CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-196

APPROVAL LETTER

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
7/17/02 04:57:49 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVABLE LETTER

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 October 30, 2000; November 1, 16, 17 (2), 2000; December 1, 5, 6 (2), 7 (3), 11, 15, 16 and 18, 2000; January 11, 15, 19 and 31, 2001; February 1, 5, 6, 12, 13 (2), 15 and 23, 2001; March 16 and 23, 2001; April 10, 11, 12 and 19, 2001; May 4, and June 18, 2001.

We also refer to the meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee of June 6, 2001, at which your NDA was discussed.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved; however, it will be necessary for you to address the following:

Clinical Issues

1. As recommended by the Advisory Committee, the approval of your application will be contingent upon your adoption of an adequate Risk Management Program (RMP). You have proposed an extensive program, described in the attachment to this letter (the description attached is based on several of your submissions to the NDA and represents our understanding of the key elements of your proposal). We consider the proposed program a condition of approval with the following modifications:

    a) Prescribers must state, in writing, that a patient has narcolepsy with cataplexy before drug will be released to the patient.
    b) Prescribers must state, in writing, that they have read the educational materials provided to them before educational materials will be sent to the patient.
    c) Patients must state, in writing, that they have read the educational materials provided to them before their first prescription is filled.
    d) A single prescription must be limited to a maximum of 3 months supply of drug, and the maximum dose prescribed must be no more than 9 gms/day, given in 2 equally divided doses. Prescriptions for a dose greater than 9 gms/day, or for more than 3 months supply, must not be filled by the pharmacist.
    e) Patients must be seen and evaluated by the prescriber with the issuance of each new prescription (every 3 months), at which time a detailed account of the patient's experience on treatment must be provided. Prescribers must submit reports of all serious adverse reactions to

3. The status of the 11 patients who were enrolled in the Scharf study and had not entered the treatment IND study #OMC-SXB-7 as of 5/31/99, needs to be described to the extent possible. These patients are listed below by ID# and initials:

   01-004/
   01-027/ [redacted]
   01-054/
   01-065/
   01-228/
   01-240/
   01-262/
   01-269/
   01-283/
   01-268/
   01-256/

4. An analysis should be provided of all patients in the entire safety database listed as having "sleepwalking" as an adverse event. Such an analysis should include detailed clinical descriptions of the episodes, whenever they can be obtained from source documents, and the following additional elements: demographics, relationship to dose, frequency, seriousness, reason for discontinuation, further evaluations (e.g., EEGs and polysomnograms) and outcome.

5. As a CNS depressant, sodium oxybate is capable of producing respiratory depression. However, your application contains no formal assessment of this potential. Such assessments are routinely required in the evaluation of sedative-hypnotic drug products. For this reason, you should perform such a study. The study should examine the effects of the recommended dosing regimen (2 doses nightly, including the highest recommended dose-9 gms divided), with both doses given in the fasted state. The study should include patients who are and who are not receiving concomitant stimulant treatment, a positive control, and patients with concomitant illnesses that might increase their risk of respiratory depression (e.g., patients with COPD, sleep apnea, etc.). In addition, plasma level data should be obtained at appropriate times. We would be happy to discuss the design of such a study with you. We believe there is sufficient suggestion of occasional respiratory depression in the clinical studies to ask that these data be collected prior to marketing.

6. While there do not appear to be any important effects of sodium oxybate on the major CYP 450 metabolizing enzymes, the levels of sodium oxybate used in your studies were far below those expected to be seen clinically. Please assess the effects of sodium oxybate on these enzymes at clinically relevant exposures.

Labeling Issues

Accompanying this letter as an attachment is our proposal for the labeling of Xyrem® Oral Solution. In some places, we have extensively revised the text that you proposed; we request that you adopt the language we have proposed verbatim. In several places in labeling, we have embedded bolded requests for you to draft appropriate language. We would be happy to discuss these proposed changes in more detail through a teleconference if you wish.

you every 3 months initially, with the longer term reporting requirements to be further negotiated with the Agency. The patient registry that is an intrinsic part of this program must also be used to actively monitor for evidence of abuse, misuse, and diversion. You will need to incorporate these elements into your RMP documents.

f) The educational materials you have prepared must note prominently that Xyrem® is gamma hydroxybutyrate, or GHB, and that this is the same compound that is used illicitly.

g) The individual dosing cups must be labeled with the dose and name of the drug.

These provisions are required because, given the safety data available in the NDA, and the potential risks of sodium oxybate, we believe that the drug can be used safely only with the restrictions imposed by the RMP. Use beyond the population for whom the drug will be indicated poses an unreasonable risk, and, therefore, all reasonable efforts should be made to restrict its use to the appropriate population, and to avoid, to the extent possible, accidental use by members of the patient's household, as well as to restrict, extra-label, recreational use. Further, because of the small database in the NDA, we believe that the registry should be maximally utilized to obtain additional data on serious adverse events as quickly as possible after approval.

