient has been disenrolled.
 - Recommend that a prescriber who has demonstrated behavior that suggests potential abuse, misuse, or diversion be disenrolled by submitting a *Sodium Oxybate REMS Program RMR* to the Sodium Oxybate REMS Program. The Sodium Oxybate REMS Program will notify the Xyrem REMS Program that the prescriber has been disenrolled if disenrollment is determined to be the appropriate corrective action.
- Review the patient's Sodium Oxybate REMS Program RMR history and alerts in the Sodium Oxybate REMS Program using the secure pharmacy web viewing portal for the patient 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 Sodium Oxybate REMS Program RMRs to the Sodium Oxybate REMS Program by completing and submitting the *Sodium Oxybate REMS Program RMR*.
- Determine whether an alert should be placed in the patient's profile in the patient database within the Sodium Oxybate REMS Program for repeated reports of lost, stolen, destroyed, or spilled drug for review prior to shipping sodium oxybate.
- Inform a pharmacist immediately if certified pharmacy staff suspects patients or prescribers of abuse, misuse, or diversion.

Adverse Event Reporting

- Everyone on staff in each certified pharmacy has an essential role to play in the process of collecting information on potential adverse events for reporting to the Sodium Oxybate REMS Program.

- 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 by calling the Sodium Oxybate REMS Program at 855-705-2424.
- Report all potential adverse events related to suspected abuse, misuse, or diversion, by completing and submitting the *Sodium Oxybate REMS Program RMR* to the Sodium Oxybate REMS Program online at www.SodiumOxybateREMSProgram.com or by fax to 800-353-0987.

Ongoing Patient Education

Patients in the Sodium Oxybate REMS Program have access to ongoing education while taking sodium oxybate through:

- 24-hour toll-free telephone help line staffed by a pharmacist trained in the Sodium Oxybate REMS Program.
- Continued contact with the certified pharmacy for every refill.
- Sodium Oxybate REMS Program website (www.SodiumOxybateREMSProgram.com).

Sodium Oxybate REMS Program

Certified Pharmacy Training Module B

Sodium Oxybate REMS Program Training for Pharmacists Involved in the Dispensing of Sodium Oxybate

All Sodium Oxybate 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 sodium oxybate, training must be completed annually.

MODULE B: SODIUM OXYBATE REMS PROGRAM TRAINING FOR PHARMACISTS

All pharmacists involved in dispensing sodium oxybate must complete the following additional training at least annually. The Sodium Oxybate REMS Program requires that pharmacists within a certified pharmacy are thoroughly trained on the requirements of the Sodium Oxybate REMS Program. Training will be conducted by reviewing the Sodium Oxybate REMS Program materials and successfully completing a Knowledge Assessment with 100% accuracy on the requirements of certified pharmacies and pharmacists working within a certified pharmacy. These duties will include:

- Review of PI
- Review of certified pharmacy's internal processes and procedures established to support the Sodium Oxybate REMS Program with an experienced pharmacist
- Execution of the Sodium Oxybate REMS Program Patient Counseling Checklist
- Detailed monitoring including completion of a *Sodium Oxybate REMS Program RMR*, as needed
- Follow-up interactions with patients and prescribers
- Sodium Oxybate REMS Program documentation and processes

Sodium Oxybate REMS Program Requirements

Sodium oxybate may be prescribed and dispensed only to patients enrolled in the Sodium Oxybate REMS Program. Because of the risks of CNS depression, abuse, misuse, and diversion, sodium oxybate is available only through a restricted distribution program called the Sodium Oxybate REMS Program.

Required components of this program include:

- Use of a certified pharmacy.
- Healthcare providers who prescribe sodium oxybate must complete and submit the following to the Sodium Oxybate REMS Program:
 - *The Sodium Oxybate REMS Program Prescriber Enrollment Form*
 - *The Sodium Oxybate REMS Program Patient Enrollment Form*
- Healthcare providers who prescribe sodium oxybate must complete prescriptions for sodium oxybate on the *Sodium Oxybate REMS Program Prescription Form* and submit the completed form to one of the certified pharmacies.
 - After completion of prescription processing, the pharmacy will fax the prescription form to the Sodium Oxybate REMS Program and retain the original.
 - Prescription refills and renewals may be conveyed by phone or fax and must be documented in the Sodium Oxybate REMS Program.
- To receive sodium oxybate, patients must be:
 - Enrolled in the Sodium Oxybate REMS Program.
 - Prescribed sodium oxybate by a prescriber certified in the Sodium Oxybate REMS Program.
 - Counseled on the serious risks and safe use of sodium oxybate.
 - Have only one active sodium oxybate prescription.

Certified Pharmacy Responsibilities

Certified pharmacies will:

- Limit the first prescription fill to a one-month supply of sodium oxybate and no more than a 3-month supply for subsequent prescription fills.
- Report potential adverse events to the Sodium Oxybate 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.
- Certified pharmacies must complete and submit a *Sodium Oxybate REMS Program RMR* to the Sodium Oxybate REMS Program for all instances of potential abuse, misuse, or diversion.
- Utilize the Sodium Oxybate REMS Program, which has access to the secure, validated, separate and distinct Sodium Oxybate REMS Program databases (patient database, certified prescriber database, certified pharmacy database, and disenrolled prescriber database) that will only be queried independently through electronic verification, to verify the following:
 - Complete patient enrollment information
 - Complete prescriber certification information
 - 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
- Prescription information including:
 - Date
 - Dose
 - Titration instructions
 - Number of refills
 - Directions
 - Total quantity (volume and number of days' supply)
 - Concomitant medications
- Sodium Oxybate REMS Program 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 sodium oxybate dispensed daily
- Documentation of interactions with prescribers, patients, and other parties.

These data must be available to the Sodium Oxybate REMS Program for review on an ongoing basis to ensure that sodium oxybate 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 Sodium Oxybate REMS Program using the certified pharmacy secure web viewing portal for the patient database and review it prior to dispensing sodium oxybate.

Patient Counseling and Screening

- Certified pharmacies must complete the *Sodium Oxybate REMS Program Patient Counseling Checklist* and submit to the Sodium Oxybate REMS Program for each patient prior to every shipment of sodium oxybate.
- Each time a pharmacist completes the *Sodium Oxybate REMS Program Patient Counseling Checklist*, the pharmacist must:
 - Verify that early refill requests have been thoroughly questioned and approved through the Sodium Oxybate REMS Program RMR procedure (see below).
 - Screen the patient for concomitant use of contraindicated medications (sedative hypnotics), alcohol, other CNS depressants, and other potentially interacting agents.
 - The pharmacist asks the patient if he or she 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 sodium oxybate.
 - Screen the patient for other medical conditions.
 - The pharmacist asks the patient what other medical conditions he or she has.
 - If the patient indicates that he or she has a certain medical condition listed on the *Sodium Oxybate REMS Program Patient Counseling Checklist*, the pharmacist counsels the patient, and notifies the prescriber about the medical condition prior to shipping sodium oxybate.
 - Document the results of the patient screening, all reported concomitant medications and comorbid medical conditions, the action(s) taken, and the date the *Sodium Oxybate REMS Program Patient Counseling Checklist* is completed in the Sodium Oxybate REMS Program.
 - Submit the *Sodium Oxybate REMS Program Patient Counseling Checklist* to the Sodium Oxybate REMS Program online at www.SodiumOxybateREMSProgram.com or complete a print version and fax to the Sodium Oxybate REMS Program at 800-353-0987.
- Certified pharmacies must provide patients with 24/7 access to a pharmacist.

Clinical Usage Clarifications

The pharmacist must:

- Review the information on each *Sodium Oxybate 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

If the issue is not resolved with the prescriber, the pharmacist may consult with the Pharmacist in Charge at their certified pharmacy and with the Sodium Oxybate REMS Program.

Prescription Refills

- Up to 5 refills are allowed on a sodium oxybate prescription (per DEA regulations for CIII controlled substances).
- Refills may be conveyed by phone or fax from the prescriber or patient and communicated to the Sodium Oxybate REMS Program by obtaining a PDA.
- For information on the prescription processing requirements see Module A – [Prescription Processing](#)
- Changes in dose require a new prescription.
- Refill orders should be opened at a patient's certified pharmacy when the patient has approximately 10 days of therapy remaining from the previous shipment.
 - A certified pharmacy technician will contact the patient and schedule a shipment. The technician will ask the patient if there has been any change in his or her medications or medical history.
 - The technician will transfer him or her to a pharmacist who must complete the *Sodium Oxybate REMS Program Patient Counseling Checklist*. The patient should be counseled on the use or diagnosis of:
 - Sedative hypnotics (for example, diazepam, phenobarbital, or 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 his or her breathing
 - Other current medical conditions
 - The pharmacist must complete refill counseling and confirmation of prescriber consultation or notification by completing and submitting the *Sodium Oxybate REMS Program Patient Counseling Checklist* to the Sodium Oxybate REMS Program online (www.SodiumOxybateREMSProgram.com) or by fax (800-353-0987).
- All patient requests for early refills are to be questioned and documented by the pharmacist.
 - An early refill request is a request for sodium oxybate shipment prior to the date of the next shipment.
 - Requests to accommodate shipment logistics (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 to evaluate his/her compliance with therapy, assessing for misuse, abuse, and diversion.
 - Evaluate the patient's record in the Sodium Oxybate REMS Program using the certified pharmacy secure web viewing portal for the patient database and review the patient's prior Sodium Oxybate 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 sodium oxybate to the patient only if approved by the prescriber.
 - Send new shipments to replace sodium oxybate reported stolen by a patient only after obtaining a copy of the police report filed by the patient.
 - Document the discussion and outcome by completing and submitting the *Sodium Oxybate REMS Program RMR* to the Sodium Oxybate REMS Program online (www.SodiumOxybateREMSProgram.com) or by fax (800-353-0987).

Monitoring and Assessing for Signs of Abuse, Misuse, and Diversion

- Risk management events must be documented in the Sodium Oxybate REMS Program.
 - 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 a Sodium Oxybate REMS Program 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
 - Sodium Oxybate REMS Program RMRs must document:
 - Patient and/or prescriber identifying information (patient names to be concealed)
 - Reason for report
 - Certified Pharmacy actions
 - Prescriber contact
 - Supporting documentation (if applicable, such as a police report, fire report, DEA Form 106, or shipper investigation report)
 - Pharmacies can request that a patient is monitored by the Sodium Oxybate REMS Program if serious or repeated events give rise to reasonable suspicion of misuse, abuse or diversion.
 - If abuse, misuse, or diversion is suspected, the pharmacist must review the patient's Sodium Oxybate REMS Program RMR history and discuss the incident with the prescriber prior to shipping sodium oxybate.
 - Repeated reports of lost, stolen, destroyed, or spilled drug will be documented as an alert to the patient record stored in the patient database of the Sodium Oxybate REMS Program and will be accessible to the dispensing pharmacist using the secure web viewing portal for the patient database for review prior to shipping drug.
 - Certified pharmacies and/or prescribers may direct the Sodium Oxybate REMS Program to disenroll a patient after review and discussion of incidents suggestive of abuse and misuse, or diversion by completing and submitting a *Sodium Oxybate REMS Program RMR Form* to the Sodium Oxybate REMS Program.. All requests from prescribers to disenroll a patient will be submitted to a certified pharmacy. The certified pharmacy is required to intake the request, then complete and submit the *Sodium Oxybate REMS Program RMR* to the Sodium Oxybate REMS Program to notify of disenrollment.
 - Pharmacies may recommend that a prescriber be disenrolled by submitting a Sodium Oxybate REMS Program RMR Form to the Sodium Oxybate REMS Program. Sodium Oxybate sponsors will review the information and determine if the prescriber should be disenrolled.
 - All *Sodium Oxybate REMS Program RMRs* must be reported to the Sodium Oxybate REMS Program online (www.SodiumOxybateREMSProgram.com) or by fax (800-353-0987).

Shipping Procedures

- Sodium oxybate must be shipped via an overnight service with receipt signature required.
 - Sodium oxybate 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 may request an alternate shipping address, which is then subject to approval by a pharmacist.
- If the patient requests Saturday delivery, his or her certified pharmacy will verify with the overnight shipping service that it is available for the shipping address.
- Each sodium oxybate shipment must include:
 - The prescribed amount of medication, contained in one or more bottles of sodium oxybate
 - A press-in-bottle adaptor (PIBA) inserted into the bottle at the certified pharmacies
 - A sodium oxybate-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 (sodium oxybate dose mixed with water)
 - A sodium oxybate Medication Guide
- Daily tracking reports must be generated by each certified pharmacy to confirm the receipt of each order shipped during the previous 48 hours. Saturday deliveries are confirmed the following Monday.
 - A patient 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.
- Receipt of each shipment of sodium oxybate by a patient must be reported to the Sodium Oxybate REMS Program through the website (www.SodiumOxybateREMSProgram.com) or by calling (855-705-2424) by the patient's certified pharmacy.

Inventory Control

The sodium oxybate inventory must be reconciled at the start and end of each business day and recorded in the pharmacy management system. A physical count must match the count in the pharmacy management system). If the sodium oxybate inventory cannot be reconciled for any reason, no other patient orders can be processed until an investigation is completed by the Pharmacist in Charge and approved by the Sodium Oxybate REMS Program. Internal procedures for reconciling the sodium oxybate inventory are subject to audit.

(To be completed by the pharmacist online at www.SodiumOxybateREMSProgram.com or complete a print version and fax to the Sodium Oxybate REMS Program at 800-353-0987 prior to dispensing each sodium oxybate shipment. 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

- New/restart
- Scheduled refill
- Early refill approved through Risk Management Report (RMR) process

Patient Name: _____ Patient ID Number: _____

Include Pharmacist Name and Date Time Stamp for each section completed

Step 2: Counseling

- Verify that the patient will receive the *Sodium Oxybate REMS Program Patient Quick Start Guide* (if not already received) and that the drug shipment to the patient will include the sodium oxybate Medication Guide.

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

- Verify that patient has been counseled on **Therapy Expectations** below:

- During clinical trials with sodium oxybate, many patients with narcolepsy saw some improvement with excessive daytime sleepiness and/or cataplexy in the first weeks after beginning sodium oxybate therapy. However, the response to sodium oxybate varies from patient to patient. It may also take time to find the right dose that works for you. Your doctor will determine the dose that is appropriate for you.
- Be sure to talk to your doctor about any troubling side effects or if you don't feel any benefits while taking sodium oxybate.
- For any changes to your prescription, have your doctor call or fax the new prescription change to the pharmacy and NEVER attempt to change the dose yourself.

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

□ Verify that patient has been counseled on **Preparation and Administration** information below:

- Sodium oxybate should be taken as directed by your doctor (review prescriber's instructions with patient).
 - Prepare each of your doses by placing _____ grams of sodium oxybate in one of the provided pharmacy containers and place _____ grams in the second container. Add 1/4 cup of water to each pharmacy container. The water does not come with sodium oxybate. You can use either tap or bottled water. The solution should remain clear and it will taste salty. Place the child-resistant cap onto the containers and put them in a safe place, out of the reach of children or pets, by your bed.
- Feel free to call your certified pharmacy if you have any questions regarding preparation or how to take your sodium oxybate doses. The Sodium Oxybate REMS Program is also available Monday through Friday, from 8 am to 8 pm Eastern Time, at 855-705-2424, and a pharmacist is always available 24 hours a day, 7 days a week at your certified pharmacy, if needed.

Refer to the Medication Guide for additional information on preparation of your sodium oxybate doses.

- Set alarm to go off 2.5 to 4 hours after you take your first dose.
- When you are ready to go to sleep, sit at your bedside and drink one dose of sodium oxybate and then lie down.
 - Your first dose of sodium oxybate should be taken at least 2 hours after eating as food will decrease the amount of sodium oxybate that your body absorbs.
 - 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 may take longer to fall asleep. The time that it takes to fall asleep might be different from night to night.
 - Upon waking up, take the second dose of medication as prescribed by your physician.
 - A minimum of 2.5 hours must separate each dose.
 - If you happen to miss a dose, NEVER take two doses of sodium oxybate at once.
- The diluted medication MUST be used within 24 hours of preparation. Discard any unused medication down the sink drain or toilet.
- When you can no longer draw medication out of the bottle with the dispensing device, dispose of your bottle. Use a marker or pen to deface the bottle to protect your confidentiality.
- Be sure to store sodium oxybate in the original bottle in a safe and secure place out of the reach of children and pets. Get emergency help (call 911) right away if a child drinks your sodium oxybate.
- Sodium oxybate should be stored at room temperature.

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

- Verify that patient has been counseled on **Precautions needed for sodium oxybate use:**
 - Sodium oxybate is classified as a controlled substance medication. Sodium oxybate 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 is sodium oxybate. Sodium oxybate is converted to gamma-hydroxybutyrate (GHB) in the body. 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 CNS depressants (for example, nortriptyline, oxycodone, or heroin) including alcohol can lead to seizure, trouble breathing, decreases in the level of consciousness, coma, and death.
 - Tell your doctor if you:
 - Are pregnant or plan to become pregnant. It is not known if sodium oxybate can affect your unborn baby.
 - Are breastfeeding. It is not known whether sodium oxybate can pass through the breast milk. Talk to your doctor about the best way to feed your baby if you take sodium oxybate.
 - Have or had depression or tried to harm yourself. You should be watched for new signs of depression.
 - Have liver problems. Your dose may need to be adjusted.
 - Have sleep apnea (short periods of not breathing while you sleep), snoring, or breathing or lung problems. You may have a higher chance of serious breathing problems with sodium oxybate.
 - Have mental health problems.
 - Walk in your sleep.
 - Are on a salt-restricted diet, have high blood pressure, heart failure, or kidney problems. Sodium oxybate contains sodium (salt) and may not be right for you.

_____ (Pharmacist Name) ___/___/____ (Date Time)

□ Verify that patient has been counseled on **Side Effects**:

- In clinical trials, the most commonly observed side effects associated with the use of sodium oxybate included: headache, nausea, dizziness, sleepiness, vomiting, urinary incontinence, and inflammation of the area around the nostrils and the back of the mouth. Some side effects may be more likely to be observed with higher doses of sodium oxybate.
- Sodium oxybate 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 doctor if you have any of these problems while taking sodium oxybate.
- Remember that you must not drive a car, operate heavy machinery, or perform any activity that is dangerous or that requires mental alertness or motor coordination for the first 6 hours after taking a dose of sodium oxybate.
- When taking sodium oxybate, do not drink alcohol or take medicines that make you sleepy, including antidepressants, antipsychotics, anti-epileptics, opioids, general anesthetics, muscle relaxants and/or illicit CNS depressants (for example, heroin or GHB).
- These are not all of the side effects that you might experience. Contact your doctor if you are concerned about any possible side effects. Refer to the Medication Guide for additional information on possible side effects.

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

Step 3: Screening

1. Is the patient taking sedative hypnotics (for example, diazepam, phenobarbital, or zolpidem)?

- Yes Counseled Patient
 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 (for example, heroin or GHB)?

- Yes Counseled Patient
 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
 No

5. Has the patient been diagnosed with sleep apnea (short periods of not breathing while asleep)?

- Yes Counseled Patient
 No

6. Does the patient have a diagnosis of or suffer from asthma, COPD, or other conditions affecting his/her breathing (slower breathing, trouble breathing)?
- Yes
 - No
 - Counseled Patient

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
 - No
 - Counseled Patient

Please list the condition(s), if known:

8. Does the patient have any clinical questions about sodium oxybate?
- Yes
 - No
 - Counseled Patient
 - Referred Patient to Prescriber

Please list the question(s):

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

Step 4: Concomitant Medication & Comorbidity Summary

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 GHB)

Medical Conditions:

- Sleep apnea
- Asthma
- COPD
- Other conditions affecting their breathing
- History of depression or suicidality
- History of drug or alcohol abuse
- Seizure disorders
- Hepatic impairment
- High blood pressure, heart problems, kidney problems, or are on a salt-restricted diet

If any of the medication types or medical conditions listed above are checked, or any of the questions in Section 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: ____/____/____

Name of prescriber consulted: _____

Prescriber NPI or DEA: _____

Prescriber consult outcome: _____

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

Step 5: Completion Summary

Checklist Completed: Yes No (Sodium oxybate is not shipped until checklist is completed.)

If yes, date checklist completed: _____/_____/_____ (Date Time)

If no, document the reason for non-completion:

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

**SODIUM OXYBATE REMS PROGRAM
RISK MANAGEMENT REPORT**

Sodium oxybate oral solution 500 mg/mL

Sodium Oxybate
REMS Program

Instructions

Risk Management Reports (RMRs) are filled out by pharmacies that are certified in the Sodium Oxybate REMS Program 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. For immediate reporting, RMRs can be completed by the pharmacist online at www.SodiumOxybateREMSProgram.com. Alternatively, a pharmacist can complete a print version and fax to the Sodium Oxybate REMS Program at 800-353-0987.

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 Sodium Oxybate 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, stolen, or delivered to an incorrect address and was not returned.
- Tampering with or counterfeiting or contamination of 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 *Sodium Oxybate REMS Program Prescriber Enrollment Form, Prescription Form, or Patient Enrollment Form*.

To complete a RMR:

- Contact the Sodium Oxybate REMS Program to assign a unique Control Number to each report in the Sodium Oxybate REMS Program.
- 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 of 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 database or patient database of the Sodium Oxybate REMS Program to ensure prescriber and pharmacist awareness.
 - The Sodium Oxybate REMS Program will monitor any associated patient or prescriber activity during the course of the investigation and for a period after the investigation, where appropriate.
 - The certified pharmacies will complete and submit the RMR to the Sodium Oxybate REMS Program. The Sodium Oxybate REMS Program will work with the sponsors to determine the need to notify local, state, or federal authorities.
- Send the RMR to the Sodium Oxybate REMS Program within one business day.
- If the RMR includes a potential adverse event, the potential adverse event is reported to the FDA through the Sodium Oxybate sponsors. If the RMR includes a product complaint, the event is also reported to the FDA through the Sodium Oxybate sponsors.

Sodium Oxybate REMS Program Risk Management Report

Date:	Control Number:	Type of Reporter:	<input type="checkbox"/> Patient	<input type="checkbox"/> Prescribing Physician	<input type="checkbox"/> Pharmacist	<input type="checkbox"/> Other
Name of Reporter (if not a patient):			Name and Address of Pharmacy:			
Nature of Report (e.g., early refill request, lost or stolen bottle, package not received, other):						
Identification Number (patient and/or prescriber ID associated with RMR):					Date Enrolled in Program:	
Have the alerts and RMR history been reviewed with the patient?				<input type="checkbox"/> Yes	<input type="checkbox"/> No	Date(s) of RMR Event (Start/End):
RMR Event (please provide detail):						
Early Refill Requested? <input type="checkbox"/> Yes <input type="checkbox"/> No						
If yes, reason for early refill request (e.g., dose increase, spilled medication, lost/stolen product):						
Prescriber Contacted?		If yes, what was the outcome of the conversation?				
<input type="checkbox"/> Yes						
<input type="checkbox"/> No		If no, what is the reason?				
Was early refill approved?			<input type="checkbox"/> Yes	<input type="checkbox"/> No	Early refill status reason:	
Potential adverse event associated with report?			<input type="checkbox"/> Yes	<input type="checkbox"/> No	If yes, AE number:	
Summary of investigation: <input type="checkbox"/> Yes <input type="checkbox"/> No						
Attachments (check all that apply): <input type="checkbox"/> DEA 106 Form <input type="checkbox"/> Police/Fire Report <input type="checkbox"/> Shipping Service Report <input type="checkbox"/> Other (specify):						
Should patient be monitored (alert placed)? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A						
Are you requesting disenrollment for suspected abuse, misuse, or diversion?		For the patient? <input type="checkbox"/> Yes <input type="checkbox"/> No		For the prescriber? <input type="checkbox"/> Yes <input type="checkbox"/> No		
<input type="checkbox"/> Yes <input type="checkbox"/> No		Patient Name: _____		Prescriber Name: _____		
Pharmacist in Charge Name:		Signature:		Date:		

Risk Evaluation and Mitigation Strategy (REMS)

The goal of the Sodium Oxybate REMS Program is to mitigate the risk of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of sodium oxybate by:

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

Sodium Oxybate REMS Program Overview

- All prescribers and pharmacies must enroll in the Sodium Oxybate REMS Program and comply with requirements for prescribing and dispensing sodium oxybate
- All patients must be enrolled in the Sodium Oxybate REMS Program to receive sodium oxybate
- All patients are required to be counseled on the serious risks and safe use of sodium oxybate
- Sodium oxybate will be dispensed only by pharmacies that are specially certified through the Sodium Oxybate REMS Program

Sodium oxybate is approved for:

- Treatment of cataplexy in patients with narcolepsy
- Treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy

If you require any additional assistance or information, please call the Sodium Oxybate REMS Program at 855-705-2424

Contact Us

Sodium Oxybate REMS Program

Phone

U.S. Phone 855 705 2424

Outside the U.S. Phone +1 855 705 2424

Fax

800 353 0987

Mailing Address

Sodium Oxybate REMS Program

P.O. Box XXXXX

City, ST XXXXX XXXX

If you require any additional assistance or information, please call the Sodium Oxybate REMS Program at 855-705-2424

Create an Account

Pharmacists and prescribers can create a web account in the Sodium Oxybate REMS Program by completing the fields below. The Username you specify must be unique within this website. All fields below are required unless otherwise indicated.

First Name	<input type="text"/>
Last Name	<input type="text"/>
Email Address	<input type="text"/>
Certification ID (opt)	<input type="text"/> ⓘ <i>(If you certified via fax, please enter your Certification ID)</i>
Username	<input type="text"/>
	<input checked="" type="checkbox"/> Suggest Username <input type="checkbox"/> Check Username Availability
	<input type="checkbox"/> Use Email Address as Username
Password	<input type="password"/>
Confirm Password	<input type="password"/>
	<input type="button" value="Cancel"/> <input type="button" value="Submit"/>

If you require any additional assistance or information, please call the Sodium Oxybate REMS Program at 855-705-2424

Frequently Asked Questions

– Is it still possible to enroll offline?

Yes, you can still enroll offline. Enrollment forms are located under the [Resources](#) tab.

– Do I need to complete the online version of the Prescriber Enrollment Form if I am already enrolled in the Sodium Oxybate REMS Program?

No. If you are already enrolled in the Sodium Oxybate REMS Program or have completed the prescriber enrollment process offline and faxed it, you do not need to complete the online version of the prescriber enrollment form.

You can still use the online enrollment form to enroll your patients.

– How long does it take to process my enrollment so I can enroll patients?

Generally, the Sodium Oxybate REMS Program will process your enrollment within 2 to 3 business days.

– How will I be notified that my patient is enrolled?

Once you complete the patient enrollment form, both you and the patient have signed the form, and the form has been submitted, the Sodium Oxybate REMS Program will process the enrollment form within 2 to 3 business days.

Once the enrollment has been processed you will receive a notification from the Sodium Oxybate REMS Program.

– Will my or my patient's information be shared with any third parties?

Your or your patient's information will only be shared with other sodium oxybate REMS programs, its agents, contractors, and affiliates.

If you require any additional assistance or information, please call the Sodium Oxybate REMS Program at 855-705-2424

[FAQs](#) | [Contact Us](#) | [Privacy Policy](#) | © 2016

Prescriber Roles & Responsibilities

To become certified, each prescriber must complete a one-time enrollment by completing the Sodium Oxybate REMS Program Prescriber Enrollment Form and submitting it to the Sodium Oxybate REMS program online or office via fax or mail.

Enroll Now

Prescribers enrolled in the Sodium Oxybate REMS Program agree to:

1. Review the Prescribing Information (PI) and the Sodium Oxybate 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 sodium oxybate on the serious risks and safe use and handling of sodium oxybate using the Sodium Oxybate REMS Program Quick Start Guide.
4. Enroll each patient in the Sodium Oxybate REMS Program by completing the Sodium Oxybate REMS Program Patient Enrollment Form and submitting the form to the Sodium Oxybate REMS Program.
5. Evaluate each patient within the first three (3) months of starting sodium oxybate therapy, including an evaluation of the following. It is recommended that patients be re-evaluated every three (3) months thereafter while taking sodium oxybate.
 - 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:
 - i. an increase in dose or frequency of dosing
 - ii. reports of lost, stolen, or spilt 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 the Sodium Oxybate REMS Program.

The prescriber will complete the *Sodium Oxybate REMS Program Prescription Form* for each new prescription and submit the form to one of the certified pharmacies, based on the patient's zip code, as indicated by the online certified pharmacy lookup on www.SodiumOxybateREMSProgram.com. By completing and signing this form, the prescriber acknowledges:

1. Having an understanding of:
 - a. The approved indications for sodium oxybate:
 - i. Treatment of cataplexy in narcolepsy
 - ii. Treatment of excessive daytime sleepiness in narcolepsy
 - b. The serious risks associated with sodium oxybate
 - c. The Prescribing Information and Sodium Oxybate REMS Program Prescriber Brochure
2. Having screened the patient for the following:
 - a. History of alcohol or substance abuse
 - b. History of sleep-related breathing disorder
 - 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
3. Having counseled the patient on:
 - a. The serious risks associated with sodium oxybate
 - b. Contraindications (alcohol and sedative hypnotics) and implications of concomitant use of sodium oxybate with other potentially interacting agents
 - c. Preparation and dosing instructions for sodium oxybate
 - d. Risk of abuse and misuse associated with sodium oxybate
 - e. Risk of operating hazardous machinery including automobiles or airplanes for the first six (6) hours after taking a dose of sodium oxybate
 - f. Safe use, handling, and storage of sodium oxybate
4. That sodium oxybate is medically appropriate for the patient
5. Having listed all known prescription and non-prescription medications and doses on the Sodium Oxybate REMS Program Prescription Form

Materials for Prescriber

- [APPROVED INDICATIONS PROCESSES ON Sodium Oxybate REMS Program Enrollment Form](#)
- [Sodium Oxybate Prescribing Information](#)
- [Sodium Oxybate REMS Program Prescriber Enrollment Form](#)
- [Sodium Oxybate REMS Program Patient Enrollment Form](#)
- [Sodium Oxybate REMS Program Quick Start Guide](#)
- [Sodium Oxybate REMS Program Prescriber Brochure](#)

Pharmacy

Certification in the Sodium Oxybate REMS Program requires pharmacies to agree to:

1. Designate an authorized representative to complete and submit the Sodium Oxybate REMS Pharmacy Enrollment Form on behalf of the pharmacy
2. Ensure that the authorized representative oversees implementation and compliance with the Sodium Oxybate REMS Program by the following:
 - i. Ensure that all pharmacy staff involved in the Sodium Oxybate REMS Program complete the *Sodium Oxybate REMS Program Certified Pharmacy Training Program* Module A
 - ii. Ensure that all pharmacists who dispense sodium oxybate complete the *Sodium Oxybate REMS Program Certified Pharmacy Training Program* Modules A and B
3. Dispense sodium oxybate only to patients enrolled in the Sodium Oxybate REMS Program pursuant to a valid prescription written by a prescriber specially certified in the Sodium Oxybate REMS Program
4. Dispense only after obtaining a Pre Dispense Authorization (PDA) for each sodium oxybate prescription
5. Recertify in the Sodium Oxybate REMS Program if the pharmacy designates a new authorized representative
6. Provide 24/7 toll free access to a pharmacist at a Sodium Oxybate REMS Program specially certified pharmacy
7. Ship sodium oxybate directly to each patient or a patient authorized adult designee, and track and verify receipt of each shipment of sodium oxybate
8. Limit the first shipment for each patient to a one month supply of sodium oxybate, and subsequent shipments to no more than a three month supply of sodium oxybate
9. 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 the Sodium Oxybate REMS Program for documentation

Enroll Now

Materials for Pharmacy

[Medication Guide](#)



[Sodium Oxybate REMS Program Pharmacy Enrollment Form](#)

If you require any additional assistance or information, please call the Sodium Oxybate REMS Program at 855-705-2424

Patient

Patients prescribed sodium oxybate must enroll in the Sodium Oxybate REMS Program. If you were previously registered in the XYREM REMS, your certified prescriber will need to enroll you in the Sodium Oxybate REMS Program.

Materials for Patients

[Medication Guide](#)

 [Sodium Oxybate REMS Program Patient Quick Start Guide](#)

 [Sodium Oxybate REMS Program Patient Enrollment Form](#)

If you require any additional assistance or information, please call the Sodium Oxybate REMS Program at 855-705-2424

Resources

Resources for Prescribers

 [Download All](#)

 [Sodium Oxybate Prescribing Information](#)

 [Sodium Oxybate REMS Program Prescriber Enrollment Form](#)

 [Sodium Oxybate REMS Program Patient Enrollment Form](#)

 [Sodium Oxybate REMS Program Prescriber Brochure](#)

Resources for Patients

 [Download All](#)

[Medication Guide](#)

 [Sodium Oxybate REMS Program Patient Quick Start Guide](#)

Resources for Pharmacies

 [Download All](#)

[Medication Guide](#)

 [Sodium Oxybate REMS Program Patient Quick Start Guide](#)

 [Sodium Oxybate REMS Program Pharmacy Enrollment Form](#)

If you require any additional assistance or information, please call the Sodium Oxybate REMS Program at 855-705-2424

Medication Guide - Sodium Oxybate (soe' dee um ox' i bate) Oral Solution, CIII

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

What is the most important information I should know about sodium oxybate?

Sodium oxybate can cause serious side effects including slow breathing or changes in your alertness. Do not drink alcohol or take medicines intended to make you fall asleep while you are taking sodium oxybate because they can make these side effects worse. Call your doctor right away if you have any of these serious side effects.

- The active ingredient of Sodium Oxybate Oral Solution is a form of gamma-hydroxybutyrate (GHB). GHB is a chemical that has been abused and misused. Abuse and misuse of sodium oxybate can cause serious medical problems, including:
 - seizures
 - trouble breathing
 - changes in alertness
 - coma
 - death
- Do not drive a car, use heavy machinery, fly an airplane, or do anything that is dangerous or that requires you to be fully awake for at least 6 hours after you take sodium oxybate. You should not do those activities until you know how sodium oxybate affects you.
- Sodium oxybate is available only by prescription and filled through the Sodium Oxybate REMS Program. Before you receive sodium oxybate, your doctor or pharmacist will make sure that you understand how to use sodium oxybate safely and effectively. If you have any questions about sodium oxybate, ask your doctor or call the Sodium Oxybate REMS Program at 1-800-XXX-XXXX.

What is sodium oxybate?

Sodium oxybate is a prescription medicine used to treat the following symptoms in people who fall asleep frequently during the day, often at unexpected times (narcolepsy):

- suddenly weak or paralyzed muscles when they feel strong emotions (cataplexy)
- excessive daytime sleepiness (EDS) in people who have narcolepsy

It is not known if sodium oxybate is safe and effective in children.

Sodium Oxybate Oral Solution is a controlled substance (CIII) because it contains sodium oxybate that can be a target for people who abuse prescription medicines or street drugs. Keep your sodium oxybate in a safe place to protect it from theft. Never give your sodium oxybate to anyone else because it may cause death or harm them. Selling or giving away this medicine is against the law.

Who should not take sodium oxybate?

Do not take sodium oxybate if you:

- take other sleep medicines or sedatives (medicines that cause sleepiness)
- drink alcohol
- have a rare problem called succinic semialdehyde dehydrogenase deficiency

Before you take sodium oxybate, tell your doctor if you:

- have short periods of not breathing while you sleep (sleep apnea).
- snore, have trouble breathing, or have lung problems. You may have a higher chance of having serious breathing problems when you take sodium oxybate.
- have or had depression or have tried to harm yourself. You should be watched carefully for new symptoms of depression.
- have liver problems.
- are on a salt-restricted diet. Sodium oxybate contains a lot of sodium (salt) and may not be right for you.
- have high blood pressure.
- have heart failure.
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if sodium oxybate can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if sodium oxybate passes into your breast milk. You and your doctor should decide if you will take sodium oxybate or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially, tell your doctor if you take other medicines to help you sleep (sedatives). Do not take medicines that make you sleepy with sodium oxybate.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take sodium oxybate?

- Read the **Instructions for Use** at the end of this Medication Guide for detailed instructions on how to take sodium oxybate.
- Take sodium oxybate exactly as your doctor tells you to take it.
- Never change your sodium oxybate dose without talking to your doctor.
- Sodium oxybate can cause sleep very quickly. You 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 to fall asleep might be different from night to night.
- Take your first sodium oxybate dose at bedtime while you are in bed. Take your second sodium oxybate dose 2.5 to 4 hours after you take your first sodium oxybate dose. You may want to set an alarm clock to make sure you wake up to take your second sodium oxybate dose. You should remain in bed after taking the first and second doses of sodium oxybate.
- If you miss your second sodium oxybate dose, skip that dose and do not take sodium oxybate again until the next night. Never take 2 sodium oxybate doses at 1 time.
- Wait at least 2 hours after eating before you take sodium oxybate.
- You should see your doctor every 3 months for a check-up while taking sodium oxybate. Your doctor should check to see if sodium oxybate is helping to lessen your symptoms and if you feel any side effects while you take sodium oxybate.
- If you take too much sodium oxybate, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of sodium oxybate?

Sodium oxybate can cause serious side effects, including:

- See **“What is the most important information I should know about sodium oxybate?”**
- **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 sodium oxybate.
- **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 symptoms of mental health problems.

- **Sleepwalking.** Sleepwalking can cause injuries. Call your doctor if you start sleepwalking. Your doctor should check you.

The most common side effects of sodium oxybate include:

- nausea
- dizziness
- vomiting
- bedwetting
- diarrhea

Your side effects may increase when you take higher doses of sodium oxybate. Sodium oxybate can cause physical dependence and craving for the medicine when it is not taken as directed.

These are not all the possible side effects of sodium oxybate. 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 sodium oxybate?

- **Always store sodium oxybate in the original bottle or in the dosing cups with child-resistant caps provided with your prescription.**
- **Keep sodium oxybate in a safe place out of the reach of children and pets.**
- **Get emergency medical help right away if a child drinks your sodium oxybate.**
- Store sodium oxybate between 68°F to 77°F (20°C to 24°C). When you have finished using a sodium oxybate bottle:
 - empty any unused sodium oxybate down the sink drain
 - cross out the label on the sodium oxybate bottle with a marker
 - place the empty sodium oxybate bottle in the trash

General information about the safe and effective use of sodium oxybate

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

This Medication Guide summarizes the most important information about sodium oxybate. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about sodium oxybate that is written for health professionals.

For more information, call the Sodium Oxybate REMS Program at 1-800-XXX-XXXX.

What are the ingredients in Sodium Oxybate Oral Solution?

Active Ingredients: sodium oxybate

Inactive Ingredients: purified water, USP

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

Distr. By:

West-Ward Pharmaceuticals Corp.

Eatontown, NJ 07724

10006869/01

Revised July 2016



Carol
Holquist

Digitally signed by Carol Holquist
Date: 1/17/2017 02:38:30PM
GUID: 508da712000293e0f6d8acfd3c5e67fe

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 202090

LABELING REVIEWS

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	July 19, 2016
ANDA Number(s)	202090
Review Number	6
Applicant Name	Roxane Laboratories, Inc.
Established Name & Strength(s)	Sodium Oxybate Oral Solution, 500 mg/mL
Proposed Proprietary Name	None
Submission Received Date	July 14, 2016 (amendment)
Labeling Reviewer	Lily Chua
Labeling Team Leader	Adolph Vezza
<p>Review Conclusion</p> <p><input type="checkbox"/> ACCEPTABLE – No Comments.</p> <p><input checked="" type="checkbox"/> ACCEPTABLE – Include Post Approval Comments</p> <p><input type="checkbox"/> Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.</p> <p><small>*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.</small></p> <p><input type="checkbox"/> On Policy Alert List</p>	

1. LABELING COMMENTS

1.1 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission dated July 14, 2016.

1.2 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.

These comments will be addressed post approval (in the first labeling supplement review).

1. PRESCRIBING INFORMATION

- a. HIGHLIGHTS, WARNING box, third paragraph: Please revise to read “Because of the risks of CNS depression, abuse, and misuse, sodium oxybate is available only through the Sodium Oxybate REMS Program using certified pharmacies. Prescribers and patients must enroll in the program (5.3).” [Add “using certified pharmacies”].
- b. HIGHLIGHTS, DOSAGE AND ADMINISTRATION: Please revise the spacing of the table so the whole table will be together and not be separated.
- c. CONTENTS, 17 PATIENT COUNSELING INFORMATION: Please revise your proposed pronunciation of the non-proprietary name to conform to the phonetic pronunciation in the current USP Dictionary of USAN and International Drug Names as follows: [(soe' dee um ox' i bate)].
- d. Please provide the complete phone number for the Sodium Oxybate REMS Program throughout the insert labeling.
- e. FULL PRESCRIBING INFORMATION, HOW SUPPLIED, 16.2 Storage: Please use brackets for [See USP Controlled Room Temperature].

2. MEDICATION GUIDE

Please provide the complete phone number for the Sodium Oxybate REMS Program throughout the Medication Guide.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s)

Review #1 finalized date: March 18, 2013

Review #2 finalized date: July 16, 2013

Review #3 finalized date: November 6, 2013 (Acceptable)

Review #4 finalized date: May 31, 2016

Review #5 finalized date: June 29, 2016

From Response to ECD, received July 14, 2016:

GENERAL COMMENTS

Pursuant to 21 CFR 314.127(a)(7), your labeling must be the same as the labeling approved for the RLD, except for changes required because of differences approved in a petition under 21 CFR 314.93 or because your drug product and the reference listed drug (RLD) are produced or distributed by different manufacturers or because aspects of the listed drug's labeling are protected by patent or exclusivity, and such differences do not render the drug product less safe or effective than the RLD for all remaining, nonprotected conditions of use. Your P IV certifications to Patent Nos. 8,772,306 (U-1532) and 9,050,302 (U-1532) indicate that you are seeking approval of a use for the RLD that is claimed by those patents (U-1532). 21 CFR 314.94(a)(12)(i)(A). Your insert labeling submitted on June 16, 2016 (b) (4)

(b) (4), you must revise your labeling to (b) (4) since the ANDA insert labeling needs to be the same as the RLD labeling and additional or modified statements cannot be made. Please note that an applicant for a drug product whose labeling does not include any indications that are covered by the listed use patent may submit a section viii statement explaining that the method of use patent does not claim any of the proposed indications in your labeling.

• Response: (b) (4)

4. PRESCRIBING INFORMATION

- Please confirm the name of the shared Sodium Oxybate REMS Program is (b) (4) Sodium Oxybate RiskMAP Program" and revise if necessary throughout the labeling.
- WARNING box, third paragraph: Please revise to read "Because of the risks of CNS depression, abuse, and misuse, sodium oxybate is available only through the (b) (4) Sodium Oxybate RiskMAP Program using certified pharmacies. Prescribers and patients must enroll in the program (5.3)." [Add "using certified pharmacies"].
- FULL PRESCRIBING INFORMATION, WARNINGS AND PRECAUTIONS, 5.3 (b) (4) Sodium Oxybate RiskMAP Program: Please include as the first bullet "Use of certified pharmacies."
- FULL PRESCRIBING INFORMATION, DRUG ABUSE AND DEPENDENCE, 9.2 Abuse, third paragraph: Please revise (b) (4) to read "commonalities".

• Response:

- We have revised the name of the shared program to "Sodium Oxybate REMS Program" throughout the proposed insert.
- We added the text "using certified pharmacies" as requested.
- We added the first bullet "Use of certified pharmacies" as requested.
- We corrected the spelling of "commonalities" as requested.

5. MEDICATION GUIDE

Please refer to comment 2a above.

• Response: We have revised the name of the shared program to "Sodium Oxybate REMS Program" throughout the proposed insert.

Reviewer Comments: Responses are acceptable except 2b. We will ask firm to include "certified pharmacies in the WARNING box post-approval.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Not submitted in this amendment.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments: From Cover letter received June 6, 2016: At the request of the Agency, Roxane hereby submits an amendment to the Proposed REMS submitted on April 08, 2016. This submission consists of REMS Supporting document (RSD) with revisions based on communications between the Agency and ANDA sponsors. REMS review pending.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? NO

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? NO

If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

**Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)**

MOST RECENTLY APPROVED NDA MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)

NDA# /Supplement# (S-000 if original): NDA 021196/S-023

Supplement Approval Date: July 15, 2015

Proprietary Name: XYREM®

Established Name: Sodium Oxybate Oral Solution

Description of Supplement: Prescribing Information and Medication Guide to be consistent with the approved REMS program, as requested by the Division. Because the Medication Guide is an element of the REMS, the supplement also constitutes a proposed REMS modification.

MOST RECENTLY APPROVED ANDA MODEL LABELING

ANDA#/Supplement# (S-000 if original): [Click here to enter text.](#)

Supplement Approval Date: [Click here to enter text.](#)

Proprietary Name: [Click here to enter text.](#)

Established Name: [Click here to enter text.](#)

Description of Supplement:

TEMPLATE (e.g., BPCA, PREA, Carve-out): [Click here to enter text.](#)

OTHER (Describe): NDA 021196/ (b) (4) S-025 is approved CMC supplement with no labeling associated with it. S-026 is pending CMC supplement with labeling to meet the implementation requirements in DSCSA.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**
 Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**
 Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments: Acceptable with post-approval comments.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: ANRPT-13 dated 08/31/2015]



3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

	Date Searched	Monograph ? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	7/20/2016	NO	NA	NA
PF	7/20/2016	NO	NA	NA

Reviewer Comments: NA

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/20/2016.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
6780889	Jul 4, 2020			P IV	12/10/2015	None
7262219	Jul 4, 2020			P IV	12/10/2015	None

7668730	Jun 16, 2024	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
7765106	Jun 16, 2024	U - 1069	A METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING AN EXCLUSIVE COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
7765107	Jun 16, 2024	U - 1070	A METHOD TO CONTROL ABUSE OF A SENSITIVE DRUG BY CONTROLLING WITH A COMPUTER PROCESSOR THE DISTRIBUTION OF THE SENSITIVE DRUG VIA AN EXCLUSIVITY CENTRAL PHARMACY THAT MAINTAINS A CENTRAL DATABASE	P IV	12/10/2015	None
7851506	Dec 22, 2019	U - 1101	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
7851506	Dec 22, 2019	U - 1102	METHOD OF TREATING CATAPLEXY IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
7895059	Dec 17, 2022	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
8263650	Dec 22, 2019	U - 1101	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8263650	Dec 22, 2019	U -1102	METHOD OF TREATING CATAPLEXY IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8324275	Dec 22, 2019	U - 1101	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8324275	Dec 22, 2019	U - 1102	METHOD OF TREATING CATAPLEXY IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8457988	Dec 17, 2022	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
8589182	Dec 17, 2022	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
8731963	Dec 17, 2022	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
8772306	Mar 15, 2033	U -1532	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS AND/OR CATAPLEXY IN NARCOLEPSY PATIENTS WITH SODIUM OXYBATE WHEN DIVALPROEX SODIUM IS CONCOMITANTLY ADMINISTERED.	P IV	12/10/2015	None
8859619	Dec 22, 2019			P IV	12/10/2015	None
8952062	Dec 22, 2019	U -1101	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8952062	Dec 22, 2019	U -1102	METHOD OF TREATING CATAPLEXY IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
9050302	Mar 15, 2033	U-1532	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS AND/OR CATAPLEXY IN NARCOLEPSY PATIENTS WITH SODIUM OXYBATE WHEN DIVALPROEX SODIUM IS CONCOMITANTLY ADMINISTERED.	P IV	12/10/2015	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments: From Cover Letter received June 10, 2016: With respect to the original complaint from 11/22/2010, this complaint remains unresolved and in litigation. There has been no decision in the litigation at this time.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: There is no unexpired exclusivity for this product.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment
Each mL of Sodium Oxybate Oral Solution contains 0.5 g of sodium oxybate in purified water, USP.	Each mL of Sodium Oxybate Oral Solution contains 0.5 g of sodium oxybate in purified water, USP.	No Change

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

<p>Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution. It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert. Two 75 mL dosing cups with child-resistant caps are included with each Sodium Oxybate Oral Solution shipment. Each white oblong HDPE bottle contains 180 mL of Sodium Oxybate Oral Solution at a concentration of 500 mg/mL and is sealed with a child resistant cap. NDC 0054-0314-57: Each tamper evident single unit carton contains one 180 mL bottle (500 mg/mL) of Sodium Oxybate Oral Solution, one press-in-bottle adaptor and one oral dispensing syringe</p> <p>16.2 Storage Keep out of reach of children. Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature. Solutions prepared following dilution should be consumed within 24 hours.</p>	<p>Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution. It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert. Two 75 mL dosing cups with child-resistant caps are included with each Sodium Oxybate Oral Solution shipment. Each white oblong HDPE bottle contains 180 mL of Sodium Oxybate Oral Solution at a concentration of 500 mg/mL and is sealed with a child resistant cap. NDC 0054-0314-57: Each tamper evident single unit carton contains one 180 mL bottle (500 mg/mL) of Sodium Oxybate Oral Solution, one press-in-bottle adaptor and one oral dispensing syringe</p> <p>16.2 Storage Keep out of reach of children. Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature. Solutions prepared following dilution should be consumed within 24 hours.</p>	<p style="text-align: center;">No Change</p>
--	--	--

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
<p>Distr. By: West-Ward Pharmaceuticals Corp. Eatontown, NJ 07724</p>	<p>Distr. By: West-Ward Pharmaceuticals Corp. Eatontown, NJ 07724</p>	<p style="text-align: center;">No Change</p>

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: CMC adequate.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments: NA

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	(bottle of 180 mL)	06/16/2016	Satisfactory
Carton	Final	(1 bottle)	06/16/2016	Satisfactory

Table 9 Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	July 2016	07/14/2016	Satisfactory*
Medication Guide	Draft	Attached to Prescribing Information	07/14/2016	Satisfactory*
SPL Data Elements		5/2016	05/12/2016	Satisfactory**

* Post-approval revision

**Response from firm received June 16, 2016: We have revised our SPL data elements table to reflect the package description as requested. Note: We have not included the SPL with this submission.



