DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-196

Orphan Medical
Attention: Dayton Reardan, Ph.D.
Vice President, Regulatory Affairs
13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305

Dear Dr. Reardan:

Please refer to your new drug application (NDA) dated September 30, 2000, received October 2, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xyrem® (sodium oxybate) Oral Solution.

We acknowledge receipt of your submissions dated May 8 and 28; June 6 ; July 1, 12 and 15, 2002. Your submission of May 16, 2002 constituted a complete response to our April 9, 2002 action letter.

This new drug application provides for the use of Xyrem® Oral Solution for the treatment of cataplexy associated with narcolepsy.

We also refer to your March 12, 2002, correspondence requesting review of Xyrem® Oral Solution under the provisions of Subpart H for restricted distribution. Therefore, as previously agreed, we have reviewed this application under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) to assure safe use of the product.

Finally, we refer to the July 17, 2002, teleconference between representatives of Orphan Medical Inc. and this division during which the final language of the labeling text was agreed upon.

We have completed the review of this application, including the Xyrem® Risk Management Program, as amended, and have concluded that adequate information has been presented to approve Xyrem® (sodium oxybate) Oral Solution under 21 CFR 314 Subpart H. Accordingly, the application is approved under the provisions of 21 CFR 314, Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of all FDA regulations and the specific restrictions on distribution and use described below.

Xyrem® Risk Management Program

We remind you that Xyrem is being approved with a Risk Management Program (RMP) that must include each of the following components:

1) Implementation of a restricted distribution program for Xyrem.
2) Implementation of a program to educate physicians and patients about the risks and benefits of Xyrem, including critical information necessary for the safe use and handling of the drug.
3) Filling of the initial prescription only after the prescriber and patient have received and read the educational materials.
4) Maintenance of a registry of all patients and a record of all prescribers.

The RMP, as described in the attached documents, adequately addresses each of these requirements. Any proposed change in the RMP must be discussed with FDA prior to its institution. FDA will determine whether the proposed change is subject to FDA approval before implementation. We expect your continued cooperation to resolve any problems regarding the RMP that may be identified following approval of this NDA.

Medication Guide

As previously communicated to you in our December 13, 2001, letter, we have determined that Xyrem® poses a serious and significant public health concern requiring distribution of a Medication Guide. This Medication Guide is necessary to help prevent serious adverse effects due to Xyrem® pursuant to 21 CFR Part 208.1 (c)(1).

In accordance with 21 CFR Part 208, Orphan Medical is responsible for ensuring that:

- A Medication Guide for Xyrem® is available for every patient who is dispensed a prescription for Xyrem®.
- The label of each carton container of Xyrem® include a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom Xyrem® is dispensed.
- The label of each container includes a statement about how the Medication Guide is dispensed.

Post Marketing Commitments

You have made a commitment to conduct the following post marketing studies, as specified in your submission dated July 1, 2002, and our telephone conversation of July 12, 2002:

1. *Description:* conduct a drug interaction study to evaluate the pharmacokinetics of Xyrem® when administered concomitantly with a proton pump inhibitor in normal human volunteers.

   Protocol Submission: within three months of FDA approval of the NDA
   Study Start: within three months of FDA approval of the protocol
   Final Report: within six months of study initiation

2. *Description:* conduct a clinical study in subjects with respiratory compromise.

   Protocol Submission: within three months of FDA approval of the NDA
   Study Start: within three months of FDA approval of the protocol
   Final Report: completion of the study within 12 months of initiation with the final report three months following completion of the study.

3. *Description:* assess the post marketing safety of Xyrem in a prospective cohort of one thousand (1,000) patients prescribed Xyrem by evaluating physician-filed adverse event data sheets; each patient will be assessed for at least 6 months.

   Submission of Plans: within one month of approval
   Start Date: immediately upon treatment of any patient
   Reports to FDA: every three months from time of approval

Clinical protocols should be submitted to your IND for this product and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a summary of the status of each commitment in your annual report to this NDA. The summary should include expected study completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies. The number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled " Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

The final printed labeling (FPL) must be identical to the enclosed agreed upon labeling text for the Product Information Insert and Medication Guide. The immediate container and carton labels must be identical to those submitted on January 8, 2002. Marketing the product with FPL text that is not identical to the agreed upon approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21 -196." Approval of this submission by FDA is not required before the labeling is used.

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must directly submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement to the Division of Drug Marketing, Advertising and Communications. Please submit all

proposed materials in draft or mock up form, not final print and send one copy to the Division of Neuropharmacological Drug Products. We acknowledge your agreement to submit the reprint with the citation Sleep 2002; 25:42-49, under 21 U.S.C. § 360aaa.

We have approved an expiration date of 36 months for this drug product.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80, 314.81, 314.520, 314.550 and 314.560.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Professional Labeling
Patient Medication Guide
Risk Management Plan
Post Marketing Evaluation Program
Physician and Patient Educational Programs

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

/s/

Robert Temple

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