DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

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.S. Patent Number	Expiration Date
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 patents[1] 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 (consoliated)], 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 month[2] 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.

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[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
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