Adolph
Veza

Digitally signed by Adolph Veza
Date: 7/25/2016 11:21:34PM
GUID: 508da70600028a9e6a494d73e6454d09
Comments: labeling is satisfactory for approval



Lily
Chua

Digitally signed by Lily Chua
Date: 7/22/2016 09:29:58AM
GUID: 5277fc6700089cebb6783d59b3e106fa

LABELING REVIEW

Division of Labeling Review
 Office of Regulatory Operations
 Office of Generic Drugs (OGD)
 Center for Drug Evaluation and Research (CDER)

Date of This Review	June 21, 2016
ANDA Number(s)	202090
Review Number	5
Applicant Name	Roxane Laboratories, Inc.
Established Name & Strength(s)	Sodium Oxybate Oral Solution, 500 mg/mL
Proposed Proprietary Name	None
Submission Received Date	June 16, 2016 (amendment)
Labeling Reviewer	Lily Chua
Labeling Team Leader	Adolph Vezza
<p>Review Conclusion</p> <p><input type="checkbox"/> ACCEPTABLE – No Comments.</p> <p><input type="checkbox"/> ACCEPTABLE – Include Post Approval Comments</p> <p><input checked="" type="checkbox"/> Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.</p> <p>*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.</p> <p><input type="checkbox"/> On Policy Alert List</p>	

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on June 21, 2016 based on your submission dated June 16, 2016:

1. GENERAL COMMENTS

Pursuant to 21 CFR 314.127(a)(7), your labeling must be the same as the labeling approved for the RLD, except for changes required because of differences approved in a petition under 21 CFR 314.93 or because your drug product and the reference listed drug (RLD) are produced or distributed by different manufacturers or because aspects of the listed drug's labeling are protected by patent or exclusivity, and such differences do not render the drug product less safe or effective than the RLD for all remaining, non-protected conditions of use. Your P IV certifications to Patent Nos. 8,772,306 (U-1532) and 9,050,302 (U-1532) indicate that you are seeking approval of a use for the RLD that is claimed by those patents (U-1532). 21 CFR 314.94(a)(12)(i)(A). Your insert labeling submitted on June 16, 2016 (b) (4)

you must revise your labeling to (b) (4) since the ANDA insert labeling needs to be the same as the RLD labeling and additional or modified statements cannot be made. Please note that an applicant for a drug product whose labeling does not include any indications that are covered by the listed use patent may submit a section viii statement explaining that the method of use patent does not claim any of the proposed indications in your labeling.

2. PRESCRIBING INFORMATION

- a. Please confirm the name of the shared Sodium Oxybate REMS Program is “(b) (4) Sodium Oxybate RiskMAP Program” and revise if necessary throughout the labeling.
- b. WARNING box, third paragraph: Please revise to read “Because of the risks of CNS depression, abuse, and misuse, sodium oxybate is available only through the (b) (4) Sodium Oxybate RiskMAP Program using certified pharmacies. Prescribers and patients must enroll in the program (5.3).” [Add “using certified pharmacies”].
- c. FULL PRESCRIBING INFORMATION, WARNINGS AND PRECAUTIONS, 5.3 (b) (4) Sodium Oxybate RiskMAP Program: Please include as the first bullet “Use of certified pharmacies.”
- d. FULL PRESCRIBING INFORMATION, DRUG ABUSE AND DEPENDENCE, 9.2 Abuse, third paragraph: Please revise (b) (4) to read “commonalities”.

3. MEDICATION GUIDE

Please refer to comment 2a above.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.

These comments will be addressed post approval (in the first labeling supplement review).

Click here to enter text.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s)

Review #1 finalized date: March 18, 2013

Review #2 finalized date: July 16, 2013

Review #3 finalized date: November 6, 2013 (Acceptable)

Review #4 finalized date: May 31, 2016

From Response to ECD, received June 16, 2016:

GENERAL COMMENTS

Your insert labeling submitted on May 12, 2016 contains

(b) (4)

(b) (4)

Please revise your labeling

(b) (4)

• **Response: We feel that the**

(b) (4)

(b) (4)

2. CONTAINER LABEL

We recommend revising the presentation of the established name from all upper case letters to title case (i.e., Sodium Oxybate Oral Solution) to improve its readability.

• **Response: We have revised the established name to appear in title case.**

3. CARTON LABEL

a. We recommend revising the presentation of the established name from all upper case letters to title case (i.e., Sodium Oxybate Oral Solution) to improve its readability.

b. Please include these statements (b) (4) Pharmacists: (b) (4)

(b) (4) and "Sodium oxybate oral solution must be dispensed to the patient in the original packaging."

• **Response:**

a. **We have revised the established name to appear in title case.**

b. **We have added the following statement: "PHARMACIST: Dispense with enclosed Medication Guide. Sodium oxybate oral solution must be dispensed to the patient in the original packaging."**

4. PRESCRIBING INFORMATION

a. HIGHLIGHTS OF PRESCRIBING INFORMATION: Please revise (b) (4) to read "SODIUM OXYBATE ORAL SOLUTION" in the first two sentences.

[Revise the presentation of the established name to appear in all upper case bolded letters].

b. HIGHLIGHTS, Title: Please revise the title to read "SODIUM OXYBATE oral solution, CIII" [lowercase bolded letters for "oral solution"].

c. Please delete (b) (4)

d. FULL PRESCRIBING INFORMATION, CLINICAL STUDIES, 14.2 Excessive Daytime Sleepiness in Narcolepsy, first paragraph: Please revise (b) (4) to read "(see Tables 5 to 7)".

• **Response:**

a. **We have revised the presentation of the established name to read as requested.**

b. **We have revised the title read as requested.**

c. **We have kept the (b) (4) as described in response #1.**

d. **We have revised the table numbering as requested.**

5. MEDICATION GUIDE

Please revise your proposed pronunciation of the non-proprietary name to conform to the phonetic pronunciation in the current USP Dictionary of USAN and International Drug Names as follows: [(soe' dee um ox' i bate)].

• **Response: We have revised our phonetic pronunciation to comply with the current USP Dictionary of USAN and International Drug Names.**

6. STRUCTURED PRODUCT LABELING

Packaging, Package Description: Please revise to read "(b) (4)".

• **Response: We have revised our SPL data elements table to reflect the package description as requested. Note: We have not included the SPL with this submission.**

Reviewer Comments: Acceptable except the response “

(b) (4)

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Acceptable.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments: From Cover letter received June 6, 2016: At the request of the Agency, Roxane hereby submits an amendment to the Proposed REMS submitted on April 08, 2016. This submission consists of REMS Supporting document (RSD) with revisions based on communications between the Agency and ANDA sponsors. REMS review pending.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? **NO**

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? **NO**

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)

MOST RECENTLY APPROVED NDA MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)

NDA# /Supplement# (S-000 if original): NDA 021196/S-023

Supplement Approval Date: July 15, 2015

Proprietary Name: XYREM®

Established Name: Sodium Oxybate Oral Solution

Description of Supplement: Prescribing Information and Medication Guide to be consistent with the approved REMS program, as requested by the Division. Because the Medication Guide is an element of the REMS, the supplement also constitutes a proposed REMS modification.

**Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)**

MOST RECENTLY APPROVED ANDA MODEL LABELING

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

TEMPLATE (e.g., BPCA, PREA, Carve-out): Click here to enter text.

OTHER (Describe): (b) (4), S-025 is pending CMC supplement with no labeling associated with it. S-026 is pending labeling supplement provides changes to the container closure system, final packaging process, and labeling components. The changes proposed in this supplement are (b) (4) to ensure compliance with the Drug Supply Chain Security Act (DSCSA) by November 2017.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

(b) (4)
We will ask firm to confirm the name of the shared Sodium Oxybate REMS Program is “(b) (4) Sodium Oxybate RiskMAP Program” and revise if necessary throughout the labeling. We will also ask firm to include “certified pharmacies in the WARNING box and in section 5.3 and revise (b) (4) to read “commonalities” in 9.2 Abuse section.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: ANRPT-13 dated 08/31/2015]



3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph ? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	6/21/2016	NO	NA	NA
PF	6/21/2016	NO	NA	NA

Reviewer Comments: NA

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 6/21/2016.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Certification Submission	Labeling Impact
6780889	Jul 4, 2020			P IV	12/10/2015	None
7262219	Jul 4, 2020			P IV	12/10/2015	None
7668730	Jun 16, 2024	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
7765106	Jun 16, 2024	U - 1069	A METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING AN EXCLUSIVE COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
7765107	Jun 16, 2024	U - 1070	A METHOD TO CONTROL ABUSE OF A SENSITIVE DRUG BY CONTROLLING WITH A COMPUTER PROCESSOR THE DISTRIBUTION OF THE SENSITIVE DRUG VIA AN EXCLUSIVITY CENTRAL PHARMACY THAT MAINTAINS A CENTRAL DATABASE	P IV	12/10/2015	None
7851506	Dec 22, 2019	U - 1101	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
7851506	Dec 22, 2019	U - 1102	METHOD OF TREATING CATAPLEXY IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
7895059	Dec 17, 2022	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
8263650	Dec 22, 2019	U - 1101	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8263650	Dec 22, 2019	U - 1102	METHOD OF TREATING CATAPLEXY IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8324275	Dec 22, 2019	U - 1101	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8324275	Dec 22, 2019	U - 1102	METHOD OF TREATING CATAPLEXY IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None

8457988	Dec 17, 2022	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
8589182	Dec 17, 2022	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
8731963	Dec 17, 2022	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
8772306	Mar 15, 2033	U -1532	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS AND/OR CATAPLEXY IN NARCOLEPSY PATIENTS WITH SODIUM OXYBATE WHEN DIVALPROEX SODIUM IS CONCOMITANTLY ADMINISTERED.	P IV	12/10/2015	None
8859619	Dec 22, 2019			P IV	12/10/2015	None
8952062	Dec 22, 2019	U -1101	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8952062	Dec 22, 2019	U -1102	METHOD OF TREATING CATAPLEXY IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
9050302	Mar 15, 2033	U-1532	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS AND/OR CATAPLEXY IN NARCOLEPSY PATIENTS WITH SODIUM OXYBATE WHEN DIVALPROEX SODIUM IS CONCOMITANTLY ADMINISTERED.	P IV	12/10/2015	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments: From Cover Letter received June 10, 2016: With respect to the original complaint from 11/22/2010, this complaint remains unresolved and in litigation. There has been no decision in the litigation at this time.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: There is no unexpired exclusivity for this product.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**

Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**

Are there changes to the manufacturer/distributor/packer statements? **NO**

If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
Each mL of Sodium Oxybate Oral Solution contains 0.5 g of sodium oxybate in purified water, USP.	Each mL of Sodium Oxybate Oral Solution contains 0.5 g of sodium oxybate in purified water, USP.	No Change

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment
Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution. It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert. Two 75 mL dosing cups with child-resistant caps are included with each Sodium Oxybate Oral Solution shipment. Each white oblong HDPE bottle contains 180 mL of Sodium Oxybate Oral Solution at a concentration of 500 mg/mL and is sealed with a child resistant cap. NDC 0054-0314-57: Each tamper evident single unit carton contains one 180 mL bottle (500 mg/mL) of Sodium Oxybate Oral Solution, one press-in-bottle adaptor and one oral dispensing syringe 16.2 Storage Keep out of reach of children. Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.	Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution. It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert. Two 75 mL dosing cups with child-resistant caps are included with each Sodium Oxybate Oral Solution shipment. Each white oblong HDPE bottle contains 180 mL of Sodium Oxybate Oral Solution at a concentration of 500 mg/mL and is sealed with a child resistant cap. NDC 0054-0314-57: Each tamper evident single unit carton contains one 180 mL bottle (500 mg/mL) of Sodium Oxybate Oral Solution, one press-in-bottle adaptor and one oral dispensing syringe 16.2 Storage Keep out of reach of children. Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.	No Change

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
Distr. By: West-Ward Pharmaceuticals Corp. Eatontown, NJ 07724	Distr. By: West-Ward Pharmaceuticals Corp. Eatontown, NJ 07724	No Change

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: From CMC review dated 08/21/2013:

Based upon the results of using Sodium Oxybate Oral Solution, 500mg/mL and water as the delivery mediums for oral dispenser (b)(4) it was determined that the syringe delivered as required in the specification. It was also determined that the percentage of theoretical delivery between the two mediums was comparable and therefore, water may be used as an alternate delivery medium for delivery testing. The syringe proposed is acceptable.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments: NA

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	(bottle of 180 mL)	06/16/2016	Satisfactory
Carton	Final	(1 bottle)	06/16/2016	Satisfactory

Table 9 Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	June 2016	06/16/2016	Revise
Medication Guide	Draft	Attached to Prescribing Information	06/16/2016	Revise
SPL Data Elements		5/2016	05/12/2016	Satisfactory**

**Response from firm received June 16, 2016: We have revised our SPL data elements table to reflect the package description as requested. Note: We have not included the SPL with this submission.



Adolph
Veza

Digitally signed by Adolph Veza
Date: 1/22/2017 01:23:46PM
GUID: 508da70600028a9e6a494d73e6454d09



Lily
Chua

Digitally signed by Lily Chua
Date: 6/29/2016 08:09:50AM
GUID: 5277fc6700089cebb6783d59b3e106fa
Comments: Issue resolved.

LABELING REVIEW

Division of Labeling Review
 Office of Regulatory Operations
 Office of Generic Drugs (OGD)

Center for Drug Evaluation and Research (CDER)

Date of This Review	May 17, 2016
ANDA Number(s)	202090
Review Number	4
Applicant Name	Roxane Laboratories, Inc.
Established Name & Strength(s)	Sodium Oxybate Oral Solution, 500 mg/mL
Proposed Proprietary Name	None
Submission Received Date	May 12, 2016 (amendment)
Labeling Reviewer	Lily Chua
Labeling Team Leader	Adolph Vezza
<p>Review Conclusion</p> <p><input type="checkbox"/> ACCEPTABLE – No Comments.</p> <p><input type="checkbox"/> ACCEPTABLE – Include Post Approval Comments</p> <p><input checked="" type="checkbox"/> Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.</p> <p>*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.</p> <p><input type="checkbox"/> On Policy Alert List</p>	

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on May 17, 2016 based on your submission dated May 12, 2016:

1. GENERAL COMMENTS

Your insert labeling submitted on May 12, 2016 (b) (4)

(b) (4)
Please revise your labeling (b) (4)

2. CONTAINER LABEL

We recommend revising the presentation of the established name from all upper case letters to title case (i.e., Sodium Oxybate Oral Solution) to improve its readability.

3. CARTON LABELING

- a. We recommend revising the presentation of the established name from all upper case letters to title case (i.e., Sodium Oxybate Oral Solution) to improve its readability.
- b. Please include these statements (b) (4) **Pharmacists:** (b) (4)
(b) (4) and “Sodium oxybate oral solution must be dispensed to the patient in the original packaging.”

4. PRESCRIBING INFORMATION

- a. HIGHLIGHTS OF PRESCRIBING INFORMATION: Please revise “(b) (4)” to read “**SODIUM OXYBATE ORAL SOLUTION**” in the first two sentences. [Revise the presentation of the established name to appear in all upper case bolded letters].
- b. HIGHLIGHTS, Title: Please revise the title to read “**SODIUM OXYBATE oral solution, CIII**” [lowercase bolded letters for “oral solution”].
- c. Please delete all (b) (4).
- d. FULL PRESCRIBING INFORMATION, CLINICAL STUDIES, 14.2 Excessive Daytime Sleepiness in Narcolepsy, first paragraph: Please revise (b) (4) to read “(see Tables 5 to 7)”.

5. MEDICATION GUIDE

Please revise your proposed pronunciation of the non-proprietary name to conform to the phonetic pronunciation in the current USP Dictionary of USAN and International Drug Names as follows: [(soe' dee um ox' i bate)].

6. STRUCTURED PRODUCT LABELING (SPL) Data Elements

Packaging, Package Description: Please revise to read (b) (4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.

These comments will be addressed post approval (in the first labeling supplement review).

NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s)

Review #1 finalized date: March 18, 2013

Review #2 finalized date: July 16, 2013

Review #3 finalized date: November 6, 2013 (Acceptable)

From Cover Letter received May 12, 2016:

We have updated our labeling in accordance with the most recently approved labeling for the RLD, approved on July 15, 2015.

In addition, West-Ward Pharmaceuticals Corp., will be the labeler and distributor for the above referenced application. The carton and container labeling will be updated to include the new company name and submitted as defined in the guidance "ANDA Submissions –Amendments and Easily Correctable Deficiencies Under GDUF A" or post-approval per the requirements of 21 CFR 314.70, as applicable.

Reviewer Comments: Responses are acceptable.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Not submitted in this amendment.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments: REQUEST FOR CONSULTATION to OSE: Waived Shared System REMS has been submitted by the ANDA applicants, ANDAs: 202090, 203631, (b) (4) and 203351 on 04/25/2016.

From Cover letter received April 8, 2016: "In response to the Agency's Pre-Approval REMS Notification Letter dated January 13, 2014, and in light of subsequent communications between the Agency and the ANDA sponsors, Roxane hereby provides the Agency with draft shared REMS documentation developed jointly by the current Sodium Oxybate ANDA sponsors" and REMS Review is pending as of May 31, 2016.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? **NO**

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? **NO**

If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

**Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)**

MOST RECENTLY APPROVED NDA MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)

NDA# /Supplement# (S-000 if original): NDA 021196/S-023

Supplement Approval Date: July 15, 2015

Proprietary Name: XYREM®

Established Name: Sodium Oxybate Oral Solution

Description of Supplement: Prescribing Information and Medication Guide to be consistent with the approved REMS program, as requested by the Division. Because the Medication Guide is an element of the REMS, the supplement also constitutes a proposed REMS modification.

MOST RECENTLY APPROVED ANDA MODEL LABELING

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

TEMPLATE (e.g., BPCA, PREA, Carve-out): Click here to enter text.

OTHER (Describe): NDA 021196/ (b) (4), S-025 is pending CMC supplement with no labeling associated with it.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**

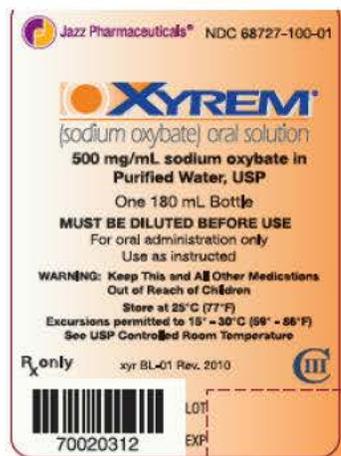
Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments: We will ask firm to (b) (4) to read “(see Tables 5 to 7)” in 14.2 Excessive Daytime Sleepiness in Narcolepsy section.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: ANRPT-13 dated 08/31/2015]



The original container must be provided to the patient. Xyrem must be dispensed in the original container. Contents: One 180 mL bottle with in bottle adapter and 4 Exact-Med Dispense (oral syringe). Dosage and Administration: See prescribing information for administration instructions. 68727-100-01

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	5/17/2016	NO	NA	NA
PF	5/17/2016	NO	NA	NA

Reviewer Comments: NA

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 5/17/2016.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
6780889	Jul 4, 2020			P IV	12/10/2015	None
7262219	Jul 4, 2020			P IV	12/10/2015	None
7668730	Jun 16, 2024	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
7765106	Jun 16, 2024	U - 1069	A METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING AN EXCLUSIVE COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
7765107	Jun 16, 2024	U - 1070	A METHOD TO CONTROL ABUSE OF A SENSITIVE DRUG BY CONTROLLING WITH A COMPUTER PROCESSOR THE DISTRIBUTION OF THE SENSITIVE DRUG VIA AN EXCLUSIVITY CENTRAL PHARMACY THAT MAINTAINS A CENTRAL DATABASE	P IV	12/10/2015	None
7851506	Dec 22, 2019	U - 1101	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
7851506	Dec 22, 2019	U - 1102	METHOD OF TREATING CATAPLEXY IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
7895059	Dec 17, 2022	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
8263650	Dec 22, 2019	U - 1101	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8263650	Dec 22, 2019	U - 1102	METHOD OF TREATING CATAPLEXY IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8324275	Dec 22, 2019	U - 1101	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8324275	Dec 22, 2019	U - 1102	METHOD OF TREATING CATAPLEXY IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8457988	Dec 17, 2022	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
8589182	Dec 17, 2022	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
8731963	Dec 17, 2022	U - 1110	METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION	P IV	12/10/2015	None
8772306	Mar 15, 2033	U - 1532	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS AND/OR CATAPLEXY IN NARCOLEPSY PATIENTS WITH SODIUM OXYBATE WHEN DIVALPROEX SODIUM IS CONCOMITANTLY ADMINISTERED.	P IV	12/10/2015	None

8859619	Dec 22, 2019			P IV	12/10/2015	None
8952062	Dec 22, 2019	U -1101	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
8952062	Dec 22, 2019	U -1102	METHOD OF TREATING CATAPLEXY IN PATIENTS WITH NARCOLEPSY	P IV	12/10/2015	None
9050302	Mar 15, 2033	U-1532	METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS AND/OR CATAPLEXY IN NARCOLEPSY PATIENTS WITH SODIUM OXYBATE WHEN DIVALPROEX SODIUM IS CONCOMITANTLY ADMINISTERED.	P IV	12/10/2015	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments: Roxane Laboratories, Inc. also certifies that it will comply with the notice requirements under 314.95(a) with respect to providing notice to each owner of the U.S. Patents listed above or their representatives and to the holder of the approved application for the listed drug product, and with the requirements under 314.95(c) with respect to the content of the notice.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: There is no unexpired exclusivity for this product.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
 Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
 Are there changes to the manufacturer/distributor/packer statements? **YES**
 If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment
Each mL of Sodium Oxybate Oral Solution contains 0.5 g of sodium oxybate in purified water, USP.	Each mL of Sodium Oxybate Oral Solution contains 0.5 g of sodium oxybate in purified water, USP.	No Change

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment
<p>Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution. It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert. Two 75 mL dosing cups with child-resistant caps are included with each Sodium Oxybate Oral Solution shipment. Each white oblong HDPE bottle contains 180 mL of Sodium Oxybate Oral Solution at a concentration of 500 mg/mL and is sealed with a child resistant cap.</p> <p>NDC 0054-0314-57: Each tamper evident single unit carton contains one 180 mL bottle (500 mg/mL) of Sodium Oxybate Oral Solution, one press-in-bottle-adaptor and one oral dispensing syringe</p> <p>16.2 Storage</p> <p>Keep out of reach of children.</p> <p>Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.</p>	<p>Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution. It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert. Two 75 mL dosing cups with child-resistant caps are included with each Sodium Oxybate Oral Solution shipment. Each white oblong HDPE bottle contains 180 mL of Sodium Oxybate Oral Solution at a concentration of 500 mg/mL and is sealed with a child resistant cap.</p> <p>NDC 0054-0314-57: Each tamper evident single unit carton contains one 180 mL bottle (500 mg/mL) of Sodium Oxybate Oral Solution, one press-in-bottle adaptor and one oral dispensing syringe</p> <p>16.2 Storage</p> <p>Keep out of reach of children.</p> <p>Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.</p>	No Change

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	Currently Proposed	Assessment
<p>(b) (4)</p>	<p>Distr. By: West-Ward Pharmaceuticals Corp. Eatontown, NJ 07724</p>	<p>From Cover Letter received 05/12/2016: West-Ward Pharmaceuticals Corp., will be the labeler and distributor for the above referenced application. The carton and container labeling will be updated to include the new company name and submitted as defined in the guidance "ANDA Submissions –Amendments and Easily Correctable Deficiencies Under GDUF A" or post-approval per the requirements of 21 CFR 314.70, as applicable.</p>

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: From CMC review dated 08/21/2013:

Based upon the results of using Sodium Oxybate Oral Solution, 500mg/mL and water as the delivery mediums for oral dispenser ((b) (4)), it was determined that the syringe delivered as required in the specification. It was also determined that the percentage of theoretical delivery between the two mediums was comparable and therefore, water may be used as an alternate delivery medium for delivery testing. The syringe proposed is acceptable.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments: NA

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	(bottle of 180 mL)	04/16/2013	Revise
Carton	Final	(1 bottle)	04/16/2013	Revise
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	May 2016	05/12/2016	Revise
Medication Guide	Draft	Attached to Prescribing Information	05/12/2016	Revise
SPL Data Elements		5/2016	05/12/2016	Revise

APPROVAL SUMMARY

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (Third Cycle)

ANDA Number: **202090**
Date of Submission: **September 30, 2013**
Applicant: **Roxane Laboratories, Inc.**
Established Name and Strength: **Sodium Oxybate Oral Solution, 500 mg/mL**
Proposed Proprietary Name: **None**

Labeling Comments below are considered:

No Comments (Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated September 30, 2013.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

For TA SUMMARY:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated September 30, 2013.

Prior to the submission of your final printed labeling, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL? YES

INSERT

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

TITLE – Place the following text immediately above “Initial U.S. ...”

SODIUM OXYBATE Oral Solution, for oral use, CIII

2. FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING STATEMENT

“... **SYSTEM (CNS) DEPRESSION and MISUSE AND ABUSE**”

[note lower case “**and**”]

3. FULL PRESCRIBING INFORMATION

Medication Guide - Sodium Oxybate Oral Solution, CIII

How should I take ..., first bullet – “... **Instructions for Use** attached to this Medication Guide for ...”

[Please note that the patient or caregiver will not be receiving the package insert, only the Medication Guide and the Instructions for Use – These two documents will be detached upon dispensing the drug product]

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER: none

Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER 180 mL	4-16-13	FINAL	APPROVE
CARTON 1 x 180 mL	4-16-13	FINAL	APPROVE
INSERT	9-30-13	FINAL	APPROVE
MEDICATION GUIDE	9-30-13	FINAL	APPROVE
REMS PLAN	10-19-11	DRAFT	CONSULT
RISKMAP	4-16-13	DRAFT	CONSULT
SPL	NONE	N/A	SUBMIT

REMS required? YES

MedGuides and/or PPIs (505-1(e))

Yes No

Communication plan (505-1(e))

Yes No

Elements to assure safe use (ETASU) (505-1(f)(3))	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
Implementation system if certain ETASU (505-1(f)(4))	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
Timetable for assessment (505-1(d))	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
ANDA REMS acceptable?	<input type="checkbox"/> Yes	<input type="checkbox"/> No <input type="checkbox"/> N/A

FOR THE RECORD:

- MODEL LABELING** - XYREM® (NDA 21-196/S-013) [Jazz Pharmaceuticals], approved 12/17/12.
- USP & PF** - Drug Product does not have a USP monograph.
- PATENT AND EXCLUSIVITY**

Patents 21-196

No	Expiration	Use Code	Use	File	Labeling Impact
7895059	12-17-22	U-1110		PIV	NONE
7851506	12-22-19	U-1101 & U-1102		PIV	NONE
6780889	7-4-20			PIV	NONE
7262219	7-4-20			PIV	NONE
7668730	3-7-24	U-1110		PIV	NONE
7765106	6-16-24	U-1069		PIV	NONE
7765107	6-16-24	U-1070		PIV	NONE
8263650	12-22-19	U-1101 & U-1102		PIV	NONE
8324275	12-22-19	U-1101 & U-1102		PIV	NONE
8457988	12-17-22	U-1110		PIV	NONE

U-1101 Method of treating excessive daytime sleepiness in patients with narcolepsy

U-1102 Method of treating cataplexy in patients with narcolepsy

U-1110 Method of treating a patient with a prescription drug using a computer database in a computer system for distribution

U-1069 A method of treating a patient with a prescription drug using an exclusive computer database in a computer system for distribution

U-1070 A method to control abuse of a sensitive drug by controlling with a computer processor the distribution of the sensitive drug via an exclusive central pharmacy that maintains a central database

Exclusivity Data 21-196

Code/Sup	Expiration	Use Code	Description	Labeling Impact
ODE	11-18-12		Treatment of excessive daytime sleepiness in patients with narcolepsy	None – EXPIRED

5. MANUFACTURING FACILITY - Boehringer Ingelheim Roxane, Inc – USA

6. FINISHED PRODUCT DESCRIPTION

ANDA – It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), two 75 mL dosing cups,,a Medication Guide, Instructions for Use and a professional insert.

The following table summarizes the elements from the RLD packaging and from RLI packaging.

Brand Packaging	RLI Packaging
Leaflet	Leaflet
Amber Plastic Bottle	White HDPE Plastic Bottle with Window Stripe
Plastic White Closure CR	Plastic White Closure CR with neckband
Syringe in grams	1 – 10mL Syringe in mL - Need grams for commercial
(b) (4)	PIBA/Dip Tube
Dose cups supplied by pharmacist	2 – 75mL Dose cups White HDPE w/ CR Closure
Printed Folding Carton	Printed Folding Carton

RLI packaging will match every element present in the brand packaging. The Container Closure System will be neck banded for tamper evidence. The final version of the syringe will be graduated in grams similarly to the one enclosed in the RLD packaging and will be protected by a polybag. The product container, syringe, 2 dose containers, and leaflet are shipped in a preprinted folding carton. Please note that the final version of the syringe will have similar dimensions compared to the syringe presently included in the sample of the finished drug product and only the graduation marking will vary. Therefore, the included syringe is adequate to check for compatibility with the PIBA, the dose cup, and for fitting in the carton.

Patient acceptability will not be impacted by the different bottle, closure system, PIBA, syringe, and dose cups used in RLI packaging since global handling is comparable to that of the brand. Furthermore, RLI bottle will present the advantage of a graduated window strip permitting a quantification of the product remaining in the bottle to monitor usage.

Per your September 1, 2011 telephone call RLI will provide samples of the placebo in our proposed commercial packaging (bottle, Syringe Oral/PBA (b) (4) Dip Tube) within one week under separate cover.

7. STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS

RLD: Store Xyrem between (b) (4) 77°F ((b) (4) 24°C).

ANDA: Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.

8. PRODUCT LINE – See comparison of RLD and ANDA in FTR # 6

RLD - KIT

ANDA – KIT

9. **CONTAINER/CLOSURE – see FTR # 6 & # 8 above**
10. **MEDICATION GUIDES/PATIENT PACKAGE INSERT – Medication Guide + Instructions for Use**
11. **RELATED APPLICATIONS - NONE**
12. **SPL DATA ELEMENTS - Not submitted.**
13. **CITIZENS PETITION/PROPRIETARY NAME/CONSULTS - Two consults – one from chemistry and the other from the LRB -**

(b) (4)

LABELING – OSE/DRISK - re: Please review the REMS submitted for ANDA 202090. It can be found in DARRTS under date 10/19/11. The RLD is XYREM (NDA 021196) held by Jazz Pharmaceuticals – Xyrem (sodium oxybate) is a drug deemed by FDA to have a REMS – Xyrem does not currently have an approved REMS but it currently is being developed by DNP – and so OGD has no model to use as a reference – this ANDA (202090) is the first generic ANDA for this drug product and we are requesting an expeditious review for that reason. [consult submitted 5-3-12].

Division of Medical Policy Programs -- PATIENT LABELING REVIEW

Date: May 15, 2012 – The Medication Guide submitted was reviewed by Twanda Scales and her recommended revisions were sent to the firm with this review except for one – it was felt by the labeling reviewer that there was no need to use (b) (4), [rather than “sodium oxybate”] for the established name throughout the Med Guide. Please note that since the Med Guide (as well as the insert) were revised and approved in S-013 on 12-17-12 after Ms Scales review was done and finalized I have asked the firm to update as per the RLD.

An answer for the consult re: the appropriateness of the REMS materials submitted by Roxane vs the innovator’s XYREM (RLD) “deemed” REMS – by Jazz Pharmaceuticals has not been forthcoming as of 3-13-13 and so labeling review of the firm’s submitted REMS materials was not undertaken. Per the LRB PM – Carrie Lemley – who has been in contact with Roxane regarding this ANDA – the firm is intending to submit a RISKMAP for this drug product which would incorporate much of the same materials as their submitted REMS with the hope that it would be more expeditiously reviewed than their submitted proposed REMS and since XYREM has a RiskMAP currently in place it may be possible to approve a generic with a RiskMAP before the full approval of a REMS for the innovator. Update from Carrie Lemley as of 10-29-13 – Agency is leaning towards allowing approval of a REMS from ROXANE with a waiver.

14. **This is a FIRST GENERIC.**

Date of Review: October 30, 2013

Primary Reviewer: Adolph Vezza

Team Leader: Captain Koung Lee

Appears This Way On
Original

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

/s/

ADOLPH E VEZZA
10/31/2013

KOUNG U LEE
11/06/2013

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **202090**

Date of Submission: **April 16, 2013**

Applicant's Name: **Roxane Laboratories, Inc.**

Established Name and Strength: **Sodium Oxybate Oral Solution, 500 mg/mL**

Proposed Proprietary Name: **None**

Labeling Comments below are considered:

NOT easily correctable (applicant cannot respond within 10 business days)

Easily correctable (respond within 10 business days)

No Comments (Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies determined on 7-5-13 based on your submission dated 4-16-13:

PATENT

You have not addressed Patent # 8457988 which expires on December 17, 2022.

CARTON

How will the two 75 cc dosing cups accompany the drug product?

INSERT

1. HIGHLIGHTS OF PRESCRIBING INFORMATION
 - a. TITLE – Place the following text immediately above “Initial U.S. ...”

SODIUM OXYBATE Oral Solution, CIII
 - b. INDICATIONS AND USAGE

No further comments will be made on your (b) (4) Sodium Oxybate (b) (4) Program at this time.

2. FULL PRESCRIBING INFORMATION: CONTENTS*

- a. (b) (4)
- b. WARNING STATEMENT
“... **SYSTEM (CNS) DEPRESSION and MISUSE AND ABUSE**”
- c. 5.1 Central Nervous System Depression
Revise the title to read as shown above.
- d. 5.3 - See comment under (1) (b) above.
- e. (b) (4),,
- f. (b) (4),,

3. FULL PRESCRIBING INFORMATION

- a. GENERAL COMMENT – Format parenthetical statements referencing other parts of the insert labeling as shown below:
[see WARNINGS AND PRECAUTIONS (5.3)].
 - i. Note there is no numerical designation before “WARNINGS”.
 - ii. Note the blank space between “PRECAUTIONS” and the parenthesis.
- b. 1.1 Cataplexy in Narcolepsy – [see CLINICAL STUDIES (14.1)]
- c. 1.2 Excessive Daytime Sleepiness in Narcolepsy – [see CLINICAL STUDIES (14.2)]
- d. 2 DOSAGE AND ADMINISTRATION
See comment under (1) (b) above.
- e. 2.1 Dosing Information, Table 1 Title
“(g = grams)” [spacing]

f. 4 CONTRAINDICATIONS

(b) (4)

g. 5.1 Central Nervous System Depression

Revise the title to be as shown above.

h. 5.3 - See comment under (1) (b) above.

i. 5.8 Use in Patients Sensitive to High Sodium Intake, Table 2 Title

“(g = grams)” [spacing]

j. 8.1 Pregnancy, last sentence – “postnatal” (b) (4)

k. 10.1 Human Experience, first paragraph, last sentence – “was” rather than “is”

l. 17 PATIENT COUNSELING INFORMATION

See comment under (1) (b) above.

m. **Instructions for Use - Sodium Oxybate Oral Solution, CIII**

Revise the title to appear as shown above.

n. **Medication Guide - Sodium Oxybate Oral Solution, CIII**

i. Revise the title to appear as shown above.

ii. What is the most important ... - See comment under (1) (b) above.

iii. How should I take ..., first bullet – “... **Instructions for Use** at the end of this Medication Guide for ...”

iv. What are the possible ... - **Bold** the last two sentences [“**Call your doctor ... side effects. You may ... at 1-800-FDA-1088.**”].

v. General information about ... - See comment under (1) (b) above.

o. Please note that the “**Instructions for Use**” should follow the “**Medication Guide**”.

REMS (b) (4)

Please note that these documents are under review and no other comments will be made at this time.

Revise your labeling, as instructed above, and submit electronically.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with [the reference listed drug's labeling **or** your last submitted labeling] with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

REMS required? RLD has RiskMAP and DEEMED REMS **(OTC do NOT require)**

- MedGuides and/or PPIs (505-1(e)) Yes No
- Communication plan (505-1(e)) Yes No
- Elements to assure safe use (ETASU) (505-1(f)(3)) Yes No
- Implementation system if certain ETASU (505-1(f)(4)) Yes No
- Timetable for assessment (505-1(d)) Yes No

ANDA REMS acceptable?

Yes No n/a

	Date submitted	Final or Draft	Recommendation
CARTON 1 x 180 mL	4-16-13	FINAL	APPROVE
CONTAINER 180 mL	4-16-13	FINAL	APPROVE
INSERT	4-16-13	FINAL	REVISE
MEDICATION GUIDE	4-16-13	FINAL	REVISE
REMS	10-19-11	DRAFT	CONSULT
RISKMAP	4-16-13	DRAFT	CONSULT

SPL	NONE	N/A	SUBMIT
-----	------	-----	--------

REVISIONS NEEDED POST APPROVAL?

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER: None

FOR THE RECORD:

- MODEL LABELING** - XYREM® (NDA 21-196/S-013) [Jazz Pharmaceuticals], approved 12/17/12.
- USP & PF** - Drug Product does not have a USP monograph.
- PATENT AND EXCLUSIVITY**

Patents 21-196

No	Expiration	Use Code	Use	File	Labeling Impact
7895059	12-17-22	U-1110		PIV	NONE
7851506	12-22-19	U-1101 & U-1102		PIV	NONE
6780889	7-4-20			PIV	NONE
7262219	7-4-20			PIV	NONE
7668730	3-7-24	U-1110		PIV	NONE
7765106	6-16-24	U-1069		PIV	NONE
7765107	6-16-24	U-1070		PIV	NONE
8263650	12-22-19	U-1101 & U-1102		PIV	NONE
8324275	12-22-19	U-1101 & U-1102		PIV	NONE
8457988	12-17-22	U-1110			

U-1101 Method of treating excessive daytime sleepiness in patients with narcolepsy

U-1102 Method of treating cataplexy in patients with narcolepsy

U-1110 Method of treating a patient with a prescription drug using a computer database in a computer system for distribution

U-1069 A method of treating a patient with a prescription drug using an exclusive computer database in a computer system for distribution

U-1070 A method to control abuse of a sensitive drug by controlling with a computer processor the distribution of the sensitive drug via an exclusive central pharmacy that maintains a central database

Exclusivity Data 21-196

Code/sup	Expiration	Use Code	Description	Labeling Impact
ODE	11-18-12		Treatment of excessive daytime sleepiness in patients with narcolepsy	None – EXPIRED

4. INACTIVE INGREDIENTS



5. MANUFACTURING FACILITY - Boehringer Ingelheim Roxane, Inc – USA

6. FINISHED PRODUCT DESCRIPTION

ANDA – It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert.

The following table summarizes the elements from the RLD packaging and from RLI packaging.

Brand Packaging	RLI Packaging
Leaflet	Leaflet
Amber Plastic Bottle	White HDPE Plastic Bottle with Window Stripe
Plastic White Closure CR	Plastic White Closure CR with neckband
Syringe in grams	1 – 10mL Syringe in mL - Need grams for commercial
(b) (4)	PIBA/Dip Tube
Dose cups supplied by pharmacist	2 – 75mL Dose cups White HDPE w/ CR Closure
Printed Folding Carton	Printed Folding Carton

RLI packaging will match every element present in the brand packaging. The Container Closure System will be neck banded for tamper evidence. The final version of the syringe will be graduated in grams similarly to the one enclosed in the RLD packaging and will be protected by a polybag. The product container, syringe, 2 dose containers, and leaflet are shipped in a preprinted folding carton. Please note that the final version of the syringe will have similar dimensions compared to the syringe presently included in the sample of the finished drug product and only the graduation marking will vary. Therefore, the included syringe is adequate to check for compatibility with the PIBA, the dose cup, and for fitting in the carton.

Patient acceptability will not be impacted by the different bottle, closure system, PIBA, syringe, and dose cups used in RLI packaging since global handling is comparable to that of the brand. Furthermore, RLI bottle will present the advantage of a graduated window strip permitting a quantification of the product remaining in the bottle to monitor usage.

Per your September 1, 2011 telephone call RLI will provide samples of the placebo in our proposed commercial packaging (bottle, Syringe Oral/PBA (b) (4) Dip Tube) within one week under separate cover.

7. STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS

RLD: Store Xyrem between (b) (4) 77°F (b) (4) 24°C).

ANDA: Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.

8. PRODUCT LINE – See comparison of RLD and ANDA in FTR # 6

RLD - KIT

ANDA – KIT

9. CONTAINER/CLOSURE – see FTR # 6 & # 8 above

10. MEDICATION GUIDES/PATIENT PACKAGE INSERT – Medication Guide

11. RELATED APPLICATIONS - NONE

12. SPL DATA ELEMENTS - Not submitted.

13. CITIZENS PETITION/PROPRIETARY NAME/CONSULTS - Two consults – one from chemistry and the other from the LRB -



LABELING – OSE/DRISK - re: Please review the REMS submitted for ANDA 202090. It can be found in DARRTS under date 10/19/11. The RLD is XYREM (NDA 021196) held by Jazz Pharmaceuticals – Xyrem (sodium oxybate) is a drug deemed by FDA to have a REMS – Xyrem does not currently have an approved REMS but it currently is being developed by DNP – and so OGD has no model to use as a reference – this ANDA (202090) is the first generic ANDA for this drug product and we are requesting an expeditious review for that reason. [consult submitted 5-3-12].

Division of Medical Policy Programs -- PATIENT LABELING REVIEW

Date: May 15, 2012 – The Medication Guide submitted was reviewed by Twanda Scales and her recommended revisions were sent to the firm with this review except for one – it was felt by the labeling reviewer that there was no need to use (b) (4) [rather than “sodium oxybate”] for the established name throughout the Med Guide. Please note that since the Med Guide (as well as the insert) were revised and approved in S-013 on 12-17-12 after Ms Scales review was done and finalized I have asked the firm to update as per the RLD.

An answer for the consult re: the appropriateness of the REMS materials submitted by Roxane vs the innovator’s XYREM (RLD) “deemed” REMS – by Jazz Pharmaceuticals

has not been forthcoming as of 3-13-13 and so labeling review of the firm's submitted REMS materials was not undertaken. Per the LRB PM – Carrie Lemley – who has been in contact with Roxane regarding this ANDA – the firm is intending to submit a RISKMAP for this drug product which would incorporate much of the same materials as their submitted REMS with the hope that it would be more expeditiously reviewed than their submitted proposed REMS and since XYREM has a RiskMAP currently in place it may be possible to approve a generic with a RiskMAP before the full approval of a REMS for the innovator. Update from Carrie Lemley as of 7-5-13 – Agency is leaning towards allowing approval of a REMS from ROXANE with a waiver.

14. **This is a FIRST GENERIC.**

Date of Review: 7-5-13

Primary Reviewer: Adolph Vezza

Team Leader: Captain Koung Lee

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

/s/

ADOLPH E VEZZA
07/12/2013

KOUNG U LEE
07/16/2013

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **202090**

Dates of Submission: **July 8, 2010 and April 6 and October 19, 2011**

Applicant's Name: **Roxane Laboratories, Inc.**

Established Name and Strength: **Sodium Oxybate Oral Solution, 500 mg/mL**

Proposed Proprietary Name: **None**

Labeling Comments below are considered:

NOT easily correctable (applicant cannot respond within 10 business days)

Easily correctable (respond within 10 business days)

No Comments (Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies determined on 3-14-13 based on your submissions dated 7-8-10 and 4-6 and 10-19-11:

CONTAINER 180 mL

1. Add the following statement to appear immediately above “For oral administration only.”:

“MUST BE DILUTED BEFORE USE”

2. Add the following statement to appear immediately above the storage temperature recommendations:

“WARNING: Keep This and All Other Medications Out of Reach of Children”

3. “Each mL contains ...” statement – “... purified water, USP [add comma]

4. (b) (4).

5. Add the following statement to appear immediately below “For oral administration

only.”:

“Use as instructed”

CARTON

1. See comments (2) and (4) under CONTAINER above.
2. Add the following statement to appear immediately above “Rx only”:
“WARNING: Keep This and All Other Medications Out of Reach of Children”
3. We note that you have included the following statement while the innovator does not have it. Please comment.
“Solutions prepared following dilution should be consumed within 24 hours (b) (4)
(b) (4)
4. How will the two 75 cc dosing cups accompany the drug product?

INSERT

1. GENERAL COMMENT
Revise your insert labeling to be the same as that of the reference listed drug, Xyrem® (NDA 21-196/S-013); approved December 17, 2012.
2. DESCRIPTION
(b) (4)
3. MEDICATION GUIDE
Revise your Medication Guide and associated Instructions for Use to be the same as that of the reference listed drug, Xyrem® (NDA 21-196/S-013); approved December 17, 2012.

REMS

Your submitted REMS was consulted and remains under review. You are encouraged to work towards a single-shared system REMS with the innovator. You may also opt to develop and submit a RiskMAP.

Revise your labeling, as instructed above, and submit electronically.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with [the reference listed drug's labeling **or** your last submitted labeling] with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

REMS required? RLD has RiskMAP and DEEMED REMS **(OTC do NOT require)**

MedGuides and/or PPIs (505-1(e)) Yes No

Communication plan (505-1(e)) Yes No

Elements to assure safe use (ETASU) (505-1(f)(3)) Yes No

Implementation system if certain ETASU (505-1(f)(4)) Yes No

Timetable for assessment (505-1(d)) Yes No

ANDA REMS acceptable?

Yes No n/a

	Date submitted	Final or Draft	Recommendation
CARTON 1 x 180 mL	7-8-10	DRAFT	REVISE
CONTAINER 180 mL	7-8-10	DRAFT	REVISE
INSERT	7-8-10	DRAFT	REVISE
MEDICATION GUIDE	7-8-10	DRAFT	REVISE
REMS	10-19-11	DRAFT	CONSULT
SPL	NONE	N/A	SUBMIT

REVISIONS NEEDED POST APPROVAL?

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER: None

FOR THE RECORD:

1. **MODEL LABELING** - XYREM® (NDA 21-196/S-013) [Jazz Pharmaceuticals], approved 12/17/12.
2. **USP & PF** - Drug Product does not have a USP monograph.
3. **PATENT AND EXCLUSIVITY**

Patents 21-196

No	Expiration	Use Code	Use	File	Labeling Impact
7895059	12-17-22	U-1110		PIV	NONE
7851506	12-22-19	U-1101 & U-1102		PIV	NONE
6780889	7-4-20			PIV	NONE
7262219	7-4-20			PIV	NONE
7668730	3-7-24	U-1110		PIV	NONE
7765106	6-16-24	U-1069		PIV	NONE
7765107	6-16-24	U-1070		PIV	NONE

U-1101 Method of treating excessive daytime sleepiness in patients with narcolepsy

U-1102 Method of treating cataplexy in patients with narcolepsy

U-1110 Method of treating a patient with a prescription drug using a computer database in a computer system for distribution

U-1069 A method of treating a patient with a prescription drug using an exclusive computer database in a computer system for distribution

U-1070 A method to control abuse of a sensitive drug by controlling with a computer processor the distribution of the sensitive drug via an exclusive central pharmacy that maintains a central database

Exclusivity Data 21-196

Code/sup	Expiration	Use Code	Description	Labeling Impact
ODE	11-18-12		Treatment of excessive daytime sleepiness in patients with narcolepsy	None – EXPIRED

4. INACTIVE INGREDIENTS



(b) (4)

5. **MANUFACTURING FACILITY - Boehringer Ingelheim Roxane, Inc – USA**

6. **FINISHED PRODUCT DESCRIPTION**

ANDA – It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert.

The following table summarizes the elements from the RLD packaging and from RLI packaging.

Brand Packaging	RLI Packaging
Leaflet	Leaflet
Amber Plastic Bottle	White HDPE Plastic Bottle with Window Stripe
Plastic White Closure CR	Plastic White Closure CR with neckband
Syringe in grams	1 – 10mL Syringe in mL - Need grams for commercial
(b) (4)	PIBA/Dip Tube
Dose cups supplied by pharmacist	2 – 75mL Dose cups White HDPE w/ CR Closure
Printed Folding Carton	Printed Folding Carton

RLI packaging will match every element present in the brand packaging. The Container Closure System will be neck banded for tamper evidence. The final version of the syringe will be graduated in grams similarly to the one enclosed in the RLD packaging and will be protected by a polybag. The product container, syringe, 2 dose containers, and leaflet are shipped in a preprinted folding carton. Please note that the final version of the syringe will have similar dimensions compared to the syringe presently included in the sample of the finished drug product and only the graduation marking will vary. Therefore, the included syringe is adequate to check for compatibility with the PIBA, the dose cup, and for fitting in the carton.

Patient acceptability will not be impacted by the different bottle, closure system, PIBA, syringe, and dose cups used in RLI packaging since global handling is comparable to that of the brand. Furthermore, RLI bottle will present the advantage of a graduated window strip permitting a quantification of the product remaining in the bottle to monitor usage.

Per your September 1, 2011 telephone call RLI will provide samples of the placebo in our proposed commercial packaging (bottle, Syringe Oral/PBA (b) (4) Dip Tube) within one week under separate cover.

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Store Xyrem between (b) (4) 7°F ((b) (4) 24°C).

ANDA: Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.

8. **PRODUCT LINE – See comparison of RLD and ANDA in FTR # 6**

RLD - KIT

ANDA - KIT

9. **CONTAINER/CLOSURE – see FTR # 6 & # 8 above**

10. **MEDICATION GUIDES/PATIENT PACKAGE INSERT – Medication Guide**
11. **RELATED APPLICATIONS - NONE**
12. **SPL DATA ELEMENTS - Not submitted.**
13. **CITIZENS PETITION/PROPRIETARY NAME/CONSULTS - Two consults – one from chemistry and the other from the LRB -**



LABELING – OSE/DRISK - re: Please review the REMS submitted for ANDA 202090. It can be found in DARRTS under date 10/19/11. The RLD is XYREM (NDA 021196) held by Jazz Pharmaceuticals – Xyrem (sodium oxybate) is a drug deemed by FDA to have a REMS – Xyrem does not currently have an approved REMS but it currently is being developed by DNP – and so OGD has no model to use as a reference – this ANDA (202090) is the first generic ANDA for this drug product and we are requesting an expeditious review for that reason. [consult submitted 5-3-12].

Division of Medical Policy Programs -- PATIENT LABELING REVIEW

Date: May 15, 2012 – The Medication Guide submitted was reviewed by Twanda Scales and her recommended revisions were sent to the firm with this review except for one – it was felt by the labeling reviewer that there was no need to use [redacted] (b) (4) [rather than “sodium oxybate”] for the established name throughout the Med Guide. Please note that since the Med Guide (as well as the insert) were revised and approved in S-013 on 12-17-12 after Ms Scales review was done and finalized I have asked the firm to update as per the RLD.

An answer for the consult re: the appropriateness of the REMS materials submitted by Roxane vs the innovator’s XYREM (RLD) “deemed” REMS – by Jazz Pharmaceuticals has not been forthcoming as of 3-13-13 and so labeling review of the firm’s submitted REMS materials was not undertaken. Per the LRB PM – Carrie Lemley – who has been in contact with Roxane regarding this ANDA – the firm is intending to submit a RISKMAP for this drug product which would incorporate much of the same materials as their submitted REMS with the hope that it would be more expeditiously reviewed than their submitted proposed REMS and since XYREM has a RiskMAP currently in place it may be possible to approve a generic with a RiskMAP before the full approval of a REMS for the innovator.

14. **This is a FIRST GENERIC.**

Date of Review: 3-14-13

Primary Reviewer: Adolph Vezza

Team Leader: Captain Koung Lee

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

/s/

ADOLPH E VEZZA
03/18/2013

KOUNG U LEE
03/18/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: May 15, 2012

To: Russell Katz, M.D., Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Associate Director, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling Medication Guide (MG)
and Instructions for Use (IFU)

Drug Name: Sodium Oxybate

Dosage Form and Route: 500mg/mL Oral Solution

Application
Type/Number: ANDA 202090

Applicant: Roxane Laboratories, Inc.

1 INTRODUCTION

On July 8, 2010, Roxane Laboratories, Inc. submitted an abbreviated new drug application (ANDA) for Sodium Oxybate, 500 mg/mL, oral solution. This ANDA refers to the listed drug XYREM (sodium oxybate) oral solution, indicated for the treatment of cataplexy in patients with narcolepsy and for excessive daytime sleepiness in patient with narcolepsy, held by Jazz Pharmaceuticals.

This review is written in response to a request from the Office of Generic Drugs, through the Division of Neurology Products (DNP), for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for Sodium Oxybate, 500mg/mL, oral solution.

Supplement 013 (S-013) is currently pending approval for listed drug XYREM (sodium oxybate) oral solution. DMPP provided a review of the Medication Guide for XYREM S-013 on November 14, 2011. When action is taken on the XYREM S-013, modifications to the Sodium Oxybate medication guide will be required.

The Risk Evaluation and Mitigation Strategy (REMS) for Sodium Oxybate oral solution will be provided by The Division of Risk Management (DRISK) under separate cover.

2 MATERIAL REVIEWED

- Draft Sodium Oxybate oral solution, (MG/IFU) received on July 8, 2010, and received by DMPP on May 10, 2012.
- Draft Sodium Oxybate oral solution, Prescribing Information (PI) received on July 8, 2010, and received by DMPP May 10, 2012.
- Approved XYREM (sodium oxybate) oral solution reference listed drug, comparator labeling dated November 2005.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our review of the MG and IFU we have:

- ensured that the MG is consistent with the prescribing information (PI)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved reference listed comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated version of the MG and IFU is appended to this memo. Consult DMPP 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.

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

/s/

TWANDA D SCALES
05/15/2012

MELISSA I HULETT
05/15/2012

LASHAWN M GRIFFITHS
05/16/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 202090

CHEMISTRY REVIEWS

ANDA 202090

**Sodium Oxybate Oral Solution
500 mg/mL**

Roxane Laboratories, Inc.

First Generic Product

Review # 4; CMC Adequate

Yanning Lin, Ph.D.

OGD, DC II

Table of Contents

Chemistry Review Data Sheet.....

The Executive Summary

I. Recommendations.....

 A. Recommendation and Conclusion on Approvability.....

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....

II. Summary of Chemistry Assessments

 A. Description of the Drug Product(s) and Drug Substance(s).....

 B. Description of How the Drug Product is Intended to be Used.....

 C. Basis for Approvability or Not-Approval Recommendation

2.3.S DRUG SUBSTANCE.....

 2.3.S.1 General Information.....

 2.3.S.2 Manufacturer.....

 2.3.S.3 Characterization.....

 2.3.S.4 Control of Drug Substance.....

 2.3.S.5 Reference Standards and Materials.....

 2.3.S.6 Container Closure System.....

 2.3.S.7 Stability.....

2.3.P DRUG PRODUCT.....

 2.3.P.1 Description and Composition of the Drug Product.....

 2.3.P.2 Pharmaceutical Development

 2.3.P.2.1 Components of the Drug Product

 2.3.P.2.2 Drug Product.....

 2.3.P.2.3 Manufacturing Process Development.....

 2.3.P.2.4 Container/Closure System

 2.3.P.3 Manufacture.....

 2.3.P.3.1 Manufacturing Process and Controls

 2.3.P.3.3 Reconciliation of the Exhibit Batch.....

 2.3.P.3.4 Unit and Batch Composition.....

 2.3.P.4 Control of Excipients

 2.3.P.5 Control of Drug Product

 2.3.P.5.1 Specifications.....

 2.3.P.5.2 Justification of Specifications.....

 2.3.P.6 Reference Standards and Materials.....

 2.3.P.7 Container/Closure System

 2.3.P.8 Stability.....

 2.3.P.8.1 Specifications.....

Chemistry Review Data Sheet

1. ANDA#: 202090
2. REVIEW#: 4
3. REVIEW DATE: 08-May-2013
4. REVIEWER: Yanning Lin, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
General Consult Review	February 05, 2013
Minor Amendment (Patent & Exclusivity/Patent Info)	August 01, 2011
Minor Amendment	September 02, 2011
Minor Amendment	September 09, 2011
Minor Amendment (REMS Proposal/Standard Timeframe)	October 19, 2011
Minor Amendment	January 11, 2011
Minor Amendment	December 03, 2010
Telephone Amendment	September 13, 2010
Minor Amendment	August 03, 2010
Filing Acknowledgment	September 22, 2010
Original Submission	July 8, 2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Minor Amendment	April 16, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc
 Address: 1809 Wilson Road
 Columbus, Ohio 43228
 Contact person: Elizabeth Ernst
 Director, Drug Regulatory Affairs and Medical Affairs
 Telephone: (614) 272-4785
 Fax: (614) 272-2470

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Sodium Oxybate Oral Solution, 500 mg/mL
- c) Code Name/# (ONDC only):None
- d) Chem. Type/Submission Priority (ONDC only):NA

- Chem. Type: N/A
- Submission Priority: N/A

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: Xyrem® (NDA #21-196)
Innovator Company: Jazz Pharmaceuticals

10. PHARMACOL. CATEGORY: Indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 500 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

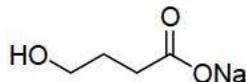
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical name:

Butanoic acid, 4-hydroxy-, sodium salt (1:1)

Butanoic acid, 4-hydroxy-, monosodium salt (9CI)

Butyric acid, 4-hydroxy-, monosodium salt (8CI)

4-Hydroxybutanoic acid sodium salt

4-Hydroxybutyrate sodium

4-Hydroxybutyric acid monosodium salt

4-Hydroxybutyric acid sodium salt

Oxybate sodium

Sodium 4-hydroxybutyrate

Sodium hydroxybutyrate

Sodium oxybate

Sodium γ -hydroxybutyrate

Sodium γ -oxybutyrate
 γ -Hydroxybutyrate sodium
 γ -Hydroxybutyric acid sodium salt
 GHB
 NaGHB

Chemical Formula: $C_4H_7NaO_3$
 Molecular Weight: 126.09
 Cas Number: [502-85-2] (for Sodium Oxybate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: (LOA see section 1.4.1)

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	by Y. Lin on 02-21-13
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Adequate	08-May-2013	Y. Lin
Labeling	Inadequate	18-Mar-2013	A. E. Vezza
Bioequivalence	Waiver Granted	29-Mar-2011	C. Chaurasia
EES	Overall Acceptable <div style="background-color: #cccccc; width: 100px; height: 15px; margin: 2px 0;"></div> (b) (4) DP: Boehringer Ingelheim Roxane Inc. Acceptable	13-Dec-2012 31-Dec-2012	OC
Microbiology	N/A		
Methods Validation	Not requested per current OGD policy (USP)		
EA	Exclusion from requirement for environmental assessment		21 CFR 25.31(a)
Radiopharmaceutical	N/A		
Pharm/Tox Consult	Adequate	1/14/13	David Hawver

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
 Yes No If no, explain reason(s) below:

The Chemistry Review for ANDA 202090

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry review is considered adequate per Y. Lin on 08-May-2013. The labeling review is inadequate as per A. E. Vezza on 18-Mar-2013. Waiver to bioequivalence has been granted by C. Chaurasia on 29-Mar-2011. The inspection of the drug product manufacturing facility, Boehringer Ingelheim Roxane Inc. is acceptable per OC on 31-Dec-2012. (b) (4)

(b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance: Maximum Daily Dose: 9 g

Sodium Oxybate (aqueous concentrate) drug substance is a clear, colorless, (b) (4) solution. (b) (4) Sodium Oxybate is soluble in aqueous (b) (4) solution. (b) (4)

(b) (4)

2. Drug product

Name	Sodium Oxybate Oral Solution
Strength/Potency	500 mg/mL
Dosage Form	Oral solution
Product Description	Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution.
Indication	Indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.
Packaging	It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert.

3. Drug Product Manufacturing:

51 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

needed changes to the labeling with our labeling review staff. Submit all revised documents.

How Supplied: Sodium Oxybate Oral Solution, 500 mg/mL for oral administration:

It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert. (b) (4) two (b) (4) dosing cups with child-resistant caps with each Sodium Oxybate Oral Solution shipment. Each white oblong HDPE bottle contains 180 mL of Sodium Oxybate Oral Solution at a concentration of 500 mg/mL and is sealed with a child resistant cap.

Storage conditions:

Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.

Tentative expiration dating: 24 months based on 3 months accelerated data and 12 months CRT data.

Solutions prepared following dilution should be consumed within 24 hours (b) (4)
(b) (4)

Sodium Oxybate Oral Solution is a Schedule III drug under the Controlled Substances Act.

Sodium Oxybate Oral Solution should be handled according to state and federal regulations. It is safe to dispose of Sodium Oxybate Oral Solution down the sanitary sewer.

CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

For questions of a medical nature or to order Sodium Oxybate Oral Solution call the Sodium Oxybate Risk Management Program at 1-800-962-8364.

Conclusion: Satisfactory from chemistry's perspective.

C. Basis for Approvability or Not-Approval Recommendation

ESTABLISHMENT INSPECTION

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Overall Acceptable (b) (4) DP: Boehringer Ingelheim Roxane Inc. Acceptable	13-Dec-2012 31-Dec-2012	OC

BIOEQUIVALENCE

Waiver to bioequivalence has been granted by C. Chaurasia on 29-Mar-2011.

ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

An Environmental Assessment was included on Module 1.on v.1.1. The firm requested a categorical exclusion.

Chemistry comments to be provided to the Applicant

ANDA: 202090

APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Sodium Oxybate Oral Solution, 500 mg/mL

CMC is adequate.

Sincerely yours,

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 202090 Original

Endorsements:

HFD-647/Yanning Lin/08-May-2013

HFD-617/ R. Presto/August 12, 2013

HFD-647/U.V.Venkataram/ 16-May-2013

HFD-640/G. J. Smith/H.Teng on behalf of G.Smith 8/2/2013

CMC Adequate

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

/s/

YANNING LIN
08/21/2013

RYAN S PRESTO
08/21/2013

NASHED I SAMAN on behalf of UBRANI V VENKATARAM
08/21/2013

GLEN J SMITH
08/21/2013

ANDA 202090

**Sodium Oxybate Oral Solution
500 mg/mL**

Roxane Laboratories, Inc.

First Generic Product

Review # 3; CMC Inadequate

Yanning Lin, Ph.D.

OGD, DC II

Table of Contents

Chemistry Review Data Sheet.....

The Executive Summary

I. Recommendations.....

A. Recommendation and Conclusion on Approvability.....

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s).....

B. Description of How the Drug Product is Intended to be Used.....

C. Basis for Approvability or Not-Approval Recommendation

2.3.S DRUG SUBSTANCE.....

2.3.S.1 General Information.....

2.3.S.2 Manufacturer.....

2.3.S.3 Characterization.....

2.3.S.4 Control of Drug Substance.....

2.3.S.5 Reference Standards and Materials.....

2.3.S.6 Container Closure System.....

2.3.S.7 Stability.....

2.3.P DRUG PRODUCT.....

2.3.P.1 Description and Composition of the Drug Product.....

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Components of the Drug Product

2.3.P.2.2 Drug Product.....

2.3.P.2.3 Manufacturing Process Development.....

2.3.P.2.4 Container/Closure System

2.3.P.3 Manufacture.....

2.3.P.3.1 Manufacturing Process and Controls

2.3.P.3.3 Reconciliation of the Exhibit Batch.....

2.3.P.3.4 Unit and Batch Composition.....

2.3.P.4 Control of Excipients

2.3.P.5 Control of Drug Product

2.3.P.5.1 Specifications.....

2.3.P.5.2 Justification of Specifications.....

2.3.P.6 Reference Standards and Materials.....

2.3.P.7 Container/Closure System

2.3.P.8 Stability.....

2.3.P.8.1 Specifications.....

Chemistry Review Data Sheet

1. ANDA#: 202090
2. REVIEW#: 3
3. REVIEW DATE: 26-Feb-2013
4. REVIEWER: Yanning Lin, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Minor Amendment (Patent & Exclusivity/Patent Info)
Minor Amendment
Minor Amendment
Minor Amendment (REMS Proposal/Standard
Timeframe)
Minor Amendment
Minor Amendment
Telephone Amendment
Minor Amendment
Filing Acknowledgment
Original Submission

Document Date

August 01, 2011
September 02, 2011
September 09, 2011
October 19, 2011
January 11, 2011
December 03, 2010
September 13, 2010
August 03, 2010
September 22, 2010
July 8, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

General Consult Review

Document Date

February 05, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc
Address: 1809 Wilson Road
Columbus, Ohio 43228
Contact person: Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs
Telephone: (614) 272-4785
Fax: (614) 272-2470

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Sodium Oxybate Oral Solution, 500 mg/mL
- c) Code Name/# (ONDC only):None
- d) Chem. Type/Submission Priority (ONDC only):NA
 - Chem. Type: N/A

- Submission Priority: N/A

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: Xyrem® (NDA #21-196)
Innovator Company: Jazz Pharmaceuticals

10. PHARMACOL. CATEGORY: Indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 500 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

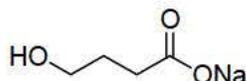
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical name:

Butanoic acid, 4-hydroxy-, sodium salt (1:1)

Butanoic acid, 4-hydroxy-, monosodium salt (9CI)

Butyric acid, 4-hydroxy-, monosodium salt (8CI)

4-Hydroxybutanoic acid sodium salt

4-Hydroxybutyrate sodium

4-Hydroxybutyric acid monosodium salt

4-Hydroxybutyric acid sodium salt

Oxybate sodium

Sodium 4-hydroxybutyrate

Sodium hydroxybutyrate

Sodium oxybate

Sodium γ -hydroxybutyrate

Sodium γ -oxybutyrate

γ-Hydroxybutyrate sodium
 γ-Hydroxybutyric acid sodium salt
 GHB
 NaGHB

Chemical Formula: C₄H₇NaO₃
 Molecular Weight: 126.09
 Cas Number: [502-85-2] (for Sodium Oxybate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: (LOA see section 1.4.1)

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	by Y. Lin on 02-21-13
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

- 6 – DMF not available
7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Inadequate	26-Feb-2013	Y. Lin
Labeling	Pending		
Bioequivalence	Waiver Granted	29-Mar-2011	C. Chaurasia
EES	Overall Acceptable (b) (4) DP: Boehringer Ingelheim Roxane Inc. Acceptable	13-Dec-2012 31-Dec-2012	OC
Microbiology	N/A		
Methods Validation	Not requested per current OGD policy (USP)		
EA	Exclusion from requirement for environmental assessment		21 CFR 25.31(a)
Radiopharmaceutical	N/A		
Pharm/Tox Consult	Adequate	1/14/13	David Hawver

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
 Yes No If no, explain reason(s) below:

The Chemistry Review for ANDA 202090

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry review is considered inadequate per Y. Lin on 26-Feb-2013. The labeling review is pending. Waiver to bioequivalence has been granted by C. Chaurasia on 29-Mar-2011. The inspection of the drug product manufacturing facility, Boehringer Ingelheim Roxane Inc. is acceptable per OC on 31-Dec-2012. (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance: Maximum Daily Dose: 9 g

Sodium Oxybate (aqueous concentrate) drug substance is a clear, colorless, (b) (4) solution. (b) (4) Sodium Oxybate is soluble in aqueous (b) (4) solution. (b) (4)

2. Drug product

Name	Sodium Oxybate Oral Solution
Strength/Potency	500 mg/mL
Dosage Form	Oral solution
Product Description	Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution.
Indication	Indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.
Packaging	It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert.

3. Drug Product Manufacturing:

51 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

needed changes to the labeling with our labeling review staff. Submit all revised documents.

How Supplied: Sodium Oxybate Oral Solution, 500 mg/mL for oral administration:

It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert. (b) (4) two (b) (4) dosing cups with child-resistant caps with each Sodium Oxybate Oral Solution shipment. Each white oblong HDPE bottle contains 180 mL of Sodium Oxybate Oral Solution at a concentration of 500 mg/mL and is sealed with a child resistant cap.

Storage conditions:

Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.

Tentative expiration dating: 24 months based on 3 months accelerated data and 12 months CRT data.

Solutions prepared following dilution should be consumed within 24 hours (b) (4)
(b) (4)

Sodium Oxybate Oral Solution is a Schedule III drug under the Controlled Substances Act.

Sodium Oxybate Oral Solution should be handled according to state and federal regulations. It is safe to dispose of Sodium Oxybate Oral Solution down the sanitary sewer.

CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

For questions of a medical nature or to order Sodium Oxybate Oral Solution call the Sodium Oxybate Risk Management Program at 1-800-962-8364.

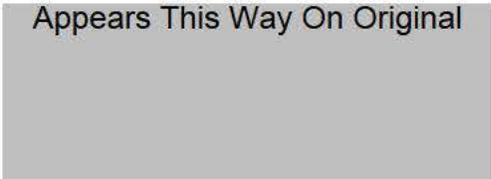
Conclusion: Satisfactory from chemistry's perspective.

C. Basis for Approvability or Not-Approval Recommendation

ESTABLISHMENT INSPECTION

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Overall Acceptable (b) (4) DP: Boehringer Ingelheim Roxane Inc. Acceptable	13-Dec-2012 31-Dec-2012	OC

Appears This Way On Original



BIOEQUIVALENCE

Waiver to bioequivalence has been granted by C. Chaurasia on 29-Mar-2011.

ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

An Environmental Assessment was included on Module 1.on v.1.1. The firm requested a categorical exclusion.

Chemistry comments to be provided to the Applicant

ANDA: 202090

APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Sodium Oxybate Oral Solution, 500 mg/mL

The deficiencies presented below represent MINOR deficiencies:

A. Chemistry Deficiencies:

1.



(b) (4)

2.

Sincerely yours,

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 202090 Original

Endorsements:

HFD-647/Yanning Lin/26-Feb-2013

HFD-617/ T. Nhu/28-Feb-2013

HFD-647/U.V.Venkataram/ 28-Feb-2013

HFD-640/G. J. Smith/28-Feb-2013

CMC Inadequate

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

/s/

YANNING LIN
02/28/2013

TINA T NHU
02/28/2013

UBRANI V VENKATARAM
02/28/2013

GLEN J SMITH
03/01/2013

ANDA 202090

**Sodium Oxybate Oral Solution
500 mg/mL**

Roxane Laboratories, Inc.

First Generic Product

Review # 2

Yanning Lin, Ph.D.

OGD, DC II

Table of Contents

Chemistry Review Data Sheet	
The Executive Summary	
I. Recommendations	
A. Recommendation and Conclusion on Approvability	
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	
II. Summary of Chemistry Assessments	
A. Description of the Drug Product(s) and Drug Substance(s).....	
B. Description of How the Drug Product is Intended to be Used.....	
C. Basis for Approvability or Not-Approval Recommendation	
2.3.S DRUG SUBSTANCE	
2.3.S.1 General Information.....	
2.3.S.2 Manufacturer.....	
2.3.S.3 Characterization.....	
2.3.S.4 Control of Drug Substance.....	
2.3.S.5 Reference Standards and Materials.....	
2.3.S.6 Container Closure System.....	
2.3.S.7 Stability.....	
2.3.P DRUG PRODUCT	
2.3.P.1 Description and Composition of the Drug Product.....	
2.3.P.2 Pharmaceutical Development	
2.3.P.2.1 Components of the Drug Product	
2.3.P.2.2 Drug Product.....	
2.3.P.2.3 Manufacturing Process Development.....	
2.3.P.2.4 Container/Closure System	
2.3.P.3 Manufacture.....	
2.3.P.3.1 Manufacturing Process and Controls	
2.3.P.3.3 Reconciliation of the Exhibit Batch.....	
2.3.P.3.4 Unit and Batch Composition.....	
2.3.P.4 Control of Excipients	
2.3.P.5 Control of Drug Product	
2.3.P.5.1 Specifications.....	
2.3.P.5.2 Justification of Specifications.....	
2.3.P.6 Reference Standards and Materials.....	
2.3.P.7 Container/Closure System	
2.3.P.8 Stability.....	
2.3.P.8.1 Specifications.....	

Chemistry Review Data Sheet

1. ANDA#: 202090
2. REVIEW#: 2
3. REVIEW DATE: 27-Oct-2011 and 03-Nov-2011
4. REVIEWER: Yanning Lin, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Minor Amendment
Minor Amendment
Telephone Amendment
Minor Amendment
Filing Acknowledgment
Original Submission

Document Date

January 11, 2011
December 03, 2010
September 13, 2010
August 03, 2010
September 22, 2010
July 8, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Minor Amendment (Patent & Exclusivity/Patent Info)
Minor Amendment
Minor Amendment
Minor Amendment (REMS Proposal/Standard
Timeframe)

Document Date

August 01, 2011
September 02, 2011
September 09, 2011
October 19, 2011

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc
Address: 1809 Wilson Road
Columbus, Ohio 43228
Contact person: Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs
Telephone: (614) 272-4785
Fax: (614) 272-2470

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Sodium Oxybate Oral Solution, 500 mg/mL
- c) Code Name/# (ONDC only):None
- d) Chem. Type/Submission Priority (ONDC only):NA
 - Chem. Type: N/A
 - Submission Priority: N/A

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: Xyrem® (NDA #21-196)

Innovator Company: Jazz Pharmaceuticals

10. PHARMACOL. CATEGORY: Indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy

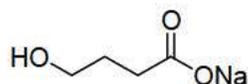
11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 500 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical name:

Butanoic acid, 4-hydroxy-, sodium salt (1:1)

Butanoic acid, 4-hydroxy-, monosodium salt (9CI)

Butyric acid, 4-hydroxy-, monosodium salt (8CI)

4-Hydroxybutanoic acid sodium salt

4-Hydroxybutyrate sodium

4-Hydroxybutyric acid monosodium salt

4-Hydroxybutyric acid sodium salt

Oxybate sodium

Sodium 4-hydroxybutyrate

Sodium hydroxybutyrate

Sodium oxybate

Sodium γ -hydroxybutyrateSodium γ -oxybutyrate γ -Hydroxybutyrate sodium

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Inadequate	27-Oct-2011 and 03-Nov-2011	Y. Lin
Labeling	Pending		
Bioequivalence	Waiver Granted	29-Mar-2011	C. Chaurasia
EES	Overall Pending <div style="background-color: #cccccc; width: 100px; height: 1em; margin-bottom: 5px;"></div> (b) (4) DP: Boehringer Ingelheim Roxane Inc. Acceptable	03-Oct-2011 10-Jan-2011	OC
Microbiology	N/A		
Methods Validation	Not requested per current OGD policy (USP)		
EA	Exclusion from requirement for environmental assessment		21 CFR 25.31(a)
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
 Yes No If no, explain reason(s) below:

The Chemistry Review for ANDA 202090

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry review is considered inadequate per Y. Lin on 27-Oct-2011 and 03-Nov-2011. The labeling review is pending. Waiver to bioequivalence has been granted by C. Chaurasia on 29-Mar-2011. The inspection of the drug product manufacturing facility, Boehringer Ingelheim Roxane Inc. is acceptable per OC on 10-Jan-2011. (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance: Maximum Daily Dose: 9 g

Sodium Oxybate (aqueous concentrate) drug substance is a clear, colorless, (b) (4) (b) (4) Sodium Oxybate is soluble in aqueous solution. (b) (4)

2. Drug product

Name	Sodium Oxybate Oral Solution
Strength/Potency	500 mg/mL
Dosage Form	Oral solution
Product Description	Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution.
Indication	Indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.
Packaging	It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert.

3. Drug Product Manufacturing:

50 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert. (b) (4) two (b) (4) dosing cups with child-resistant caps with each Sodium Oxybate Oral Solution shipment. Each white oblong HDPE bottle contains 180 mL of Sodium Oxybate Oral Solution at a concentration of 500 mg/mL and is sealed with a child resistant cap.

Storage conditions:

Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.

Tentative expiration dating: 24 months based on 3 months accelerated data and 3 months CRT data.

Solutions prepared following dilution should be consumed within 24 hours (b) (4)
(b) (4)

Sodium Oxybate Oral Solution is a Schedule III drug under the Controlled Substances Act.

Sodium Oxybate Oral Solution should be handled according to state and federal regulations. It is safe to dispose of Sodium Oxybate Oral Solution down the sanitary sewer.

CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

For questions of a medical nature or to order Sodium Oxybate Oral Solution call the Sodium Oxybate Risk Management Program at 1-800-962-8364.

Conclusion: Satisfactory from chemistry's perspective.

C. Basis for Approvability or Not-Approval Recommendation

ESTABLISHMENT INSPECTION

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Overall Pending (b) (4) DP: Boehringer Ingelheim Roxane Inc. Acceptable	03-Oct-2011 10-Jan-2011	OC

BIOEQUIVALENCE

Waiver to bioequivalence has been granted by C. Chaurasia on 29-Mar-2011.

ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

An Environmental Assessment was included on Module 1.on v.1.1. The firm requested a categorical exclusion.

Chemistry comments to be provided to the Applicant

ANDA: 202090

APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Sodium Oxybate Oral Solution, 500 mg/mL

The deficiencies presented below represent MINOR deficiencies:

A.



B.

Sincerely yours,

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 202090 Original
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-647/Yanning Lin, Ph.D./27-Oct-2011 and 03-Nov-2011

HFD-647/U.V.Venkataram Ph.D./ 03-Nov-2011

HFD-617/ T. Nhu/4-Nov-2011

F/T by UV

V:\\Chemistry Division II\\Team 22\\Final Version for Dartrts\\202090N002_RYL.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

YANNING LIN
11/04/2011

UBRANI V VENKATARAM
11/04/2011

TINA T NHU
11/04/2011

ANDA 202090

**Sodium Oxybate Oral Solution
500 mg/mL**

Roxane Laboratories, Inc.

First Generic Product

Review # 1

Yanning Lin, Ph.D.

OGD, DC II

Table of Contents

Chemistry Review Data Sheet	
The Executive Summary	
I. Recommendations	
A. Recommendation and Conclusion on Approvability	
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	
II. Summary of Chemistry Assessments	
A. Description of the Drug Product(s) and Drug Substance(s).....	
B. Description of How the Drug Product is Intended to be Used.....	
C. Basis for Approvability or Not-Approval Recommendation	
2.3.S DRUG SUBSTANCE	
2.3.S.1 General Information.....	
2.3.S.2 Manufacturer.....	
2.3.S.3 Characterization.....	
2.3.S.4 Control of Drug Substance.....	
2.3.S.5 Reference Standards and Materials.....	
2.3.S.6 Container Closure System.....	
2.3.S.7 Stability.....	
2.3.P DRUG PRODUCT	
2.3.P.1 Description and Composition of the Drug Product.....	
2.3.P.2 Pharmaceutical Development	
2.3.P.2.1 Components of the Drug Product	
2.3.P.2.2 Drug Product.....	
2.3.P.2.3 Manufacturing Process Development.....	
2.3.P.2.4 Container/Closure System	
2.3.P.3 Manufacture.....	
2.3.P.3.1 Manufacturing Process and Controls	
2.3.P.3.3 Reconciliation of the Exhibit Batch.....	
2.3.P.3.4 Unit and Batch Composition.....	
2.3.P.4 Control of Excipients	
2.3.P.5 Control of Drug Product	
2.3.P.5.1 Specifications.....	
2.3.P.5.2 Justification of Specifications.....	
2.3.P.6 Reference Standards and Materials.....	
2.3.P.7 Container/Closure System	
2.3.P.8 Stability.....	
2.3.P.8.1 Specifications.....	

Chemistry Review Data Sheet

1. ANDA#: 202090
2. REVIEW#: 1
3. REVIEW DATE: 31-Mar-2011, 02-Jun-2011 and 30-Jun-2011
4. REVIEWER: Yanning Lin, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Minor Amendment

January 11, 2011

Minor Amendment

December 03, 2010

Telephone Amendment

September 13, 2010

Minor Amendment

August 03, 2010

Filing Acknowledgment

September 22, 2010

Original Submission

July 8, 2010

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc
Address: 1809 Wilson Road
Columbus, Ohio 43228
Contact person: Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs
Telephone: (614) 272-4785
Fax: (614) 272-2470

8. DRUG PRODUCT NAME/CODE/TYPE:

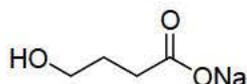
- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Sodium Oxybate Oral Solution, 500 mg/mL
- c) Code Name/# (ONDC only):None
- d) Chem. Type/Submission Priority (ONDC only):NA
 - Chem. Type: N/A
 - Submission Priority: N/A

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: Xyrem® (NDA #21-196)

Innovator Company: Jazz Pharmaceuticals

10. PHARMACOL. CATEGORY: Indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy
11. DOSAGE FORM: Oral Solution
12. STRENGTH/POTENCY: 500 mg/mL
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical name:

Butanoic acid, 4-hydroxy-, sodium salt (1:1)
 Butanoic acid, 4-hydroxy-, monosodium salt (9CI)
 Butyric acid, 4-hydroxy-, monosodium salt (8CI)
 4-Hydroxybutanoic acid sodium salt
 4-Hydroxybutyrate sodium
 4-Hydroxybutyric acid monosodium salt
 4-Hydroxybutyric acid sodium salt
 Oxybate sodium
 Sodium 4-hydroxybutyrate
 Sodium hydroxybutyrate
 Sodium oxybate
 Sodium γ -hydroxybutyrate
 Sodium γ -oxybutyrate
 γ -Hydroxybutyrate sodium
 γ -Hydroxybutyric acid sodium salt
 GHB
 NaGHB

Chemical Formula: C₄H₇NaO₃
Molecular Weight: 126.09
Cas Number: [502-85-2] (for Sodium Oxybate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: (LOA see section 1.4.1)

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	by Y. Lin on 03-31-2011 and 06-02-2011
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	
	III		4	NA	NA	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Inadequate	31-Mar-11, 02-Jun-11 and 30-Jun-11	Y. Lin
Labeling	Pending		
Bioequivalence	Waiver Granted	29-Mar-2011	C. Chaurasia
EES	Overall Pending <div style="background-color: #cccccc; padding: 2px;">(b) (4)</div> DP: Boehringer Ingelheim Roxane Inc. Acceptable	28-Sep-2010 10-Jan-2011	OC
Microbiology	N/A		
Methods Validation	Not requested per current OGD policy (USP)		
EA	Exclusion from requirement for environmental assessment		21 CFR 25.31(a)
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
 Yes No If no, explain reason(s) below:

The Chemistry Review for ANDA 202090

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry review is considered inadequate per Y. Lin on 31-Mar-2011 and 02-Jun-2011. The labeling review is pending. Waiver to bioequivalence has been granted by C. Chaurasia on 29-Mar-2011. The inspection of the drug product manufacturing facility, Boehringer Ingelheim Roxane Inc. is acceptable per OC on 10-Jan-2011. (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance: Maximum Daily Dose: 9 g

Sodium Oxybate (aqueous concentrate) drug substance is a clear, colorless, (b) (4) solution. (b) (4) Sodium Oxybate is soluble in aqueous (b) (4) solution. (b) (4)

2. Drug product

Name	Sodium Oxybate Oral Solution
Strength/Potency	500 mg/mL
Dosage Form	Oral solution
Product Description	Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution.
Indication	Indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.
Packaging	It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert.

3. Drug Product Manufacturing:

a. Formulation:

It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert. (b) (4) two (b) (4) dosing cups with child-resistant caps with each Sodium Oxybate Oral Solution shipment. Each white oblong HDPE bottle contains 180 mL of Sodium Oxybate Oral Solution at a concentration of 500 mg/mL and is sealed with a child resistant cap.

Storage conditions:

Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.

Tentative expiration dating: 24 months based on 3 months accelerated data and 3 months CRT data.

Solutions prepared following dilution should be consumed within 24 hours (b) (4)
(b) (4)

Sodium Oxybate Oral Solution is a Schedule III drug under the Controlled Substances Act.

Sodium Oxybate Oral Solution should be handled according to state and federal regulations. It is safe to dispose of Sodium Oxybate Oral Solution down the sanitary sewer.

CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

For questions of a medical nature or to order Sodium Oxybate Oral Solution call the Sodium Oxybate Risk Management Program at 1-800-962-8364.

Conclusion: Satisfactory from chemistry's perspective.

C. Basis for Approvability or Not-Approval Recommendation

ESTABLISHMENT INSPECTION

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Overall Pending (b) (4) DP: Boehringer Ingelheim Roxane Inc. Acceptable	28-Sep-2010 10-Jan-2011	OC

BIOEQUIVALENCE

Waiver to bioequivalence has been granted by C. Chaurasia on 29-Mar-2011.

ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

An Environmental Assessment was included on Module 1.on v.1.1. The firm requested a categorical exclusion.

cc: ANDA # 202090 Original
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-647/Yanning Lin, Ph.D./31-Mar-2011, 02-Jun-2011 and 30-Jun-2011

HFD-647/U.V.Venkataram Ph.D./14-Jun-2011; 30-Jun-2011 (after DDD review)

HFD-617/ T. Nhu/6-July-2011

F/T by UV

V:\\Chemistry Division II\\Team 22\\Final Version for Darrts\\202090N001_RYL.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

YANNING LIN
07/06/2011

UBRANI V VENKATARAM
07/06/2011

TINA T NHU
07/06/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 202090

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202090
Drug Product Name	Sodium Oxybate Oral Solution
Strength(s)	500 mg/mL
Applicant Name	Roxane Laboratories
Address	1809 Wilson Road Columbus, Ohio 43228
Applicant's Point of Contact	Elizabeth A. Ernst
Contact's Telephone Number	(614) 272-4785
Contact's Fax Number	(614) 276-2470
Original Submission Date(s)	July 08, 2010
Submission Date(s) of Amendment(s) Under Review	
Reviewer	Chandra S. Chaurasia, Ph.D.
Study Number (s)	N/A ¹
OUTCOME DECISION	ADEQAUTE

OVERALL REVIEW RESULT	ADEQUATE		
WAIVER REQUEST RESULT	ADEQUATE		
DSI REPORT RESULT	N/A		
BIOEQUIVALENCE STUDY	N/A		
TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	Waiver Request	500 mg/mL	ADEQUATE

¹ Not Applicable

1 EXECUTIVE SUMMARY

Roxane Laboratories is requesting a waiver of *in vivo* bioequivalence studies for its Sodium Oxybate Oral Solution, 500 mg/mL. The reference listed drug (RLD) is Xyrem[®] (Sodium Oxybate) Oral Solution, 500 mg/mL manufactured by Jazz Pharmaceuticals.

The test product contains the same amount of the active ingredient as the reference product, and does not contain any inactive ingredients, except for purified water.

The Division of Bioequivalence grants a waiver request for *in vivo* bioequivalence study requirements for the test Sodium Oxybate Oral Solution, 500 mg/mL under 21 CFR § 320.22(b)(3).

The application is acceptable with no deficiencies.

2 TABLE OF CONTENTS

1	Executive Summary	2
2	Table of Contents	3
3	Submission Summary.....	4
3.1	Drug Product Information.....	4
3.2	PK/PD Information	4
3.3	OGD Recommendations for Drug Product	5
3.4	Contents of Submission.....	6
3.5	Formulation.....	6
3.6	Waiver Request(s).....	6
3.7	Deficiency Comments	6
3.8	Recommendations.....	6
3.9	Comments for Other OGD Disciplines	7
4	Appendix	7
4.1	Formulation Data	7
4.1.1	Comments on Test Formulations.....	8
4.2	Consult Reviews.....	8
4.3	Additional Attachments.....	8
4.4	Outcome Page	10

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Sodium Oxybate Oral Solution, 500 mg/mL
Reference Product	Xyrem [®] (Sodium Oxybate) Oral Solution, 500 mg/mL
RLD Manufacturer	Jazz Pharmaceuticals
NDA No.	021196
RLD Approval Date	Jul 17, 2002
Indication²	Xyrem [®] (sodium oxybate) oral solution is indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy

3.2 PK/PD Information²

Bioavailability	Following oral administration, sodium oxybate is absorbed rapidly but incompletely, with an absolute bioavailability of about 25%. The average peak plasma concentrations (1 st and 2 nd peak) following administration of a 9 g daily dose divided into two equivalent doses given four hours apart were 78 µg/mL and 142 µg/mL, respectively.
Food Effect	Administration of sodium oxybate immediately after a high fat meal delayed the t _{max} from 0.75 hr to 2.0 hr, decreased the C _{max} by a mean of 58% and AUC by 37%.
Tmax	0.5 to 1.25 hrs
Metabolism	Metabolism is the major elimination pathway for sodium oxybate, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. No active metabolites have been identified.
Distribution	V _d ≅ 190-384 mL/kg Plasma protein binding: < 1%
Excretion	The clearance of sodium oxybate is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. Renal Excretion: < 5% of unchanged drug . Fecal Excretion: Negligible.
Half-life	0.5 to 1 hrs
Dosage and Administration	It is recommended to be taken at bedtime while in bed and again 2.5 to 4 hrs later. The dose of Xyrem [®] should be titrated to effect. The recommended starting dose is 4.5 g/night divided into two equal doses of 2.25 g. The starting dosage can then be increased to a maximum of 9 g/night in increments of 1.5 g/night (0.75 g per dose). Each dose of Xyrem [®] must be diluted with two ounces (60 mL) of water in the child-resistant dosing cups provided prior to ingestion.

² Label for Xyrem[®] solution (NDA 021196) from drugs@fda.gov as approved on 11/18/2005 (last accessed: 02/15/2010)

	<p>Because food significantly reduces the bioavailability of sodium oxybate, the patient should allow at least 2 hrs after eating before taking the first dose of sodium oxybate. Patients should try to minimize variability in the timing of dosing in relation to meals.</p>
Black-Box Warnings	<p><u>WARNING: Central nervous system depressant with abuse potential. Should not be used with alcohol or other CNS depressants.</u></p> <p>Sodium oxybate is a gamma hydroxybutyrate (GHB), a known drug of abuse. Abuse has been associated with some important central nervous system (CNS) adverse events (including death). Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Reports of respiratory depression occurred in clinical trials. Almost all of the patients who received sodium oxybate during clinical trials were receiving CNS stimulants.</p> <p>Important CNS adverse events associated with abuse of GHB include seizure, respiratory depression and profound decreases in level of consciousness, with instances of coma and death. For events that occurred outside of clinical trials, in people taking GHB for recreational purposes, the circumstances surrounding the events are often unclear (e.g., dose of GHB taken, the nature and amount of alcohol or any concomitant drugs).</p> <p>Xyrem is available through the Xyrem Success Program, using a centralized pharmacy 1-866-XYREM88[®]. The Success Program provides educational materials to the prescriber and the patient explaining the risks and proper use of sodium oxybate, and the required prescription form. Once it is documented that the patient has read and/or understood the materials, the drug will be shipped to the patient. The Xyrem Success Program also recommends patient follow-up every 3 months. Physicians are expected to report all serious adverse events to the manufacturer.</p>
Drug Specific Issues (if any)	N/A

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	N/A
Summary of OGD or DBE History	<p>The Orange Book lists Jazz Pharmaceutical's Xyrem[®] (sodium oxybate) solution, 500 mg/mL as the RLD. Presently, there is no generic product approved for the RLD.</p> <p>This application has been identified as a first generic for sodium oxybate solution, 500 mg/mL by the Regulatory Support Branch (DARRTS, ANDA 202090, REV-RPM-03(Filing Review), final date: 09/27/2010).</p>

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	---
Single-dose fed	No	---
Steady-state	No	---
In vitro dissolution	No	---
Waiver requests	Yes	1
BCS Waivers	No	---
Clinical Endpoints	No	---
Failed Studies	No	---
Amendments	No	---

3.5 Formulation

Location in appendix	Section 4.1, Page 7
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	ACCEPTABLE
If not acceptable, why?	

3.6 Waiver Request(s)

Strengths for which waivers are requested	500 mg/mL
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	YES
If not then why?	N/A

3.7 Deficiency Comments

None

3.8 Recommendations

The Division of Bioequivalence (DBE) agrees that the information submitted by Roxane Laboratories demonstrate that its Sodium Oxybate Oral Solution, 500 mg/mL meets the requirement of Section 21 CFR § 320.22(b)(3). The DBE recommends the waiver of *in vivo* bioequivalence testing be granted.

The Division of Bioequivalence deems the test product, Sodium Oxybate Oral

Solution, 500 mg/mL manufactured by Roxane Laboratories to be bioequivalent to the reference product, Xyrem® (Sodium Oxybate) Oral Solution, 500 mg/ mL, manufactured by Jazz Pharmaceuticals.

3.9 Comments for Other OGD Disciplines

Discipline	Comment
	None

4 APPENDIX

4.1 Formulation Data³

Ingredients	Function	Amount (mg/mL)	Amount (%w/w)
Sodium Oxybate (b) (4)	Active Ingredient	500 ¹ mg	100.0%
Water, Purified, USP	(b) (4)	QS	QS

¹ (b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	The test product formulation is acceptable (for detail comments, please refer to section 4.1.1 of this review).

RLD Formulation⁴ (Not to be released under FOIA)

Component	Role	Targeted Composition (b) (4)	Amount (mg/mL)
Sodium Oxybate	Active	(b) (4)	500
Purified Water, USP	(b) (4)	(b) (4)	(b) (4)
(b) (4) Malic Acid, (b) (4), NF	pH Adjustment	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

³ DARRTS, ANDA 202090, Supporting document#1, Module 2.3.P. Page# 1

⁴ DARRTS, NDA 021196, REV-QUALITY-03(General Review), final date: 06/21/2001

Comment on RLD Formulation:

(b) (4)

(b) (4)

In the supplement application NDA 21196 S 016, the RLD applicant made the changes in

(b) (4)

(b) (4) which was found acceptable⁵.

Comparative Formulation Data for Test vs. Reference, 500 mg/mL Strength

Ingredient	Amount (mg) /mL	
	Test	Reference
Sodium Oxybate	500.0	500.0
(b) (4) Malic Acid, (b) (4) NF	-	(b) (4)
(b) (4)	-	(b) (4)
Purified Water	QS	QS

4.1.1 Comments on Test Formulations

1. The test product is an oral solution, containing active ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application.
2. The test product, 500 mg/mL does not contain any inactive ingredients, except for purified water, whereas the reference product, 500 mg/mL contains malic acid (b) (4) as needed for pH adjustment. However, the pH (b) (4) (b) (4) for release and stability of the test product, 500 mg/mL are similar to the pH (b) (4) for release and stability of the reference product, 500 mg/mL. The role of malic acid in the reference product is pH adjuster. Absence of malic acid in the test product formulation is not expected to significantly affect the absorption of the active drug ingredient compared to the reference drug product. Therefore, the test product formulation is acceptable.

4.2 Consult Reviews

N/A

4.3 Additional Attachments

None

⁵ DARRTS, NDA 021196, REV-QUALITY-03(General Review), final date: 04/28/2010

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 202090

APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Sodium Oxybate Oral Solution, 500 mg/mL

The Division of Bioequivalence (DBE) has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.4 Outcome Page

ANDA: 202090

Completed Assignment for 202090 ID: 13275

Reviewer: Kaur, Paramjeet

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description:

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>		
13275	7/8/2010	Other	Waiver Oral Solution	1	1	Edit	Delete
				Bean Total:	1		

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Oral Solution Waiver(s)	
Strength 1	1
<i>Oral Solution/Waiver Total</i>	<i>1</i>

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

/s/

CHANDRA S CHAURASIA
03/29/2011

ETHAN M STIER on behalf of BARBARA M DAVIT
03/29/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 202090

OTHER REVIEWS

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	ANDA
Application Number	(b) (4) 203631, 203351, 202090
Goal Date (internal)	January 17, 2017
OSE RCM #	2016-954
Reviewer Name(s)	Laura Zendel, PharmD
Health Communications Analyst	Anahita Tavakoli, M.A.
Acting DRISK Team Leader	Donella Fitzgerald, PharmD
Acting DRISK Deputy Director	Jamie Wilkins Parker, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	1/13/2017
Subject	Final Evaluation of proposed shared ANDA REMS for sodium oxybate
Established Name	sodium oxybate
Sponsors	(b) (4) 203631 Amneal Pharmaceuticals 203351 Ohm Laboratories Inc. 202090 Roxane Laboratories Inc.
Review Division	Office of Generic Drugs (OGD)
Therapeutic Class	Central Nervous System depressant
Formulation(s)	Oral solution in concentration of 0.5 g/mL
Dosing Regimen	Recommended starting dose of 4.5g (maximum 9.0g) administered orally at bedtime in two divided doses

Table of Contents

1 Executive Summary	4
2 Introduction	5
3 Background	5
3.1 Product Information	5
Table 1. Xyrem Dose Regimen	5
3.2 Xyrem REMS	6
Table 2. Abbreviated Summary of Approved Xyrem REMS	7
3.3 Regulatory History.....	7
4 Results of the Review of the ANDA Group’s Proposed REMS.....	12
4.1 REMS Goals	12
4.2 REMS Elements	12
4.2.1 Medication Guide	12
4.2.2 Elements to Assure Safe Use	12
4.2.3 Implementation System	19
4.3 REMS Supporting Document	20
4.3.1 REMS Assessment Plan.....	20
4.4 REMS Appended Materials.....	20
4.4.1 Sodium Oxybate REMS Program Prescriber Enrollment Form	21
4.4.2 Sodium Oxybate REMS Program Prescriber Brochure	21
4.4.3 Sodium Oxybate REMS Program Patient Enrollment Form	21
4.4.4 Sodium Oxybate REMS Program Prescription Form.....	21
4.4.5 Sodium Oxybate REMS Program Quick Start Guide for Patients	22
4.4.6 Sodium Oxybate REMS Program Certified Pharmacy Training Modules A and B	22
4.4.7 Sodium Oxybate REMS Program Patient Counseling Checklist.....	27

4.4.8 Sodium oxybate REMS Program Risk Management Report (RMR)	27
4.4.9 Sodium Oxybate REMS Program Pharmacy Enrollment Form	28
4.4.10 Sodium Oxybate REMS Program Website Screen Shots	28
5 Discussion	29
6 Conclusion and Recommendations	31
7 Appendices	36
7.1 Materials Reviewed	36
7.2 Appended materials	36

1 Executive Summary

This review by the Division of Risk Management (DRISK) evaluates the proposed shared risk evaluation and mitigation strategy (REMS) for generic products referencing Xyrem (sodium oxybate), received by the Office of Generic Drugs (OGD) on April 8, 2016, and amended on June 6, 2016, August 22, 2016, and December 2, 2016 by the abbreviated new drug applications (ANDAs): (b) (4)

(b) (4) Amneal Pharmaceuticals (ANDA 203631), Ohm Laboratories Inc. (ANDA 203351), and Roxane Laboratories Inc. (ANDA 202090). (b) (4)

Per statutory requirements described in section 505-1(h)(9)(i)(1) of the Food, Drug, and Cosmetic Act (FDCA) as amended by the Food and Drug Administration Amendments Act (FDAAA), the ANDAs of sodium oxybate shall use a single, shared system (SSS) REMS with the reference label drug (RLD) unless FDA waives that requirement and permits the ANDAs to use a different, but comparable aspect of the elements to assure safe use (ETASU). The ANDAs for sodium oxybate seek a waiver of the SSS requirement and approval of a separate REMS for the generic products referencing Xyrem.

The Xyrem REMS, approved on February 27, 2015 and most recently modified on July 15, 2015, includes a Medication Guide (MG) and ETASU to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion¹ of Xyrem.

The ANDA group submitted a separate proposed REMS, herein referred to as the ANDA REMS, which has the same goals and the same ETASU as the Xyrem REMS. It proposes operational differences in certain aspects of the ETASU that are comparable to the Xyrem REMS. DRISK has determined that, as designed, the proposed REMS for sodium oxybate will achieve the same level of patient safety as the approved Xyrem REMS. The ANDA group's proposed ANDA program differs operationally from the Xyrem REMS program by: 1) including a requirement for the prescriber to submit the sodium oxybate prescription form to one of the certified pharmacies; 2) proposing the use of multiple certified pharmacies with use of a duplicate claim safeguard; and 3) use of multiple databases which are connected through an electronic telecommunication verification, commonly referred to as a "switch." Preliminary comments were shared with the ANDA group via teleconference on 7/21/2016. Additional comments were shared with the ANDA group in a review dated 10/12/2016. To facilitate discussion and gain clarity on certain aspects of the ANDA REMS Program, face-to-face meetings were held between the Agency and the ANDA group on 11/9/2016 and 11/10/2016 with additional teleconferences on 11/30/2016 and 12/1/2016. The ANDA group submitted an amended REMS document, supporting document and appended materials in response on December 2, 2016.

¹ The goal of mitigating diversion in this REMS refers to preventing the sale or transfer of the drug outside the framework of the REMS in order to mitigate the risks of central nervous system depression, respiratory depression, abuse, and misuse.

2 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed shared risk evaluation and mitigation strategy (REMS) for generic sodium oxybate oral solution (received on April 8, 2016, and amended on June 6, 2016, August 22 2016, and December 2, 2016) submitted by following the abbreviated new drug applications (ANDAs) [REDACTED] (b) (4) [REDACTED] (b) (4) Amneal Pharmaceuticals (ANDA 203631), Ohm Laboratories Inc. (ANDA 203351), and Roxane Laboratories Inc. (ANDA 202090), herein referred to in this review as the ANDA group. Preliminary comments were shared with the ANDA group (via teleconference) on 7/21/2016. The ANDA group submitted an amended REMS document, supporting document and REMS appended materials on August 22, 2016 and additional comments were provided to the ANDA group on October 12, 2016. On November 3, 2016, the ANDA group and the Agency met via teleconference to discuss the comments. The ANDA group and the Agency met face to face on November 9 and 10, 2016 to further discuss the REMS Program. The ANDA group submitted an amended REMS document, supporting document and appended materials on December 2, 2016, which is the subject of this review.

3 Background

3.1 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 depressant. Xyrem was approved with restrictions to assure safe use under 21 CFR 314.520 (subpart H) in 2002 for the treatment of cataplexy in narcolepsy and in 2005 for the treatment of excessive daytime sleepiness (EDS) in narcolepsy.

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 (see Table 1).

Table 1. Xyrem Dose Regimen

If a Patient's Total Nightly Dose is:	Take at Bedtime:	Take 2.5-4 hours later:
4.5 g/night	2.25 g	2.25 g
6.0 g/night	3.0 g	3.0 g
7.5 g/night	3.75 g	3.75 g
9.0 g/night	4.5 g	4.5 g

Recommended dosing states to increase the dose 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 g to 9 g per night

orally. As stated in the package insert, *doses higher than 9 g per night have not been studied and should not ordinarily be administered.*²

The Medication Guide includes the following instructions: “Take your first Xyrem dose at bedtime while you are in bed. Take your second Xyrem dose 2 ½ to 4 hours after you take your first Xyrem dose. You may want to set an alarm clock to make sure you wake up to take your second Xyrem dose. You should remain in bed after taking the first and second doses of Xyrem.”

3.2 Xyrem REMS

Xyrem (sodium oxybate) oral solution formulation was approved by the FDA on July 17, 2002 for the treatment of cataplexy in patients with narcolepsy, and on November 18, 2005 for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. Sodium oxybate is a controlled substance classified as schedule III in its approved form and as schedule I for illicit use (gamma-hydroxybutyrate, or GHB, is known as the “date rape drug”) and is also associated with central nervous system and respiratory depression. The Xyrem approval was under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) with a risk management plan to assure safe use of the product. The risk management plan proposed by Jazz contained a requirement that the drug be dispensed only from a single, central pharmacy. Xyrem was approved with a risk management plan which included implementation of a restricted distribution program, patient and prescriber education regarding the risks and benefits of Xyrem including critical information necessary for the safe use and handling of the drug, filling of the initial prescription only after the prescriber and patient have received and read the educational materials, and maintenance of a registry of all patients and a record of all prescribers.

On the effective date of Food and Drug Administration Amendments Act of 2007 (FDAAA), Xyrem was identified as a product deemed to have in effect an approved REMS because there were elements to assure safe use in effect. As part of the negotiations for a final REMS, Jazz proposed removing the requirement for a single pharmacy and instead allowing certification of multiple pharmacies. Later that year (2009), Jazz also submitted a supplement for a new indication for fibromyalgia, and in that supplement proposed a REMS with multiple certified pharmacies. FDA rejected the application for fibromyalgia, but did so on grounds unrelated to the multiple pharmacy certification.³ Following the rejection of the fibromyalgia application, negotiation of the final REMS for Xyrem continued. FDA explained to Jazz that its final REMS should not contain the restriction to a single pharmacy, but should instead contain the stringent requirements for pharmacy certification necessary to control distribution of the drug. By early 2011, however, Jazz changed its position and began insisting that the single

² Xyrem (sodium oxybate) [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. Revised April 2015.

³ Complete Response Letter for NDA 022531, dated October 8, 2010

pharmacy requirement remain.⁴ In December 2013, the Agency sent a REMS modification notification letter to Jazz that included required removal of the single pharmacy requirement. Jazz filed a dispute resolution request. When the request was denied, Jazz appealed. On February 27, 2015, in the hopes of bringing the protracted negotiations and dispute to a close, the Agency approved the REMS Jazz proposed (i.e., with the single, central pharmacy requirement). The approval letter included language making clear the Agency does not think the requirement of a single pharmacy is the only way to safely distribute the drug. The approval letter also stated the Agency would consider future modifications as necessary and the dispute was denied as moot.

Table 2. Abbreviated Summary of Approved Xyrem REMS

REMS Goals	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, and patients 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.
REMS Elements	Medication Guide
	Prescriber Certification - Special certification of healthcare providers (HCPs) who prescribe Xyrem: ensures enrollment in the Xyrem REMS Program and understanding of Prescriber Brochure.
	Pharmacy Certification – Special certification of central pharmacy (not stocked in retail pharmacy outlets): ensures enrollment in Xyrem REMS Program, completion of pharmacy training, completion of Patient Counseling Checklist, review of Central Database, shipment directly to patient
	Documentation of safe use conditions – Patients must sign Patient Enrollment Form
Implementation System	Monitor compliance with prescriber, pharmacy, and patient enrollment, maintenance of Central Database

3.3 Regulatory History

The following is a summary of the regulatory history for the ANDAs for sodium oxybate and Xyrem, relevant to this review:

- 07/07/2002: The Agency approved Xyrem for the treatment of cataplexy (orphan designation) with restricted distribution under a Risk Management and Action Plan (RiskMAP) called the Xyrem Success Program. The key features of the RiskMAP included: Mandatory enrollment and education of prescribers and patients; restricted distribution of Xyrem dispensed via a single central pharmacy by direct shipping after verification of the prescription, and prescriber/patient information.

⁴ Kumar, J. DRISK. Final REMS Review for Xyrem, dated February 27, 2015.

- 03/28/2008: After the FDAAA of 2007 was passed, the Agency published in the Federal Register (FR)14 a list of drugs that were deemed to have an approved REMS and directed holders of approved applications for those products to submit a proposed REMS by September 21, 2008; Xyrem was included in the list of deemed products.
- 07/08/2010: The Agency received ANDA 202090 for sodium oxybate oral solution from Roxane.
- 10/19/2011: Roxane submitted a proposed REMS for sodium oxybate oral solution.
- [REDACTED] (b) (4)
- 09/27/2012: The Agency sent a REMS Notification Letter/"Information Request Letter" to Roxane regarding requirements for a single shared REMS program for Sodium Oxybate Oral Solution. This letter identified Jennifer Ekelund as the Jazz Pharmaceuticals contact person for the development of the single shared system (SSS)
- 10/14/2012: Roxane (Gregory Hicks, Associate Director, REMS, Labeling, and Drug Safety) sent letter to Jennifer Ekelund (Executive Director, Regulatory Affairs, Jazz Pharmaceuticals) to request a teleconference with appropriate representatives from each company to begin the process of developing a SSS REMS for sodium oxybate.
- [REDACTED] (b) (4)
- 03/20/2013: Roxane received a Complete Response Letter (CRL) for ANDA 202090, which included product quality and labeling deficiencies. The CRL encouraged the Sponsor to work towards a SSS REMS with the innovator or opt to develop and submit a RiskMAP.
- 04/16/2013: Roxane submitted an amendment to the proposed REMS in response to receiving the CRL on 03/20/2013.
- [REDACTED] (b) (4)
- [REDACTED]
- 01/23/2014: The Agency facilitated a "kick-off" meeting between the Agency, Jazz and ANDA sponsors (Roxane, Amneal, [REDACTED] (b) (4)) to assist in the development of a SSS REMS for sodium oxybate. [REDACTED] (b) (4)
- [REDACTED] (b) (4) It was determined that Roxane would provide a draft confidential disclosure agreement (CDA) to the group for discussion shortly after the meeting.
- 03/05/2014: Teleconference with Amneal, Roxane, [REDACTED] (b) (4) to discuss recent information identified in Jazz's Q4 2013 earnings call regarding Jazz entering into formal dispute resolution with FDA. The ANDAs inquired whether they should proceed with REMS negotiations without

Jazz until the dispute was resolved. The Agency responded that all parties should continue to work together to form a SSS REMS unless otherwise notified by FDA.

- [REDACTED] (b) (4)
- [REDACTED]
- 2/04/2015: Meeting between the Agency and ANDAs to discuss the possibility of a waiver of the SSS requirement and the ANDA's proposed distribution model for use in a separate REMS.
- 02/27/2015: The Agency approved the Xyrem REMS, although it contained areas where the Agency was not aligned with Jazz, including the use of the word “diversion” and restriction to a “single, central pharmacy.” The Agency noted that the action of approving the REMS submitted by Jazz should not be construed or understood as agreement with Jazz that limiting the dispensing to a single pharmacy is the only way to ensure that the benefits of Xyrem outweigh the risks under section 505-1 of the FD&C Act.
- 06/09/2015: The ANDAs met with the Agency and discussed the status of the SSS REMS negotiations. The Agency and the ANDAs discussed the REMS requirements for the ANDAs if they were to seek a waiver of the SSS requirement and propose a separate REMS.
- 07/15/2015: The Agency approved a REMS Modification for Xyrem. The modification included revisions to labeling including: “Xyrem Success Program” modified to “Xyrem REMS Program” and references to a “centralized pharmacy” or a “central pharmacy” revised to “central pharmacy that is specially certified” throughout the Xyrem labeling and Medication Guide to be consistent with the approved REMS.
- [REDACTED] (b) (4)
- 08/19/2015: The ANDAs emailed the Agency to report a “lack of progress with Jazz on key terms for an operating agreement.” The ANDAs indicated that, as a result of the lack of progress, they intended to develop a proposal for a separate REMS
- 10/13/2015: The Agency met with the ANDAs and Jazz via teleconference to find out more about the status of the negotiations and understand what the major issues are to accurately assess the status of the development process. Two threshold issues were identified, the first being voting rights and the second being related to the process for negotiating a SSS – parallel vs. sequential legal and operational discussions.
- 12/04/2015: Jazz submitted a letter to the Agency expressing its opposition to a potential waiver of the SSS requirement.
- 1/20/2016: The Agency met with the ANDAs as a follow-up to the meetings on 06/09/2015 and 10/13/2015. The ANDAs provided a diagram of their proposed Sodium Oxybate REMS Model. During the meeting, the draft diagram was reviewed and the sponsors provided additional information.

- 03/23/2016: Teleconference between Jazz, the ANDAs, and the Agency to provide the Agency with a status of SSS REMS negotiations. The Agency was made aware that the sponsors still have not agreed on basic terms such as voting rights.
- 04/08/2016: The ANDAs submitted a draft shared sodium oxybate REMS Document, Appended Materials, and Supporting Document developed jointly by the current ANDAs.
- 05/06/2016: Teleconference between the Agency and the ANDAs to clarify components of the proposed sodium oxybate ANDA REMS submission. The ANDAs clarified that an electronic telecommunication system or “switch system” would be used to check prescriptions within the separate, distinct, REMS databases. The Agency communicated that an updated Supporting Document was needed to provide details of the REMS functionality.
- 06/06/2016: A REMS amendment was submitted by the ANDAs to include proposed changes to the Sodium Oxybate REMS Supporting Document.
- 06/16/2016: Teleconference between the Agency and the ANDAs to discuss Agency proposed changes to the Sodium Oxybate REMS and discuss procedural timelines for implementation of the REMS program. The Agency proposed to mitigate the risk of duplicate dispensing by requiring the ANDA pharmacies to report all prescriptions received for sodium oxybate and report and verify disenrollment of prescribers/patients that is specifically related to abuse, misuse, and diversion to the Xyrem REMS Program Central Database.
- 7/21/2016: Teleconference between the Agency and the ANDAs during which the Agency provided feedback on its initial review of the proposed Sodium Oxybate REMS Document, Supporting Document, and Appended Materials.
- 8/22/2016: A REMS amendment was submitted by the ANDA group to include proposed changes to the Sodium Oxybate REMS Document, Supporting Document and Appended Materials.
- 9/2/2016: An Information Request (IR) was sent to the ANDA group requesting clarification of the disenrollment process including time to disenrollment from the initial decision to disenroll and how patient and prescriber data will be reflected in the databases post-disenrollment.
- 9/9/2016: An IR was sent to the ANDA group requesting clarification of terms necessary to describe the databases, the definition of “(b) (4)” with regard to enrollment status, and the necessity to qualify the patient database as “enrolled patient database.”
- 9/14/2016: The ANDA group submitted an IR response via email for both the 9/2/2016 and 9/9/2016 IRs clarifying the disenrollment process, terms necessary to describe the databases, and agreed to remove the term “(b) (4)” to describe enrollment status and the term “enrolled” to describe the patient database.
- 10/12/2016: Interim comments were sent to the ANDA group regarding the 8/22/2016 submission.

- 11/3/2016: Teleconference between the ANDA group and the Agency in which the ANDA group requested a face-to-face meeting with the agency to discuss the interim comments. The ANDA group explained that although many of the recommendations were typographical in nature from the Agency's perspective, they might have a larger impact on the functionality of the REMS program than anticipated. The Agency agreed that a face-to-face meeting would be beneficial.
- 11/9/2016 – 11/10/2016: Face to Face meeting between the ANDA group and the Agency. The ANDA group clarified that the certified pharmacies will not have access to the databases and proposed that the patient counseling checklist be completed with every dispensation of sodium oxybate and faxed or sent electronically via the website to the Sodium Oxybate REMS program who will then update the databases. Additionally, there will be a secure web portal where pharmacies will be able to access data from the patient database to evaluate concomitant medications and RMR histories. The ANDA group noted that different terms were used to describe prescribers (enrolled vs. certified) and proposed the use of "certified prescribers" to be used throughout the REMS document and appended materials, to which the Agency agreed. The ANDA group clarified the disenrollment procedures for patients and prescribers and proposed the use of the RMR form for certified pharmacies to direct the Sodium Oxybate REMS Program to disenroll a patient or prescriber and that the Sodium Oxybate REMS Program, not the certified pharmacy, would alert the Xyrem REMS Program of the disenrollment. The Agency requested that the ANDA group create a knowledge assessment for the certified pharmacy training to be included as an appendix in the supporting document, as well as to expand on the PDA process and audit plan for pharmacies and wholesalers in the supporting document.
- 11/30/2016: Teleconference between the ANDA group and the Agency to discuss database terminology in the REMS document and Sodium Oxybate REMS Program Pharmacist terminology. The ANDA group agreed to refer to the databases as secure, validated, separate, and distinct Sodium Oxybate REMS Program databases, (patient database, specially certified prescriber database, specially certified pharmacy database and disenrolled prescriber database) are maintained and will only be queried independently through electronic telecommunication verification and agreed to include a statement to ensure that all pharmacists who dispense sodium oxybate complete the Sodium Oxybate REMS Program Certified Pharmacy Training.
- 12/1/2016: Teleconference between the ANDA group and the Agency to discuss the Supporting Document and Certified Pharmacy Training. The ANDA group proposed to change the language stating that the prescription form would be sent to the Sodium Oxybate REMS Program to state that the Patient Counseling Checklist would instead be sent to the Sodium Oxybate REMS Program and used to update the patient database. The Agency requested that the ANDAs create a registration form for the wholesalers/distributors to be included as an appendix in the Supporting Document.
- 12/2/2016: A REMS amendment was submitted by the ANDA group to include proposed changes to the Sodium Oxybate REMS Document, Supporting Document and Appended Materials.

- 1/3/2017: The Agency received formal requests from Roxane, Amneal, (b) (4) (b) (4) to waive the requirement to form a single shared system REMS with the NDA holder.

4 Results of the Review of the ANDA Group's Proposed REMS

The ANDA group incorporated and responded appropriately to all of the Agency's comments and revisions requested in the 7/21/2016 teleconference, 9/2/2016, 9/9/2016, and 10/12/2016 Information Requests regarding the REMS Document and appended REMS Materials and as discussed in the 11/9/2016-11/10/2016 face to face meetings and 11/30/2016 and 12/1/2016 teleconferences.

4.1 REMS Goals

The goal of the Sodium Oxybate REMS Program is to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of sodium oxybate by:

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

Reviewer Comment:

The proposed goals of the ANDA REMS are the same as in the Xyrem REMS and are acceptable to DRISK.

4.2 REMS Elements

4.2.1 Medication Guide

The Office of Generic Drugs (OGD) Division of Labeling Review will review the Medication Guide (MG) during their review of the label for ANDAs (b) (4) 203631, 203351, 202090, and provide their comments under separate cover.

4.2.2 Elements to Assure Safe Use

The ANDA group's proposed elements to assure safe use (ETASU) are the same as the Xyrem REMS. The ANDA REMS proposes operational differences in certain aspects of the ETASU that are comparable to the Xyrem REMS. DRISK has determined that, as designed, the proposed REMS for sodium oxybate will achieve the same level of patient safety as the approved Xyrem REMS.

Displayed below are the components of the proposed ANDA REMS with corresponding reviewer

comments:

1. Healthcare Providers who prescribe sodium oxybate products are specially certified

To become specially certified to prescribe sodium oxybate, each prescriber must complete and submit to the *Sodium Oxybate REMS Program the Prescriber Enrollment Form*. By signing the form, the prescriber agrees to review the Prescribing Information and *Prescriber Brochure*; screen, counsel, enroll, and evaluate each patient, and to report adverse events and cases of abuse, misuse, or diversion to the Sodium Oxybate REMS Program. The prescriber will complete the *Prescription Form* and submit the form to one of the specially certified pharmacies.

Reviewer Comments:

The healthcare provider certification requirements for the ANDA REMS are the same as in the Xyrem REMS.

The ANDA group proposed to change (b) (4) prescribers” to “certified prescribers” as both terms were used in the REMS. Prescribers are also described as certified in the Xyrem REMS and DRISK found this to be acceptable.

The ANDA REMS differs operationally from the Xyrem REMS in that the prescriber faxes the Prescription Form to a certified pharmacy instead of the REMS program. This operational difference is justified as the certified pharmacies and the Sodium Oxybate REMS Program are separate entities in the ANDA REMS.

There are additional operational differences between the the ANDA REMS and the Xyrem REMS. The ANDA group proposes to maintain separate and distinct databases that will be queried independently through electronic telecommunication verification compared to a single central database that the Xyrem REMS sponsor maintains. The type of information collected in the databases, however, will be the same. The ANDA REMS databases will be queried via electronic telecommunication verification commonly known as a “switch.” The switch will allow the databases to be queried simultaneously behind the scenes for real time verification of the databases in a matter of seconds. DRISK finds the use of multiple databases that collect the same information as the single central database to be acceptable and offer the same level of safety.

The creation of two REMS will create some inefficiencies for prescribers. Healthcare providers who wish to have the ability to prescribe Xyrem as well as the generic product will have to enroll in both REMS programs. Thus, a prescriber already enrolled in the Xyrem REMS who wishes to prescribe generic sodium oxybate, must complete and submit a separate prescriber enrollment form to the ANDA REMS. That step need only be completed once, and the prescribing information and prescriber brochure a prescriber must review are essentially identical to the Xyrem labeling and prescriber brochure, and the required attestations on the enrollment form

are the same. Once enrolled in the ANDA REMS, the remaining requirements the prescriber carries out (patient enrollment, counseling, assessment, and adverse event reporting) are the same as under the Xyrem REMS. As such, the creation of two REMS should not impose an additional burden beyond the requirement for prescribers to separately enroll in both programs.

2. Sodium oxybate will be dispensed only by pharmacies that are specially certified

The ANDA REMS will require that all pharmacies that dispense generic sodium oxybate are certified and ANDA sponsors will ensure that generic sodium oxybate will not be stocked in retail pharmacy outlets. To become certified in the ANDA REMS, the pharmacy must agree to designate an authorized representative to complete and submit the *Pharmacy Enrollment Form* on behalf of the pharmacy and oversee implementation and compliance with the ANDA REMS by ensuring that all pharmacy staff involved in the ANDA REMS complete the *Certified Pharmacy Training Program*. The pharmacy is required to re-certify in the ANDA REMS if the pharmacy designates a new authorized representative. Other certification requirements include agreeing to provide 24-7 toll free access to a pharmacist; shipping sodium oxybate directly to each patient or patient-authorized adult designee and track and verify receipt of each shipment; to limit the first shipment to a one-month supply and subsequent shipments to no more than a three month supply; and to report adverse events to the Sodium Oxybate REMS Program.

Generic sodium oxybate will be dispensed only to patients enrolled in the Sodium Oxybate REMS Program pursuant to a valid prescription written by a prescriber specially certified in the Sodium Oxybate REMS Program. The pharmacy uses the Sodium Oxybate REMS Program to access the databases through electronic telecommunication verification to obtain a Pre-Dispense Authorization (PDA) for each prescription to verify that the pharmacy is specially certified, the prescriber is specially certified, the patient is enrolled, and the patient has no other known active generic sodium oxybate prescriptions.

Prior to dispensing generic sodium oxybate, a pharmacist completes the *Patient Counseling Checklist* and submits the checklist to the Sodium Oxybate REMS Program. Additionally, each prescription is validated by obtaining a pre-dispense authorization (PDA); reviewing patient information obtained from the website pertaining to concomitant use of sedative hypnotics, CNS depressants, or potentially interacting agents and risk management reports and alerts regarding potential abuse, misuse, or diversion; and confirming all prescription information. Lastly, the certified pharmacy will contact the Xyrem REMS Program to verify that the patient has no other active prescriptions for Xyrem that overlap with the current generic sodium oxybate prescription, verify that the patient/prescriber has not been disenrolled in the Xyrem REMS Program for suspected abuse, misuse, or diversion, and to report all prescriptions filled for generic sodium oxybate.

The certified pharmacies will monitor and report to the Sodium Oxybate REMS Program all

instances of patient or prescriber behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion of generic sodium oxybate. Pharmacies will document these events, including all requests for early refills by completing and submitting a *Sodium Oxybate REMS Program RMR Form* to the Sodium Oxybate REMS Program. 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 obtained from the Sodium Oxybate REMS Program website and ensure the request or concern has been discussed with the prescriber prior to shipping generic sodium oxybate. Pharmacies and/or prescribers that are certified in the Sodium Oxybate REMS Program may direct that a patient be disenrolled from the Sodium Oxybate REMS Program after reviewing or receiving reports of incidents suggestive of abuse, misuse, or diversion by completing and submitting a *Sodium Oxybate REMS Program RMR Form* to the Sodium Oxybate REMS Program. Pharmacies may recommend that a prescriber be disenrolled by submitting a *Sodium Oxybate REMS Program RMR Form* to the Sodium Oxybate REMS Program. The ANDA sodium oxybate sponsors will review the information and determine if the prescriber should be disenrolled.

Reviewer Comments:

Just as in the Xyrem REMS, any pharmacy that wishes to dispense generic sodium oxybate must be certified to dispense sodium oxybate. Certification requirements include the completion of an enrollment form and that the pharmacists and other staff complete a training program. Additionally, just as in the Xyrem REMS, generic sodium oxybate will not be stocked in retail pharmacies, there will be 24-7 toll free access to a pharmacist, and generic sodium oxybate will be dispensed only to enrolled patients pursuant to a valid prescription written by a certified prescriber and will be tracked and shipped by an overnight service. The certified pharmacies will also document and report adverse events as well as any cases of suspected abuse, misuse, or diversion using the risk management report (RMR).

The ANDA REMS differs from the Xyrem REMS in the following ways:

- The ANDA REMS allows for the certification of multiple pharmacies. The Agency has stated that it does not believe that limiting dispensing to a single pharmacy is the only way to ensure that the benefits of sodium oxybate outweigh the risks and has expressed concern that limiting the distribution to one pharmacy imposes burdens on patient access and the healthcare delivery system.⁵ No other currently approved REMS requires a sponsor to limit dispensing to a single pharmacy. Because the Xyrem REMS currently specifies use of only a single pharmacy, any pharmacy other than the Xyrem pharmacy would only be enrolling in the ANDA REMS and would not be enrolling in both. Therefore, any pharmacy dispensing generic sodium oxybate would need to take only one training program. To accommodate the*

⁵ Dispute Appeal Denied Letter to Jazz from Office of New Drugs, dated February 27, 2015

certification of multiple pharmacies, the ANDA group added the role of the authorized representative who will be responsible for submitting the pharmacy enrollment form and overseeing implementation and compliance with the ANDA REMS program. The inclusion of the authorized representative is a necessary addition as the pharmacies will be separate entities from the REMS program and will require a representative to perform these functions. The pharmacy is required to re-certify if the pharmacy designates a new authorized representative.

- *The ANDA REMS will use multiple databases compared to a single database used in the Xyrem REMS. The ANDA REMS program will use a switch system to query each separate database simultaneously to generate a PDA which will verify that the pharmacy is certified, the prescriber is certified, the patient is enrolled and the patient does not have any known active overlapping prescription for sodium oxybate. Obtaining a PDA is not additional burden because it is done seamlessly behind the scenes in seconds when the pharmacy enters the prescription information in to the pharmacy management system.*
- *Communication between the certified pharmacies and the Xyrem REMS is required. Pharmacies certified in the ANDA REMS must contact the Xyrem REMS Program to verify that the patient does not have an overlapping active prescription for Xyrem, that the patient/prescriber were not disenrolled from Xyrem due to suspected abuse, misuse, or diversion, and to report prescriptions being filled for sodium oxybate. This communication will be documented. The pharmacy certified in the Xyrem REMS will receive these reports and enter all relevant safety information into the Xyrem central database, as it is required to do under its REMS.⁶ The reporting of fills and disenrollment will be only a minimal additional burden on the pharmacies in both programs.*
- *In the ANDA REMS, completed forms are submitted to the Sodium Oxybate REMS Program who is responsible for updating and maintaining the databases whereas the central pharmacy updates the databases in the Xyrem REMS. A pharmacist at the certified pharmacies will complete the patient counseling checklist before every dispensation of sodium oxybate and submit it to the Sodium Oxybate REMS Program for documentation in the databases. Similarly, the completed RMR form is also submitted to the Sodium Oxybate REMS program so that RMR histories and alerts can be documented in the databases. The responsibility of maintaining and updating the databases has been removed from the certified pharmacies and transferred to the Sodium Oxybate REMS Program.*

⁶ Xyrem REMS section II(B)(2)(a)(iv), section II(B)(2)(c)(iv), section II(B)(2)(d)(i), and section II(C)(1)(c)

- *The action of reviewing concomitant medications and RMR histories and alerts was moved to the “Validate each Sodium Oxybate REMS Program prescription” section to include this action as a step in prescription validation. The same step exists in a separate section in the Xyrem REMS. The ANDA group propose that the certified pharmacies will have access to historical information contained in the patient database via the website.*
- *The RMR form is used in both REMS programs, but has additional functionality in the Sodium Oxybate REMS. As in the Xyrem REMS, the RMR form is used to record early refill requests as well as incidents suggestive of abuse, misuse, or diversion. In the Sodium Oxybate REMS, the RMR form is also used by a certified pharmacy to direct the Sodium Oxybate REMS Program to disenroll patients or prescribers due to abuse, misuse, or diversion. At the time of disenrollment, the Sodium Oxybate REMS Program will notify the Xyrem REMS program that the patient/prescriber was disenrolled. This communication to the Xyrem REMS ensures that the Xyrem REMS is aware of patients and prescribers who have been disenrolled from the ANDA REMS for suspected abuse, misuse, or diversion should they attempt to enroll in the Xyrem REMS.*
- *The ANDA sodium oxybate sponsors have an additional role in terms of pharmacy certification that is not included in the Xyrem REMS including making the enrollment form available, verification that the enrollment form is accurate and complete, notifying the pharmacy when they are successfully certified, maintaining the databases, and decertifying the pharmacies for non-compliance.*

DRISK finds these operational changes to be acceptable and comparable to the Xyrem REMS. DRISK has determined that, as designed, the ANDA REMS will achieve the same level of safety as the Xyrem REMS.

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

ANDA Sodium Oxybate sponsors will ensure that generic sodium oxybate is dispensed only by pharmacies that are specially certified in the ANDA REMS, by direct shipment, to patients (or patient-authorized adult designees) enrolled in the Sodium Oxybate REMS Program. Patients are enrolled in the ANDA REMS only if a certified prescriber completes the *Patient Enrollment Form* and submits the form to the Sodium Oxybate REMS Program. By signing the *Patient Enrollment Form*, patients acknowledge that they have been counseled and have asked the prescriber any questions they may have about sodium oxybate. Following enrollment, the patient remains in the Sodium Oxybate REMS Program unless they are disenrolled by the Sodium Oxybate REMS Program at the direction of a certified prescriber and/or pharmacy. Following disenrollment, the Sodium Oxybate REMS Program will contact the Xyrem REMS Program to report instances of patient/prescriber disenrollment in Sodium Oxybate REMS

Program due to suspected abuse, misuse, or diversion and document that the call was completed in the appropriate database.

A disenrolled patient may be re-enrolled in the Sodium Oxybate REMS Program if both the certified pharmacy and the requesting certified prescriber agree to re-enroll the patient. A patient may change prescribers if the new prescriber is also certified in the Sodium Oxybate REMS Program, and the new prescription does not overlap with another active prescription for sodium oxybate.

Reviewer Comments:

The ANDA REMS will preserve the same strong protections for patient safety as the Xyrem REMS. Patient enrollment in the ANDA REMS is the same as the Xyrem REMS. Some patients may need to be enrolled in both REMS programs by their prescriber, for instance, if they would like to switch from using the brand product to a generic. The materials required in both programs will contain the same safety messages about sodium oxybate and the Agency does not believe that the co-existence of the two REMS will be a significant burden to patients or compromise the clarity of the safety messages communicated to them. If patients do switch between the programs, the patient history data that are relevant to identifying any abuse, misuse, or diversion will not be lost. The ANDA REMS requires its certified pharmacies to contact the Xyrem REMS Program to verify that a patient has not been disenrolled from the Xyrem REMS due to suspected abuse, misuse, or diversion and identify any overlapping prescriptions prior to dispensing. The ANDA REMS further requires its certified pharmacies to communicate the patient's corresponding prescription information to the Xyrem central pharmacy who is required to enter all relevant safety information into its central database to use for prescription verification.⁷ This pharmacy-to-pharmacy communication would ensure that each REMS program can access a patient's relevant sodium oxybate history.

The ANDA REMS differs from the Xyrem REMS when it comes to disenrollment procedures. When a patient or prescriber is disenrolled in the ANDA REMS for suspected abuse, misuse or diversion, the Sodium Oxybate REMS Program will contact the Xyrem REMS Program to notify them of this disenrollment. Again, this communication would ensure that each REMS program can access a patient's relevant sodium oxybate history.

The ANDA group added language here stating that generic sodium oxybate is dispensed by direct shipment to patients or patient authorized adult designees enrolled in the Sodium Oxybate REMS Program. This reviewer has identified that a reader could interpret that the designees were enrolled, however, the REMS materials clearly state that the designees are not enrolled. Additionally, both the Xyrem REMS and ANDA REMS allow for sodium oxybate to be shipped to patient-authorized adult designees, and DRISK has determined that as stated does not result in a safety issue.

4.2.3 Implementation System

ANDA sodium oxybate sponsors will ensure that generic sodium oxybate is distributed only by wholesalers/ distributors that have registered with the ANDA REMS to pharmacies specially certified in the ANDA REMS. Generic sodium oxybate will not be stocked in retail pharmacy outlets. Generic sodium oxybate will be shipped only to patients enrolled in the ANDA REMS pursuant to a valid prescription written by a prescriber specially certified in the ANDA REMS that does not overlap with another active prescription for sodium oxybate and will include a Medication Guide with each shipment.

ANDA sodium oxybate sponsors will ensure that the secure, validated, separate, and distinct Sodium Oxybate REMS Program databases are maintained and will be queried independently through electronic telecommunication verification. Completed data forms, prescription and distribution data, as well as information related to dosing, concomitant medications, and behavior that raises suspicion of abuse, misuse, or diversion, including complete RMR histories, will be contained only in the appropriate database (patient database, specially certified prescriber database, disenrolled prescriber database, specially certified pharmacy database, wholesaler/distributor database). ANDA sodium oxybate sponsors will monitor the databases for timely reporting to specially certified prescribers and pharmacies of any behavior by enrolled patients or specially certified prescribers in the Sodium Oxybate REMS Program that raises suspicion of abuse, misuse, or diversion and to evaluate the implementation of the ANDA REMS and will ensure that appropriate corrective actions are implemented to address compliance concerns.

ANDA sodium oxybate sponsors must audit the registered wholesalers/distributors within 90 calendar days after the wholesaler/distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Sodium Oxybate REMS Program. Corrective action must be instituted by ANDA sodium oxybate sponsors if noncompliance is identified. ANDA sodium oxybate sponsors will audit all specially certified pharmacies after approval of the Sodium Oxybate REMS Program to ensure that each pharmacy implements the Sodium Oxybate REMS Program as directed within 90 calendar days after the pharmacy places its first order of sodium oxybate. Thereafter, ANDA sodium oxybate sponsors will audit at least 50% of the Sodium Oxybate REMS Program specially certified pharmacy dispensing locations at least annually, identify all issues of noncompliance, and institute appropriate corrective actions, potentially including pharmacy decertification.

ANDA sodium oxybate sponsors will monitor the Sodium Oxybate REMS Program for timely reporting of all potential adverse events and will monitor and evaluate the implementation of the ETASU and take reasonable steps to work to improve implementation of these elements.

Reviewer Comments:

The ANDA group made changes to the Implementation System to account for the operational differences between the programs. The ANDA REMS involves multiple wholesalers/distributors. As a result, each wholesaler/distributor will be registered with the ANDA REMS and will need to confirm that the

pharmacy is certified in the ANDA REMS before selling/distributing generic sodium oxybate to the pharmacy. Additionally, the ANDA Sodium Oxybate sponsors will perform audits on the wholesalers/distributors as well as the certified pharmacies to ensure that all processes and procedures are in place and functioning to support the requirements of the ANDA REMS. DRISK has determined that this is a secure and cohesive system and it does not create an increased risk of abuse, misuse, or diversion.

DRISK finds these operational changes to be acceptable and comparable to the Xyrem REMS. DRISK has determined that, as designed, the ANDA REMS will achieve the same level of safety as the Xyrem REMS.

4.3 REMS Supporting Document

The proposed REMS Supporting Document submitted describes how the ANDA REMS will implement controls to ensure appropriate prescribing, that patients are informed of the risks associated with sodium oxybate prior to initiating treatment, and appropriate dispensing.

Reviewer Comments:

The Supporting Document is consistent with the REMS and appended REMS materials. The background provides an overview of sodium oxybate product history, REMS history and the risk management approach taken by the ANDA group. The goals of the ANDA REMS are the same as the Xyrem REMS. The ETASU used in the ANDA REMS are the same as the Xyrem REMS in that healthcare providers who prescribe generic sodium oxybate are specially certified, generic sodium oxybate will be dispensed by pharmacies that are specially certified to patients who are enrolled in the Sodium Oxybate REMS Program with documentation of safe use conditions. The Supporting Document includes an Implementation System and Assessment Plan. The Supporting Document also contains the knowledge assessments for Modules A and B of the Certified Pharmacy Training as well as a Registration Form for wholesalers/distributors as an appendix. The education requirements, patient screening, counseling, and monitoring, and dispensing requirements described in the Supporting Document will ensure that the ANDA REMS maintains the same level of safety as the established Xyrem REMS.

4.3.1 REMS Assessment Plan

The Assessment Plan is appended to the supporting document and is intended to capture the metrics currently being reported for the RLD as well as additional metrics based on the operational differences for the ANDA REMS (e.g. multiple pharmacies, use of electronic PDA).

Reviewer Comments:

For the waived SSS REMS section 505-1(g)(2)(C) of the FDCA authorizes the FDA to require REMS assessments for ANDA drugs at pre-specified intervals because such assessments are necessary to evaluate whether the approved strategy should be modified. The waiver-granted REMS for generic sodium oxybate is comparable to the REMS for Xyrem, therefore the assessments being required of generic sodium oxybate will be comparable to the assessments required for Xyrem and should be submitted 18 months following the approval and every 12 months thereafter.

4.4 REMS Appended Materials

The proposed ANDA REMS includes the same appended materials as the Xyrem REMS program with the addition of a pharmacy enrollment form. The ANDA group incorporated and responded appropriately to all of the Agency's comments and revisions.

4.4.1 Sodium Oxybate REMS Program Prescriber Enrollment Form

By signing the Prescriber Enrollment Form, the prescriber attests to understand the indications for sodium oxybate, to have read the Prescribing Information and Prescriber Brochure, and agrees to enroll, screen, counsel and evaluate each patient, and to report all potential adverse events to the Sodium Oxybate REMS Program. The form includes all prescriber information including DEA number, state license number, NPI number, and facility or practice location.

Reviewer Comment:

The Sodium Oxybate REMS Program Prescriber Enrollment Form is the same as the Xyrem Prescriber Enrollment Form.

4.4.2 Sodium Oxybate REMS Program Prescriber Brochure

The Prescriber Brochure provides an overview of the ANDA REMS including important prescribing information, educational and counseling requirements and materials necessary for program certification and prescribing sodium oxybate.

Reviewer Comment:

The Sodium Oxybate Prescriber Brochure is the same as the Xyrem Prescriber Brochure except for operational differences in the programs reflected in the brochure. In the ANDA REMS the prescriber submits the enrollment forms to the Sodium Oxybate REMS Program and faxes the prescription form directly to a certified pharmacy while in the Xyrem REMS, the prescriber submits all forms to the REMS Program.

4.4.3 Sodium Oxybate REMS Program Patient Enrollment Form

By signing the Patient Enrollment Form, patients acknowledge that they have been counseled about the risks of sodium oxybate, have asked their prescriber any questions, and have been provided information that their personally identifiable information will be shared with the Sodium Oxybate REMS Program and other sodium oxybate REMS programs. By signing the Patient Enrollment Form, the prescriber acknowledges that the patient has been counseled. The Form includes patient information, insurance information and prescriber information.

Reviewer Comment:

The Sodium Oxybate Patient Enrollment form is the same as the Xyrem Patient Enrollment form except that the ANDA group added language for the patient to acknowledge that personally identifiable information provided will be shared with other sodium oxybate REMS programs, its agents, contractors, and affiliates. DRISK finds this to be acceptable as patient information will be shared with the Xyrem REMS Program as part of the duplicate claim safeguard.

4.4.4 Sodium Oxybate REMS Program Prescription Form

By signing the prescription form, the prescriber attests to understanding the approved indications of sodium oxybate and important safety information, to have read the prescribing information and prescriber brochure, and that the patient has been screened and counseled. The form includes prescriber information, patient information, fixed or titrated dosing schedules, dispensing instructions, and a pharmacy section to document that the Xyrem REMS program has been contacted to confirm that the patient has no other active prescriptions for sodium oxybate, that the patient and prescriber have not been disenrolled in the Xyrem REMS Program for suspected abuse, misuse, or diversion, and to report that a prescription for generic sodium oxybate is being filled for the patient. The Prescription Form also notes that that the form may not satisfy all legal requirements for prescribing sodium oxybate in all states and instructs prescribers to submit all prescriptions in accordance with applicable state laws.

Reviewer Comment:

The Sodium Oxybate Prescription form is the same as the Xyrem Prescription Form except for changes resulting from operational differences in the programs. Before dispensing generic sodium oxybate, the pharmacy will contact the Xyrem REMS program to verify that the patient has no other active prescriptions for sodium oxybate (Xyrem) that overlap with the current prescription for generic sodium oxybate; to verify that the patient and prescriber have not been disenrolled in the Xyrem REMS Program for suspected abuse, misuse, or diversion; and to report to the Xyrem REMS Program that a prescription for generic sodium oxybate will be filled for the patient. The ANDA group proposes adding a section at the end of the Prescription Form “For Pharmacy Use Only” to document this interaction. DRISK finds this to be acceptable. Additionally, this prescription form may not meet legal requirements for prescribing controlled substances in all states. Therefore, the ANDA group added a disclaimer informing prescribers to follow applicable requirements for writing prescriptions for controlled substances per their state law that may be required in addition to completing this prescription form.

4.4.5 Sodium Oxybate REMS Program Quick Start Guide for Patients

The Quick Start Guide for Patients informs patients of the serious side effects and drug interactions associated with sodium oxybate and how to obtain, use, and store sodium oxybate safely.

Reviewer Comment:

The Sodium Oxybate REMS Program Quick Start Guide for Patients is the same as the Xyrem Quick Start Guide aside from a caption on the pictogram on page 14. DRISK finds the caption to be appropriate to indicate that products from different companies may not be identical.

4.4.6 Sodium Oxybate REMS Program Certified Pharmacy Training Modules A and B

The Certified Pharmacy Training consists of two modules, A and B. Module A is for all pharmacy staff who handle generic sodium oxybate, including pharmacists. Module A reviews the indications and usage, how supplied, controlled substance scheduling, boxed warning, contraindications, as well as warnings and precautions. Module A also goes over ANDA REMS requirements including details of certified pharmacy responsibilities, prescription processing, shipping, and monitoring for inappropriate prescribing, abuse, misuse and diversion. Module B provides additional training for pharmacists

involved with dispensing of generic sodium oxybate. It reiterates the ANDA REMS requirements and certified pharmacy responsibilities and focuses on patient counseling and screening, clinical usage clarifications, prescription refills, monitoring and assessing for signs of abuse, misuse, and diversion, shipping procedures and inventory control.

Reviewer Comment:

While there are differences in the Sodium Oxybate REMS Program Certified Training compared to the approved Xyrem REMS Program, these differences reflect the operational functions of the Sodium Oxybate REMS Program. These functional changes include use of multiple certified pharmacies, multiple databases that are connected, and use of the Sodium Oxybate REMS secure web portal to view patient information housed in the Sodium Oxybate REMS Program patient database.

Module A:

The ANDA REMS Pharmacy Training contains identical important safety information, indications and usage, how supplied, controlled substance scheduling, boxed warning, contraindications, warnings and precautions, shipping procedures, and ongoing patient education. The training for the ANDA REMS Program contains differences in some nuances in wording. For example, Xyrem refers to enrolled prescribers and central pharmacy while the ANDA REMS refers to certified prescribers and certified pharmacies.

The section on databases was removed from the ANDA REMS Pharmacy Training because maintenance of the databases is a function of the Sodium Oxybate REMS Program, not the pharmacies. DRISK agrees that training on maintenance of databases is not applicable to the certified pharmacies in the ANDA REMS.

Enrollment processing and maintenance was changed to enrollment verification because the pharmacies are not responsible for enrollment processing/maintenance, but do need to verify prescriber and patient enrollment. The content in the enrollment verification section in the ANDA REMS Pharmacy Training is identical to the content in the enrollment processing/maintenance section of Xyrem pharmacy training with the following exceptions:

- *Information from the enrollment forms is maintained in the appropriate Sodium Oxybate REMS Program database by the Sodium Oxybate REMS Program instead of the certified pharmacies.*
- *Information regarding procedures to follow when a new patient enrollment form is received was removed, as this is a function of the Sodium Oxybate REMS Program, not the certified pharmacies.*
- *The ANDA REMS pharmacies will provide patient counseling with every dispensation.*
- *The Sodium Oxybate REMS Program will notify prescribers of successful enrollment and successful patient enrollment in the ANDA REMS instead of the certified pharmacies.*

- *Procedures for verification of enrollment (ex. confirm the prescriber’s DEA and state license numbers are active, etc.) were removed, as this is a function of the Sodium Oxybate REMS Program.*
- *The ANDA REMS has added, “A certified prescriber and/or a certified pharmacy can direct that a patient be disenrolled from the Sodium Oxybate REMS Program” to align with differences in disenrollment procedures. Reasons for patient disenrollment are the same.*
- *The Sodium Oxybate REMS Program will contact a prescriber if an enrollment form is received for a patient previously disenrolled in the program for suspicions of abuse, misuse, or diversion instead of the pharmacy.*

DRISK finds these changes to be acceptable as some of the responsibilities of the central pharmacy in the Xyrem REMS have been shifted to the Sodium Oxybate REMS Program instead of the certified pharmacies in the ANDA REMS. The responsibilities are the same, simply performed by a separate entity in a different location.

Both pharmacy training programs have a section for prescription processing. Some of the processes differ but they achieve the same results. The Xyrem REMS states that the prescription information will be entered into the central database. In the ANDA REMS, the pharmacy does not have access to update the database directly, so it skips this and moves on to prescription validation. The information will be entered into the databases by the Sodium Oxybate REMS Program by obtaining a PDA and by submitting the prescription form and patient counseling checklist. Steps that are the same include:

- *Verify that the prescription form is complete and signed by the prescriber*
- *Verify that the prescription form was received from the prescriber’s office*
- *The prescription is for only a 1-month supply on a patient’s first sodium oxybate fill and no more than a 3 month supply on subsequent fills*
- *There are no discrepancies or concerns with dosing and titration (contact prescriber if discrepancies or concerns are found)*
- *Contact the prescriber if overlapping prescriptions are received*
- *If there is suspected abuse, misuse, or diversion, the prescription is not filled and an RMR is completed*
- *Valid reasons for overlapping prescriptions*
 - *If the pharmacy determines that the reason for an overlapping prescription is valid, the pharmacy must ensure that the patient does not receive multiple overlapping prescriptions.*

Both programs also need to verify that the prescriber is enrolled/certified, the patient is enrolled and the patient has no other active sodium oxybate prescriptions. The process for doing this is different. In Xyrem, this information is verified by checking the databases. In the ANDA REMS, this is done by obtaining a PDA which will also confirm that the pharmacy is certified. Obtaining a PDA is not additional burden because it is done seamlessly behind the scenes in seconds when the pharmacy

enters the prescription information in to the pharmacy management system. Additionally, the ANDA REMS includes an extra step which involves the certified pharmacy contacting the Xyrem REMS to verify that the patient does not have any overlapping prescription for Xyrem, that the patient/prescriber was not disenrolled from Xyrem for suspected abuse, misuse, or diversion, and to report that a generic sodium oxybate prescription is being filled for the patient. This could be perceived as additional burden since it requires an extra step, but this burden is minimal and it is a necessary step to ensure that there is no overlapping Xyrem/sodium oxybate prescription.

The ANDA REMS has moved the step for reviewing for use on concomitant use of sedative hypnotics and RMR histories to the prescription verification process. Both programs must review this information; however, the location of this step is different.

Once the prescription is validated, both programs contact the patient to schedule shipment and complete required counseling. The ANDA REMS differs in that it instructs the pharmacy to provide the Patient Quick Start Guide to all new patients (not only to those who have not received it from the prescriber) and to complete the patient-counseling checklist prior every dispensation of generic sodium oxybate. The completed checklist is then submitted to the Sodium Oxybate REMS Program.

Both programs require monitoring for inappropriate prescribing, abuse, misuse, and diversion. Both programs use the RMR to document early refill requests and instances of patient and prescriber behavior that suggest potential abuse, misuse, or diversion and both require that the information be maintained in the database(s). Because the certified pharmacies in the ANDA REMS cannot update the databases, they are required to submit the RMR to the Sodium Oxybate REMS Program who will use it to update the databases. The RMR has an additional purpose in the ANDA REMS as it can be used to direct that a patient or prescriber be disenrolled due to suspected abuse, misuse, or diversion. Adverse event reporting differs in the ANDA REMS in that adverse events related to suspected abuse, misuse, or diversion are reported using the RMR form while all other adverse events are reported by calling the Sodium Oxybate REMS Program who will then notify the ANDA sodium oxybate sponsors. Adverse events are reported directly to Jazz Pharmaceuticals in the Xyrem REMS.

Module B

Both programs require all pharmacists to complete the pharmacist training at least annually. The ANDA REMS differs in the explanation of the training pertaining to new pharmacists. Xyrem explains that training typically lasts from three to four weeks, extended as information retention of the trainee dictates, conducted by a pharmacist currently specializing in the Xyrem REMS Program and continues with a senior pharmacist acting as a mentor. The ANDA REMS requires that pharmacists be thoroughly trained on the requirements of the Sodium Oxybate REMS Program including review of the certified pharmacy's internal processes and procedures established to support the Sodium Oxybate REMs Program with an experienced pharmacist. The ANDA REMS does not specify the duration of training, but does include the same duties that a pharmacist must perform to ensure competency.

Sodium Oxybate REMS Program Requirements are nearly identical to the Xyrem REMS Requirements. The ANDA REMS requires prescription forms to be submitted to the certified pharmacies instead of the REMS program. The ANDA group added that after completion of prescription processing, the pharmacy will fax the prescription form to the Sodium Oxybate REMS Program and retain the original. Upon review, the Agency does not find this to present a safety issue.

Certified pharmacy responsibilities are also nearly the same in both programs. The ANDA REMS has added that the RMR should be submitted to the Sodium Oxybate REMS Program [for documentation in the databases]. The databases are described in the ANDA REMS as secure, validated, separate and distinct (patient database, certified prescriber database, certified pharmacy database, and disenrolled prescriber database) that will only be queried independently through electronic telecommunication verification. The information contained within the databases is the same. Historical data contained in the databases is accessed using the certified pharmacy secure web-viewing portal in the ANDA REMS that gives the pharmacy direct access for viewing pertinent information without the ability to update the databases.

Patient counseling and screening is the same in both programs except for the timing of the counseling. In the Xyrem REMS, the patient counseling checklist is required to be completed in its entirety for initial prescriptions and for patients who are restarting after not receiving Xyrem for six or more months. The patient counseling checklist steps one, three, four, and five are completed for renewals and refills if the patient has indicated a change in his or her health or medications. In the ANDA REMS, the patient counseling checklist is required to be completed in its entirety for all dispensations of generic sodium oxybate and submitted to the Sodium Oxybate REMS Program for documentation.

Clinical usage clarifications and shipping procedures are the same in both programs.

The prescription refill process is nearly identical in both programs. The ANDA REMS differs in that it specifies that refills may be conveyed by phone or fax from the prescriber or patient indicating that the patient can contact the pharmacy to request a refill and that refills are communicated to the Sodium Oxybate REMS Program by obtaining a PDA. The patient counseling checklist is completed for all refills and the completed checklist is submitted to the Sodium Oxybate REMS Program for documentation. For early refill requests, the patient's record is evaluated similarly by using the certified pharmacy secure web-viewing portal for the patient database. Documentation of the discussion between the pharmacy and the prescriber regarding the early refill request is performed by submitting the RMR to the Sodium Oxybate REMS Program.

Both programs require monitoring and assessing for signs of abuse, misuse, and diversion and recording the events using the RMR form. Examples of events that should generate an RMR are the same and information documented on the RMR is the same. The ANDA REMS adds that pharmacies can request that a patient is monitored by the Sodium Oxybate REMS Program if serious or repeated events give rise to reasonable suspicion of misuse, abuse, or diversion. The RMR form has additional

functionality in the ANDA REMS in that it can be used to direct that a patient or prescriber be disenrolled for suspected abuse, misuse or diversion. RMRs are submitted to the Sodium Oxybate REMS Program online or by fax.

Inventory control is similar. Inventory is recorded in the central database in the Xyrem REMS and in the pharmacy management system in the ANDA REMS. Both require that inventory be reconciled at the start and end of each business day and a physical count must match the count in the database/pharmacy management system. If the inventory cannot be reconciled, no orders can be processed until an investigation is completed by the pharmacist in charge. The ANDA REMS has added that internal procedures for reconciling the generic sodium oxybate inventory are subject to audit.

Some of the responsibility is removed from the certified pharmacies surrounding updating and maintaining the databases. This becomes a function of the Sodium Oxybate REMS Program. While the certified pharmacies gather much of the data through prescription processing, the patient counseling checklist and the RMR, they do not have to spend extra time updating the databases with the information which allows them to focus on patient safety aspects surrounding use of this medication. DRISK finds this to be acceptable and believes it will achieve the same level of safety as the Xyrem REMS.

4.4.7 Sodium Oxybate REMS Program Patient Counseling Checklist

The Patient Counseling Checklist is a tool that pharmacists use to screen and counsel patients before each dispensation of generic sodium oxybate. The Pharmacist counsels the patient on therapy expectations, preparation and administration, precautions needed and side effects of sodium oxybate. The pharmacist screens the patient for concomitant medications and medical conditions that may put the patient at risk for CNS or respiratory depression. The pharmacist also lists all of the patient's prescription and non-prescription medications and all current medical conditions for which the patient is under a healthcare provider's care as well as answers the patient's clinical questions about sodium oxybate. If concomitant medications or comorbidities are discovered that the prescriber has not indicated awareness, the pharmacist will consult the prescriber and document the outcome.

Reviewer Comment:

The Sodium Oxybate Patient Counseling Checklist is the same as the Xyrem Patient Counseling Checklist except that the ANDA group removed the restrictions from each step (ex. Complete this section ONLY for new patients and existing patients who are restarting sodium oxybate treatment after not receiving sodium oxybate for 6 months or longer) to indicate that the checklist is to be completed prior to dispensing each generic sodium oxybate shipment. The prescriber information was moved from step one to step four so that prescriber information can be documented when a prescriber consult is required.

4.4.8 Sodium oxybate REMS Program Risk Management Report (RMR)

The RMR is completed by pharmacies 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 can be completed online or printed and faxed to the Sodium Oxybate REMS Program. The RMR history allows for the review of prior events of suspected abuse, misuse, or diversion and gives a more complete picture of the patient's history. A trend or pattern of behavior can be an indicator of abuse, misuse, or diversion and identified patients or prescribers who may require additional scrutiny when another event occurs. The pharmacy can use the RMR form to direct the Sodium Oxybate REMS Program to disenroll a patient or prescriber for suspected abuse, misuse, or diversion based on this history.

Reviewer Comment:

The Sodium Oxybate RMR form is the same as the Xyrem RMR form except for changes due to operational differences in the ANDA REMS. The RMRs must be submitted to the Sodium Oxybate REMS Program where the information will be documented in the databases. The Sodium Oxybate REMS Program will work with the sponsors to determine the need to notify local, state, or federal authorities. Additionally, the ANDA group included a section to allow the certified pharmacies to request that a patient or prescriber be disenrolled by the Sodium Oxybate REMS Program for suspected abuse, misuse, or diversion. The pharmacies do not have direct access to the databases, therefore, if the pharmacy determines that a patient or prescriber should be disenrolled due to suspected abuse, misuse, or diversion, the pharmacy will use this form to communicate the decision to the REMS Program which will perform the disenrollment and update the databases.

4.4.9 Sodium Oxybate REMS Program Pharmacy Enrollment Form

The Pharmacy Enrollment Form is completed and submitted by the pharmacy's authorized representative. The authorized representative is responsible for ensuring that pharmacy staff complete the required training and ensure that the pharmacy enables its pharmacy management system to support electronic communication with the Sodium Oxybate REMS Program using established telecommunication standards. By signing the form, the authorized representative attests that the pharmacy has put processes and procedures in place to comply with the ANDA REMS including dispensing sodium oxybate only to enrolled patients pursuant to a valid prescription written by a certified prescriber.

Reviewer Comment:

DRISK finds it acceptable to include the Sodium Oxybate REMS Program Pharmacy Enrollment form as part of the REMS, but recognizes that this is an addition that differs from the Xyrem REMS Program. Use of a pharmacy enrollment form is necessary for the ANDA sodium oxybate sponsors to ensure the pharmacies agree to adhere to all of the requirements necessary to comply with the Sodium Oxybate REMS Program. The content reflects the responsibilities of a certified pharmacy as outlined in the REMS document.

4.4.10 Sodium Oxybate REMS Program Website Screen Shots

The ANDA REMS website contains pages with information for prescribers, patients, and pharmacies including certification requirements as outlined in the REMS document. Other pages include a Frequently Asked Questions page directed at prescribers, a Contact Us page with contact information

for the Sodium Oxybate REMS Program, a Resources page for access to enrollment forms and educational materials, and a Create an Account page for prescribers and pharmacists for access to the secure section of the website.

Reviewer Comment:

The ANDA REMS website is the same as the Xyrem REMS except for changes reflecting the operational differences in the programs. The home page contains the same goals, program overview, and approved indications for sodium oxybate, with the exception that there are multiple certified pharmacies in the ANDA REMS compared to a single central pharmacy in the Xyrem REMS. The prescriber roles and responsibilities are the same with the exception that the prescriber submits the prescription form to one of the certified pharmacies in the ANDA REMS instead of the REMS Program as in the Xyrem REMS.

The ANDA REMS website has additional pages that are not included in the Xyrem REMS Website. The ANDA REMS includes a page with pharmacy certification requirements that are outlined in the REMS Document. A page for patients exists to inform them that patients prescribed generic sodium oxybate must enroll in the Sodium Oxybate REMS Program: If you were previously registered in the Xyrem REMS, your certified prescriber will need to enroll you in the Sodium Oxybate REMS Program. A Resources page is included which contains links to resources including prescribing information, enrollment forms, prescriber brochure, medication guide, and patient quick start guide. The ANDA group included a FAQ page that focuses on prescriber enrollment and patient enrollment. Additionally, the ANDA group included a Create an Account Page for pharmacists and prescribers to access the secure section of the website. The secure section will contain the pharmacy look up for prescribers to choose a pharmacy based on the patient's zip code and will hold the prescription form so that only (b) (4) prescribers can have access to it.

5 Discussion

The ANDA group submitted amendments integrating comments provided by the Agency from the 10/12/2016 review and the 11/9/2016 and 11/10/2016 face-to-face meetings and 11/30/2016 and 12/1/2016 teleconferences into their proposed REMS. DRISK finds the most recent submission (12/2/2016) acceptable.

Section 505-1(i)(1)(B) of the FD&C Act provides that an ANDA is subject to the ETASU for the RLD, but a separate REMS for ANDA applicants that is waived from the SSS requirement can use a “different, comparable aspect of the [ETASU].” FDA interprets this standard to mean that a waived system for ETASU must include the same general elements as described in the statute. FDA further interprets this to allow a separate REMS for ANDA applicants to use different methods or operational means to effectuate a REMS requirement, provided the program achieves the same level of safety.

The ANDA group's proposed REMS has the same goals and ETASU as those in the Xyrem REMS. Specifically, both the Xyrem REMS and the ANDA REMS require that 1) healthcare providers who

prescribe the drug are specially certified, 2) the drug will be dispensed only by pharmacies that are specially certified, and 3) the drug will be dispensed and shipped only to patients who are enrolled in the REMS program with documentation of safe use conditions.

The ANDA REMS has the same enrollment requirements for patients and prescribers, provides the same education on the safe use of sodium oxybate, and requires the same screening, counseling, and evaluation of patients and reporting of adverse events as the Xyrem REMS. The ANDA REMS will offer the same level of safety as the Xyrem REMS by ensuring that generic sodium oxybate is dispensed only to patients enrolled in the Sodium Oxybate REMS Program pursuant to a valid prescription written by a certified prescriber by a certified pharmacy. Only a certified pharmacy that coordinates secure shipment to patients and is not open to the public can dispense sodium oxybate. The ANDA REMS contains the same statement as the Xyrem REMS that generic sodium oxybate will not be stocked in retail pharmacy outlets.

There are some differences in the operational aspects of the ETASU. Specifically, the ANDA REMS does not include the same limitations on the number of pharmacies and databases used. While the Xyrem REMS uses a single pharmacy and a single database, the ANDA REMS will use multiple certified pharmacies and multiple databases that are connected via an electronic telecommunication verification mechanism known as a switch system. The switch system ensures coordination among pharmacies such that a drug is dispensed only after there is verification that all safe use requirements are met namely that: 1) the patient is enrolled in the REMS meaning that, among other things, the patient has been screened by a certified prescriber and been educated about the safe use of sodium oxybate; 2) the prescriber is certified in the REMS, meaning that, among other things, the prescriber has reviewed the prescribing information regarding the safe use of sodium oxybate and agreed to report adverse events promptly; 3) a pharmacy is certified in the REMS, meaning that, among other things, the staff has been trained about the particular risks of sodium oxybate and the REMS program requirements including prescription validation and patient counseling; and 4) the patient does not have any overlapping active prescription for generic sodium oxybate. If all of these requirements are met, a PDA will be generated. Obtaining a PDA will not introduce additional burden because it is done seamlessly behind the scenes in seconds when the pharmacy enters the prescription information in to the pharmacy management system allowing for real-time verification of enrollment status in the databases.

The ANDA REMS has built in a duplicate claim safeguard in which a certified pharmacy will contact the Xyrem REMS Program prior to dispensing generic sodium oxybate to ensure that the patient does not have an overlapping active prescription for Xyrem. The pharmacy will also verify that the patient and prescriber have not been disenrolled from the Xyrem REMS due to abuse, misuse, or diversion, and will report prescriptions filled for generic sodium oxybate for each patient.

Once all checks are completed, the medication is shipped directly to the patient just as it is in the Xyrem REMS.

DRISK has concluded that the Sodium Oxybate REMS Program, as designed, achieves the same level of safety as the Xyrem REMS. The different aspects of the ETASU in the REMS proposed by the ANDA group are comparable to those in the Xyrem REMS. In each case, the drug is shipped directly to the patient and not stocked on retail pharmacy shelves, the same patient counseling takes place prior to dispensing, and multiple checks are built in to ensure that safe use conditions have been met and that there have been no attempts at diversion, abuse, or misuse. Accordingly, this conclusion is consistent with the Agency's stated position that limiting dispensing to a single pharmacy is not the only way to meet the necessary requirements for certification and ensure the benefits of sodium oxybate outweigh the risks.

6 Conclusion and Recommendations

DRISK finds the proposed ANDA REMS and its appended materials, and the supporting document, as submitted on December 2, 2016 to be acceptable. DRISK recommends approval of the REMS and as designed has determined that it will offer the same level of safety as the Xyrem REMS.

For the waived SSS REMS section 505-1(g)(2)(C) of the FDCA authorizes the FDA to require REMS assessments for ANDA drugs at pre-specified intervals because such assessments are necessary to evaluate whether the approved strategy should be modified. The waiver-granted REMS for sodium oxybate is comparable to the REMS for Xyrem, therefore the assessments being required of sodium oxybate will be comparable to the assessments required for Xyrem and should be submitted 18 months following the approval and every 12 months thereafter.

The following assessment plan is to be included in the approval letter:

1. Program Implementation

- a. Product Launch Date
- b. Date when REMS materials became available to healthcare providers (HCPs) on the website and via the contact center
- c. The dates stakeholders could become specially certified and/or enrolled online, by mail, by fax, by email:
 - i. Prescribers
 - ii. Pharmacies
 - iii. Patients
- d. Date when the Sodium Oxybate REMS Program website went live
- e. Sodium Oxybate REMS Program website utilization
 - i. Number of unique site visits

2. REMS Program Utilization

- a. Prescribers
 - i. Number of specially certified prescribers, status of certification, and method of certification

- ii. Summary of reasons certification is incomplete for prescribers (e.g. “Prescriber missing information on form”, etc.)
 - iii. Number of specially certified prescribers by specialty
 - iv. Number of specially certified prescribers who were disenrolled during the reporting period and reasons for disenrollment
 - v. Number of patients by current specially certified prescriber
 - b. Pharmacies
 - i. Number of specially certified pharmacies, status of certification, and method of certification
 - ii. Summary of reasons certification is incomplete for pharmacies (e.g. “Pharmacy authorized representative changed, no replacement given”, etc.)
 - iii. Number of specially certified pharmacy decertifications during the reporting period and reasons for decertification
 - c. Patient Status
 - i. Number, age, and gender of enrolled patients
 - ii. Number of disenrolled patients and reason(s) for disenrollment
 - iii. Number of active patients (patients enrolled who received at least one shipment of sodium oxybate during the reporting period)
 - iv. Number of duplicate patients detected by the specially certified pharmacies
 - v. Number of patients associated with more than one prescriber during their therapy
 - vi. Number of patients who have discontinued sodium oxybate after receiving at least one shipment of sodium oxybate
 - vii. Number of discontinued patients who were associated with an adverse event, including death
- 3. Contact Center Report**
- a. Number of Contacts
 - b. Summary of reason for call (i.e. “Enrollment question”, etc.) by reporter (i.e. pharmacy, prescriber, patient)
 - c. Summary of any REMS-related problems identified
 - d. Narrative of any corrective actions resulting from issues identified
- 4. Sodium Oxybate REMS Program Compliance**
- a. Prescriptions
 - i. Total number of prescriptions dispensed; stratify by the number of new and the number of refills
 - ii. Number of patients with overlapping prescriptions (more than one active prescription)
 - iii. Number of patients prescribed a daily dose >9 g
 - iv. Number of prescriptions requiring contact with Xyrem REMS program

1. Status of these prescriptions (dispensed, not dispensed); report any delays in shipment of product related to inability to contact Xyrem REMS program
 - v. Number of sodium oxybate prescriptions that were written by non-certified or disenrolled prescribers (reported or detected through audit)
 1. Actions taken (e.g. "Provision of sodium oxybate program materials", "Prescriber certified", etc.)
 2. Outcome of actions taken
- b. Shipments
- i. Total number of bottles and shipments sent
 - ii. Number of shipments lost in delivery that were unrecovered and the number of corresponding DEA 106 forms and RMRs completed
 - iii. Number of prescriptions dispensed by noncertified pharmacies and actions taken to prevent future occurrences (reported or detected through audit)
 - iv. Number of shipments sent to noncertified pharmacies, source of report, and actions taken to prevent future occurrences
 - v. Number of duplicate patients who were shipped Sodium Oxybate under more than one name or identifier
 - vi. Number of patients who were shipped Sodium Oxybate after being disenrolled
 - vii. Number of initial shipments sent to patients without completion of the Sodium Oxybate REMS Program Patient Counseling Checklist
- c. Early refills
- i. Number of patients who requested an early refill and reason for the request
 - ii. Number of requests approved
 - iii. Number of requests denied by the prescriber
 - iv. Number of requests denied by the specially certified pharmacies
 - v. Number of patients with multiple requests for early refills
- d. Concomitant medications - Summary table from Sodium Oxybate REMS Program Patient Counseling Checklists of the number of patients taking the following concomitant medications and who subsequently received at least one shipment of Sodium oxybate:
- i. Sedative hypnotics
 - ii. Alcohol
 - iii. Other potentially interacting agents:
 - iv. Sedating antidepressants, antipsychotics, or anti-epileptics
 - v. General anesthetics
 - vi. Muscle relaxants
 - vii. Opioid analgesics
 - viii. Divalproex sodium or other valproate drug (e.g., valproic acid)
 - ix. Illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB])
- e. Concomitant diagnoses - Summary table from Sodium oxybate 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 Sodium Oxybate:

- i. Sleep apnea
 - ii. Asthma, COPD, or other conditions affecting the respiratory system
 - f. Number of notifications by pharmacists to prescribers for the following situations and the outcome of the notification (e.g., dispensed Sodium oxybate, counseled patient, or other actions)
 - i. Patient report of alcohol use
 - ii. Patient report of diagnosis of sleep apnea
 - iii. Patient report of diagnosis of asthma, COPD, or other conditions affecting the respiratory system
 - iv. Suspected abuse, misuse, or diversion
 - v. Alerts regarding potential abuse, misuse, or diversion on the patient profiles
 - g. Risk Management Reports submitted
 - i. Number of patients with an RMR
 - ii. Number of patients with multiple RMRs
 - iii. Number of alerts generated from RMRs
 - iv. Number of RMRs generated from early refill requests
 - v. Number of RMRs generated for other reasons (list reasons)
 - vi. Number of prescriber-related RMRs
 - vii. Early refill requests
 - h. Any other reports of non-compliance with the Sodium oxybate REMS program, source of report, and any corrective actions or resolution.
 - i. A summary report of audits of the specially certified pharmacies conducted during the assessment period including any actions taken to address findings
- 5. Barriers or Delays in Patient Access**
 - a. False negatives: i.e., all REMS and safe use requirements were met, but a PDA was not provided by the Sodium Oxybate REMS Program
 - b. Inadvertent disenrollments
 - c. Unintended system interruptions and resolutions
 - d. Total number of PDA rejections, the number of these that were subsequently approved and the duration of time from rejection to approval
- 6. Inappropriate Patient Access**
 - a. False positives: e.g., all REMS and safe use requirements were not met, but a PDA was provided by the Sodium Oxybate REMS Program
- 7. Evaluation of Safe Use Procedures**
 - a. Provide reasons for prescription rejections/PDA rejected by the Sodium Oxybate REMS Program
 - b. Summary and count of RMR events and the corrective actions taken
- 8. Evaluation of Knowledge/Surveys**

- a. An evaluation of knowledge of specially certified prescribers of the risk of respiratory depression, contraindication with sedative hypnotics and alcohol, and the potential for abuse, misuse, and overdose associated with sodium oxybate
- b. An evaluation of knowledge of specially certified pharmacy authorized representatives and pharmacists of the risk of respiratory depression, contraindication with sedative hypnotics and alcohol, and the potential for abuse, misuse, and overdose associated with sodium oxybate
- c. An evaluation of knowledge of patients of the risk of respiratory depression, contraindication with sedative hypnotics and alcohol, and the potential for abuse, misuse, and overdose associated with sodium oxybate

9. Adverse Events

- a. Total aggregate number of the following potential adverse event reports received by the Sodium Oxybate REMS Program and sent to the Sodium Oxybate sponsors during the reporting period, and cumulatively:
 - i. Aggregate number of reports of abuse, misuse, diversion, overdose, accidental exposure, respiratory depression associated with sodium oxybate
 - ii. Aggregate number of potential adverse events associated with dispensed and unused sodium oxybate
 - iii. Aggregate number of potential adverse events associated with a non-certified pharmacy, disenrolled prescriber, disenrolled prescriber, or disenrolled patient
 - iv. Aggregate number of potential adverse events associated with a sodium oxybate medication error
 - v. Aggregate number of potential adverse events associated with use with concurrent sedative hypnotics and alcohol
- b. Total aggregate number of potential adverse event reports in Section III.E.9.a. that were received by the Sodium Oxybate sponsors from all sources during the reporting period
- c. Total aggregate number of potential adverse event reports in Section III.E.9.a. received by the Sodium Oxybate REMS Program and sent to the Sodium Oxybate sponsors that were subsequently reported as an adverse event by a Sodium Oxybate sponsor, during the reporting period and cumulatively
- d. Total aggregate number of potential adverse event reports in Section III.E.9.a. received by the Sodium Oxybate sponsors from all sources that were subsequently reported as an adverse event by a Sodium Oxybate sponsor, during the reporting period and cumulatively

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

- a. Sodium Oxybate REMS Program will report to FDA on the dispensing of the Medication Guide as part of the REMS assessments

11. Surveillance and monitoring

- a. The Sodium Oxybate REMS program 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 Society for Forensic Toxicologists (SOFT) for any information regarding abuse, misuse, or diversion of sodium oxybate. Any relevant information will be included in the REMS assessments

7 Appendices

7.1 Materials Reviewed

The following is a list of materials informing this review:

1. (b) (4) Amneal Pharmaceuticals, Ohm Laboratories Inc., Roxane Laboratories Inc., (b) (4) Proposed REMS for Sodium Oxybate ANDAs (b) (4), 203631, 203351, 202090, dated April 8, 2016, amended June 6, 2016, August 22, 2016, and December 2, 2016
2. FDA. Division of Neurology Products. Supplement Approval for NDA 21196, dated July 15, 2015.
3. Kumar, J. Division of Risk Management. Evaluation of proposed shared ANDA REMS for sodium oxybate, dated September 1, 2016
4. Zendel, L. Division of Risk Management. Evaluation of proposed shared ANDA REMS for sodium oxybate, dated October 22, 2016

7.2 Appended materials

1. Sodium Oxybate REMS Document
2. Sodium Oxybate Appended Materials
 - a. Sodium Oxybate REMS Program Prescriber Enrollment Form
 - b. Sodium Oxybate REMS Program Prescriber Brochure
 - c. Sodium Oxybate REMS Program Prescription Form
 - d. Sodium Oxybate REMS Program Patient Enrollment Form
 - e. Sodium Oxybate REMS Program Quick Start Guide for Patient
 - f. Sodium Oxybate REMS Program Pharmacy Enrollment Form
 - g. Sodium Oxybate REMS Program Certified Pharmacy Training Modules A and B
 - h. Sodium Oxybate REMS Program Patient Counseling Checklist
 - i. Sodium Oxybate REMS Program Risk Management Report
 - j. Sodium Oxybate REMS Program Website Screen Shots

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

/s/

LAURA A ZENDEL
01/13/2017

JAMIE C WILKINS PARKER
01/13/2017

CYNTHIA L LACIVITA
01/13/2017
Concur

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	ANDA
Application Number	(b) (4), 203631, 203351, 202090,
Goal Date (internal)	November 10, 2016
OSE RCM #	2016-954
Reviewer Name(s)	Laura Zendel, PharmD
Health Communications Analyst	Anahita Tavakoli, M.A.
DRISK Team Leader	Jamie Wilkins Parker, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	10/12/2016
Subject	Evaluation of proposed shared ANDA REMS for sodium oxybate
Established Name	sodium oxybate
Applicants	(b) (4), Amneal Pharmaceuticals, Ohm Laboratories Inc., Roxane Laboratories Inc.
Review Division	Office of Generic Drugs (OGD)
Therapeutic Class	Central Nervous System depressant
Formulation(s)	Oral solution in concentration of 0.5 g/mL
Dosing Regimen	Recommended starting dose of 4.5g (maximum 9.0g) administered orally at bedtime in two divided doses

Table of Contents

1	Executive Summary	3
2	Introduction	4
3	Background	4
	Product Information.....	4
	Xyrem REMS	5
	Regulatory History	7
4	Results of the Review of the Applicant Holders Proposed REMS	10
	REMS Goals.....	10
	REMS Elements.....	10
	Medication Guide	10
	Elements to Assure Safe Use	10
	Implementation System	15
	REMS Supporting Document.....	17
	REMS Assessment Plan.....	18
	REMS Appended Materials	18
	Sodium Oxybate REMS Program Prescriber Enrollment Form	18
	Sodium Oxybate REMS Program Prescriber Brochure	19
	Sodium Oxybate REMS Program Patient Enrollment Form.....	19
	Sodium Oxybate REMS Program Prescription Form.....	19
	Sodium oxybate REMS Program Quick Start Guide for Patient	20
	Sodium Oxybate REMS Program Certified Pharmacy Training Modules A and B.....	20
	Sodium Oxybate REMS Program Patient Counseling Checklist.....	22
	Sodium oxybate REMS Program Risk Management Report.....	22
	Sodium Oxybate REMS Program Pharmacy Enrollment Form	23

5	Discussion	23
6	Conclusion and Recommendations	24
7	Comments to the Applicants	24
8	Appendices	31
	Materials Reviewed	31
	Appended materials	31

1 Executive Summary

This review by the Division of Risk Management (DRISK) evaluates the proposed shared risk evaluation and mitigation strategy (REMS) for generic products referencing Xyrem (sodium oxybate), received by the Office of Generic Drugs (OGD) on April 8, 2016, and amended on June 6, 2016 and August 22, 2016, by the abbreviated new drug applications (ANDAs): (b) (4)

(b) (4) Amneal Pharmaceuticals (ANDA 203631), Ohm Laboratories Inc. (ANDA 203351), and Roxane Laboratories Inc. (ANDA 202090). (b) (4)

(b) (4). Per statutory requirements described in section 505-1(h)(9)(i)(1) of the Food, Drug, and Cosmetic Act (FDCA) as amended by the Food and Drug Administration Amendments Act (FDAAA), the ANDAs of sodium oxybate shall use a single, shared system (SSS) REMS with the reference label drug (RLD) unless FDA waives that requirement and permits the ANDAs to use a different, but comparable aspect of the Elements to Assure Safe Use (ETASU). The ANDAs for sodium oxybate seek a waiver of the SSS requirement and approval of a separate REMS for the generic products referencing Xyrem.

The Xyrem REMS, approved on February 27, 2015 and most recently modified on July 15, 2015, includes a Medication Guide (MG) and ETASU to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion¹ of Xyrem.

The generic sodium oxybate applicants submitted a separate proposed REMS, herein referred to as the ANDA REMS, which has the same goals and the same ETASU as the Xyrem REMS. It proposes operational differences in certain aspects of the ETASU which, with the requested changes described below, will be comparable to the Xyrem REMS. DRISK believes the proposed REMS for sodium oxybate, with required DRISK edits, will achieve the same level of patient safety as the approved Xyrem REMS.

¹ The goal of mitigating diversion in this REMS refers to preventing the sale or transfer of the drug outside the framework of the REMS in order to mitigate the risks of central nervous system depression, respiratory depression, abuse, and misuse.

The Applicant's proposed ANDA program differs from the Xyrem REMS program by: 1) including a requirement for the prescriber to submit the sodium oxybate prescription form to one of the certified pharmacies; 2) proposing the use of multiple (b) (4) pharmacies (i.e., mail order pharmacies), use of a duplicate claim safeguard; and 3) use of multiple databases which are connected through an electronic telecommunication verification, commonly referred to as a "switch system." Preliminary comments were shared with the Applicant group via teleconference on 7/21/2016. The Applicant group submitted an amended REMS document, supporting document and appended materials in response on August 22, 2016. This review provides comments on the amended REMS materials and REMS document to clarify the pharmacy enrollment process, duplicate claim safeguard provision, and terminology describing the databases, as well as changes to the Supporting Document to include more details of operations, and general comments to Appended Materials.

2 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed shared risk evaluation and mitigation strategy (REMS) for sodium oxybate oral solution (received on April 8, 2016, and amended on June 6, 2016 and August 22 2016) submitted by following the abbreviated new drug applications (ANDAs): (b) (4)

(b) (4) Amneal Pharmaceuticals (ANDA 203631), Ohm Laboratories Inc. (ANDA 203351), and Roxane Laboratories Inc. (ANDA 202090), herein referred to in this review as the Applicant Group. Preliminary comments were shared with the Applicant group (via teleconference) on 7/21/2016. The Applicant group submitted an amended REMS document, supporting document and appended materials on August 22, 2016 which is the subject of this review.

This is second of several reviews that will evaluate this proposed ANDA REMS. The background information is contained in the review dated Sept. 1 2016².

3 Background

PRODUCT INFORMATION

Xyrem (sodium oxybate), a Schedule III controlled substance, is the sodium salt of gammahydroxybutyrate (GHB). GHB is a potent central nervous system depressant. Xyrem was approved under subpart H6 in 2002 for the treatment of cataplexy in narcolepsy and in 2005 for the treatment of excessive daytime sleepiness (EDS) in narcolepsy.

²Kumar J. Division of Risk Management. Evaluation of proposed shared ANDA REMS for sodium oxybate. 09/01/2016

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 (see Table 1).

If a Patient's Total Nightly Dose is:	Take at Bedtime:	Take 2.5-4 hours later:
4.5 g/night	2.25 g	2.25 g
6.0 g/night	3.0 g	3.0 g
7.5 g/night	3.75 g	3.75 g
9.0 g/night	4.5 g	4.5 g

Recommended dosing states to increase the dose 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 g to 9 g per night orally. As stated in the package insert, *doses higher than 9 g per night have not been studied and should not ordinarily be administered.*³

The Medication Guide includes the following instructions: "Take your first Xyrem dose at bedtime while you are in bed. Take your second Xyrem dose 2 ½ to 4 hours after you take your first Xyrem dose. You may want to set an alarm clock to make sure you wake up to take your second Xyrem dose. You should remain in bed after taking the first and second doses of Xyrem."

XYREM REMS

Xyrem (sodium oxybate) oral solution formulation was approved by the FDA on July 17, 2002 for the treatment of cataplexy in patients with narcolepsy, and on November 18, 2005 for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. Sodium oxybate is a controlled substance classified as schedule III in its approved form and as schedule I for illicit use (gamma-hydroxybutyric acid, or GHB, is known as the "date rape drug") and is also associated with central nervous system and respiratory depression. The Xyrem approval was under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) with a risk management plan to assure safe use of the product. The risk management plan proposed by Jazz contained a requirement that the drug be dispensed only from a single, central pharmacy. Xyrem was approved with a risk management plan which included implementation of a restricted distribution program, patient and prescriber education regarding the risks and benefits of Xyrem including critical information necessary for the safe use and handling of the drug, filling of the initial prescription only after the prescriber and patient have received and read the educational materials, and maintenance of a registry of all patients and a record of all prescribers. The FDA allowed the limitation of the single central pharmacy to remain in the risk management plan, believing it to be a way to effectuate the overall restrictions on distribution necessary for safe use of the drug.

³ Xyrem (sodium oxybate) [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. Revised April 2015.

On the effective date of Food and Drug Administration Amendments Act of 2007 (FDAAA), Xyrem was identified as a product deemed to have in effect an approved REMS because there were elements to assure safe use in effect. As part of the negotiations for a final REMS, Jazz proposed removing the requirement for a single pharmacy and instead allowing certification of multiple pharmacies. Later that year (2009) Jazz also submitted a supplement for a new indication for fibromyalgia, and in that supplement proposed a REMS with multiple certified pharmacies. FDA rejected the application for fibromyalgia, but did so on grounds unrelated to the multiple pharmacy certification. Following the rejection of the fibromyalgia application, negotiation of the final REMS for Xyrem continued. FDA explained to Jazz that its final REMS should not contain the restriction to a single pharmacy, but should instead contain the stringent requirements for pharmacy certification necessary to control distribution of the drug. By early 2011, however, Jazz changed its position and began insisting that the single pharmacy requirement remain.⁴ In December 2013, the Agency sent a REMS modification notification letter to Jazz which included required removal of the single pharmacy requirement. Jazz filed a dispute resolution request. When the request was denied, Jazz appealed. On February 27, 2015, in the hopes of bringing the protracted negotiations and dispute to a close, the Agency approved the REMS Jazz proposed (i.e., with the single, central pharmacy requirement). The approval letter included language making clear the Agency did not think the requirement of a single pharmacy is the only way to safely distribute the drug. The approval letter also stated the Agency would consider future modifications as necessary and the dispute was denied as moot.

Table 1. Abbreviated Summary of Approved Xyrem REMS

REMS Goals	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, and patients 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.
REMS Elements	Medication Guide
	Prescriber Certification - Special certification of healthcare providers (HCPs) who prescribe Xyrem: ensures enrollment in the Xyrem REMS Program and understanding of Prescriber Brochure.
	Pharmacy Certification – Special certification of central pharmacy (not stocked in retail pharmacy outlets): ensures enrollment in Xyrem REMS Program, completion of pharmacy training, completion of Patient Counseling Checklist, review of Central Database, shipment directly to patient
	Documentation of safe use conditions – Patients must sign Patient Enrollment Form

⁴ Kumar, J. DRISK. Final REMS Review, dated February 27, 2015.

Implementation System	Monitor compliance with prescriber, pharmacy, and patient enrollment, maintenance of Central Database
-----------------------	---

REGULATORY HISTORY

The following is a summary of the regulatory history for the ANDAs for sodium oxybate and Xyrem, relevant to this review:

- 07/07/2002: The Agency approved Xyrem for the treatment of cataplexy (orphan designation) with restricted distribution under a Risk Management and Action Plan (RiskMAP) called the Xyrem Success Program. The key features of the RiskMAP included: Mandatory enrollment and education of prescribers and patients; restricted distribution of Xyrem dispensed via an exclusive, single central pharmacy by direct shipping after verification of the prescription, and prescriber/patient information.
- 03/28/2008: After the FDAAA of 2007 was passed, the Agency published in the Federal Register (FR)14 a list of drugs that were deemed to have an approved REMS and directed holders of approved applications for those products to submit a proposed REMS by September 21, 2008; Xyrem was included in the list of deemed products.
- 07/08/2010: The Agency received ANDA 202090 for sodium oxybate oral solution from Roxane.
- 10/19/2011: Roxane submitted a proposed REMS for sodium oxybate oral solution.
- [REDACTED] (b) (4)
- 09/27/2012: The Agency sent a REMS Notification Letter/“Information Request Letter” to Roxane regarding requirements for a single shared REMS program for Sodium Oxybate Oral Solution. This letter identified Jennifer Ekelund as the Jazz Pharmaceuticals contact person for the development of the single shared system (SSS)
- 10/14/2012: Roxane (Gregory Hicks, Associate Director, REMS, Labeling, and Drug Safety) sent letter to Jennifer Ekelund (Executive Director, Regulatory Affairs, Jazz Pharmaceuticals) to request a teleconference with appropriate representatives from each company to begin the process of developing a SSS REMS for sodium oxybate.
- [REDACTED] (b) (4)
- 03/20/2013: Roxane received a Complete Response Letter (CRL) for ANDA 202090, which included product quality and labeling deficiencies. The CRL encouraged the Sponsor to work towards a SSS REMS with the innovator or opt to develop and submit a RiskMAP.
- 04/16/2013: Roxane submitted an amendment to the proposed REMS in response to receiving the CRL on 03/20/2013.

- [REDACTED] (b) (4)
- [REDACTED]
- 01/23/2014: The Agency facilitated a "kick-off" meeting between the Agency, Jazz and ANDA applicants (Roxane, Amneal, (b) (4) to assist in the development of a SSS REMS for sodium oxybate. [REDACTED] (b) (4). It was determined that Roxane would provide a draft confidential disclosure agreement (CDA) to the group for discussion shortly after the meeting.
- 03/05/2014: Teleconference with Amneal, Roxane, (b) (4) to discuss recent information identified in Jazz's Q4 2013 earnings call regarding Jazz entering into formal dispute resolution with FDA. ANDAs inquired whether they should proceed with REMS negotiations without Jazz until the dispute was resolved. The Agency responded that all parties should continue to work together to form a SSS REMS unless otherwise notified by FDA.
- [REDACTED] (b) (4)
- [REDACTED]
- 2/04/2015: Meeting between the Agency and ANDA sponsors to discuss the possibility of a waiver of the SSS requirement and the ANDA sponsors' proposed distribution model for use in a separate REMS.
- 02/27/2015: The Agency approved the Xyrem REMS, although it contained areas where the Agency was not aligned with Jazz, including the use of the word "diversion" and restriction to a "single, central pharmacy." The Agency noted that the action of approving the REMS submitted by Jazz should not be construed or understood as agreement with Jazz that limiting the dispensing to a single pharmacy is the only way to ensure that the benefits of Xyrem outweigh the risks under section 505-1 of the FD&C Act.
- 06/09/2015: ANDAs met with the Agency and discussed the status of the single shared system negotiations. The Agency and the ANDA applicants discussed the REMS requirements for ANDA applicants if they were to seek a waiver of the SSS requirement and propose a separate REMS.
- 07/15/2015: The Agency approved a REMS Modification for Xyrem. The modification included revisions to labeling including: "Xyrem Success Program" modified to "Xyrem REMS Program" and references to a "centralized pharmacy" or a "central pharmacy" revised to "central pharmacy that is specially certified" throughout the Xyrem labeling and Medication Guide to be consistent with the approved REMS.
- [REDACTED] (b) (4)

- 10/13/2015: The Agency met with the ANDAs and RLD to find out more about the status of the negotiations and understand what the major issues are to accurately assess the status of the development process.
- 1/20/2016: The Agency met with the ANDAs as a follow-up to the meetings on 06/09/2015 and 10/13/2015. The ANDA Sponsors provided a diagram of their proposed Sodium Oxybate REMS Model. During the meeting, the draft diagram was reviewed and the sponsors provided additional information.
- 03/23/2016: Teleconference between Jazz, the sodium oxybate ANDAs, and the Agency to provide the Agency with a status of SSS negotiations. The Agency was made aware that the sponsors still have not agreed on basic terms such as voting rights.
- 04/08/2016: The ANDAs submitted a draft shared sodium oxybate REMS Document, Appended Materials, and Supporting Document developed jointly by the current Sodium Oxybate ANDA Sponsors.
- 05/06/2016: Teleconference between the Agency and the ANDA sponsor group to clarify components of the proposed sodium oxybate ANDA REMS submission. The ANDA sponsor group clarified that an electronic telecommunication system or “switch system” would be used to check prescriptions within the separate, distinct, REMS databases. The Agency communicated that an updated Supporting Document was needed to provide details of the REMS functionality.
- 06/06/2016: A REMS amendment was submitted by the ANDAs to include proposed changes to the Sodium Oxybate REMS Supporting Document.
- 06/16/2016: Teleconference between the Agency and the ANDA sponsor group to discuss Agency proposed changes to the Sodium Oxybate REMS and discuss procedural timelines for implementation of the REMS program. The Agency proposed to mitigate the risk of duplicate dispensing by requiring the ANDA pharmacies to report all prescriptions received for sodium oxybate and report and verify disenrollment of prescribers/patients that is specifically related to abuse, misuse, and diversion to the Xyrem REMS Program Central Database.
- 7/21/2016: Teleconference between the Agency and the ANDA sponsor group during which the Agency provided feedback on its initial review of the proposed Sodium Oxybate REMS Document, Supporting Document, and Appended Materials.
- 8/22/2016: A REMS amendment was submitted by the ANDAs to include proposed changes to the Sodium Oxybate REMS Document, Supporting Document and Appended Materials.
- 9/1/2016: The DRISK REMS review finalized in DARRTS reflected the comments discussed with the Applicant group on 7/21/2016
- 9/2/2016: An Information Request (IR) was sent to the ANDAs requesting clarification of the disenrollment process including time to disenrollment from the initial decision to disenroll and how patient and prescriber data will be reflected in the databases post-enrollment.

- 9/9/2016: An IR was sent to the ANDAs requesting clarification of terms necessary to describe the databases, the definition of [REDACTED] (b) (4) with regard to enrollment status, and the necessity to qualify the patient database as “enrolled patient database.”
- 9/14/2016: The Applicant Group submitted an IR response via email for both the 9/2/2016 and 9/9/2016 IRs clarifying the disenrollment process, terms necessary to describe the databases, and agreed to remove the term [REDACTED] (b) (4) to describe enrollment status and the term “enrolled” to describe the patient database.

4 Results of the Review of the Applicant Holders Proposed REMS

The Applicant group has submitted amendments integrating comments addressed in the DRISK 9/1/2016 review⁵ to their proposed REMS; however, more changes are required. Provided the Applicant group makes all necessary changes outlined in this review, this would allow for submission of a REMS that DRISK could find acceptable. A summary of the proposed ANDA REMS and respective Reviewer Comments follows:

REMS GOALS

The proposed goals of the Sodium Oxybate REMS are the same as in the Xyrem REMS.

Reviewer Comment:

The proposed goals are acceptable to DRISK.

REMS ELEMENTS

Medication Guide

The Sodium Oxybate REMS website address and the telephone number for the REMS call center should be included in the Medication Guide. The Office of Generic Drugs (OGD) Division of Labeling Review will review the Medication Guide (MG) during their review of the label for ANDAs [REDACTED] (b) (4) 203631, 203351, 202090, and provide their comments under separate cover.

Elements to Assure Safe Use

Any modifications proposed by the Applicant Group are described in detail below. Changes that have been accepted by the Applicant Group have been omitted but will be retained in final documents (see attached redlined documents for further information). The text below focuses on new proposed text submitted by the Applicant Group.

General Reviewer Comments:

Overall, the Applicant Group accepted the changes addressed in the DRISK review from 9/1/2016,

⁵ Kumar J. Division of Risk Management. Evaluation of proposed shared ANDA REMS for sodium oxybate. 09/01/2016

8 Appendices

MATERIALS REVIEWED

The following is a list of materials informing this review:

1. [REDACTED] (b) (4) Amneal Pharmaceuticals, Ohm Laboratories Inc., Roxane Laboratories Inc., [REDACTED] (b) (4) Proposed REMS for Sodium Oxybate ANDAs [REDACTED] (b) (4), 203631, 203351, 202090, dated April 8, 2016, amended June 6, 2016.
2. FDA. Division of Neurology Products. Supplement Approval for NDA 21196, dated July 15, 2015.
3. Kumar, J. Division of Risk Management. Evaluation of proposed shared ANDa REMS for sodium oxybate, dated September 1, 2016

APPENDED MATERIALS

1. Red-lined Sodium Oxybate REMS Document
2. Red-lined Sodium Oxybate Appended Materials
 - a. Sodium Oxybate REMS Program Supporting Document
 - b. Sodium Oxybate REMS Program Prescriber Enrollment Form
 - c. Sodium Oxybate REMS Program Prescriber Brochure
 - d. Sodium Oxybate REMS Program Patient Enrollment Form
 - e. Sodium Oxybate REMS Program Prescription Form
 - f. Sodium Oxybate REMS Program Quick Start Guide for Patient
 - g. Sodium Oxybate REMS Program Certified Pharmacy Training Modules A and B
 - h. Sodium Oxybate REMS Program Patient Counseling Checklist
 - i. Sodium Oxybate REMS Program Risk Management Report
 - j. Sodium Oxybate REMS Program Pharmacy Enrollment Form
 - k. Sodium Oxybate REMS Program Website

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

/s/

LAURA A ZENDEL
10/12/2016

CYNTHIA L LACIVITA
10/12/2016
Concur

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	ANDA
Application Number	(b) (4), 203631, 203351, 202090,
Goal Date (internal)	October 31, 2016
OSE RCM #	2016-954
Reviewer Name(s)	Jasminder Kumar, PharmD
Health Communications Analyst	Anahita Tavakoli, M.A.
DRISK Team Leader	Jamie Wilkins Parker, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	September 1, 2016
Subject	Evaluation of proposed shared ANDA REMS for sodium oxybate
Established Name	sodium oxybate
Applicants	(b) (4) (b) (4) Amneal Pharmaceuticals, Ohm Laboratories Inc., Roxane Laboratories Inc.
Review Division	Office of Generic Drugs (OGD)
Therapeutic Class	Central Nervous System depressant
Formulation(s)	Oral solution in concentration of 0.5 g/mL
Dosing Regimen	Recommended starting dose of 4.5g (maximum 9.0g) administered orally at bedtime in two divided doses

*** This document contains proprietary and confidential information that should not be released to the public. ***

Table of Contents

1	Executive Summary	3
2	Introduction.....	4
3	Background	4
4	Results of the Review of the Applicant Holders Proposed REMS	9
4.1	REMS Goals	9
4.2	REMS Elements	9
4.3	REMS Supporting Document.....	19
4.4	REMS Appended Materials.....	20
4.4.1	Sodium Oxybate REMS Program Prescriber Enrollment Form.....	20
4.4.2	Sodium Oxybate REMS Program Prescriber Brochure	20
4.4.3	Sodium Oxybate REMS Program Patient Enrollment Form.....	21
4.4.4	Sodium Oxybate REMS Program Prescription Form	21
4.4.5	Sodium oxybate REMS Program Quick Start Guide for Patient.....	21
4.4.6	Sodium Oxybate REMS Program Certified Pharmacy Training Modules A and B	21
4.4.7	Sodium Oxybate REMS Program Patient Counseling Checklist.....	23
4.4.8	Sodium oxybate REMS Program Risk Management Report.....	23
4.4.9	Sodium oxybate REMS Program Website.....	24
5	Discussion	24
6	Conclusion.....	26
7	Recommendations.....	27
8	Comments to the Applicants	27
9	Appendices	31

1 Executive Summary

This review by the Division of Risk Management (DRISK) evaluates the proposed shared risk evaluation and mitigation strategy (REMS) for generic products referencing Xyrem (sodium oxybate), received by the Office of Generic Drugs (OGD) on April 8, 2016, and amended on June 6, 2016, by the abbreviated new drug applications (ANDAs): [REDACTED] (b) (4)

[REDACTED] (b) (4) Amneal Pharmaceuticals (ANDA 203631), Ohm Laboratories Inc. (ANDA 203351), and Roxane Laboratories Inc. (ANDA 202090). Per statutory requirements described in section 505-1(h)(9)(i)(1) of the Food, Drug, and Cosmetic Act (FDCA) as amended by the Food and Drug Administration Amendments Act (FDAAA), the ANDAs of sodium oxybate shall use a single shared system (SSS) REMS with the RLD unless FDA waives that requirement and permits the ANDAs to use a different, but comparable aspect of the elements to assure safe use (ETASU). The ANDAs for sodium oxybate seek a waiver of the SSS requirement and approval of a separate REMS for the generic products referencing Xyrem.

The Xyrem REMS, approved on February 27, 2015 and most recently modified on July 15, 2015, includes a Medication Guide (MG) and ETASU to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion¹ of Xyrem.

The generic sodium oxybate applicants submitted a separate proposed REMS, herein referred to as the ANDA REMS, which has the same goals and the same ETASU as the Xyrem REMS. It proposes operational differences in certain aspects of the ETASU which, with the requested changes described below, will be comparable to the Xyrem REMS. DRISK believes the proposed REMS for sodium oxybate, with required DRISK edits, will achieve the same level of patient safety as the approved Xyrem REMS. The Applicant's proposed ANDA program differs from the Xyrem REMS program by: 1) including a requirement for the prescriber to submit the sodium oxybate prescription form to one of the certified pharmacies; 2) proposing the use of multiple [REDACTED] (b) (4) pharmacies (i.e., mail order pharmacies), use of a duplicate claim safeguard; and 3) use of multiple databases which are connected through an electronic telecommunication verification, commonly referred to as a "switch system." This review provides preliminary comments that include edits to the REMS document to remove reference to payers and comments on the duplicate claim safeguard provision, revisions to the Supporting Document to include more details of operations, and general comments to Appended Materials.

¹ The goal of mitigating diversion in this REMS refers to preventing the sale or transfer of the drug outside the framework of the REMS in order to mitigate the risks of central nervous system depression, respiratory depression, abuse, and misuse.

2 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed shared risk evaluation and mitigation strategy (REMS) for sodium oxybate oral solution (received on April 8, 2016, and amended on June 6, 2016) submitted by following the abbreviated new drug applications (ANDAs):

(b) (4)

(b) (4) Amneal Pharmaceuticals (ANDA 203631), Ohm Laboratories Inc. (ANDA 203351), and Roxane Laboratories Inc. (ANDA 202090), herein referred to in this review as the Applicant Group.

3 Background

3.1 PRODUCT INFORMATION

Xyrem (sodium oxybate), a Schedule III controlled substance, is the sodium salt of gammahydroxybutyrate (GHB). GHB is a potent central nervous system depressant. Xyrem was approved under subpart H6 in 2002 for the treatment of cataplexy in narcolepsy and in 2005 for the treatment of excessive daytime sleepiness (EDS) in narcolepsy.

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 (see Table 1).

If a Patient's Total Nightly Dose is:	Take at Bedtime:	Take 2.5-4 hours later:
4.5 g/night	2.25 g	2.25 g
6.0 g/night	3.0 g	3.0 g
7.5 g/night	3.75 g	3.75 g
9.0 g/night	4.5 g	4.5 g

Recommended dosing states to increase the dose 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 g to 9 g per night orally. As stated in the package insert, *doses higher than 9 g per night have not been studied and should not ordinarily be administered.*²

The MG includes the following instructions: "Take your first Xyrem dose at bedtime while you are in bed. Take your second Xyrem dose 2 ½ to 4 hours after you take your first Xyrem dose. You may want to set an alarm clock to make sure you wake up to take your second Xyrem dose. You should remain in bed after taking the first and second doses of Xyrem."

² Xyrem (sodium oxybate) [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. Revised April 2015.

3.2 XYREM REMS

Xyrem (sodium oxybate) oral solution formulation was approved by the FDA on July 17, 2002 for the treatment of cataplexy in patients with narcolepsy, and on November 18, 2005 for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. Sodium oxybate is a controlled substance classified as schedule III in its approved form and as schedule I for illicit use (gamma-hydroxybutyric acid, or GHB, is known as the “date rape drug”) and is also associated with central nervous system and respiratory depression. The Xyrem approval was under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) with a risk management plan to assure safe use of the product. The risk management plan proposed by Jazz contained a requirement that the drug be dispensed only from a single, central pharmacy. FDA approved the plan with this limitation, believing it to be a way to effectuate the overall restrictions on distribution necessary for safe use of the drug.

On the effective date of Food and Drug Administration Amendments Act of 2007 (FDAAA), Xyrem was identified as a product deemed to have in effect an approved REMS because there were elements to assure safe use in effect. As part of the negotiations for a final REMS Jazz proposed removing the requirement for a single pharmacy and instead allowing certification of multiple pharmacies. Later that year (2009) Jazz also submitted a supplement for a new indication for fibromyalgia, and in that supplement proposed a REMS with multiple certified pharmacies. FDA rejected the application for fibromyalgia, but did so on grounds unrelated to the multiple pharmacy certification. Following the rejection of the fibromyalgia application, negotiation of the final REMS for Xyrem continued. FDA explained to Jazz that its final REMS should not contain the restriction to a single pharmacy, but should instead contain the stringent requirements for pharmacy certification necessary to control distribution of the drug. By early 2011, however, Jazz changed its position and began insisting that the single pharmacy requirement remain.³ In December 2013, the Agency sent a REMS modification notification letter to Jazz which, which included, required removal of the single pharmacy requirement. Jazz filed a dispute resolution request. When the request was denied, Jazz appealed. On February 27, 2015, in the hopes of bringing the protracted negotiations and dispute to a close, the Agency approved the REMS Jazz proposed (i.e., with the single, central pharmacy requirement). The approval letter included language making clear the Agency did not think the requirement of a single pharmacy is the only way to safely distribute the drug. The approval letter also stated the Agency would consider future modifications as necessary and the dispute was denied as moot.

³ Kumar, J. DRISK. Final REMS Review, dated February 27, 2015.

Table 1. Abbreviated Summary of Approved Xyrem REMS

REMS Goals	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, and patients 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.
REMS Elements	Medication Guide
	Prescriber Certification - Special certification of healthcare providers (HCPs) who prescribe Xyrem: ensures enrollment in the Xyrem REMS Program and understanding of Prescriber Brochure.
	Pharmacy Certification – Special certification of central pharmacy (not stocked in retail pharmacy outlets): ensures enrollment in Xyrem REMS Program, completion of pharmacy training, completion of Patient Counseling Checklist, review of Central Database, shipment directly to patient
	Documentation of safe use conditions – Patients must sign Patient Enrollment Form
Implementation System	Monitor compliance with prescriber, pharmacy, and patient enrollment, maintenance of Central Database

3.3 REGULATORY HISTORY

The following is a summary of the regulatory history for the ANDAs for sodium oxybate and Xyrem, relevant to this review:

- 07/07/2002: The Agency approved Xyrem for the treatment of cataplexy (orphan designation) with restricted distribution under a Risk Management and Action Plan (RiskMAP) called the Xyrem Success Program. The key features of the RiskMAP included: Mandatory enrollment and education of prescribers and patients; restricted distribution of Xyrem dispensed via an exclusive, single central pharmacy by direct shipping after verification of the prescription, and prescriber/patient information.
- 03/28/2008: After the FDAAA of 2007 was passed, the Agency published in the Federal Register (FR)14 a list of drugs that were deemed to have an approved REMS and directed holders of approved applications for those products to submit a proposed REMS by September 21, 2008; Xyrem was included in the list of deemed products.
- 07/08/2010: The Agency received ANDA 202090 for sodium oxybate oral solution from Roxane.
- 10/19/2011: Roxane submitted a proposed REMS for sodium oxybate oral solution.
- [REDACTED] (b) (4)
- 09/27/2012: The Agency sent a REMS Notification Letter/“Information Request Letter” to Roxane regarding requirements for a single shared REMS program for Sodium Oxybate Oral

Solution. This letter identified Jennifer Ekelund as the Jazz Pharmaceuticals contact person for the development of the single shared system

- 10/14/2012: Roxane (Gregory Hicks, Associate Director, REMS, Labeling, and Drug Safety) sent letter to Jennifer Ekelund (Executive Director, Regulatory Affairs, Jazz Pharmaceuticals) to request a teleconference with appropriate representatives from each company to begin the process of developing a single shared system REMS for sodium oxybate.

- [REDACTED] (b) (4)

- 03/20/2013: Roxane received a Complete Response Letter (CRL) for ANDA 202090, which included product quality and labeling deficiencies. The CRL encouraged the Sponsor to work towards a single-shared system REMS with the innovator or opt to develop and submit a RiskMAP.

- 04/16/2013: Roxane submitted an amendment to the proposed REMS in response to receiving the CRL on 03/20/2013.

- [REDACTED] (b) (4)
- [REDACTED]

- 01/23/2014: The Agency facilitated a "kick-off" meeting between the Agency, Jazz and ANDA applicants (Roxane, Amneal, [REDACTED] (b) (4)) to assist in the development of a SSS REMS for sodium oxybate. [REDACTED] (b) (4)

[REDACTED] (b) (4) It was determined that Roxane would provide a draft Confidential Disclosure Agreement (CDA) to the group for discussion shortly after the meeting.

- 03/05/2014: Teleconference with Amneal, Roxane, [REDACTED] (b) (4) to discuss recent information identified in Jazz's Q4 2013 earnings call regarding Jazz entering into formal dispute resolution with FDA. ANDAs inquired whether they should proceed with REMS negotiations without Jazz until the dispute was resolved. The Agency responded that all parties should continue to work together to form a SSS REMS unless otherwise notified by FDA.

- [REDACTED] (b) (4)
- [REDACTED]

- 2/04/2015: Meeting between the Agency and ANDA sponsors to discuss the possibility of a waiver of the SSS requirement and the ANDA sponsors' proposed distribution model for use in a separate REMS.

- 02/27/2015: The Agency approved the Xyrem REMS, although it contained areas where the Agency was not aligned with Jazz, including the use of the word "diversion" and restriction to a

“single, central pharmacy.” The Agency noted that the action of approving the REMS submitted by Jazz should not be construed or understood as agreement with Jazz that limiting the dispensing to a single pharmacy is the only way to ensure that the benefits of Xyrem outweigh the risks under section 505-1 of the FD&C Act.

- 06/09/2015: ANDAs met with the Agency and discussed the status of the single shared system negotiations. The Agency and the ANDA applicants discussed the REMS requirements for ANDA applicants if they were to seek a waiver of the SSS requirement and propose a separate REMS..
- 07/15/2015: The Agency approved a REMS Modification for Xyrem. The modification included revisions to labeling including: “Xyrem Success Program” modified to “Xyrem REMS Program” and references to a “centralized pharmacy” or a “central pharmacy” revised to “central pharmacy that is specially certified” throughout the Xyrem labeling and Medication Guide to be consistent with the approved REMS.
- [REDACTED] (b) (4) .
- 10/13/2015: The Agency met with the ANDAs and RLD to find out more about the status of the negotiations and understand what the major issues are to accurately assess the status of the development process.
- 1/20/2016: The Agency met with the ANDAs as a follow-up to the meetings on 06/09/2015 and 10/13/2015. The ANDA Sponsors provided a diagram of their proposed Sodium Oxybate REMS Model. During the meeting, the draft diagram was reviewed and the sponsors provided additional information.
- 03/23/2016: Teleconference between Jazz, the sodium oxybate ANDAs, and the Agency to provide the Agency with a status of SSS negotiations. The Agency was made aware that the sponsors still have not agreed on basic terms such as voting rights.
- 04/08/2016: The ANDAs submitted a draft shared sodium oxybate REMS Document, Appended Materials, and Supporting Document developed jointly by the current Sodium Oxybate ANDA Sponsors.
- 05/06/2016: Teleconference between the Agency and the ANDA sponsor group to clarify components of the proposed sodium oxybate ANDA REMS submission. The ANDA sponsor group clarified that a switch system would be used to check prescriptions within the separate, distinct, REMS databases. The Agency communicated that an updated Supporting Document was needed to provide details of the REMS functionality.
- 06/06/2016: A REMS amendment was submitted by the ANDAs to include proposed changes to the Sodium Oxybate REMS Supporting Document.
- 06/16/2016: Teleconference between the Agency and the ANDA sponsor group to discuss Agency proposed changes to the Sodium Oxybate REMS and discuss procedural timelines for implementation of the REMS program. The Agency proposed to mitigate the risk of duplicate dispensing by requiring the ANDA pharmacies to report all prescriptions received for sodium

oxybate and report and verify disenrollment of prescribers/patients that is specifically related to abuse, misuse, and diversion to the Xyrem REMS Program Central Database.

- 7/21/2016: Teleconference between the Agency and the ANDA sponsor group during which the Agency provided feedback on its initial review of the proposed Sodium Oxybate REMS Document, Supporting Document, and Appended Materials.

4 Results of the Review of the Applicant Holders Proposed REMS

The applicants for sodium oxybate submitted a proposed REMS, which, with the required edits described in this review, will be comparable to the Xyrem REMS. If DRISK identifies additional necessary changes in amended sponsor's submissions; they will be addressed in subsequent DRISK reviews. The operational differences in the proposed program are expected to achieve the same level of safety.

A summary of the proposed ANDA REMS and respective Reviewer Comments follows:

4.1 REMS GOALS

The proposed goals of the Sodium Oxybate REMS are the same as in the Xyrem REMS.

Reviewer Comment:

The proposed goals are acceptable to DRISK.

4.2 REMS ELEMENTS

4.2.1 Medication Guide (MG)

The Sodium Oxybate REMS website address and the telephone number for the REMS call center should be included in the MG. The Office of Generic Drugs (OGD) Division of Labeling Review will review the MG during their review of the label for (b) (4), 203631, 203351, 202090, and provide their comments under separate cover.

4.2.2 Elements to Assure Safe Use

1. *Healthcare providers who prescribe sodium oxybate must be specially certified*

- a. Sodium Oxybate REMS Program Sponsors will ensure that healthcare providers who prescribe sodium oxybate are certified in the Sodium Oxybate REMS Program. To become certified to prescribe sodium oxybate, each prescriber must complete and submit to the Sodium Oxybate REMS Program the *Sodium Oxybate REMS Program Prescriber Enrollment Form*, which includes the prescriber agreeing to:
 - i. Review the sodium oxybate Prescribing Information (PI) and the Sodium Oxybate REMS Program Prescriber Brochure.
 - ii. Screen each patient for whom sodium oxybate is prescribed for:
 - 1) History of alcohol or substance abuse
 - 2) History of sleep-related breathing disorders
 - 3) History of compromised respiratory function
 - 4) Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents

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

/s/

JASMINDER N KUMAR
09/01/2016

CYNTHIA L LACIVITA
09/01/2016
Concur

ANDA 202090

PRE-APPROVAL REMS NOTIFICATION

Roxane Laboratories Inc.
Attention: Gregory Hicks
1809 Wilson Road
Columbus, OH 43228

Dear Mr. Hicks:

Please refer to your pending Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for sodium oxybate oral solution, 500 mg/mL.

We refer to your risk evaluation and mitigation strategy (REMS) submission dated October 19, 2011 and your risk minimization action plan (RiskMAP) submission dated April 16, 2013.

We refer to our letter dated September 27, 2012, informing you that a REMS is necessary for products containing sodium oxybate to ensure that the benefits of the drug outweigh the risk of developing central nervous system and respiratory depression, and the potential for abuse, misuse, and overdose associated with sodium oxybate. In addition, we informed you that Xyrem (sodium oxybate) is deemed to have in effect an approved REMS under section 909(b)(1) of the Food and Drug Administration Amendments Act (FDAAA) of 2007. Finally, we informed you that a drug that is subject to an ANDA is required to have a REMS if the applicable listed drug has an approved REMS and that the elements to assure safe use must be implemented through a single shared system with the listed drug unless FDA waives that requirement.

To facilitate the development of a single shared system REMS with the listed drug, please submit a REMS document based on the attached sodium oxybate REMS template document. The REMS program will be required to include the following elements: Medication Guide, elements to assure safe use including prescriber certification, pharmacy certification, and documentation of safe use conditions, and an implementation system. Your REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Additionally, all relevant proposed REMS materials including enrollment forms, and educational or training materials should be appended to the proposed REMS. The REMS supporting document should explain the rationale for each of the elements included in the proposed REMS.

A multiple-sponsor meeting will be held with the Agency in January, 2014, to facilitate the development of the single shared system REMS program.

Use the following designator at the top of the first page of your proposed REMS submission in bold, capital letters:

AMENDMENT FOR ANDA 202090 PROPOSED REMS

If you have any questions, call Tina Nhu, Regulatory Project Manager at (240) 276-8548.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosures:
REMS document

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

/s/

MARY J DEMPSEY

01/13/2014

entered into DARRTS on behalf of Tina Nhu

KATHLEEN UHL

01/13/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 202090

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Approval Type: <input checked="" type="checkbox"/> FULL APPROVAL <input type="checkbox"/> TENTATIVE APPROVAL <input type="checkbox"/> SUPPLEMENTAL APPROVAL (NEW STRENGTH)		
RPM: John Ibrahim Team:		Approval Date: 1/17/2017
<input type="checkbox"/> PI <input type="checkbox"/> PII <input type="checkbox"/> PIII <input checked="" type="checkbox"/> PIV (eligible for 180 day exclusivity) <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> MOU <input checked="" type="checkbox"/> RX or <input type="checkbox"/> OTC		
ANDA #: 202090 Applicant: Roxane Laboratories, Inc. Established Product Name: Sodium Oxybate Oral Solution, 500 mg/mL		
Basis of Submission (RLD): Xyrem/NDA 021196 (Is ANDA based on an approved Suitability Petition? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No)		
Does the ANDA contain REMS? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (If YES, initiate approval action 6 weeks prior to target action date)		
Regulatory Project Manager Evaluation:		Date: 9/9/2016
<input checked="" type="checkbox"/> Date last Complete Response (CR) letter was issued -- Date 9/19/2013 <input type="checkbox"/> Previously reviewed and tentatively approved (if applicable) --- Date N/A		
Date of Application 7/8/2010	Original Received Date 7/8/2010	Date Acceptable for Filing 7/8/2010
YES	NO	
<input checked="" type="checkbox"/>	<input type="checkbox"/>	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A) Date of Acceptable Quality 8/21/2013 Date of Acceptable Dissolution N/A Date of Acceptable Bioequivalence 3/29/2011 Date of Acceptable Labeling 7/26/2016 If applicable: Date of Acceptable Microbiology N/A Date of Acceptable Clinical Review N/A Date of Acceptable REMS 1/13/2017
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Are consults pending for any discipline?
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES → Verify a second filing review was completed and that all disciplines completed new reviews <input type="checkbox"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Is there a pending Citizen Petition (CP)?
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Overall OC Recommendation is acceptable (EES is acceptable) Date Acceptable: 4/16/2015 Re-evaluation Date: _____
<input checked="" type="checkbox"/>	<input type="checkbox"/>	OSI Clinical Endpoint and Bioequivalence Site Inspections are acceptable
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff (OGDREQUEST) 30 to 60 days prior to approval, Date emailed _____
Draft Approval/Tentative Approval Letter		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Approval/Tentative Approval letter is drafted and uploaded to the Final Decision task
Review Discipline/Division Endorsements		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Division of Legal and Regulatory Support Endorsement completed, Date 1/17/2017
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Paragraph IV Evaluation completed (if applicable), Date 1/16/2017
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Quality Endorsement completed, Date 12/27/2016
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Bioequivalence Endorsement completed, Date 12/19/2016
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Labeling Endorsement completed, Date 1/6/2017
<input checked="" type="checkbox"/>	<input type="checkbox"/>	REMS Endorsement (if applicable), Date 1/17/2017
RPM Team Leader Endorsement and Action Package Verification		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	RPM Team Leader Endorsement completed, Date 1/17/2017
Final Decision and Letter Sign-off		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Final Decision recommending approval/tentative approval completed, Date 1/17/2017
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Approval/Tentative Approval letter electronically signed, Date: 1/17/2017
Project Close-Out		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Notify applicant of approval and provide a courtesy copy of the electronically signed letter
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Is there a Post Marketing Agreement (PMA)? IF YES → Send email to PMA coordinator, Date emailed N/A
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Email OGD Approval distribution list (CDER-OGDAPPROVALS) with approval information



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form		Author: Heather Strandberg

This page to be completed by the RPM

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 12/6/2016

Name/Title: HS

Contains GDEA certification: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	
(required if sub after 6/1/92)	Pediatric Exclusivity System
Patent/Exclusivity Certification: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	RLD = Xyrem NDA# 21196
If Para. IV Certification- did applicant:	Date Checked 12/6/2016
Notify patent holder/NDA holder Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	Nothing Submitted <input type="checkbox"/>
Was applicant sued w/in 45 days: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	Written request issued <input type="checkbox"/>
Has case been settled: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Study Submitted <input type="checkbox"/>
Date settled:	
Is applicant eligible for 180 day Yes	
Is a forfeiture memo needed: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	
If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	
Date of latest Labeling Review/Approval Summary	
Any filing status changes requiring addition Labeling Review Yes <input type="checkbox"/> No <input type="checkbox"/>	
Type of Letter:	
<input checked="" type="checkbox"/> APPROVAL <input type="checkbox"/> TENTATIVE APPROVAL <input type="checkbox"/> SUPPLEMENTAL APPROVAL (NEW STRENGTH)	
<input type="checkbox"/> OTHER:	
Comments:	
<p>ANDA submitted on 7/8/2010, BOS = Xyrem, NDA 21196. Provided PIV certification to the '889, '219, and '730 patents. Provided an exclusivity statement to address ODE listed in the OB at the time of submission. Roxane will not market their product prior to expiration of the ODE on 11/18/2012. Patent amendment received prior to ANDA acknowledgment on 8/3/2010 – revised patent certification to include PIV certification to the '106 and '107 patents. The patents were received for listing in the OB under NDA 21196 on 7/27/2010. The patents were issued by the USPTO on 7/27/2010 and were timely filed for the NDA. They are considered later listed for this ANDA. ANDA ack for filing with PIV certification on 7/8/2010 (LO date 9/27/2010).</p> <p>Patent Amendment rec'd 12/3/2010 – provided documentation of receipt of notice sent via USPS for the '889, '219, '730, '106, and '107 patents. RR provided for notice sent to Bruce Cozzad, Jazz Pharmaceuticals (Palo Alto, CA) delivery receipt is signed but not dated, Carol Gamble, Jazz Pharmaceuticals (Palo Alto, CA) delivered 10/20/2010, JPI Commercial, LLC (Palo Alto, CA) delivered 10/25/2010, Schwegman, Lundberg & Woessner, P.A. (Minneapolis, MN) X2 delivered 10/19/2010, General Counsel, Silicon Valley Bank (San Francisco, CA) delivered 10/22/2010, LBI Group Inc. (New York, NY) delivery receipt not provided (it is noted that the 30 month stay expired on 4/25/2013, therefore a copy of the delivery receipt will not be requested), and Twist Merger Sub, Inc. (Palo Alto, CA) notice was returned to sender. Roxane provided a copy of complaint filed in the D of NJ within the statutory 45-day period on 11/22/2010 for infringement of the '889, '219, '730, '106, and '107 patents (CA No. 10-6108). As suit was brought within 45 days of notice, there is an automatic 30 month stay of approval wrt to the '889, '219, and '730 patents that expired on 4/25/2013. The '106 and '107 patents are considered later listed and litigation wrt these patents does not create a statutory stay of approval.</p> <p>Patent Amendment rec'd 1/11/2011 – revised patent certification to include PIV certification to the newly listed '506 patent. The patent was received for listing in the OB under NDA 21196 on 12/16/2010. The patent was issued by the USPTO on 12/14/2010 and is timely filed for the NDA. It is considered later listed for this ANDA.</p> <p>Patent Amendment rec'd 11/16/2011 – amendment to acknowledge revised expiration date for the '730 patent and</p>	

Lead Division: Program Management **Effective Date:** 10/1/2014

Page 2 of 13

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

Please ensure you are using the most current version of this Form. It is available at:

[OGD QMS Approved Documents](#)



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

provided PIV certification to the newly listed '059 patent. The '059 patent was received for listing in the OB under NDA 21196 on 2/24/2011. The patent was issued by the USPTO on 2/22/2011 and is timely filed for the NDA. It is considered later listed for this ANDA.

Patent Amendment rec'd 7/17/2012 - provided documentation of receipt of notice sent via USPS for the '506 and '059 patents. RR provided for notice sent to Bruce Cozzad, Jazz Pharmaceuticals (Palo Alto, CA) delivered 1/14/2011, General Counsel Silicon Valley Bank (San Francisco, CA) delivered 1/14/2011, and Carol Gamble, Jazz Pharmaceuticals (Palo Alto, CA) delivery receipt is signed but not dated. RR provided for notice sent to Bruce Cozzad, Jazz Pharmaceuticals (Palo Alto, CA) delivered 4/4/2011, Carol Gamble, General Counsel, Jazz Pharmaceuticals (Palo Alto, CA) delivered 4/4/2011, and General Counsel, Silicon Valley Bank (San Francisco, CA) delivered 3/25/2011.

Patent Amendment rec'd 10/9/2012 - revised patent certification to include PIV certification to the newly listed '650 patent. The '650 patent was received for listing in the OB under NDA 21196 on 9/20/2012. The patent was issued by the USPTO on 9/11/2012 and is timely filed for the NDA. It is considered later listed for this ANDA.

Patent Amendment rec'd 6/7/2013 - revised patent certification to include PIV certification to the newly listed '275 patent. The '275 patent was received for listing in the OB under NDA 21196 on 12/5/2012. The patent was issued by the USPTO on 12/4/2012 and is timely filed for the NDA. It is considered later listed for this ANDA.

Patent Amendment rec'd 6/20/2013 - provided documentation of receipt of notice sent via (b) (4) for the '275 patent. RR provided for notice sent to General Counsel, Barclays Bank PLC (New York, NY) delivered 6/10/2013 and Jazz Pharmaceuticals (Palo Alto, CA) delivered 6/10/2013.

Patent Amendment rec'd 9/30/2013 - revised patent certification to include PIV certification to the newly listed '988 patent. The '988 patent was received for listing in the OB under NDA 21196 on 7/3/2013. The patent was issued by the USPTO on 6/4/2013 and is timely filed for the NDA. It is considered later listed for this ANDA.

Patent Amendment rec'd 10/22/2013 - provided documentation of receipt of notice sent via USPS for the '988 patent. RR provided for notice sent to Jazz Pharmaceuticals (Palo Alto, CA) X2, signed but not dated.

Patent Amendment rec'd 11/8/2013 - submitted a letter contesting forfeiture of Roxane's 180 day exclusivity

Patent Amendment rec'd 4/1/2014 - revised patent certification to include PIV certification to the newly listed '182 patent. The '182 patent was received for listing in the OB under NDA 21196 on 12/19/2013. The patent was issued by the USPTO on 11/19/2013 and is timely filed for the NDA. It is considered later listed for this ANDA.

Patent Amendment rec'd 5/9/2014 - provided documentation of receipt of notice sent via USPS for the '182 patent. RR provided for notice sent to Jazz Pharmaceuticals (Palo Alto, CA) X2 delivered 4/4/2014.

Patent Amendment rec'd 1/15/2015 - revised patent certification to include PIV certifications to the newly listed '619, '963, and '306 patents. The '619, '963, and '306 patents were received for listing in the OB under NDA 21196 on 10/28/2014, 5/30/2014, and 7/9/2014, respectively. The patents were issued by the USPTO on 10/14/2014, 5/20/2014, and 7/8/2014, respectively, and are considered timely filed for the NDA. The patents are considered later listed for this ANDA.

Patent Amendment rec'd 2/12/2015 - provided documentation of receipt of notice sent via USPS for the '619, '963, and '306 patents. RR provided for notice sent to Jazz Pharmaceuticals (Palo Alto, CA) X2 delivered 1/23/2015.

Patent Amendment rec'd 4/15/2015 - revised patent certification to include PIV certifications to the newly listed '062 patent. The '062 patent was received for listing in the OB under NDA 21196 on 2/19/2015. The patent was issued by the USPTO on 2/10/2015 and is considered timely filed for the NDA. The patent is considered later listed for this ANDA.

Patent Amendment rec'd 12/10/2015 - revised patent certification to include PIV certifications to the newly listed '302 patent. The '302 patent was received for listing in the OB under NDA 21196 on 7/8/2015. The patent was issued by the USPTO on 6/9/2015 and is considered timely filed for the NDA. The patent is considered later listed for this ANDA.

Patent Amendment rec'd 6/10/2016 - provided documentation of receipt of notice sent via (b) (4) for the '650, '062, and '302 patents. RR provided for notice sent wrt the '650 patent to Jazz Pharmaceuticals (Palo Alto, CA) X2 delivered 10/10/2012 and CT Lien Solutions (Columbus, OH) delivered 10/10/2012, and General Counsel Barclays Bank PLC (New York, NY) delivered 10/18/2012. RR provided for notice sent wrt the '062 patent to Jazz Pharmaceuticals (Palo Alto, CA) X2 delivered 12/14/2015. RR provided for notice sent wrt the '302 patent to Jazz Pharmaceuticals (Palo Alto, CA) X2 delivered 4/16/2015. Roxane also provided copies of complaints filed in the D of NJ, including CA No. 12-6761 filed on 10/26/2012 for infringement of the '650 patent, CA No. 15-3684 filed on 6/1/2015 for infringement of the '062



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

patent and CA No. 16-0469 filed on 1/27/2016 for infringement of the '302 patent. These patents are considered later listed and litigation does not create a 30 month stay of approval. In the cover letter, Roxane also confirms that litigation wrt CA No. 10-6108 remains ongoing.

Patent Amendment rec'd 11/16/2016 – submitted in response to requests from FDA sent 11/7/2016 and 11/10/2016, requesting an update of litigation status for all listed patents. Roxane provided copies of the following complaints, not previously submitted, filed in the D of NJ: CA No. 11-0660 filed on 2/4/2011 for infringement of the '431 patent (not listed in the OB) and the '506 patent (CA No. confirmed via PACER), CA No. 11-2523 filed on 5/2/2011 for infringement of the '059 patent, CA No. 12-7459 filed on 12/5/2012 for infringement of the '275 patent, CA No. 16-4971 filed on 8/12/2016 for infringement of the '963 patent, CA No. 15-1360 filed on 2/20/2015 for infringement of the '306 and '619 patents. Roxane also provided a covenant not to sue for the '988 patent filed on 11/8/2013 under CA. No. 10-6108, and notified the agency that they were not sued wrt the '182 patent. Roxane further stated in their cover letter that CA. No. 12-6761 and all other actions filed between 2010 and 2012 have been consolidated with CA No. 10-6108 (e.g. CA Nos. 11-0660, consolidation order filed 4/6/2011; 11-2523, consolidation order filed 6/15/2011; 12-6761 and 12-7459 consolidation order filed 4/12/2013. Copies of consolidation orders were not provided by Roxane. Consolidation orders and filing dates were confirmed for each case via PACER). Roxane also confirmed that CA Nos. 15-3684 and 16-0469 were consolidated with CA No. 15-1360 (consolidation orders filed 11/23/2015 and 3/24/2016, respectively. Information confirmed via PACER). Roxane further notified the agency that open CA Nos. 10-6108, 15-1360, and 16-4971 are ongoing.

Patent Summary:

'889 patent – PIV; sued, CA No. 10-6108, ongoing, 30 month stay expired 4/25/2013
'219 patent – PIV; sued, CA No. 10-6108, ongoing, 30 month stay expired 4/25/2013
'730 patent – PIV; sued, CA No. 10-6108, ongoing, 30 month stay expired 4/25/2013
'106 patent – PIV (later listed); sued, CA No. 10-6108, ongoing
'107 patent – PIV (later listed); sued, CA No. 10-6108, ongoing
'506 patent – PIV (later listed); sued, CA No. 11-0660, consolidated with CA No. 10-6108, ongoing
'059 patent – PIV (later listed); sued, CA No. 11-2523, consolidated with CA No. 10-6108, ongoing
'650 patent – PIV (later listed); sued, CA No. 12-6761, consolidated with CA No. 10-6108, ongoing
'275 patent – PIV (later listed); sued, CA No. 12-7459, consolidated with CA No. 10-6108, ongoing
'988 patent – PIV (later listed); covenant not to sue filed on 11/8/2013 under CA No. 10-6108
'182 patent – PIV (later listed); not sued
'963 patent – PIV (later listed); sued, CA No. 16-4971, ongoing
'306 patent - PIV (later listed); sued, CA No. 15-1360
'619 patent - PIV (later listed); sued, CA No. 15-1360
'062 patent – PIV (later listed); sued, CA No. 15-3684, consolidated with CA No. 15-1360, ongoing
'302 patent – PIV (later listed); sued, CA No. 16-0469, consolidated with CA No. 15-1360, ongoing

Roxane was the first applicant to file a substantially complete application containing a PIV certification for this drug product. In order to retain eligibility for 180 day exclusivity for these strengths this ANDA needed to secure TA within 40 months of the valid submission date of 7/8/2010. This 40 month date was 11/8/2013. The agency is drafting a forfeiture memo to determine whether Roxane forfeited eligibility for 180 day exclusivity for this drug product. It is noted that this ANDA fell into the cohort of submissions that were afforded extensions under Sec 1133 of FDASIA for the 30 month period in which the applicant needed to secure TA or FA in order to keep their 180 day exclusivity. FDASIA extended timeframes for ANDAs originally submitted between 1/9/2010 and 7/9/2012, with 7/9/2012 being the enactment date of FDASIA. This ANDA was submitted 7/8/2010 and originally benefitted from a 40 month timeframe to secure TA/FA and not potentially forfeit exclusivity. However, as the ANDA was not TA/FA'd within 40 months and FDA's first opportunity to analyze 180 day exclusivity for this product fell after 9/30/2016, this period was reduced to 30 months (Sec 1133 (a)(1)(B)).



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Regardless of the agency's decision related to 180 day exclusivity, this ANDA is eligible for immediate Full Approval. Roxane has provided PIV certifications to all listed patents protecting the RLD. Roxane was sued on all patents except for the '988 and '182 patents. Only the '889, '219, and '730 patents were listed at the time of ANDA submission. Litigation wrt to these patents created an automatic 30 month stay which expired on 4/25/2013. The remaining patents were later listed and litigation with respect to these patents does not create a stay of approval.

Pending CP referencing sodium oxybate, FDA-2016-P-2672: Requests that FDA refuse to approve any sodium oxybate ANDA that does not include in its proposed labeling the portions of the Xyrem package insert and REMS related to divalproex. It is noted that the proposed labeling and REMS submitted for ANDA 202090 retains information related to divalproex. The agency will respond to the petition on the same date as approval.

Update 1/11/2017:

Per memorandum dated January 11, 2017, the Agency determined that there was a change in review of the requirements for approval such that Roxane did not forfeit eligibility for 180 day exclusivity. This ANDA is eligible for immediate Full Approval and should be granted 180 day exclusivity as the first applicant to provide PIV certification to the '889, '219, and '730 patents.

Update 1/17/2017:

Patent amendment rec'd 1/13/2017 - revised patent certification to include PIV certification to the newly listed '426 patent. The '426 patent was originally submitted for listing in the OB under NDA 21196 on 12/6/2016. The patent was resubmitted on 12/21/2016 and 1/10/2017 with additional or corrected information requested by the OB staff. The patent was issued by the USPTO on 11/8/2016. The patent was resubmitted within 15 days of each OB request, therefore the patent is considered timely filed for the NDA. It is considered later listed for this ANDA. The applicant included copies of (b) (4) shipping receipts to document that notice was also sent on 1/13/2017.

Patent Amendment rec'd 1/17/2017 – provided documentation of receipt of notice sent via (b) (4) RR provided for notice sent to Bank of America (Dallas, TX) delivered 1/17/2017 and Jazz Pharmaceuticals (Palo Alto, CA) X2 delivered 1/17/2017. It is noted that Jazz Pharmaceuticals is identified as the NDA holder and the US Agent for the patent owner, Jazz Pharmaceuticals Ireland Ltd, on the Form FDA 3542 submitted with the '426 patent.

This ANDA is still eligible for immediate Full Approval for the reasons set forth above, and should be granted 180-day exclusivity as the first applicant to submit a substantially complete ANDA with paragraph IV certification to the '889, '219, and '730 patents.



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

2. **Paragraph IV Evaluation (for ANDAs with PIV certifications or other controversial regulatory issues)**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

3. **Quality Endorsement by the Office of Pharmaceutical Science**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

4. **Bioequivalence Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

5. **Labeling Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

6. **REMS Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

7. **RPM Team Leader Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

8. **Final Decision**

Date: 1/17/2017
Name/Title: cah

Para.IV Patent Cert: Yes No
Pending Legal Action: Yes No
Petition: Yes No
Entered to APTrack database
GDUFA User Fee Obligation Status Met Unmet
Press Release Acceptable
First Generic Approval
PD or Clinical for BE
Special Scientific or Reg. Issue

Date PETS checked for first generic drug _____

Comments:

ANDA received on 7/8/2010. The BOS = Xyrem, NDA 021196, Jazz Pharmaceuticals Inc. The applicant provided PIV certifications to all patents, '889, '219, '730, '106, '107, '506, '059, '650, '275, '988, '182, '963, '306, '619, '062, '302, and '426. The applicant notified the RLD and was sued within 45 days. The 30 month stay pertaining to patents '219 and '730 expired on 4/25/13. The other patents were submitted after the application was submitted and therefore do not create a statutory stay of approval if sued. There are no new patents/exclusivities listed in the OB for this NDA (1/17/17). There is a pending CP referencing sodium oxybate, FDA-2016-P-2672. This petition requests that FDA refuse to approve any sodium oxybate ANDA that does not include in its proposed labeling the portions of the Xyrem package insert and REMS related to divalproex. This ANDA does not propose to carve out of this information. Thus, is unaffected by this CP. Additionally, the agency will respond to the petition on the same date as approval. Bio – waiver of in-vivo bioequivalence studies requested. Bio adequate and waiver granted based on 21 CFR 320.22(b)(3) per Chaurasia on 3/29/11. Bio endorsement completed by Li on 12/19/16. Drug Product is adequate per Lin/Presto/Samaan/Smith on 8/21/13. DMF (b) (4) is adequate 2/21/13. QE completed by Venkataram on 12/23/16. This endorsement indicates OPQ reviews remain adequate including DMF and facilities. REMS is adequate per DRISK, Zende/Tavakoli/Fitzerald/Parker/Lacivita, on 1/13/17. SSS Waiver memo signed by Sharp on 1/17/17. REMS endorsement completed by Barley on 1/17/17. Labeling is adequate per Chua/Vezza on 7/26/16. Review confirms medication guide is adequate. Labeling endorsement completed by Vezza on 1/6/17. The overall manufacturing inspection recommendation is approve (see screen shots below – there are no visible alerts in the platform at the time of this action). Memo from Shimer dated 1/11/17 states Roxane has not forfeited cites eligibility for the 180 day exclusivity. Thus this ANDA is ready for full approval.

(b) (4)



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Appears This Way In
Original

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

Please ensure you are using the most current version of this Form. It is available at:

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Application History:

Click here to enter text.

Appears This Way In Original

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

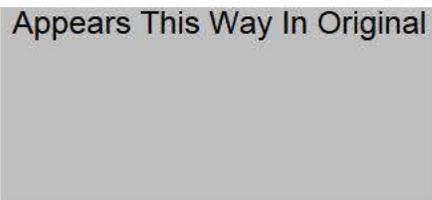


Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Orange Book Report:

Click here to enter text.

Appears This Way In Original



Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

Please ensure you are using the most current version of this Form. It is available at:
[OGD QMS Approved Documents](#)



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

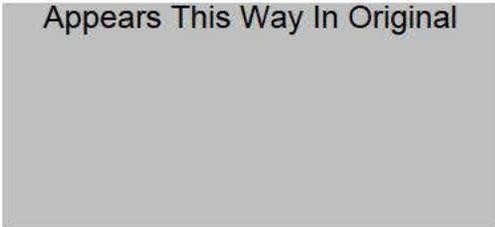
REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form

Appears This Way In Original



MEMORANDUM

DATE: January 17, 2017

TO: Abbreviated New Drug Applications (ANDAs) for sodium oxybate oral solution products

ANDA 202090 - Roxane Laboratories, Inc. (Roxane)

(b) (4)

ANDA 203351 - Ohm Laboratories, Inc. (Ohm)

ANDA 203631 - Amneal Pharmaceuticals (Amneal)

(b) (4)

THROUGH

Senior Regulatory Counsel
Office of Regulatory Policy

FROM: Trueman W. Sharp, M.D., M.P.H.

Deputy Director
Office of Bioequivalence
Office of Generic Drugs

SUBJECT: Decision to waive the requirement for a single, shared system REMS for sodium oxybate oral solution

Executive Summary

This memorandum explains the Food and Drug Administration's (FDA's or the Agency's) decision to waive the requirement for a single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for sodium oxybate oral solution drug products (sodium oxybate). Each applicant listed above currently has pending an abbreviated new drug application (ANDA) referencing Xyrem (sodium oxybate) Oral Solution (Xyrem), a product marketed under a new drug application (NDA) held by Jazz

Pharmaceuticals (Jazz), as the reference listed drug (RLD). Xyrem is approved with a REMS that includes elements to assure safe use (ETASU).¹

Section 505-1(i)(1)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that a generic drug (e.g., sodium oxybate) and the applicable listed drug (e.g., Xyrem) must use an SSS if a REMS with ETASU is required for the listed drug. It also gives FDA the authority to waive this requirement if the Agency determines that the burden of creating an SSS outweighs its benefit, taking into account the impact on the relevant stakeholders, or if an ANDA applicant certifies that it sought a license for use of an aspect of the applicable listed drug's ETASU claimed by a patent that has not expired or a method or process that, as a trade secret, is entitled to protection, and was unable to obtain one.² As explained in more detail below, although either ground would be sufficient on its own, FDA finds that both prongs of this standard have been met for sodium oxybate: the burden of creating an SSS for these products outweighs the benefit, and (b) (4) ANDA (b) (4) certified that (b) (4) sought a license for use of an aspect of Jazz's ETASU claimed by a patent and were unable to obtain one. Accordingly, the Agency has determined to waive the SSS requirement.

The ANDA (b) (4) proposed REMS³ has the same ETASU as those in the Xyrem REMS. Specifically, both the Xyrem REMS and the proposed sodium oxybate ANDA REMS require that: (1) healthcare providers who prescribe the drug are specially certified⁴; (2) the drug will be dispensed only by pharmacies that are specially certified⁵; and (3) the drug will be dispensed and shipped only to patients who are enrolled in the REMS program with documentation of safe use conditions.⁶ Although *aspects* of these requirements in the proposed sodium oxybate REMS vary because of differences in how the ETASU will be operationalized (e.g., the use of multiple, certified pharmacies rather than a single pharmacy), FDA has further determined that the different aspects of the

¹ See section 505-1 of the FD&C Act. The currently approved Xyrem REMS can be found on the FDA's Approved REMS website: <http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>. The single shared system requirement applies if the REMS for the applicable listed drug includes elements to assure safe use. For ease of reference in this memorandum, however, we refer to an SSS for the ETASU portion of a REMS as a "single, shared system REMS" or simply "single, shared system[.]"

² See section 505-1(i)(1)(B) of the FD&C Act.

³ (b) (4) the ANDA (b) (4) submitted a REMS amendment for a proposed shared ANDA REMS on April 8, 2016 or April 11, 2016, and (b) (4) submitted a subsequent amendment on December 2, 2016. The shared ANDA REMS discussed in this memorandum refers to the proposed shared ANDA REMS submitted on December 2, 2016. Contemporaneous with this memo, FDA is approving the ANDA submitted by Roxane (202090) with the ANDA REMS submitted on December 2, 2016. (b) (4)

See section 505-1(f)(3)(A) of the FD&C Act.

⁵ See section 505-1(f)(3)(B) of the FD&C Act.

⁶ See section 505-1(f)(3)(D) of the FD&C Act.

ETASU in the REMS proposed by the ANDA (b) (4) described above are comparable to those in the Xyrem REMS.

To help assure that this decision does not unduly burden health care providers, patients, or the U.S. healthcare system in general, FDA is attaching a condition to the waiver: that the ANDA (b) (4) waiver-granted REMS system be open to all future applicants of sodium oxybate products.

The remainder of this memorandum provides a summary of relevant background information and explains in further detail the Agency's rationale for waiving the requirement for an SSS REMS for sodium oxybate and for determining that the differences in the way the ETASU in the ANDA REMS are operationalized are comparable to the corresponding aspects of the ETASU in the Xyrem REMS.

I. The Statutory Standard

The Agency's authority to waive the requirement for an SSS REMS is governed by section 505-1(i)(1)(B) of the FD&C Act. In relevant part, section 505-1(i)(1)(B) states:

The Secretary may waive the [SSS REMS requirement] for a drug that is the subject of an abbreviated new drug application, and permit the applicant to use a different, comparable aspect of the elements to assure safe use, if the Secretary determines that—

- (i) the burden of creating a single, shared system outweighs the benefit of a single, system, taking into consideration the impact on health care providers, patients, the applicant for the abbreviated new drug application, and the holder of the reference drug product; or
- (ii) an aspect of the elements to assure safe use for the applicable listed drug is claimed by a patent that has not expired or is a method or process that, as a trade secret, is entitled to protection, and the applicant for the abbreviated new drug application certifies that it has sought a license for use of an aspect of the elements to assure safe use for the applicable listed drug and that it was unable to obtain a license.

Thus, FDA has explicit legal authority to waive the requirement that the RLD and an ANDA that references the RLD use an SSS for the ETASU portion of a REMS, provided

the Agency determines either that the burden of creating an SSS REMS outweighs the benefit of such an SSS REMS (taking into account the impact on the statutorily-identified stakeholders) or that the ANDA applicant certifies that it sought a license for use of an aspect of the ETASU claimed by a patent and was unable to obtain one.

II. Background

A. Xyrem (sodium oxybate) Oral Solution

On July 17, 2002, FDA approved NDA 21-196 for Xyrem for the treatment of cataplexy in patients with narcolepsy, and on November 18, 2005, FDA approved a supplemental new drug application (sNDA) for Xyrem for the treatment of excessive daytime sleepiness in patients with narcolepsy.

The prescription drug Xyrem is the sodium salt of gamma-hydroxybutyrate (GHB). GHB is a Schedule I controlled substance, while FDA-approved products containing GHB (including its salts, isomers, and salts of isomers), including Xyrem (sodium oxybate), are controlled under Schedule III.⁷ Risks associated with Xyrem at recommended doses can include central nervous system (CNS) depression, respiratory depression, confusion, and neuropsychiatric events (such as depression). Abuse of GHB either alone or in combination with other CNS depressants is associated with adverse reactions including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with amnesia, particularly when combined with alcohol, poses risks for voluntary and involuntary users (e.g., assault victims).

B. The Xyrem REMS

The Xyrem REMS requires distribution of a Medication Guide in accordance with 21 CFR Part 208. The REMS also requires ETASU to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Xyrem.⁸ Prior to filling a Xyrem prescription, the pharmacy must screen for a patient's concomitant use of sedative-hypnotics and other potentially interacting agents, monitor for inappropriate prescribing, misuse, abuse, and diversion, and notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of

⁷ 21 CFR 1308.11(e)(1) and 1308.13(c)(6).

⁸ As explained in the 2015 Xyrem REMS approval letter, 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. Supplement 15 Approval Letter at 2 (Feb. 27, 2015).

potential abuse, misuse, or diversion. In addition, the REMS is designed to mitigate the risks by informing prescribers, pharmacists, and patients of the risk of significant central nervous system 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, and the safe use, handling, and storage of Xyrem.

Finally, the Xyrem REMS also includes an implementation system through which the sponsor evaluates and monitors compliance with the REMS requirements, as well as a timetable for the submission of REMS assessments.

C. Relevant Regulatory History

The chronology of primary importance in FDA's determination to grant a waiver in this case is the history of discussions between Jazz and the ANDA (b) (4) regarding the development of an SSS. However, because the content and structure of the Xyrem REMS inevitably affects the contours of an SSS or a separate, waived system, the history of the establishment and evolution of the Xyrem REMS – including the roughly seven years of discussions and disagreements between FDA and Jazz about the REMS – is also described below. These two chronologies have proceeded in parallel from approximately 2012 to the present.

1. History of Xyrem REMS

Xyrem was originally approved in 2002 under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) with a risk management plan to assure safe use of the product. The original risk management plan proposed by Jazz contained a requirement that the drug be dispensed only from a single, central pharmacy. FDA approved the plan with this limitation, believing it to be a good way to effectuate the overall restrictions on distribution necessary for safe use of the drug.⁹

Under Section 909 of the FDA Amendments Act (FDAAA), which was enacted in 2007, a drug that was approved before the effective date of FDAAA was deemed to have in effect an approved REMS if there were in effect on the effective date of FDAAA elements to assure safe use required under section 314.520 of FDA regulations. Sponsors of these products, which included Xyrem, were required to submit a proposed REMS to FDA by September 21, 2008 (FDAAA Section 909(b)(3)). Jazz submitted such a proposal on August 29, 2008. That proposal was amended multiple times by Jazz.

⁹ See REMS modification notification letter, December 20, 2013.

In August 2009, as part of its transition from a risk management plan to a REMS, Jazz submitted a proposal to, among other things, remove the restriction to a single pharmacy and instead allow certification of multiple pharmacies. Its rationale for this proposed change was that it would “increase patient access without compromising patient safety.”¹⁰ Jazz also stated that the single pharmacy program in existence at that time “imposes numerous impediments to patient access to Xyrem, possibly depriving narcolepsy patients of an important medication to control their EDS and cataplexy and potentially affect their lives dramatically.”¹¹ Later that year Jazz also submitted a new NDA (22-531) seeking approval for a new indication for fibromyalgia, and in that application proposed a REMS with multiple certified pharmacies. FDA declined to approve the application for fibromyalgia, but did so on grounds unrelated to the multiple pharmacy certification.¹²

After FDA declined to approve the Xyrem fibromyalgia application, discussions between FDA and Jazz regarding the REMS for Xyrem continued. In early 2011, Jazz changed its position and abruptly dropped its proposal for certification of multiple pharmacies. By that time, Jazz had listed several patents related to its REMS in FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

In August 2012, FDA provided interim comments on the proposed REMS which stated that, consistent with Jazz’s earlier request, the final REMS should not contain the single pharmacy limitation, but should instead include the same stringent requirements as part of the requirements for pharmacy certification.¹³ FDA, considered, among other things, the statutory requirement under the FD&C Act that ETASU be imposed only if “necessary to assure safe use of the drug,”¹⁴ that ETASU be “commensurate with the specific serious risk[s] listed in the labeling” of the drug, that ETASU “not be unduly burdensome on patient access to the drug,” and “to the extent practicable,” that ETASU be structured “so as to minimize their burden on the health care delivery system.”¹⁵ FDA believed that the restriction to a single pharmacy was not necessary or appropriate to ensure the safe use of Xyrem, and that any pharmacy that could meet the requirements for certification could safely dispense Xyrem. FDA was also concerned that the restriction to a single pharmacy in the REMS could unduly burden patient access and the health care delivery system.¹⁶

¹⁰ Jazz REMS proposal, August 24, 2009.

¹¹ Id.

¹² See Complete Response Letter for NDA 022531, October 8, 2010.

¹³ FDA Interim Comments on proposed REMS, August 31, 2012.

¹⁴ FD&C Act Section 505-1(f)(1)

¹⁵ FD&C Act Section 505-1(f)(2)(A), (C), and (D).

¹⁶ Dispute Appeal Denied Letter, February 27, 2015.

In its 2013 SEC filings, Jazz noted that it expected FDA modifications to the Xyrem REMS and stated that, “depending on the extent to which certain provisions of our Xyrem deemed REMS which are currently protected by our method of use patents covering the distribution of Xyrem are changed as part of updating our REMS documents, the ability of our existing patents to protect our Xyrem distribution system from generic competitors may be reduced.”¹⁷

In December, 2013, in an effort to bring the protracted discussions over the Xyrem REMS to a close, FDA informed Jazz that the Agency was requiring a modification to the REMS under the Agency’s statutory authority¹⁸ which, among other things, would remove the single pharmacy limitation. FDA also sent a draft template for the REMS to the ANDA (b) (4) to facilitate the development of an SSS for sodium oxybate.

On February 28, 2014, Jazz filed a formal dispute resolution request, appealing the Division of Neurology Product’s REMS modification notification and claiming that the Agency’s “assertion that the closed-loop distribution system for Xyrem is no longer necessary is not only unsupported, it puts patients and others at risk.”¹⁹ Jazz also argued that FDA did not have authority to modify the Xyrem REMS.²⁰

FDA (through the Office of New Drug Evaluation I) denied Jazz’s dispute resolution request on May 8, 2014,²¹ and Jazz appealed this decision to the Director of the Office of New Drugs on June 23, 2014.²² At a meeting with FDA to discuss the ongoing dispute, a Jazz representative acknowledged that it might be possible for a distribution system that involves two, and perhaps more, specialty pharmacies to effectively prevent the abuse, misuse, and diversion of sodium oxybate.²³ Also at this meeting, FDA expressed two primary public health goals: (1) to have a REMS that assures safe use of the drug, and (2) to ensure that the REMS does not stand in the way of generic approval.

In light of the significant drain on Agency resources posed by the dispute, and the fact that the outcome of Jazz’s challenge to the Agency’s legal authority to require a

¹⁷ Form 10-Q, September 30, 2013, at p.54.

¹⁸ See section 505-1(g)(4)(B) of the FD&C Act, which authorizes FDA to require a modification to an approved REMS either to (1) ensure the benefits of the drug outweigh the risks of the drug; or (2) minimize the burden on the health care delivery system of complying with the strategy.

¹⁹ Jazz Formal Dispute Resolution Request (FDRR), February 28, 2014.

²⁰ Jazz argued, among other things, that FDA lacked statutory authority to modify a REMS “deemed” to be in effect by operation of FDAAA, and alternatively, even if FDA did have such authority, it could only be exercised to add restrictions to a REMS, not to modify or remove elements. Jazz FDRR, February 28, 2014.

²¹ Appeal Denied Letter to Jazz from Office of Drug Evaluation I, May 8, 2014.

²² Appeal of Decision by the Office of Drug Evaluation I, June 23, 2014.

²³ Minutes from meeting on August 13, 2014.

modification to a “deemed REMS” had the potential to affect only a small number of drug products,²⁴ the Agency decided to approve the REMS Jazz had proposed (i.e., with the single, central pharmacy limitation), and deny the dispute as moot.²⁵ However, the letter from Dr. Jenkins, Director of the Office of New Drugs, denying Jazz’s appeal states the following:

Our action approving the REMS submitted by Jazz should not be construed or understood as agreement with Jazz that limiting dispensing to a single pharmacy is the only way to ensure that the benefits of Xyrem outweigh the risks under section 505-1 of the FD&C Act. We continue to be concerned that limiting the distribution of Xyrem to one pharmacy imposes burdens on patient access and the healthcare delivery system. No other currently approved REMS requires a sponsor to limit dispensing to a single pharmacy.

At this time, FDA finds that the REMS approved today meets the applicable statutory standards. FDA intends to evaluate the Xyrem REMS, including the burdens it imposes, on an ongoing basis and will require modifications as appropriate.

2. History of SSS Development Efforts

The first ANDA to reference Xyrem, submitted by Roxane, was received by FDA on July 8, 2010. Roxane first contacted Jazz regarding the development of an SSS REMS on October 12, 2012.²⁶ (b) (4)

On January 23, 2014, FDA hosted a meeting between Jazz and the ANDA (b) (4) to facilitate the development of an SSS REMS for sodium oxybate. At this meeting, the ANDA (b) (4) provided a proposed timeline to the meeting attendees with 30, 60, and 90 day milestones with deliverables. For example, the ANDA (b) (4) committed to providing Jazz a draft confidentiality and disclosure agreement (CDA)—typically a prerequisite to substantive discussions about the formation of an SSS—shortly after the meeting with the goal of having it fully executed within 30 days. FDA requested that the parties submit bi-weekly updates to the Agency on the status of negotiations.²⁷

²⁴ At that time there were only three “deemed” REMS remaining, including Xyrem.

²⁵ Dispute Appeal Denied Letter to Jazz from Office of New Drugs, February 27, 2015.

²⁶ See ANDA 202090, Sequence 0013 (Mar. 20, 2013).

²⁷ Minutes of meeting, January 23, 2014. As noted below, the negotiations are described very differently by Jazz and the ANDA (b) (4) and both Jazz and the ANDA (b) (4) accuse the other of

The ANDA (b) (4) provided a draft CDA to Jazz on January 28, 2014. On February 14, 2014, Jazz provided a draft CDA that was substantially revised. Negotiations over the CDA ensued, and the agreement was not fully executed until the end of August 2014, more than seven months after the initial draft was shared.²⁸

In March, 2014, the ANDA (b) (4) having learned of the dispute resolution request by Jazz, expressed concern that “any dispute resolution process will be a protracted matter which will further delay the implementation of a REMS.”²⁹ FDA responded by stating that all parties should continue working together to develop an SSS for sodium oxybate products.³⁰

Over the Summer of 2015, communication between the parties showed a continued inability to agree on threshold issues in the negotiations for an SSS. For example, Jazz’s summary of a call between the parties on June 24, 2015, describes the parties’ disagreement on voting rights for the negotiations. It states:

Jazz’s proposal included provisions for consensus decision making during development of shared REMS, with voting decision making after development, after approval and after implementation changing in accordance with parties’ approval and/or market share status. ANDA (b) (4) proposal provides that all decision making will be determined by majority vote of parties who have NDA or ANDA (and who have paid any costs then due) regardless of such parties’ approval status or market share.³¹

On August 19, 2015, the ANDA (b) (4) emailed the Agency to report a “lack of progress with Jazz on key terms for an operating agreement.”³² The ANDA (b) (4) indicated that, as a result of the lack of progress, they intended to develop a proposal for a separate REMS.

On October 13, 2015, FDA hosted a tele-conference with Jazz and the ANDA (b) (4) to jointly discuss the status of their efforts to develop an SSS REMS. The ANDA

mischaracterizing events. See, e.g., September 9, 2015 email from M. Shumsky for Roxane; September 25, 2015 email from J. Gold for Jazz; December 28, 2016 letter from M. Shumsky for Roxane to K. Uhl, FDA; (b) (4)

See ANDA 202090, Sequence 0038 (Jan. 4, 2017).

²⁹ Email from Gregory Hicks to FDA, March 12, 2014.

³⁰ Email from FDA to Gregory Hicks, March 26, 2014.

³¹ Email from Jana Gold, Jazz to ANDA (b) (4) dated July 20, 2015.

³² (b) (4)

(b) (4) explained that the parties were at an impasse on several major threshold issues. The first was voting rights. The ANDA (b) (4) wanted a voting structure based on “one company-one vote” as was the structure in other SSS REMS in which they had participated, while Jazz wanted voting by consensus until after approval and implementation of the REMS. The second threshold issue related to the process for negotiating an SSS. Jazz maintained that the ANDA (b) (4) were stalling the negotiations by refusing to proceed with legal and operational discussions on a parallel track, which would require integration of operational personnel into the legal negotiations. The ANDA (b) (4) responded that the negotiations needed to be sequential rather than parallel, because the CDA they signed precluded the ANDA (b) (4) from using any of the information from the negotiations for an SSS REMS in the possible future development of a separate REMS for ANDA sponsors. Therefore, if their operations staff were involved in discussions regarding the legal agreement with Jazz for an SSS, those staff would be precluded from later working on a separate system. The ANDA (b) (4) stated that this put them in an untenable position, knowing that the SSS negotiations were by no means guaranteed to be successful, and essentially would have required the ANDA (b) (4) to forfeit their right to obtain a waiver if necessary.³³

On December 4, 2015, Jazz submitted a letter to the Agency expressing its opposition to a potential waiver of the SSS requirement for sodium oxybate.³⁴ In it, Jazz argued, among other things, that FDA cannot grant a waiver and approve a separate REMS for generics that utilizes multiple pharmacies, instead of a single, central pharmacy. The agency has carefully considered Jazz’s arguments and rejected them for the reasons described in section III below.

FDA hosted another joint tele-conference with the parties on March 23, 2016, to determine whether any progress had been made on these threshold issues. The parties did not appear to be any further along in resolving these disagreements than they had been five months before.³⁵

In April, 2016, the ANDA (b) (4) submitted a REMS amendment (b) (4) proposing a joint separate REMS system for generic sodium oxybate. On December 2, 2016, the ANDA (b) (4) submitted a subsequent REMS amendment. (b) (4), Roxane, (b) (4) submitted requests that FDA waive the SSS requirement dated

³³ Minutes of t-con, October 13, 2015.

³⁴ Letter in opposition to potential waiver of the SSS requirement, December 4, 2015 (December 4 Submission).

³⁵ Minutes of t-con, March 23, 2016.

December 28, 2016.³⁶ (b) (4) Roxane) requested a waiver pursuant to both statutory grounds described in section 505-1(i)(1)(B) of the FD&C Act.

III. Discussion

The Agency has determined that a waiver of the SSS requirement for sodium oxybate is appropriate because the burden of creating an SSS outweighs the benefit of a single system, taking into consideration the impact on health care providers, patients, the ANDA (b) (4) and the holder of the reference drug product.

Although an SSS for all sodium oxybate products, including Xyrem, would likely provide the greatest efficiencies for stakeholders once implemented, the burden of negotiating an SSS has been substantial. In the more than four years since the first ANDA applicant and Jazz first began negotiating an SSS REMS³⁷ they have been unable to develop one. In fact, during that time, the parties (b) (4) have reached an impasse on governance issues without even broaching the substantive issues involved in developing an SSS REMS.

The negotiations are described very differently by Jazz and by the ANDA (b) (4) and both Jazz and the ANDA (b) (4) accuse the other of mischaracterizing events.³⁸ For example, Jazz claims that ANDA (b) (4) are being “incentivized to hinder productive SSSR development by creating pretexts for waiver.”³⁹ The ANDA (b) (4) state that Jazz has engaged in a strategy that “entails serial attempts to impose unreasonable contractual terms and conditions on the ANDA (b) (4) while concurrently issuing self-serving statements to FDA and the ANDA (b) (4) about Jazz’s commitment to the process.”⁴⁰

We recognize that there are financial incentives and considerations on both sides that can hinder (b) (4) efforts to establish an SSS REMS. Certain statements by Jazz, including the concerns expressed in its SEC filings and its change in position regarding the necessity of the single pharmacy requirement (from urging FDA to remove the

³⁶ See ANDA 202090, Sequence 0038 (Jan. 4, 2017); (b) (4)

³⁷ Roxane’s ANDA was received on July 8, 2010. FDA sent Roxane a REMS Notification Letter on September 27, 2012. Roxane first contacted Jazz regarding formation of an SSS REMS on October 12, 2012.

³⁸ See, e.g., September 9, 2015 email from M. Shumsky for Roxane and September 25, 2015 email from J. Gold for Jazz. We note that not only are the parties prospective competitors, but patent infringement litigation has been ongoing between Jazz and one or more of the ANDA sponsors during this time.

³⁹ December 4 Submission at p.4.

⁴⁰ ANDA (b) (4) response to FDA questions, October 8, 2014.

restriction to a single pharmacy in 2009 to insisting it is critical to safe use in 2011), suggest Jazz's awareness that the Xyrem REMS could have the effect of blocking or delaying approval of generic versions of Xyrem.

Regardless of whose characterization of events is more accurate, the parties have been attempting to negotiate an SSS REMS for sodium oxybate for a substantially longer period of time than the applicants for alosetron or buprenorphine, the other drug products for which an SSS waiver has been granted.⁴¹ Further, there is little FDA can do to force the two sides to agree to particular terms, because although the FD&C Act mandates that the RLD holder and the generic applicant use an SSS REMS, the Agency has no effective enforcement mechanism to compel the parties to participate in an SSS REMS, or to do so on specific terms. The enforcement mechanisms under the FD&C Act generally are designed to further FDA's public health mission,⁴² not to mediate or resolve corporate disputes over governance issues or address behavior that one or more parties claim is anticompetitive.⁴³

⁴¹ The first waiver of the SSS requirement was issued to the ANDAs referencing Subutex (buprenorphine) or Suboxone (buprenorphine and naloxone). In that case, the ANDA products were approved with a waiver of the SSS requirement approximately one year after SSS negotiations began (see Memorandum re: decision to waive the requirement for a single, shared system REMS for buprenorphine-containing transmucosal products (submitted to ANDA 090819, et al., February 22, 2013)). The waiver of the SSS requirement for the ANDAs referencing Lotronex (alosetron) was the second and most recent occasion on which the Agency has waived the SSS REMS requirement. In that case, the waiver of the SSS requirement was granted and ANDA products were approved approximately three years after SSS negotiations began (see Memorandum re: decision to waive the requirement for a single, shared system REMS for alosetron products (submitted to ANDA 200652 on May 4, 2015)).

⁴² The enforcement tools available to FDA under the REMS provisions include finding the drug is misbranded (§ 502) (21 U.S.C. § 352(y)), seizure of a product deemed to be misbranded (§ 304(a)) (21 U.S.C. § 334(a)), withdrawal of approval of the product due to safety and efficacy concerns (§ 505(e)) (21 U.S.C. § 355(e)), seeking to enjoin violative behavior (e.g., enjoining distribution of a misbranded or unapproved product (§ 302) (21 U.S.C. § 332), prohibiting the introduction or delivery for introduction into interstate commerce of the product (§ 505(p)) (21 U.S.C. § 355(p)), and imposing civil money penalties (§ 303) (21 U.S.C. § 333(f)(4)).

⁴³ Jazz has requested that FDA refer the parties to mediation under the Administrative Dispute Resolution Act of 1996 (ADRA) to resolve their disagreement over business issues regarding the governance of any SSS REMS. FDA has declined to do so, both because the ADRA does not appear to apply by its terms and because the Agency has determined that it would not be an efficient use of limited government resources. Jazz's letter states that the ADRA gives FDA authority to refer the ongoing negotiations to mediation or another form of alternative dispute resolution as a way of resolving the parties' business issues, and that the ADRA is applicable to facilitating negotiations between parties, because it defines an "issue in controversy" as an "issue which is material to a decision concerning an administrative program of an agency, and with which there is disagreement... (B) between persons who would be substantially affected by the decision" (5 U.S.C. § 571(8)(B)). While it may be true that an "issue in controversy" can apply to two parties external to the Agency, we disagree that the business issues here are "material to a decision concerning an administrative program" of the Agency. Rather, the governance issues on which the parties disagree have little or no bearing on whether FDA can ultimately find that the standard for waiving the SSS requirement is met or whether an ANDA for sodium oxybate meets the statutory standard for approval. Moreover, under the ADRA, an "administrative program" is a federal function that involves protection of

In the absence of a waiver of the SSS requirement, the ANDA (b) (4) and Jazz's failure to agree to SSS terms is likely to further delay the approval of a generic version of sodium oxybate. Given the extensive negotiations that have occurred, the inability of the parties to agree to terms, and the Agency's lack of an effective mechanism to require them to do so, FDA concludes that, similar to the two previous instances where FDA granted a waiver of the SSS requirement, the burden of creating an SSS REMS in this instance appears to be insurmountably large.

A. The Burden of Creating a Single, Shared System Outweighs the Benefits

In accordance with section 505-1(i)(1)(B) of the FD&C Act, the Agency has considered the impacts that granting a waiver and permitting a second, separate REMS for sodium oxybate will have on health care providers, patients, the ANDA (b) (4) and the reference drug sponsor (Jazz). The Agency concludes that, on balance, the impacts on these stakeholders favor granting a waiver. While an SSS would provide benefits to stakeholders by avoiding the potential confusion and inefficiency associated with the co-existence of two REMS for sodium oxybate, these benefits do not outweigh the burdens of (1) the time and resources expended by the parties to create an SSS REMS, and (2) a

the public interest and the "determination of rights, privileges, and obligations of private persons through rule making, adjudication, licensing, or investigation" (Section 571(2)). The current negotiations for an SSS REMS for sodium oxybate do not appear to fit this description. They are negotiations between private parties regarding their business relationship, to which FDA is not a party. The FDA is not engaged in any rulemaking, adjudication, licensing, or investigation with respect to the governance of a shared system REMS. While FDA may facilitate communication and negotiation between the parties, we are not determining any rights, privileges or obligations in doing so. Moreover, FDA is not aware of any circumstances in which the Agency has utilized the provisions of the ADRA, or any other statutory provisions, to refer private parties to mediation and Jazz has provided no such examples. Jazz refers in its letter to the Department of Health and Human Services (HHS) Alternative Dispute Resolution Division program. However, this program provides alternative dispute resolution services in appeals filed with the Departmental Appeals Board's other three Divisions (Appellate, Civil Remedies and Medicare Operations Division) and is therefore inapplicable.

Jazz cited two examples where FDA purportedly "has established dispute resolution under the ADRA" by referring to guidance documents from the Center for Veterinary Medicine and the Center for Devices and Radiological Health. The guidance documents to which it refers apply to veterinary drugs and medical devices, and are not binding on FDA or the public. Each of these guidance documents explicitly applies to dispute resolution for "scientific controversies" between the Agency and a regulated party. Both were issued to aid in implementation of the dispute resolution provision in the Food and Drug Administration Modernization Act of 1997 (FDAMA), which was designed to ensure that FDA makes appropriate use of independent scientific experts to advise the agency on "scientific controversies" between FDA and a sponsor, applicant, or manufacturer (Section 562 of the FDCA). The current disagreement between Jazz and the ANDA (b) (4) regarding governance of an SSS REMS for sodium oxybate is neither a scientific controversy nor a disagreement between the Agency and a regulated party. Accordingly, we do not find these examples to be relevant.

Even assuming that the ADRA applies, its application is discretionary. It is our view that invoking the ADRA to refer the parties to mediation regarding business issues that--however they are decided--ultimately are not relevant to the statutory standard for approving a REMS, is not an efficient use of limited governmental resources. We note that the parties were not prevented from pursuing mediation on their own.

delay in the approval of one or more equally safe generic sodium oxybate alternatives. The Agency's findings with respect to the impacts on each stakeholder group of having two REMS are summarized below.

1. Health Care Providers

The creation of two REMS will create some inefficiencies for prescribers and pharmacies/pharmacists. Specifically, health care providers who wish to have the ability to prescribe Xyrem as well as a generic sodium oxybate product will have to enroll in two REMS programs. That means that a prescriber must complete and submit a separate prescriber enrollment form to the ANDA REMS. That step need only be completed once, however, and the form is short—just one page. Further, the prescribing information and prescriber brochure a prescriber must review as part of enrollment are nearly identical to the Xyrem labeling and prescriber brochure, and the required attestations (e.g., prescriber agreement to provide certain counseling, screening, and monitoring for each patient) on the enrollment form are the same.

Once enrolled in the ANDA REMS, the burden on a prescriber in operating under the REMS is the same as under the Xyrem REMS: he or she must enroll, assess, and counsel each patient, and submit a prescription form to the certified pharmacy. Again, both forms are just one page each and nearly identical to the Xyrem REMS materials. The prescriber is also required to reassess the patient within the first 3 months of starting sodium oxybate therapy, and it is recommended every 3 months thereafter. The prescriber is required to report adverse events, including any cases of suspected abuse, misuse, or diversion, to *either* the Xyrem or the ANDA REMS, as appropriate, but need not report to both. As such, the creation of two REMS should not impose an additional burden with respect to enrollment, counseling, assessment, or adverse event reporting.

A pharmacy that wishes to dispense generic sodium oxybate will need to have their pharmacists and other staff complete a training program similar to the Xyrem REMS pharmacy training program and complete a short form to become certified in the ANDA REMS. This step need only be completed once. Because the Xyrem REMS currently specifies use of only a single pharmacy, any pharmacy other than the Xyrem pharmacy would be enrolling only in the sodium oxybate REMS program. Therefore, any pharmacy dispensing sodium oxybate would need to take only one training program.

Certain communication between pharmacies will also be needed. First, a pharmacy certified in the ANDA REMS must, for each prescription received, contact the Xyrem REMS to request verification that: (1) the patient has no active overlapping prescription(s) for Xyrem; and (2) the patient and prescriber have not been disenrolled for suspected abuse, misuse, or diversion. Second, the ANDA REMS program also must report to the Xyrem REMS pharmacy on an ongoing basis each prescription filled and

any instances of patient/prescriber disenrollment in the ANDA REMS program. These communications will be documented.

The Xyrem REMS pharmacy will receive these reports from pharmacies certified in the ANDA REMS program and enter all relevant safety information into the Xyrem central database, as it is required to do under its REMS.⁴⁴

The reporting of prescription fills and disenrollment will be only a minimal additional burden on the pharmacies in both programs. We do not expect the overall number of patients or the total number of prescriptions dispensed to change substantially as a result of the approval of generic products. The difference will be that some of the prescriptions currently being filled by the Xyrem pharmacy likely will instead be filled by pharmacies certified under the ANDA REMS program. Therefore, some of the time the Xyrem REMS pharmacy previously spent on filling prescriptions for Xyrem presumably will now be spent receiving information from the ANDA REMS program pharmacies and entering it into the Xyrem REMS database. Although this shift likely will result in a reallocation of resources, we do not expect that it will result in an overall increased burden on the Xyrem pharmacy. Accordingly, FDA does not believe that the waiver of the SSS requirement will impose a significant burden on health care providers.

2. Patients

The Agency finds that, while a waiver will result in some burdens on patients due to the existence of two programs, these burdens will be minimal. As discussed further in section III(C) below, the Agency finds that the proposed sodium oxybate REMS will afford patients the same level of safety as the Xyrem REMS.

While two REMS will mean that some patients⁴⁵ may need to enroll in two REMS programs, the burden associated with enrollment (completing a form during a physician visit and receiving counseling) is a modest, one-time obligation. Moreover, the REMS materials required in both programs will contain the same safety messages about sodium

⁴⁴ See, e.g., Xyrem REMS section II(B)(2)(a)(iv) (to become certified in the REMS program, the pharmacy must agree to “Utilize the secure and validated XYREM REMS Program Central Database,”; section II(B)(2)(d)(i) (the certified pharmacy “will document these events, including all requests for early refills, in the XYREM REMS Program Central Database by completing an RMR [Risk Management Report],”); and II(C)(1)(c) (“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 Risk Management Report histories.”).

⁴⁵ The Agency anticipates that most patients will use either generic sodium oxybate or Xyrem, but not both. Existing patients wishing to use generic sodium oxybate will need to enroll in the new ANDA REMS program. New patients presumably would enroll in either the ANDA REMS program or the Xyrem REMS program, but not both. The Agency expects that only a very small number of patients would need to be enrolled in both REMS programs at the same time.

oxybate. As a result, FDA does not believe that the co-existence of the two REMS will be a significant burden to patients or compromise the clarity of the safety messages communicated to them.

Jazz has raised the concern that patients switching between the Xyrem REMS and the ANDA REMS, which uses different databases, would mean loss of access to the patient's prior sodium oxybate history, negatively impacting patient care and security.⁴⁶ The Agency does not agree.

If patients do switch between the REMS programs, the patient history data that are relevant to identifying any abuse, misuse, or diversion will not be lost. The ANDA REMS requires its certified pharmacies to contact the Xyrem central pharmacy to verify that a patient has not been disenrolled from the Xyrem REMS and identify any overlapping prescriptions prior to dispensing. The ANDA REMS further requires its certified pharmacies to communicate the patient's corresponding prescription information to the Xyrem central pharmacy. The Xyrem central pharmacy is required to enter all relevant safety information into its central database to use for prescription verifications.⁴⁷ This pharmacy-to-pharmacy communication will ensure that each REMS program can access a patient's relevant sodium oxybate history.⁴⁸

The inability of the ANDA (b) (4) and Jazz to create an SSS imposes a significant burden on patients in that it bars access to one or more equally safe generic sodium oxybate products. FDA has been waiting to approve any sodium oxybate ANDAs pending development of an SSS REMS.⁴⁹

Jazz has argued that patient access does not hinge on, and would not be realized by, a decision to waive the SSS requirement for sodium oxybate, because comprehensive resolution of intellectual property litigation between Jazz and ANDA (b) (4) is not likely to occur for some time.⁵⁰ Given the ongoing litigation, Jazz states that patient access to generic sodium oxybate could conceivably be realized more quickly through

⁴⁶ December 4 Submission at 31.

⁴⁷ See fn. 44 supra.

⁴⁸ Both the Xyrem REMS and the ANDA REMS require that documentation of instances of potential abuse, misuse, or diversion be maintained in their respective databases and reviewed prior to dispensing (Xyrem REMS section II(B)(2)(b)(iii)(b); ANDA REMS section II(B)(2)(b)(ii)(2)(b)). The Agency considered whether additional reporting between the programs would be appropriate, such as reporting of all Risk Management Reports (RMRs) generated, and concluded such information would not be useful. Most RMRs do not report issues that indicate a patient should not receive the drug (e.g., early refill request due to a prescribed dose increase), and those that do would lead to disenrollment, which is required to be communicated between the REMS programs. FDA concluded that the reporting of every RMR between the programs would potentially burden both systems without improving safety.

⁴⁹ Delay may also impose a substantial cost to the U.S. healthcare system, as Xyrem remained, until now, shielded from generic competition.

⁵⁰ December 4 Submission at 32.

continued negotiation for an SSS rather than a waiver of the SSS requirement.⁵¹ FDA is not privy to the details of the litigation and cannot comment on the merits. However, as explained above, after four years of unsuccessful negotiation for an SSS it seems unlikely that continued discussions will yield results in the near term. Thus, even if the burden on patients of the lack of access to potentially more affordable sodium oxybate alternative is not immediately ameliorated by the granting of a waiver, that burden will be removed once the first generic product comes to market. Moreover, by issuing a waiver and approving an ANDA, FDA is taking one critical and fundamental step to alleviate that burden on patients.

In short, the burden of creating an SSS here denies patients access to one or more potentially more affordable sodium oxybate alternatives, while the potential benefit of an SSS is that some patients will not have to enroll in two REMS programs and receive the duplicative educational materials associated with having two REMS programs.

3. ANDA (b) (4)

Absent a waiver, approval of pending ANDAs will be delayed until the parties reach an agreement on an SSS REMS. There are obvious incentives for any innovator company, including Jazz, to delay generic competition, including by failing to agree on SSS REMS terms. Jazz asserts that it is the ANDA (b) (4) hindering SSS development and seeking a waiver in order to avoid the time, money, and effort associated with development of an SSS.⁵² This argument assumes that the expenditure of time, money, and effort would be less significant to develop a separate REMS system. The Agency notes, however, that the ANDA REMS is a shared system (b) (4), and therefore required its own time, money, and effort to develop. Given that these factors did not prevent the ANDA (b) (4),⁵³ it does not appear that an unwillingness to invest the time, money, and effort to develop a shared program is the underlying barrier to development of an SSS in this case.

By granting a waiver, the Agency will remove a barrier to generic products coming to market. The Agency's decision to grant a waiver will benefit the ANDA (b) (4) to the extent it will allow ANDA applications that otherwise meet the statutory standard to be approved, the result intended by the Hatch-Waxman amendments. The burden of SSS development outweighs any potential benefit to ANDA applicants from such a system.

⁵¹ Id.; see also, Letter from Jazz to FDA, December 5, 2016.

⁵² Id. at 29.

⁵³ The ANDA (b) (4) began negotiations for a separate REMS in October, 2014 (see ANDA (b) (4) response to FDA questions, October 8, 2014) and (b) (4) began contracting third party vendors to build the system in August, 2015 (see (b) (4)).

4. Jazz

Jazz argues that a waiver will affect its ability to continue using its approved REMS and impact patient safety because “without access to all of the data, Jazz would lose the ability to ensure that the pharmacy has all of the data necessary to monitor for overlapping prescriptions, review for potentially interacting agents that are unknown to the prescriber, and review of alerts and RMRs regarding potential misuse, abuse, or diversion...”⁵⁴ However, Jazz will continue to have access to the data it needs to fulfill all of the safe use requirements in its approved REMS. As explained in sections III(A)(1) above and III(C) below, the ANDA REMS requires pharmacies certified in that REMS to report to the Xyrem REMS each prescription filled as well as each instance of patient/prescriber disenrollment in the ANDA REMS. This will provide the Xyrem pharmacy the data necessary to monitor for overlapping prescriptions and disenrollments for potential misuse, abuse, or diversion. Jazz will not lose data necessary to monitor potentially interacting agents unknown to prescribers, because each REMS program requires their certified pharmacies to screen for concomitant medications and document them in their respective database(s).⁵⁵ The Xyrem program will not need to check the ANDA program databases for this information, because the Xyrem pharmacy will obtain that information independently from enrolled prescribers and patients and will add that information to its own database. Therefore, Jazz will continue to have access to the data it needs to fulfill all of the safe use requirements in its approved REMS.

Jazz also argues that any negative outcomes of a separate REMS for sodium oxybate ANDAs (i.e., increased risk associated with distribution) would put Jazz at risk for increased liability. As explained below, FDA has carefully reviewed and considered the ANDA (b) (4) proposed REMS program and has determined that it describes a secure and cohesive system and does not create an increased risk of abuse, misuse, or diversion. Because FDA finds that the ANDA (b) (4) proposed REMS program would assure the same level of safety as the existing Xyrem REMS program, FDA does not anticipate that Jazz will experience a meaningful increase in liability.

Approving sodium oxybate ANDAs would allow patients and the healthcare system access to alternative versions of the drug and increase competition in the marketplace.⁵⁶

⁵⁴ December 4 submission at 33.

⁵⁵ Xyrem REMS document Section II(B)(2)(b)(i); ANDA REMS document Section II(B)(2)(b)(i).

⁵⁶ In a letter to FDA dated December 5, 2016, Jazz requested that it be informed of any effort by the ANDA (b) (4) to form a separate REMS and that Jazz have the opportunity to review and evaluate the ANDA REMS prior to approval. FDA denied a similar request made by Prometheus Laboratories, Inc. in a 2013 citizen petition (Docket No. FDA-2013-P-0572) regarding the REMS for Lotronex (alosetron), and declines to do so here as well. As explained in that petition response, FDA welcomes input from RLD sponsors at any point on whether a waiver of the SSS requirement should be granted. In this case, FDA has considered such information submitted by Jazz as described in this memorandum.

The benefit of an SSS is the potential for reducing the burden on stakeholders of having separate REMS programs. However, as described above, those burdens in this case are minimal and the potential benefit of alleviating them is far outweighed by the significant burden of continued SSS negotiations and of denying patients access to generic versions of the drug for an indefinite period of time.

B. (b) (4) ANDA (b) (4) unable to obtain a license for the aspect of the ETASU claimed by Jazz in an unexpired patent and as a trade secret entitled to protection

In accordance with Section 505-1(i)(1)(B)(ii), (b) (4), and Roxane (b) (4) certified that “an aspect of the elements to assure safe use for the applicable listed drug is claimed by a patent that has not expired or is a method or process that, as a trade secret, is entitled to protection, and the [ANDA (b) (4)] sought a license for use of an aspect of the elements to assure safe use for the applicable listed drug and (b) (4) unable to obtain a license.” This certification was made in waiver request (b) (4) to FDA dated December 28, 2016, from (b) (4) Roxane.⁵⁷

Consistent with the statutory requirement that such a certification include “a description of the efforts made by the [ANDA] applicant to obtain a license,” Roxane’s letter states that the company proposed license terms to Jazz between October 2012 and September 2013. The letter states that Jazz refused those terms and declined to offer a substantive counterproposal. Additional discussions took place in 2016, but Roxane states that those were again unsuccessful. (b) (4)

(b) (4)

⁵⁷ December 28, 2016 waiver request letter from M. Shumsky for Roxane to K. Uhl, FDA (ANDA 202090, Sequence 0038 (Jan. 4, 2017)); (b) (4)

(b) (4)

In December 2015, Jazz acknowledged that (b) (4) ANDA (b) (4) had “requested licenses to some of Jazz’s REMS patents” but stated that “(b) (4) certify that it has made reasonable efforts to obtain a license to Xyrem’s intellectual property.”⁵⁹ However, Jazz also indicated that it would be willing to discuss license terms only “once the contours of the shared REMS come into focus” and “*only* in the context of resolution of the [ongoing patent infringement] litigation, through settlement or otherwise.”⁶⁰

As with the shared REMS negotiations, the patent license negotiations seem to be described differently by Jazz and the ANDA (b) (4). It would be difficult for FDA to assess the merits of these respective positions, but the statute does not require us to do so.⁶¹ Under section 505-1(i)(B)(ii) of the FD&C Act, the Agency may waive the SSS requirement if: (1) an aspect of the ETASU for the applicable listed drug is claimed by a patent that has not expired; and (2) an ANDA applicant certifies that it has sought a license for use of an aspect of the ETASU and that it was unable to obtain a license. Both criteria are satisfied here.⁶²

C. The ANDA (b) (4) proposed REMS is comparable to the approved REMS for Xyrem

Section 505-1(i)(1)(B) of the FD&C Act provides that an ANDA is subject to the ETASU for the RLD, but a separate REMS for ANDA applicants that is waived from the SSS requirement can use a “different, comparable aspect of the [ETASU].” FDA interprets this standard to mean that a waived system for ETASU must include the same general elements as described in the statute. For example, if the RLD’s ETASU consist of prescriber certification (under 505-1(f)(3)(A)) and dispensing of a drug only in certain

⁵⁸ Id.

⁵⁹ Jazz December 4, 2015 Submission at 35.

⁶⁰ Id. (emphasis added).

⁶¹ Jazz argues that “the statute plainly gives FDA a role to play when it comes to issues concerning [REMS patent] licensing” because it authorizes the Agency to seek to negotiate a voluntary agreement with the patent owner if it receives a certification under 505-1(i)(B)(ii). Id. at 36. We agree that the statute provides the Agency with that authority, but disagree with the implication that such authority obligates FDA to second-guess the certifications made by ANDA applicants or to otherwise play a more prominent role in patent license negotiations. The authority to negotiate a voluntary agreement with the patent owner is discretionary, and given the longstanding disagreement between the parties over the SSS REMS and related patent issues, FDA declines to invoke this discretionary authority here.

⁶² Jazz further argues that even if this waiver criterion were met, it would be “inappropriate” for FDA to grant a waiver because doing so would “eliminat[e] key safety measures that are essential to ensuring that sodium oxybate can be safely distributed.” Id. at 36-39. FDA disagrees with that conclusion for the reasons described in this memorandum.

healthcare settings (under 505-1(f)(3)(C)), the ANDA system must include those elements as well. FDA further interprets “different, comparable aspect of the [ETASU]” to allow a separate REMS for ANDA applicants to use different methods or operational means to effectuate a REMS requirement, provided the program achieves the same level of safety.

The ANDA ^{(b)(4)} proposed REMS has the same ETASU as those in the Xyrem REMS. The proposed ANDA REMS operationalizes these elements differently, and FDA has determined that those aspects of the ETASU are comparable to the Xyrem REMS. Specifically, both the Xyrem REMS and the ANDA REMS require that: (1) healthcare providers who prescribe the drug are specially certified⁶³; (2) the drug will be dispensed only by pharmacies that are specially certified⁶⁴; and (3) the drug will be dispensed and shipped only to patients who are enrolled in the REMS program with documentation of safe use conditions.⁶⁵ The following specific REMS requirements are the same:

1. **Prescriber Certification.** Both REMS require healthcare providers who prescribe sodium oxybate agree to perform the same functions, including patient screening, counseling, evaluating, enrolling, and reporting adverse events.
2. **Pharmacy Certification.** Both REMS require that the drug will not be stocked in retail pharmacies, and both require that their certified pharmacies⁶⁶ perform the same functions:
 - a. Dispense only to patients that are enrolled in the REMS
 - b. Ensure that all pharmacy staff involved in the program are trained
 - c. Ensure that pharmacists involved in the program are trained
 - d. Utilize database(s) for tracking and documenting the relevant prescription and enrollment information
 - e. Provide toll-free access to a REMS program pharmacist
 - f. Ship the drug directly to each patient or designee and track the shipment
 - g. Limit the first shipment to a one-month supply and subsequent shipments to no more than a three-month supply
 - h. Document and report all potential adverse events to the sponsor(s)
 - i. Ensure completion of patient counseling checklist and its requirements and the documentation of information received

⁶³ See section 505-1(f)(3)(A) of the FD&C Act.

⁶⁴ See section 505-1(f)(3)(B) of the FD&C Act.

⁶⁵ See section 505-1(f)(3)(D) of the FD&C Act.

⁶⁶ The Xyrem REMS specifies use of the single pharmacy, while the ANDA REMS contemplates multiple certified pharmacies.

- j. Validate each prescription by
 - i. verifying that both prescriber and patient are enrolled and that the patient has no other active prescription
 - ii. confirming all prescription information
 - k. Review the patient information, including concomitant or interacting agents, and reports regarding potential abuse, misuse, or diversion
 - l. Monitor, document, and report to sponsor(s) all instances of patient or prescriber behavior that give rise to a reasonable suspicion of abuse, misuse, or diversion.
3. **Documentation of Safe Use Conditions.** Both REMS require that the drug only be shipped to patients who are enrolled in the REMS program with documentation of the same safe use conditions:
- a. The drug is dispensed only by a certified pharmacy, by direct shipment, to patients enrolled in the program
 - b. Patients are enrolled in the program only if a prescriber completes the patient enrollment form
 - c. The drug is dispensed and shipped only to patients who have signed the prescriber-completed patient enrollment form and acknowledged that he/she has been counseled and asked any questions
 - d. Patients remain in the program unless the pharmacy or prescriber determine they should be disenrolled
 - e. Disenrolled patients may re-enroll under certain conditions
 - f. Patients may change prescribers provided that the new prescriber is also enrolled in the program and that the new prescription does not overlap with another active prescription.

The ANDA REMS requires that sodium oxybate can be prescribed only by certified prescribers, and dispensed only to enrolled patients by certified pharmacies.⁶⁷ Only a mail order pharmacy that coordinates secure shipment to patients and is not open to the public can be certified to dispense sodium oxybate. The ANDA REMS also contains the same statement as the Xyrem REMS that sodium oxybate “will not be stocked in retail pharmacy outlets.”⁶⁸

There are some differences in the operational aspects of the ETASU. Specifically, the ANDA REMS does not include the same limitations on the number of pharmacies and databases used. While the Xyrem REMS uses a single pharmacy and a single database,

⁶⁷ The Xyrem REMS states that “Xyrem will be dispensed only by the central pharmacy that is specially certified.”

⁶⁸ ANDA REMS section II(B)(2)(a) and II(C)(1)(b).

the ANDA REMS will use multiple certified pharmacies and multiple databases connected via an electronic communication verification mechanism known as a switch system. The switch system ensures coordination among prescribers and pharmacies such that a drug is dispensed only after there is verification that all safe use conditions are met, namely that: (1) the patient is enrolled in the REMS, meaning that, among other things, the patient has been screened by a trained prescriber and educated about the safe use of sodium oxybate; (2) the prescriber is certified in the REMS, meaning that, among other things, the prescriber has reviewed the prescribing information regarding the safe use of sodium oxybate and agreed to report adverse events promptly; and (3) a pharmacy trained about the particular risks of sodium oxybate and the REMS program requirements has validated the prescription and provided the required patient counseling.

A switch system has been used to verify safe use conditions in other approved REMS,⁶⁹ including the REMS for Transmucosal Immediate Release Fentanyl (TIRF) products.⁷⁰ TIRF products are Schedule II controlled substances that are contraindicated in non-opioid tolerant patients (among others) due to the risk of fatal respiratory depression, and pose risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors. The switch system technology used in the TIRF REMS has been successfully implemented to verify, prior to dispensing, that the pharmacy and prescriber are enrolled and active and the patient has not been deactivated from the program.⁷¹ The switch system provides this information to pharmacists at the point-of-dispensing, and if one or more of the required enrollments cannot be verified, then the switch system will reject the prescription, and the pharmacy will receive a rejection notice.

The ANDA REMS will use a switch system similar to the TIRF REMS to perform the necessary safety checks at the point of dispensing. Once a certified pharmacy receives the prescription, it requests a pre-dispense authorization (PDA) from the ANDA REMS via the switch system, which queries databases of patients, prescribers, dis-enrolled prescribers, and pharmacies, to verify the necessary prescription information and patient and prescriber enrollments before authorizing dispensing.

In addition to verifying this necessary safety information from its own databases, the ANDA REMS will require a certified pharmacy to contact the Xyrem REMS program to verify, prior to dispensing, that the patient has no other active prescriptions for Xyrem that overlap with the prescription to be filled, and to identify any patient and prescriber

⁶⁹ The REMS for Addyi, Qsymia, and clozapine, among others, also utilize a switch system. See FDA REMS website at <http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm>.

⁷⁰ TIRF REMS document is available at <http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60>.

⁷¹ See e.g., TIRF REMS assessment review, September 28, 2016, at p.29.

dis-enrollments. A certified pharmacy in the ANDA REMS also will provide corresponding information (prescription information and enrollment status) to the Xyrem REMS program, so that the Xyrem pharmacy can include that information in its central database and verify prescriptions and enrollment status against the ANDA system.⁷²

Once all checks are completed, the medication is shipped directly to the patient just as it is under the RLD program. The drug product is never housed in a retail pharmacy.

FDA has concluded that this approach achieves the same level of safety as the RLD. We have determined that the different aspects of the ETASU in the REMS proposed by the ANDA (b) (4) are comparable to those in the Xyrem REMS. In each case, the drug is shipped directly to the patient and not stocked on retail pharmacy shelves, the same patient counseling takes place prior to dispensing, and multiple checks are built in to ensure that safe use conditions have been met and that there have been no attempts at diversion, abuse or misuse. Accordingly, this conclusion is consistent with the Agency's stated position (described above) that limiting dispensing to a single pharmacy is not the only way to meet the necessary requirements for pharmacy certification and ensure that the benefits of Xyrem outweigh the risks.

Controls under the ANDA REMS

In its submission to the Agency dated December 4, 2015, Jazz states its opposition to a waiver of the SSS REMS requirement for generic sodium oxybate products. This submission predates the submission of the ANDA (b) (4) REMS, but Jazz refers to the ANDA (b) (4) "Paragraph IV notices"⁷³ as evidence that (b) (4) intend to deviate significantly from the approved Xyrem REMS.⁷⁴ Jazz describe ANDA (b) (4) stated intent to use "multiple separate sodium oxybate databases and multiple additional points of distribution" and quotes from the (b) (4) ANDA (b) (4) Paragraph IV notices to characterize the use of multiple databases as disconnected and incomplete.⁷⁵

Jazz's description of the ANDA (b) (4) system does not accurately characterize the REMS being approved. The ANDA REMS does not permit the use of retail pharmacies, which Jazz maintains would entail shipment to, and stocking of sodium oxybate at,

⁷² The Xyrem REMS requires that the certified pharmacy access the REMS program database to verify all enrollments and prescription information prior to each dispense of the drug. See Section II(B)(2)(b)(ii).

⁷³ Pursuant to section 505(j)(2)(B) of the FD&C Act, an ANDA applicant that makes a certification described in subparagraph (A)(vii)(IV) shall give notice to certain recipients in accordance with this section. Such a "Paragraph IV notice" shall include a detailed statement of the factual and legal basis of the applicant's opinion that Jazz's REMS patents will not be infringed. See section 505(j)(2)(B)(iv)(II) of the FD&C Act.

⁷⁴ Dec.4 Submission at 9.

⁷⁵ Id. at 10.

additional sites upstream in the pharmaceutical distribution chain. On the contrary, the ANDA REMS requires that sodium oxybate only be distributed by wholesalers/distributors that are certified in the REMS, and that they distribute the drug only to certified pharmacies. As a result, sodium oxybate cannot be distributed to secondary wholesalers, which Jazz describes as “the weakest point in the U.S. pharmaceutical distribution chain.”⁷⁶ In other words, the ANDA REMS maintains strict controls on distribution and physical security of sodium oxybate.

While it is true that the ANDA REMS will use multiple pharmacies and multiple databases, these pharmacies and databases are connected in a way that accomplishes the same result as the Xyrem REMS. FDA therefore does not share Jazz’s view that the ANDA REMS significantly deviates from the approved Xyrem REMS. The differences between the programs do not reflect different ETASU, but rather are aspects of the ETASU that are being operationalized differently. Based upon the Agency’s expertise and experience with the use of switch technology in other REMS programs, we expect that the ANDA REMS for sodium oxybate will provide the same level of safety as the Xyrem REMS. Therefore, FDA has determined that these operational differences are comparable within the meaning of section 505-1(i)(1)(B) of the FD&C Act.

Use of databases

Jazz states that “the central database is necessarily one of the elements to assure safe use of Xyrem, because it is indispensable to the successful operation of the entire REMS.”⁷⁷ The Agency disagrees. From a safety perspective, the use of a central database is not “indispensable to the successful operation of the entire REMS.” As explained above, the ANDA REMS use of multiple databases connected by a switch system, together with required communications verifying and reporting key information between the ANDA REMS certified pharmacies and the Xyrem REMS certified pharmacy, assure a comprehensive review of the data necessary to ensure safe use of sodium oxybate. Consequently, FDA finds that the ANDA REMS program achieves the same level of safety as the Xyrem REMS central pharmacy’s use of a central database.

Single pharmacy requirement

We note that of the approved REMS that include pharmacy certification as an element, other than the Xyrem REMS, none requires use of a single pharmacy or even limits the pharmacies to a certain number. Though many companies *choose* to limit the number of pharmacies they utilize to implement their REMS, that is a business decision and not one

⁷⁶ Id. at 24.

⁷⁷ Id. at 20.

required by the REMS. Rather, the REMS with pharmacy certification provisions specify the substantive criteria for certification that are necessary to assure safe use of the drug without stipulating how many pharmacies can or will be permitted to be certified.

To the extent that Jazz asserts a single central pharmacy is essential to safe use of the drug and no generic program can be safe without it, FDA notes that this was the primary disagreement between Jazz and the Agency in the dispute resolution over the finalized REMS for Xyrem, and the Agency has long maintained that use of a single central pharmacy is not the only way to safely distribute the drug.⁷⁸ FDA also notes the inconsistent position Jazz has taken on this subject and the statement Jazz made⁷⁹ suggesting knowledge that this aspect of its REMS could have the effect of preventing generic competition.

“REMS regulatory science” and evidence of comparability

Jazz further argues that FDA cannot grant a waiver of the SSS requirement because “[c]urrently available REMS regulatory science cannot provide evidence adequate to demonstrate comparability of differing aspects of sodium oxybate ANDA REMS to the Xyrem REMS.”⁸⁰ It goes on to state that “[t]he current state of evolution of REMS regulatory science has not developed the standards of evidence, tools, and methodology needed to reliably evaluate whether the level of risk mitigation associated with the existing Xyrem REMS will be maintained if one or more separate, waived REMS are introduced.”⁸¹

We disagree with Jazz’s view for two reasons. First, FDA’s conclusions regarding comparability here are based on experience with the successful use of switch systems to verify safe use conditions in other REMS; they are neither theoretical nor without support. Second, we find Jazz’s reading inconsistent with FDA’s statutory waiver authority. Under Jazz’s narrow reading, the Agency must develop “standards of evidence, tools, and methodology” to determine whether different aspects of the ETASU are comparable to the Xyrem REMS. The statute does not establish such requirements, and we decline to adopt them here. FDA has carefully reviewed the proposed REMS for the ANDA (b) (4) and has concluded that the differences in the way the ETASU are operationalized are comparable to the corresponding aspects of the ETASU in the Xyrem REMS.

⁷⁸ See e.g., Meeting Minutes from August 14, 2013; dispute denial letter dated November 20, 2013.

⁷⁹ See fn. 17 supra.

⁸⁰ Dec. 4 Submission at p.25.

⁸¹ Id. at p.26.

Consistent with other REMS, periodic assessments of both of these programs will allow the Agency to monitor compliance with each and make any modifications necessary to ensure the benefits of the drug continue to outweigh its risks. The assessment plan for the ANDA REMS requires the same metrics as the Xyrem REMS in order to determine that the REMS is meeting its goals. Assessments will be submitted to FDA at 6 and 12 months following approval and annually thereafter. The assessment plan will evaluate compliance with the sodium oxybate REMS Program requirements, including compliance with and evaluations of safe use procedures, corrective and preventative actions taken to address non-compliance with distribution and dispensing requirements, incidences of overlapping prescriptions, as well as early refill requests and any reports of behavior suspicious of abuse, misuse or diversion.⁸²

IV. A Conditional Waiver is Appropriate

FDA is attaching the following condition to the waiver: the waiver-granted REMS shall be open to all current and future applicants with sodium oxybate products. The primary purpose of this condition is seek to minimize the number of ETASU systems with which patients, prescribers, and other stakeholders would need to comply.⁸³

V. Conclusion

For the foregoing reasons, FDA has decided to waive the requirement that sodium oxybate products use an SSS REMS. The waiver is conditioned on a requirement that the ANDA (b) (4) make (b) (4) REMS open to all current and future applicants for sodium oxybate products. The Agency has also determined that the ANDA REMS contains the same ETASU as the Xyrem REMS and uses comparable aspects of those ETASU.

⁸² Details of the assessment plan will be included in the approval letter for any ANDA subject to the ANDA REMS.

⁸³ FDA has imposed the same condition in both other waivers of the SSS requirement: buprenorphine and alosetron.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 11, 2017

FROM: Martin Shimer
Deputy Director, Division of Legal and Regulatory Support
Office of Generic Drug Policy

TO: ANDA 202090

SUBJECT: 180-day Exclusivity for Sodium Oxybate Oral Solution, 500 mg/mL

I. STATUTORY BACKGROUND

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) describes, among other things, certain events that can result in the forfeiture of a first applicant's¹ 180-day generic drug exclusivity as described in section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act).

The forfeiture provisions of the MMA appear at section 505(j)(5)(D) of the FD&C Act. Included among these is section 505(j)(5)(D)(i)(IV), which states the following:

FAILURE TO OBTAIN TENTATIVE APPROVAL.--The first applicant fails to obtain tentative approval of the application within 30 months² after the date on

¹ A "first applicant" is eligible for 180-day exclusivity by virtue of filing a substantially complete ANDA with a paragraph IV certification on the first day on which such an ANDA is received. Section 505(j)(5)(B)(iv)(II)(bb). If only one such ANDA is filed on the first day, there is only one first applicant; if two or more such ANDAs are filed on the first day, first applicant status is shared.

² For applications submitted between January 9, 2010, and July 9, 2012 containing a paragraph IV certification (or amended to first contain a paragraph IV certification during that period of time), and approved or tentatively approved during the period of time beginning on July 9, 2012, and ending on September 30, 2015, section 1133 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (P.L. 112-144) extends this period to 40 months. For applications submitted between January 9, 2010, and July 9, 2012 containing a paragraph IV certification (or amended to first contain a paragraph IV certification during that period of time), and approved or tentatively approved during the period of time beginning on October 1, 2015, and ending on September 30, 2016, section 1133 of FDASIA extends this period to 36 months. In addition, if an application was submitted between January 9, 2010, and July 9, 2012 containing a paragraph IV certification (or amended to first contain a paragraph IV certification during that period of time), and FDA has not approved or tentatively approved the application but must consider whether the applicant has forfeited exclusivity because a potentially blocked application is ready for approval, FDA will apply the 36-month period if it makes the forfeiture determination between the period of time beginning on October 1, 2015, and ending on September 30, 2016. For all other applications, the 30-month period set forth in FD&C Act section 505(j)(5)(D)(i)(IV) applies.

which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

The “failure to obtain tentative approval” forfeiture provision establishes a bright-line rule: If within 30 months of submission, an abbreviated new drug application (ANDA) has been determined by the Food and Drug Administration (FDA or the Agency) to meet the statutory standards for approval and it is only patent and/or exclusivity protection that prevents full approval, then an applicant will be given a tentative approval and will maintain eligibility for 180-day exclusivity. If tentative approval or approval³ is not obtained within 30 months, eligibility for 180-day exclusivity is generally forfeited unless “the failure [to obtain an approval] is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.” Under this provision, it is not sufficient to show that FDA’s review of the ANDA (to determine that the ANDA has met the pre-existing approval requirements), caused a failure to obtain a tentative approval or approval at 30 months. Nor is it sufficient for an applicant to show that FDA changed or reviewed (i.e., considered whether to change) the requirements for approval while the application was under review. The applicant must also show that its failure to obtain a tentative approval at the 30 month date is **caused by** this change in or review of approval requirements. FDA generally will presume that the failure to obtain tentative approval or approval was caused by a change in or review of approval requirements if, at the 30 month date, the evidence demonstrates that the sponsor was actively addressing the change in or review of approval requirements (or FDA was considering such efforts), and these activities precluded tentative approval (or approval) at that time. Where the evidence fails to demonstrate that the sponsor was actively addressing the change in or review of approval requirements, and these activities precluded tentative approval (or approval) at the 30-month date, FDA generally does not presume that the failure was caused by a change in or review of approval requirements. If FDA were to hold otherwise, an applicant that receives one or more deficiencies resulting from a change in approval requirements could simply delay addressing those deficiencies and avoid forfeiture.

In addition, FDA has determined that if one of the causes of failure to get tentative approval or approval by the 30-month forfeiture date was a change in or review of the requirements for approval imposed after the application was filed, an applicant will not forfeit eligibility notwithstanding that there may have been other causes for failure to obtain tentative approval or approval by the 30-month forfeiture date. Thus, to avoid forfeiture, an applicant must show that acceptability of at least one aspect of the ANDA (e.g., chemistry) was delayed, and that this delay was caused at least in part, by a change in or review of the requirements for approval (which the sponsor or FDA is actively addressing), irrespective of what other elements may also have been outstanding at the 30-month date. In other words, “but-for” causation is not required in order to qualify for this exception. FDA has determined that this interpretation best effectuates the policy embodied in the exception. It does not penalize applicants for reviews of

³ As explained below in note 4, FDA interprets this provision to also encompass the failure to obtain final approval, where applicable, within 30 months of filing.

or changes in approval requirements imposed on applicants after their ANDAs are filed that are a cause of the failure to obtain approvals or tentative approvals within 30 months (and presumes causation if, at the 30 month date, the sponsor was actively addressing those changes, and these changes precluded approval), and continues to incentivize applicants to challenge patents by preserving in many instances the opportunity to obtain 180-day exclusivity.

Under this provision, the 30-month timeframe is generally measured without regard to the length of time the ANDA was under review by the Agency. However, subsection 505(q)(1)(G) of the Act, enacted as part of the Food and Drug Administration Amendments Act of 2007 (Pub. Law 110-85) provides one exception. This subsection provides that:

If the filing of an application resulted in first-applicant status under subsection (j)(5)(D)(i)(IV) and approval of the application was delayed because of a petition, the 30-month period under such subsection is deemed to be extended by a period of time equal to the period beginning on the date on which the Secretary received the petition and ending on the date of final agency action on the petition (inclusive of such beginning and ending dates), without regard to whether the Secretary grants, in whole or in part, or denies, in whole or in part, the petition.

Thus, pursuant to this provision, if approval was delayed because of a 505(q) petition such that the application was not ready to be approved at 30 months from the date of submission because of the time it took the Agency to respond to the 505(q) petition, the 30-month-period-from-initial-submission deadline for obtaining a tentative (or final) approval will be extended by the amount of time that the 505(q) petition was under review.⁴

II. DISCUSSION

Roxane Laboratories, Inc. (Roxane) submitted ANDA 202090 for Sodium Oxybate Oral Solution, 500 mg/mL, on July 8, 2010. Roxane qualified as a “first applicant” and therefore is eligible for 180-day exclusivity for its generic Sodium Oxybate Oral Solution, 500 mg/mL,

⁴ In addition to tolling the 30-month period described in 505(j)(5)(D)(i)(IV) in certain circumstances where a petition is under review, section 505(q)(1)(G) clarified the scope of section 505(j)(5)(D)(i)(IV). If the phrase “tentative approval” in section 505(j)(5)(D)(i)(IV) is viewed in isolation, it might be suggested that this section applies only when an ANDA is eligible for a tentative approval due to a patent, 30-month stay or exclusivity blocking final approval, and that this provision cannot serve as a basis for forfeiture when an ANDA would have otherwise been eligible only for a *final* approval because there is no blocking patent, 30-month stay or exclusivity. Although section 505(j)(5)(D)(i)(IV) refers to “tentative approvals,” the terms of section 505(q)(1)(G) clearly describe a broader scope. Section 505(q)(1)(G) expressly states that if “approval” of the first applicant’s application was delayed because of a petition, the 30-month period described in section 505(j)(5)(D)(i)(IV) will be extended. Thus, Congress contemplated that section 505(j)(5)(D)(i)(IV) establishes a 30-month period within which an ANDA generally must obtain either tentative approval or final approval. This interpretation squares both with the statutory language and with not permitting the 180-day exclusivity for a first applicant whose ANDA is deficient to delay approval of subsequent applications. Therefore, FDA interprets section 505(j)(5)(D)(i)(IV) as requiring that, unless the period is extended for one of the reasons described in the FD&C Act or section 1133 of FDASIA, a first applicant that fails to obtain either tentative approval or approval for its ANDA within 30 months will forfeit eligibility for 180-day exclusivity.

absent forfeiture. FDA will consider whether there was a change in or a review of the requirements for approval that caused Roxane's failure to obtain tentative approval within 30 months from the date the application was submitted. Although Roxane submitted its ANDA within the time period identified in section 1133(a) of FDASIA, FDA did not approve or tentatively approve the application on or before September 30, 2016, and FDA did not make the forfeiture determination during the period of time beginning on October 1, 2015 and ending on September 30, 2016. Therefore, under FDA's interpretation of section 1133(a) of FDASIA, the 30-month period set forth in section 505(j)(5)(D)(i)(IV) of the FD&C Act applies.⁵

This memorandum addresses whether Roxane has forfeited its eligibility for 180-day exclusivity due to its failure to obtain tentative approval by January 8, 2013.

On November 8, 2013, Roxane submitted correspondence regarding its eligibility for 180-day exclusivity, in which it asserted that it did not forfeit exclusivity for two reasons: 1) approval of ANDA 202090 was delayed because of two citizen petitions; and 2) failure to obtain tentative approval was caused by a change in or a review of the requirements for approval.⁶ Roxane did not specify which requirements for approval may have changed or been under review. Roxane's correspondence also asserted that, under section 1133 of FDASIA, the forfeiture date was November 8, 2013, i.e., 40 months from the date that ANDA 202090 was submitted. As described above, under FDA's interpretation of section 1133 of FDASIA, the applicable forfeiture date is January 8, 2013, i.e., 30 months from the date that ANDA 202090 was submitted.

We must base our forfeiture analysis on the record before the Agency. The following is a timeline of certain key submissions and actions regarding ANDA 202090:

07/17/2002	The reference listed drug (RLD), Xyrem, is approved under the restricted distribution provisions of 21 CFR Part 314 Subpart H to assure safe use of the product, with a Risk Management Program (RMP), which later became known as a Risk Minimization Action Plan (RiskMAP) ⁷
09/27/2007	Food and Drug Administration Amendments Act of 2007 (FDAAA), Public Law 110-85 enacted
03/27/2008	FDA publishes <i>Federal Register</i> notice identifying products deemed to have in effect an approved REMS under FDAAA, including the RLD
08/29/2008	RLD proposed REMS submitted in accordance with FDAAA (NDA 021196/S-015)

⁵ See note 2, above.

⁶ Letter to I. Margand, T. Nhu, and P. Rickman (OGD) fr. A. Amann (Roxane) re "ANDA 202090, Sodium Oxybate Oral Solution, 500 mg/mL, GENERAL CORRESPONDENCE" (Nov. 8, 2013).

⁷ Letter to D. Reardan (Orphan Medical) fr. R. Temple (Office of Drug Evaluation I, Center for Drug Evaluation and Research (CDER)) re "NDA 21-196" (July 17, 2002).

11/13/2008	RLD REMS amendment submitted
08/25/2009	RLD REMS amendment submitted
08/31/2009	RLD REMS amendment submitted
10/07/2009	RLD REMS amendment submitted
07/08/2010	ANDA 202090 submitted
02/03/2011	RLD REMS amendment submitted
03/29/2011	ANDA 202090 bioequivalence review (acceptable)
04/07/2011	ANDA 202090 proposed "risk management program" submitted
07/06/2011	ANDA 202090 chemistry review (deficient); chemistry deficiencies faxed
08/26/2011	RLD REMS amendment submitted
09/02/2011	ANDA 202090 chemistry amendment
09/09/2011	ANDA 202090 chemistry amendment
10/19/2011	ANDA 202090 proposed REMS submitted
11/04/2011	ANDA 202090 chemistry review (deficient); chemistry deficiencies faxed
11/30/2011	ANDA 202090 teleconference re: chemistry
01/31/2012	RLD REMS amendment submitted
03/12/2012	ANDA 202090 REMS correspondence
04/13/2012	RLD REMS amendment submitted
05/18/2012	Citizen petition (FDA-2012-P-0499) received requesting, among other things, <i>in vivo</i> bioequivalence testing for ANDAs referencing Xyrem as the RLD
07/09/2012	Food and Drug Administration Safety and Innovation Act (FDASIA), Public Law 112-144 enacted
07/10/2012	Citizen petition (FDA-2012-P-0733) received requesting, among other things, that FDA rescind receipt of ANDAs referencing Xyrem as the RLD that did not contain a proposed risk management system at the time the ANDA was accepted for review
09/27/2012	FDA sent ANDA 202090 a REMS Notification Letter, which requested that Roxane submit a proposed REMS and noted that it should contact the NDA sponsor to discuss development of a single, shared system (SSS) REMS
11/13/2012	Citizen petition (FDA-2012-P-0499) denied
11/21/2012	RLD REMS amendment submitted
12/13/2012	Citizen petition (FDA-2012-P-0733) denied
12/17/2012	RLD labeling changes approved (S-013)
12/20/2012	RLD REMS amendment submitted
01/08/2013	07/08/2010 plus 30 months
03/01/2013	ANDA 202090 chemistry review (deficient)
03/18/2013	ANDA 202090 labeling review (deficient)

03/20/2013	ANDA 202090 Complete Response letter issued (chemistry and labeling deficiencies; notes that “Your submitted REMS was consulted and remains under review. You are encouraged to work towards a single-shared system REMS with the innovator. You may also opt to develop and submit a RiskMAP.”)
04/16/2013	ANDA 202090 response to Complete Response letter, which included a proposed RiskMAP
06/29/2013	RLD REMS amendment submitted
07/16/2013	ANDA 202090 labeling review (deficient)
07/17/2013	RLD REMS amendment submitted
08/21/2013	ANDA 202090 chemistry review (acceptable)
09/10/2013	RLD REMS amendment submitted
09/19/2013	ANDA 202090 Complete Response letter issued (labeling deficiencies; acknowledges a proposed REMS was submitted)
09/30/2013	ANDA 202090 response to Complete Response letter
10/08/2013	RLD REMS amendment submitted
11/06/2013	ANDA 202090 labeling review (acceptable)
11/08/2013	ANDA 202090 correspondence received regarding the failure to obtain tentative approval forfeiture provision
01/23/2014	FDA REMS meeting with the RLD sponsor and ANDA applicants referencing Xyrem as the RLD to initiate development of a SSS REMS
04/02/2014	ANDA 202090 REMS correspondence, which alleges that FDA informed Roxane on March 7, 2013 ⁸ that the previously submitted proposed REMS could not be approved because the RLD did not have an approved REMS ⁹ and suggested that Roxane change its proposed REMS to a RiskMAP, which Roxane did on April 16, 2013
04/11/2014	RLD labeling changes approved (S-019) and RLD REMS amendment submitted
04/22/2014	RLD REMS amendment submitted
04/30/2014	ANDA 202090 REMS status update email
05/30/2014	ANDA 202090 REMS status update email
06/30/2014	ANDA 202090 REMS status update email
08/02/2014	ANDA 202090 REMS status update email
10/02/2014	ANDA 202090 REMS status update email
11/04/2014	ANDA 202090 REMS status update email and meeting between FDA and ANDAs referencing Xyrem as the RLD regarding status of SSS REMS negotiations

⁸ Neither the Office of Regulatory Policy nor the Office of Surveillance and Epidemiology, Division of Risk Management could locate a record of this communication.

⁹ Under section 909(b) of FDAAA, Xyrem was deemed to have in effect an approved REMS.

11/07/2014	RLD REMS amendment submitted
12/01/2014	ANDA 202090 REMS status update email
01/14/2015	ANDA 202090 REMS status update email
02/04/2015	ANDA 202090 REMS status update email and meeting between FDA and ANDA applicants referencing Xyrem as the RLD regarding REMS development
02/27/2015	RLD REMS approved

Contrary to Roxane’s assertion in its November 8, 2013 correspondence, tentative approval of Roxane’s ANDA was not delayed because of a citizen petition, such that the 30-month period would be extended past January 8, 2013, under section 505(q)(1)(G) of the FD&C Act. While two citizen petitions were submitted pertaining to ANDAs referencing Xyrem as the RLD, as noted on the timeline above, both were answered before January 8, 2013, and there is no evidence that FDA’s consideration of these petitions caused a delay in approval or tentative approval. Furthermore, the citizen petitions pertained to receipt for review and bioequivalence requirements, and these discipline reviews were both acceptable as of the forfeiture date.

FDA Review of ANDA 202090

As the above timeline indicates, at the forfeiture date of January 8, 2013, bioequivalence was acceptable, chemistry and labeling were deficient, and REMS was pending.

REMS Review

Pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under 505(j) is subject to certain elements of the REMS required for the applicable RLD. If the REMS for the RLD includes elements to assure safe use (ETASU), FDA cannot approve a REMS for an ANDA unless either: 1) the generic drug and RLD use a single, shared system (SSS) for the ETASU; or 2) FDA waives the requirement for a SSS, and permits the ANDA to use a separate, comparable system for the ETASU.

At the 30-month forfeiture date of January 8, 2013, FDA was reviewing the REMS requirements for approval or tentative approval of an ANDA referencing Xyrem as the RLD. In accordance with section 909(b) of FDAAA, Xyrem was deemed to have in effect an approved REMS on March 25, 2008. Section 909(b) further provides that holders of approved applications for which a REMS is deemed to be in effect must submit a proposed REMS by September 21, 2008. The proposed REMS for Xyrem was submitted on August 29, 2008 and was amended multiple times in response to FDA comments both before and after the 30-month forfeiture date of January 8, 2013. This “post-FDAAA REMS” for Xyrem was not approved by FDA until February 27, 2015.

During FDA’s ongoing review of the REMS requirements for Sodium Oxybate Oral Solution, 500 mg/mL, Roxane actively sought to address the Agency’s risk mitigation concerns. On April 7, 2011, Roxane submitted a “proposed risk management program,” and on October 19, 2011, Roxane submitted a proposed REMS, while the post-FDAAA REMS for Xyrem was still under

review. FDA's September 27, 2012 REMS Notification Letter stated that a REMS would be required for sodium oxybate oral solution and directed Roxane to contact the RLD sponsor regarding the development of a SSS.¹⁰ According to Roxane's April 2, 2014 correspondence,¹¹ FDA then allegedly informed Roxane on March 7, 2013 that its ANDA could not be approved with a REMS because the RLD did not have a post-FDAAA approved REMS and suggested that it submit a RiskMAP. FDA's March 20, 2013 Complete Response letter noted that: "Your submitted REMS was consulted and remains under review. You are encouraged to work towards a single-shared system REMS with the innovator. You may also opt to develop and submit a RiskMAP."¹² Roxane submitted a proposed RiskMAP on April 16, 2013. However, FDA's subsequent Complete Response letter, issued September 19, 2013, stated that a REMS would in fact be necessary for approval.¹³

The REMS approval letter noted that, "FDA has sought to finalize and approve the REMS for Xyrem since 2008. In doing so, we have faced repeated, lengthy delays." These delays and FDA's ongoing review of the REMS requirements for approval of ANDAs referencing Xyrem as the RLD were a cause of Roxane's failure to obtain tentative approval by the 30-month forfeiture date. The record shows that FDA was considering whether Roxane's application could be approved with a REMS or RiskMAP as of the forfeiture date of January 8, 2013, and did not resolve the question until after the 30-month forfeiture date. FDA's ongoing review of the risk mitigation requirements for approval was a cause of Roxane's inability to obtain tentative approval.

Therefore, based on these facts, we have determined that there was a review of the requirements for approval, specifically with respect to the REMS requirements, which was a cause of Roxane's failure to obtain tentative approval by the 30-month forfeiture date.

Chemistry and Labeling Reviews

Because FDA has determined that there was a review of the approval requirements with respect to REMS, which was a cause of Roxane's failure to obtain tentative approval by January 8, 2013, we need not determine whether there is a separate basis for non-forfeiture with respect to chemistry or labeling.

III. CONCLUSION

Roxane's ANDA 202090 for Sodium Oxybate Oral Solution, 500 mg/mL, was submitted on July 8, 2010. The 30-month forfeiture date was January 8, 2013. Roxane's ANDA was not tentatively approved within this time period. Roxane's failure to obtain tentative approval within

¹⁰ Letter to G. Hicks (Roxane) fr. G. Geba (OGD) re "ANDA 202090, INFORMATION REQUEST" (Sept. 27, 2012).

¹¹ Letter to Division of Documents Management fr. A. Amann (Roxane) re "ANDA 202090 - Sodium Oxybate Oral Solution, 500mg/mL" (Apr. 2, 2014).

¹² Letter to R. Wilson (Roxane) fr. K. Uhl (OGD) re "ANDA 202090, COMPLETE RESPONSE" (Mar. 20, 2013).

¹³ Letter to A. Amann (Roxane) fr. K. Uhl (OGD) re "ANDA 202090, COMPLETE RESPONSE" (Sept. 19, 2013).

30 months was caused by a change in or review of the requirements for approval, specifically FDA's review of the REMS requirements for approval. Therefore, Roxane has not forfeited its eligibility for the 180-day exclusivity period described in section 505(j)(5)(B)(iv) of the FD&C Act for Sodium Oxybate Oral Solution, 500 mg/mL.

Martin H.
Shimer li -S

Digitally signed by Martin H.
Shimer li -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=13001
57630, cn=Martin H. Shimer li -S
Date: 2017.01.11 07:59:12 -05'00'

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 17, 2017

FROM: Martin Shimer
Deputy Director, Division of Legal and Regulatory Support
Office of Generic Drug Policy

THROUGH: Kathleen Uhl
Director, Office of Generic Drugs (OGD)

TO: Abbreviated New Drug Application (ANDA) 202090, ANDA 203351,
ANDA 203631, (b) (4)
(b) (4)

SUBJECT: Patent Certification Requirements for Certain Risk Evaluation and Mitigation
Strategy (REMS) Amendments

This memorandum documents the Food and Drug Administration's (FDA's or the Agency's) decision that ANDA applicants for sodium oxybate oral solution referencing new drug application (NDA) 022196, Xyrem, as the reference listed drug (RLD) must determine whether to submit new or amended patent certifications in connection with REMS amendments to their respective applications, submitted before December 5, 2016,¹ that propose to use a separate system for the elements to assure safe use (ETASU). FDA has not determined that REMS amendments must always contain new or amended patent certifications.

I. FACTUAL BACKGROUND

Xyrem was approved on July 17, 2002. At the time of approval, no patents were listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) for Xyrem; however, multiple patents have since been listed.

A REMS for Xyrem was approved on February 27, 2015.² Several of the patents listed in the

¹ On October 6, 2016, FDA issued a final rule on *Abbreviated New Drug Applications and 505(b)(2) Applications*, which had an effective date of December 5, 2016 (see 81 FR 69580). The final rule revised, among other things, certain patent certification requirements related to certain ANDA amendments (see 21 CFR 314.96(d)). However, the substantive REMS amendments to the sodium oxybate ANDAs at issue here were all submitted prior to December 5, 2016. In this case, the final rule does not apply to these substantive REMS amendments.

² In accordance with section 909(b) of the Food and Drug Administration Amendments Act of 2007 (FDAAA), Xyrem was deemed to have in effect an approved REMS on March 25, 2008. Section 909(b) further provided that holders of approved applications for which a REMS is deemed to be in effect must submit a proposed REMS by September 21, 2008. The proposed REMS for Xyrem was submitted on August 29, 2008 and was amended multiple

Orange Book for Xyrem are method-of-use patents, which Jazz Pharmaceuticals (Jazz), the holder of NDA 021196, claims protect aspects of its REMS program (“the Xyrem Success Program”). The following listed patents are method-of-use patents that Jazz asserts cover the Xyrem REMS program: 7,668,730; 7,765,106; 7,765,107; 7,895,059; 8,457,988; 8,589,182; 8,731,963.

The first ANDA referencing Xyrem as the RLD was submitted on July 8, 2010 (ANDA 202090). There are currently a total (b)(4) ANDAs pending:

ANDA #	Receipt Date
202090	07/08/10
203631	04/06/12
(b)(4)	
203351	12/18/13
(b)(4)	

(b)(4)

In a letter dated September 25, 2015, Jazz requested that “FDA confirm that new paragraph IV certifications must be submitted when an applicant submits a new or amended proposed Risk Evaluation and Mitigation Strategy (“REMS”) for an Abbreviated New Drug Application (“ANDA”) referencing Xyrem®, and that notice of such certification be provided to the patent holder Jazz Pharmaceuticals, Inc. (“Jazz”), as required by 21 USC 355(j)(2)(B)(ii).”⁵

Jazz asserted that an amendment containing a proposal for a REMS for sodium oxybate would require recertification because the proposal would “result in new ANDA products, with revised

times in response to FDA comments. This “post-FDAAA REMS” for Xyrem was approved by FDA on February 27, 2015.

(b)(4)

ANDA 202090, Sequence 0028 (Apr. 8, 2016); ANDA 203351, Sequence 0016 (Apr. 8, 2016); ANDA 203631, Sequence 0028 (Apr. 8, 2016); (b)(4)

(b)(4)

Subsequent REMS amendments regarding the substantive elements of the separate system for the ETASU were also received before December 5, 2016.

⁵ Letter to W. Dunn (Division of Neurology Products) fr. J. Ekelund (Jazz) re “NDA 21-196: Xyrem® (sodium oxybate) oral solution 0.5 g/mL, Correspondence Regarding Paragraph IV Certifications” (Sept. 25, 2015) (Jazz Letter), at 1.

labeling and conditions of use.”⁶

II. DISCUSSION

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), an ANDA applicant must include in its application one of four certifications with respect to each patent that claims the listed drug the ANDA references.⁷ If a new patent is timely listed while the ANDA is pending, an ANDA applicant is required to submit a patent certification to the patent prior to ANDA approval. If an ANDA applicant submits a paragraph IV certification to a listed patent, the ANDA applicant must notify the RLD holder and patent owner of the factual and legal basis for the applicant’s opinion that the patent is not valid, is unenforceable, or will not be infringed.⁸ If the NDA holder or patent owner initiates a patent infringement action against the ANDA applicant within 45 days of receiving the required notice, approval of the ANDA generally will be stayed for 30 months from the date of the notice or such shorter or longer time as the court might order.⁹ FDA has long held the position that the agency plays only a ministerial role with respect to patent listing, patent certification, and notice requirements, and this position has been upheld by the courts.¹⁰

The statute does not directly address patent certification requirements applicable to ANDA amendments. FDA’s regulations in effect at the time the REMS amendments described in the previous section were submitted provide that, with certain exceptions, an ANDA applicant must “amend a submitted certification if, at any time before the effective date of approval of the application, the applicant learns that the submitted certification is no longer accurate.”¹¹ FDA has previously explained that “[a]n applicant that submits a 505(b)(2) application or ANDA containing a paragraph IV certification to a listed patent must reevaluate whether the patent certification continues to be accurate after a change to the proposed product submitted in an amendment to the 505(b)(2) application or ANDA.”¹²

⁶ Id., at 4.

⁷ The four certifications are as follows:

- (I) that such patent information has not been filed (a paragraph I certification),
- (II) that such patent has expired (a paragraph II certification),
- (III) of the date on which such patent will expire (a paragraph III certification), or
- (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (a paragraph IV certification).

Section 505(j)(2)(A)(vii) of the FD&C Act; see also 21 CFR 314.94(a)(12)(i)(A). The FD&C Act provides one circumstance in which an applicant with a pending ANDA need not certify to a listed patent: “if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection,” the applicant can submit “a statement that the method of use patent does not claim such a use” (referred to as a “section viii statement”) (section 505(j)(2)(A)(viii) of the FD&C Act; see also 21 CFR 314.94(a)(12)(iii)).

⁸ Section 505(j)(2)(B) of the FD&C Act.

⁹ Section 505(j)(5)(B)(iii) of the FD&C Act.

¹⁰ See, e.g., *aiiPharma v. Thompson*, 296 F.3d 227, 242-43 (4th Cir. 2002); *American Biosci., Inc. v. Thompson*, 269 F.3d 1077, 1084 (D.C. Cir. 2001).

¹¹ 21 CFR 314.94(a)(12)(viii)(C)(1). See also 54 FR 28872, 28886 (July 10, 1989) (“A patent certification must also be amended if the applicant learns that its previous certification is incorrect . . .”).

¹² Citizen Petition Response to J. Dubeck and F. Stearns (Keller and Heckman LLP) fr. J. Woodcock (Center for Drug Evaluation and Research (CDER)) re “Docket No. FDA-2003-P-0519” (Feb. 6, 2015).

Under this regulatory framework, FDA has generally relied on ANDA applicants to determine whether an amendment requires a new or amended patent certification. FDA has advised applicants that recertification is necessary—and not left the determination solely to the ANDA applicants—primarily in limited situations involving certain reformulations of the proposed drug products.¹³ (b) (4)

If an ANDA applicant determines that a previous certification is no longer accurate, an amended certification and any accompanying notice would be required. FDA cannot and does not evaluate the sufficiency of such notice.¹⁵

The substantive REMS amendments to the sodium oxybate ANDAs were all submitted before December 5, 2016. On October 6, 2016, FDA published a final rule that implements portions of Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) and clarifies and updates FDA’s regulations regarding ANDAs and 505(b)(2) applications, and the rule had an effective date of December 5, 2016.¹⁶ The substantive REMS amendments are subject to the regulations in effect at the time of their submission, as described above.

Under the regulations in effect at the time the substantive REMS amendments to the sodium oxybate ANDAs were submitted, ANDA applicants were required to determine whether to recertify or to amend a previously submitted patent certification or statement in connection with submitting an amendment containing a proposed REMS. Under 21 CFR 314.94(a)(12)(viii)(C)(1), these ANDA applicants must submit amended patent certifications if they determine their patent certifications are no longer accurate. It is therefore the ANDA applicants’ responsibility to update their patent certifications if necessary. Consistent with the regulations in effect at the time the substantive REMS amendments were submitted, FDA’s ministerial role with respect to patent information, and past practice, the ANDA applicants must

¹³ See, e.g., Citizen Petition Response to G. Masoudi (Covington & Burling LLP) fr. J. Woodcock (CDER) re “Docket No. FDA-2010-P-0223” (Oct. 19, 2010).

(b) (4)

¹⁵ “Disputes involving the sufficiency of the notice must be resolved by the applicant, patent owner, and holder of the approved application rather than by action on the part of FDA.” *Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions*; Final Rule, 59 FR 50338, 50350 (Oct. 3, 1994); “The agency has neither the resources nor the expertise to engage in patent disputes or questions regarding sufficiency of notice.” *Id.*, at 50352; “The statute provides express and specific grounds for delaying an effective date of approval (see section 505(c)(3) of the act). These do not include any express authority to delay an effective date of approval based on an inadequate notice, and the agency is not prepared to infer such authority.” *Id.*, at 50339.

¹⁶ *Abbreviated New Drug Applications and 505(b)(2) Applications*, 81 FR 69580, 69615-16 (Oct. 6, 2016).

determine whether to submit new or amended patent certifications.

We note that our conclusion here is consistent with section 505-1(f)(8) of the FD&C Act, which prohibits Jazz from using ETASU required by FDA to block or delay approval of an ANDA referencing Xyrem.¹⁷

We also note that (b)(4) sodium oxybate ANDA applicants sent letters dated December 28, 2016 to FDA requesting that the Agency exercise its statutory authority under section 505-1(i)(1)(B) of the FD&C Act to waive the requirement to use a single, shared system for the ETASU and permit the ANDA applicants to use a separate system.¹⁸ These ANDA applicants also submitted the waiver request letters to their ANDAs.¹⁹ These waiver request letters do not alter any of the substantive elements of the ANDAs' proposed separate system for the ETASU.²⁰ Instead, the waiver request letters describe the ANDA applicants' analysis of why waiver of the single, shared system requirement for the ETASU is appropriate under the statute and describes the parties' unsuccessful efforts to develop a single, shared system. Jazz had requested that "FDA confirm that new paragraph IV certifications must be submitted when an applicant submits a new or amended proposed [REMS]."²¹ These waiver request letters were not submissions seeking approval of new or amended proposed REMS, so these letters were outside the scope of Jazz's request.

III. CONCLUSION

ANDA applicants for sodium oxybate referencing Xyrem as the RLD must determine whether to submit new or amended patent certifications in connection with REMS amendments to their respective applications, submitted before December 5, 2016, that propose to use a separate system for the ETASU. If any such applicant were to determine that its previous certification was no longer accurate, an amended certification and any accompanying notice would be required.

Martin H. Shimer li -S

Digitally signed by Martin H. Shimer li -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300157630, cn=Martin H. Shimer
li -S
Date: 2017.01.17 11:36:58 -05'00'

¹⁷ Section 505-1(f)(8) of the FD&C Act ("No holder of an approved covered application shall use any element to assure safe use required by the Secretary under this subsection to block or delay approval of an application under section 505(b)(2) or (j)...").

¹⁸ Letter to K. Uhl (OGD) fr. M. Shumsky (Kirkland & Ellis LLP, counsel for Roxane Laboratories, Inc.) re "ANDA No. 202090—Waiver Request Pursuant To 21 U.S.C. § 355-1(i)(1)(B)" (Dec. 28, 2016); Letter to K. Uhl (OGD) fr.

(b)(4)
(b)(4)
(b)(4)
(b)(4) Sodium Oxybate Oral Solution, 500 mg/ml – Waiver Request Pursuant to 21 U.S.C. § 355-1(i)(1)(B)" (Dec. 28, 2016); Letter to OGD fr. A. Patel (Amneal Pharmaceuticals) re "Sodium Oxybate Oral Solution, 500 mg/mL, Single Shared REMS Waiver Request Pursuant to 21 U.S.C. § 355-1(i)(1)(B), ANDA # 203631(Sequence # 0036)" (Dec. 28, 2016).

¹⁹ See ANDA 202090, Sequence 0038 (Jan. 4, 2017); (b)(4) ANDA 203631, Sequence 0036 (Dec. 28, 2016); (b)(4)

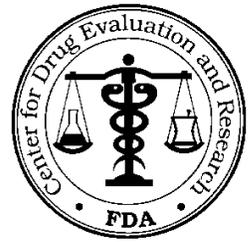
As stated above, all substantive REMS amendments to the ANDAs regarding the proposed separate system were submitted prior to December 5, 2016.

²¹ Jazz Letter, at 1.

EASILY CORRECTABLE DEFICIENCY

ANDA 202090

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Roxane Laboratories, Inc.

TEL: (614) 241-4122

ATTN: Sarah Smith

Email: sasmith@west-ward.com

FROM: Sunny Pyon

Dear Ms. Smith:

This communication is in reference to your abbreviated new drug application (ANDA) dated July 8, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sodium Oxybate Oral Solution, 500 mg/mL.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**EASILY CORRECTABLE DEFICIENCY
LABELING
REFERENCE # 8874340**

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Labeling Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

We have completed our review and have the following comments:

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

If you have questions regarding these deficiencies or would like acknowledgement of receipt of your amendment upon submission, please contact the Labeling Project Manager, Sunny Pyon, at sunny.pyon@fda.hhs.gov.

Sincerely yours,

Sunny Pyon -S

Digitally signed by Sunny Pyon -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Sunny Pyon -S,
0.9.2342.19200300.100.1.1=2001673604
Date: 2016.06.02 15:21:36 -04'00'

Sunny Pyon, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

From: [REDACTED] (b) (4)
Sent: Wednesday, February 17, 2016 2:49 PM
To: Zerislassie, Ermias
Subject: RE: Sodium Oxybate January Update to FDA by ANDA Applicants

Dear Ermias:

Pursuant to your request, and on behalf of the ANDA applicants, I am writing to provide an update on the status of our communications through January 2016 with Jazz Pharmaceuticals with regard to a possible single shared REMS for sodium oxybate.

On January 29, 2016, the ANDA applicants participated in a call with Jazz, as represented by P.J. Honerkamp and Jana Gold. Pursuant to an agreement under which Jazz agreed that it would not disclose any confidential information, Jazz provided a high-level overview of its already publicly-available, FDA-approved REMS document. The ANDA applicants expressed their appreciation to Jazz for sharing its insight and analysis of various operational issues, and the call concluded after approximately 30 minutes. During the call, governance and other MOU issues for a single shared REMS were not discussed, and the ANDA applicants believe their December 23, 2015 report to the agency regarding such issues remains accurate.

Pursuant to our agreement with Jazz, we will forward a copy of this update to them.

Best Regards,
[REDACTED] (b) (4)

[REDACTED] (b) (4)

From: Zerislassie, Ermias [mailto:Ermias.Zerislassie@fda.hhs.gov]
Sent: Tuesday, December 29, 2015 3:38 PM
To: (b) (4)
Subject: RE: Sodium Oxybate December 2015 UPDATE TO THE FDA BY ANDA APPLICANTS

Thank you for the update (b) (4)

From: (b) (4)
Sent: Wednesday, December 23, 2015 7:11 PM
To: Zerislassie, Ermias
Subject: Sodium Oxybate December 2015 UPDATE TO THE FDA BY ANDA APPLICANTS

(b) (4)

Dear Ermias:

Pursuant to your request, and on behalf of the ANDA applicants, I am writing to provide an update on the status of our communications through November 2015 with Jazz Pharmaceuticals with regards to a possible single shared REMS for sodium oxybate. On November 12, 2015 the ANDA applicants communicated with Jazz to the effect that we thought it better to communicate directly with the Agency, rather than through the submission of a joint update, and thus we submit this separate update to you today.

As both the Agency and Jazz are aware, the ANDA applicants continue to have fundamental disagreements with Jazz as to the governance procedures of a single shared REMS, and we are unable to report any progress on the resolution of the concerns we expressed during our call with you. More specifically and for example, the continued rejection by Jazz of a “one-company/one-vote” principle is fundamentally at odds with our concept of how a single shared REMS should govern itself, and thus that disagreement remains a significant obstacle to a shared program.

In addition, and as previously reported to the Agency by Jazz, on November 4, 2015, Jazz wrote to the ANDA applicants to suggest we may be “substantially underestimating” the challenges of creating a separate REMS, and offered to give us the benefit of Jazz’s insight and expertise on various operational issues. The ANDA applicants are amenable to such a call, and to that end each company has now executed a separate CDA to cover

that call. Due to a miscommunication regarding the scheduling of the call, it has not yet taken place and we are currently awaiting new suggested dates from Jazz. We appreciate Jazz's offer to share its opinions with the ANDA applicants as to their view of operational issues created by a possible separate REMS. While interesting, this discussion, unfortunately, will not affect the impasse we have reached on the material issue of governance and other previously discussed disagreements with Jazz.

Pursuant to our agreement with Jazz, we will forward a copy of this update to them, and will expect to receive from Jazz a copy of any update that they provide to you.

Best Regards

(b) (4)

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

/s/

ERMIAS ZERISLASSIE
02/17/2016

From: [Jennifer Ekelund](#)
To: [Zerlassie, Ermias](#); [Flowers, Louis](#); [Jenkins, Darrell](#)
Cc:

(b) (4)

Subject: July 2015 Update for the sodium oxybate SSS REMS
Date: Wednesday, August 12, 2015 3:20:50 PM
Attachments: [FW REMS legal call.msg](#)

Dear Ermias:

I am writing to provide an update for the sodium oxybate shared REMS group for the second half of June and July. The information below is current as of August 6th.

On June 24, the legal representatives of the parties held a teleconference to discuss proposed MOU terms circulated by Jazz on April 6 and the response from the ANDA holders on June 12, 2015. A summary of the discussion is attached. The parties were not able to reach agreement on all of the issues in the ANDA parties' markup but agreed that their discussion would continue and Jazz would provide the next draft proposal as well as a summary of the call.

Because the legal representatives of the ANDA holders stated that they would not discuss the substance of any single shared REMS without their operational colleagues, on July 7, Jazz's Single Point of Contact ("SPOC"), wrote to the individuals the ANDA holders had identified as SPOCs to request a teleconference to discuss the substance of a shared REMS. Jazz's SPOC also requested that the ANDA Holders provide a working draft of any shared REMS that the ANDA holders might be considering, as suggested in the legal call.

On July 20, Jazz's legal representative sent a revised MOU proposal based on the parties' June 24 discussion. On July 24, Par's legal representative wrote on behalf of the ANDA and proposed a follow up call on August 4.

On July 27, Jazz's SPOC wrote to the ANDA holders and asked for a response to her July 7 email. Jazz's legal representative wrote to the legal team and confirmed that the legal team was not available August 4 but would provide alternative proposed dates as soon as possible.

On July 30, 2015, outside counsel for Roxane, writing on behalf of the ANDA applicants, wrote to identify issues he had identified as having the parties "bogged down" and stated among other things that the ANDA holders would not discuss the content of a shared REMS until there is agreement on an MOU. Jazz notes that this position is contrary to the position taken by the ANDA holders in October 2014, when the ANDA holders insisted that legal and operational discussions should proceed in parallel.

On July 31, Jazz's legal representative responded that Jazz disagrees with outside counsel's statements in the July 30 email suggesting that the parties are bogged down, and that Jazz would provide dates for a follow up call as soon as possible. Jazz's legal representative followed up on

August 2, 2015, offering August 12, 13 or 14 as potential dates for a follow up call of the legal representatives.

(b) (4)

Thank you,
Jennifer

Jennifer Ekelund

*Vice President, US Regulatory Affairs
Jazz Pharmaceuticals, Inc.
3180 Porter Drive
Palo Alto, CA 94304
650.496.2630
650.496.2641 (fax)
jennifer.ekelund@jazzpharma.com*

**** ATTENTION: CONFIDENTIAL ****

This email message is for the sole use of the intended recipient(s) and may contain confidential and/or privileged information. Any unauthorized review, use, disclosure or distribution is prohibited. If you are not the intended recipient, please contact me by reply email and destroy all copies of the original message. Thank you.

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

/s/

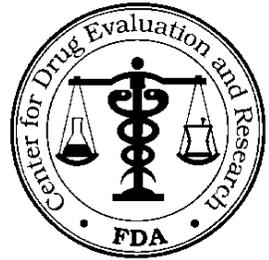
ERMIAS ZERISLASSIE

08/13/2015

COMPLETE RESPONSE

ANDA 202090

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



TO: Roxane Laboratories Inc.

TEL: 614-272-4785

ATTN: Anton (Tony) Amann, Ph.D.

FAX: 614-276-2470

FROM: Tina Nhu

FDA CONTACT PHONE: (240) 276-8548

Dear Sir:

This facsimile is in reference to your abbreviated new drug application, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

We have completed the review and have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (___ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.



ANDA 202090

COMPLETE RESPONSE

Roxane Laboratories, Inc.
Attention: Anton (Tony) Amann
1809 Wilson Road
Columbus, OH 43228

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated July 8, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Sodium Oxybate Oral Solution, 500 mg/mL.

Reference is also made to your amendment dated April 16, 2013.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The Division of Chemistry has no further questions at this time.

BIOEQUIVALENCE

The Division of Bioequivalence has no further questions at this time.

LABELING

Labeling Deficiencies determined on 7-5-13 based on your submission dated 4-16-13:

PATENT

You have not addressed Patent # 8457988 which expires on December 17, 2022.

CARTON

How will the two 75 cc dosing cups accompany the drug product?

INSERT

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

- a. TITLE – Place the following text immediately above “Initial U.S. ...”

SODIUM OXYBATE Oral Solution, CIII

- b. INDICATIONS AND USAGE

No further comments will be made on your (b) (4) Sodium Oxybate RiskMAP Program at this time.

2. FULL PRESCRIBING INFORMATION: CONTENTS*

- a. (b) (4)

- b. WARNING STATEMENT

“... **SYSTEM (CNS) DEPRESSION and MISUSE AND ABUSE**”

- c. 5.1 Central Nervous System Depression

Revise the title to read as shown above.

- d. 5.3 - See comment under (1) (b) above.

- e. (b) (4)

- f. (b) (4), .

3. FULL PRESCRIBING INFORMATION

- a. GENERAL COMMENT – Format parenthetical statements referencing other parts of the insert labeling as shown below:

[see WARNINGS AND PRECAUTIONS (5.3)].

- i. Note there is no numerical designation before “WARNINGS”.
- ii. Note the blank space between “PRECAUTIONS” and the parenthesis.

- b. 1.1 Cataplexy in Narcolepsy – [see CLINICAL STUDIES (14.1)]

- c. 1.2 Excessive Daytime Sleepiness in Narcolepsy – [see CLINICAL STUDIES (14.2)]

d. 2 DOSAGE AND ADMINISTRATION

See comment under (1) (b) above.

e. 2.1 Dosing Information, Table 1 Title

“(g = grams)” [spacing]

f. 4 CONTRAINDICATIONS

(b) (4)

g. 5.1 Central Nervous System Depression

Revise the title to be as shown above.

h. 5.3 - See comment under (1) (b) above.

i. 5.8 Use in Patients Sensitive to High Sodium Intake, Table 2 Title

“(g = grams)” [spacing]

j. 8.1 Pregnancy, last sentence – “postnatal” (b) (4)

k. 10.1 Human Experience, first paragraph, last sentence – “was” rather than “is”

l. 17 PATIENT COUNSELING INFORMATION

See comment under (1) (b) above.

m. **Instructions for Use - Sodium Oxybate Oral Solution, CIII**

Revise the title to appear as shown above.

n. **Medication Guide - Sodium Oxybate Oral Solution, CIII**

i. Revise the title to appear as shown above.

ii. What is the most important ... - See comment under (1) (b) above.

iii. How should I take ..., first bullet – “... **Instructions for Use** at the end of this Medication Guide for ...”

iv. What are the possible ... - **Bold** the last two sentences [“**Call your**”

doctor ... side effects. You may ... at 1-800-FDA-1088.”].

- v. General information about ... - See comment under (1) (b) above.
- o. Please note that the “**Instructions for Use**” should follow the “**Medication Guide**”.

Revise your labeling, as instructed above, and submit electronically.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling [the reference listed drug’s labeling or your last submitted labeling] with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Under section 909(b)(1) of the Food and Drug Administration Amendments Act (FDAAA) of 2007, we identified sodium oxybate as a product deemed to have in effect an approved REMS because there were in use on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520. A REMS will be necessary for Sodium Oxybate Oral Solution, 500 mg/mL, if it is approved, to ensure that the benefits of the drug outweigh the risk(s) of developing central nervous system and respiratory depression, and the potential for abuse and misuse associated with sodium oxybate.

We acknowledge receipt of your proposed REMS, included in your submission dated October 19, 2011. We also refer to our letter dated September 27, 2012, in which the details of the REMS requirements were outlined and you were notified of the need to work on a single shared system with the innovator. Your proposed REMS contains a Medication Guide, elements to assure safe use, an implementation system.

The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

FACILITY INSPECTIONS

Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a MINOR AMENDMENT. The designation as a **RESUBMISSION/AFTER ACTION – MINOR COMPLETE RESPONSE AMENDMENT** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Chemistry, Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to. Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dose form (FDFs) or active pharmaceutical ingredient (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States. In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

The drug product may not be legally marketed until you have been notified in writing that this application is approved. If you have any questions, call Tina Nhu, Regulatory Project Manager, at (240) 276-8548.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
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/

ROBERT L WEST

09/19/2013

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.



ANDA 202090

COMPLETE RESPONSE

Roxane Laboratories, Inc.
Attention: Randall S. Wilson, Vice President
Scientific, Medical and Regulatory Affairs
1809 Wilson Road
Columbus, OH 43228

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated July 8, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Sodium Oxybate Oral Solution, 500 mg/mL.

Reference is also made to your amendments dated September 13, 2010; April 6, September 2, September 8, October 19, 2011; and March 12, 2012.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The deficiencies presented below represent MINOR deficiencies:

A. Chemistry Deficiencies:

1.

2.

(b) (4)

BIOEQUIVALENCE

The Division of Bioequivalence (DBE) has completed its review and has no further questions at this time.

LABELING

Labeling Deficiencies determined on 3-14-13 based on your submissions dated 7-8-10 and 4-6 and 10-19-11:

CONTAINER 180 mL

1. Add the following statement to appear immediately above “For oral administration only.”:

“MUST BE DILUTED BEFORE USE”

2. Add the following statement to appear immediately above the storage temperature recommendations:

“WARNING: Keep This and All Other Medications Out of Reach of Children”

3. “Each mL contains ...” statement – “... purified water, USP [add comma]

4.  (b) (4)

5. Add the following statement to appear immediately below “For oral administration only.”:

“Use as instructed”

CARTON

1. See comments (2) and (4) under CONTAINER above.

2. Add the following statement to appear immediately above “Rx only”:

“WARNING: Keep This and All Other Medications Out of Reach of Children”

3.  (b) (4)

4. How will the two 75 cc dosing cups accompany the drug product?

INSERT

1. GENERAL COMMENT

Revise your insert labeling to be the same as that of the reference listed drug, Xyrem® (NDA 21-196/S-013); approved December 17, 2012.

2. DESCRIPTION



3. MEDICATION GUIDE

Revise your Medication Guide and associated Instructions for Use to be the same as that of the reference listed drug, Xyrem® (NDA 21-196/S-013); approved December 17, 2012.

REMS

Your submitted REMS was consulted and remains under review. You are encouraged to work towards a single-shared system REMS with the innovator. You may also opt to develop and submit a RiskMAP.

Revise your labeling, as instructed above, and submit electronically.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with [the reference listed drug's labeling **or** your last submitted labeling] with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a **MINOR AMENDMENT**. The designation as a **RESUBMISSION/AFTER ACTION – MINOR COMPLETE RESPONSE AMENDMENT** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Chemistry, Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dose form (FDFs) or active pharmaceutical ingredient (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

The drug product may not be legally marketed until you have been notified in writing that this application is approved. If you have any questions, call Sean Belouin, Regulatory Project Manager, at (240) 276-8566.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
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/

ROBERT L WEST

03/20/2013

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.



ANDA 202090

INFORMATION REQUEST

Roxane Laboratories Inc.
Attention: Gregory Hicks
1809 Wilson Road
Columbus, OH 43228

Dear Mr. Hicks:

Please refer to your pending Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sodium Oxybate Oral Solution, 500 mg/mL.

In accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for products containing sodium oxybate to ensure that the benefits of the drug outweigh the risk of developing central nervous system and respiratory depression, and the potential for abuse and misuse associated with sodium oxybate. Under section 909(b)(1) of the Food and Drug Administration Amendments Act (FDAAA) of 2007, we identified sodium oxybate as a product deemed to have in effect an approved REMS because there were in use on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520.

In addition, in accordance with section 505-1(i) of the FDCA, an abbreviated new drug application (ANDA) is required to have a REMS if the applicable listed drug has an approved REMS. Pursuant to section 505-1(i) of the FDCA, a drug that is the subject of an ANDA and the listed drug it references must use a single shared system for elements to assure safe use unless FDA waives that requirement. The REMS for Xyrem (sodium oxybate) includes elements to assure safe use. Therefore, a single shared system for the elements to assure safe use is required. The sponsor for the NDA for Xyrem is Jazz Pharmaceuticals, who has identified Jennifer Ekelund, as their contact for the development of the single shared system. Jennifer Ekelund can be reached at (650) 496-2630.

This letter is to inform you that, at minimum, the single shared system REMS program will be required to include the following elements:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide, as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that sodium oxybate poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of sodium oxybate. FDA has determined that sodium oxybate is a product for which patient labeling could help prevent serious adverse effects, and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use sodium oxybate.

Elements to Assure Safe Use:

- A requirement that healthcare providers who prescribe sodium oxybate are specially certified. To become certified, prescribers shall agree to complete the prescriber requirements in the REMS and shall enroll in the sodium oxybate REMS program.
- A requirement that sodium oxybate will only be dispensed by pharmacies that are specially certified. To become certified, pharmacies shall agree to the pharmacy/pharmacist requirements in the sodium oxybate REMS program.
- A requirement that sodium oxybate will only be dispensed to patients with documentation of safe-use conditions. Safe use conditions include confirming documentation that the pharmacy, prescriber, and patient are enrolled in the sodium oxybate REMS program.

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use. Include an intervention plan to address any findings of non-compliance with the elements to assure safe use regarding pharmacy certification and documentation of safe use conditions and to address any findings that suggest an increase in risk and take reasonable steps to work to improve implementation of these elements.

The Implementation System must include but is not limited to the following:

- A database of all enrolled entities.
- A plan to monitor compliance of the certified prescribers, patients, and pharmacies to ensure that all requirements of the sodium oxybate REMS program are being met.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for your product. Additionally, all relevant proposed REMS materials including enrollment forms, informed consents, and educational or training materials should be appended to the proposed REMS. Once FDA finds the content acceptable, we will include this document as an attachment to the approval letter that includes the REMS.

The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix A).

Use the following designator at the top of the first page of your proposed REMS submission in bold, capital letters:

AMENDMENT FOR ANDA 202090 PROPOSED REMS

If you have any questions, call Carrie Lemley, Labeling Project Manager at (240) 276-8986.

Sincerely yours,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
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/

ROBERT L WEST

09/27/2012

Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.

QUALITY DEFICIENCY - MINOR

ANDA 202090

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Roxane Laboratories, Inc.

TEL: (614) 272-4785

ATTN: Elizabeth Ernst

FAX: (614) 276-2470

FROM: Tina Nhu

FDA CONTACT PHONE: (240) 276-8548

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 8, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sodium Oxybate Solution, 500 mg/mL.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ___ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a **QUALITY MINOR AMENDMENT** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

*Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855*

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

ANDA: 202090

APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Sodium Oxybate Oral Solution, 500 mg/mL

The deficiencies presented below represent MINOR deficiencies:

A.



(b) (4)

B.

Sincerely yours,

{See appended electronic signature page}

Glen Smith
Acting Director
Division of Chemistry II
Office of Generic Drugs
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/

UBRANI V VENKATARAM
11/04/2011
For Glen Smith

QUALITY DEFICIENCY - MINOR

ANDA 202090

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Roxane Laboratories, Inc.

TEL: (614) 272-4785

ATTN: Elizabeth Ernst

FAX: (614) 276-2470

FROM: Tina Nhu

FDA CONTACT PHONE: (240) 276-8548

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 8, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sodium Oxybate Solution, 500 mg/mL.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 3 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until **all deficiencies** have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a **QUALITY MINOR AMENDMENT** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

*Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855*

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

ANDA: 202090

APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Sodium Oxybate Oral Solution, 500 mg/mL

The deficiencies presented below represent MINOR deficiencies:

A. Chemistry Deficiencies:

1.

2.

3.

4.

5.

6.

7.

8.

9.

(b) (4)

10.

11.

12.

13.

14.

15.

16.

17.

18.

19.

20.

21.

B.



(b) (4)

Sincerely yours,

{See appended electronic signature page}

Glen Smith
Acting Director
Division of Chemistry II
Office of Generic Drugs
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/

UBRANI V VENKATARAM
07/06/2011
For Glen Smith (Acting Director)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : August 10, 2010

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 202090 for Sodium Oxybate Oral Solution, 500 mg/mL to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Roxane Laboratories, Inc. has submitted ANDA 202090 for Sodium Oxybate Oral Solution, 500 mg/mL. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Roxane Laboratories, Inc. on July 8, 2010 for its Sodium Oxybate product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-202090	----- ORIG-1	----- ROXANE LABORATORIES INC	----- Sodium Oxybate

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

/s/

EDWARD WASHINGTON
08/25/2010