We will provide you with a detailed review of the Physician and Patient Success Programs once the product labeling is written and the entire RMP is defined.

We believe that adoption of this RMP is critical to the safe use of Xyrem®. Therefore, before this product can be approved, restrictions under 21 CFR 314.520 will need to be carefully defined.

2. A safety update for the ongoing studies, OMC-SXB-7 and [redacted] should be provided (the latter study is intended to assess the efficacy of Xyrem® in treating excessive daytime sleepiness). Even though the data for Study [redacted] may still be blinded, safety data may still be submitted. We would be happy to discuss with you appropriate ways in which this might be accomplished.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

While we have made extensive changes to your proposed labeling, there are two important changes that we wish to draw your attention to:

1. *'Indications'*: we have proposed that Xyrem be indicated for patients with cataplexy who are being treated with concomitant CNS stimulants. We have proposed this restriction because almost all of the clinical experience in your NDA was accrued in such patients, and we believe that it is possible that the use of stimulants may be protective of some of the CNS/respiratory depressant effects of Xyrem, especially at the higher doses. In the absence of evidence that Xyrem is devoid of important depressant effects when given alone, we believe it is appropriate to restrict its use to patients also receiving stimulants.

2. *'Contraindications'*: we have contraindicated the use of Xyrem with sedative-hypnotic drugs. We recognize that you have performed a pharmacokinetic study with zolpidem and determined no important kinetic interaction, but we believe the combination of Xyrem with potent CNS depressants is ill-advised, and should be avoided, absent data to the contrary.

Chemistry and Manufacturing Issues

——— the manufacturer of your drug product, recently received a Warning Letter from the Agency which cited numerous cGMP violations. The application cannot be approved until the Agency has re-inspected that site, and has determined that the deficiencies cited in that letter have been corrected. As of this time, ——— is not prepared for a re-inspection.

Postmarketing Issues

While the following issues need not be resolved prior to approval, the following will be required after marketing:

1. Because sodium oxybate is ionized in the GI tract, we would like you to perform drug interaction studies with drugs that alter gastric pH, such as antacids, proton-pump inhibitors, and H2 blockers, all of which may alter the absorption of sodium oxybate.

2. Please submit the results of the rat carcinogenicity study when available.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

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

Attachments (2)

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/s/

Robert Temple
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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We acknowledge receipt of your amendments dated October 5 and 23, November 7 and 27, December 13, 2001; and January 9, February 27, and March 8, 2002.

Your October 5, 2001, amendment constituted a complete response to our July 2, 2001, approvable letter.

We also acknowledge receipt of your submission dated April 3, 2002, containing the results of the completed rat carcinogenicity study.

We also refer to the April 2, 2002, meeting between you and FDA.

We have reviewed this application under the restricted distribution regulations contained in 21 CFR 314.520 of Subpart H.

We have completed the review of this application, as amended, and it is approvable. The remaining issues that you will need to address before this application may be approved are outlined below.

Assessment of Xyrem's Potential to Induce Respiratory Depression

In our July 2, 2001 Approvable Letter we asked you to perform a formal assessment of the respiratory effects of Xyrem prior to marketing. Such assessments are routinely required in the evaluation of sedative-hypnotic drug products. Subsequently, we agreed to review the results of SXB-20, an uncontrolled polysomnographic study previously performed to evaluate the effect of Xyrem on different sleep stages. You believed the results of the respiratory monitoring in SXB-20 provided enough reassurance to allow approval while formal, controlled studies could be performed post-approval.

We have reviewed the results of SXB-20 and are concerned that Xyrem may produce clinically important deleterious effects on respiratory function during sleep, especially in patients with sleep

apnea. While there was marked variability in the data collected, 2 of the 4 patients with moderate-severe sleep apnea had marked elevations over baseline in the RDI (respiratory distress index) while on treatment. Absent a control group, it is impossible to distinguish between variability and a drug effect as the cause of these elevations. As discussed in our meeting of April 2, 2002, we believe that these changes may represent a clinically significant worsening of respiratory function at night related to treatment with Xyrem in at least one, and perhaps in both, patients. We acknowledge that you believe that none of the patients experienced a clinically relevant decline in respiratory function. We agreed that you may submit a comprehensive response to our stated concerns in lieu of a definitive assessment of Xyrem's effect on respiratory function in response to this letter. While it is possible that we may find your arguments convincing (if we do, you would still need to perform an adequately designed trial to definitively address this question in Phase 4), it is also possible that we will remain concerned that Xyrem may cause an important deterioration of nighttime respiratory function. If this is the outcome, you will be required to perform an adequate study addressing this issue prior to approval.

Adequacy of the Safety Database

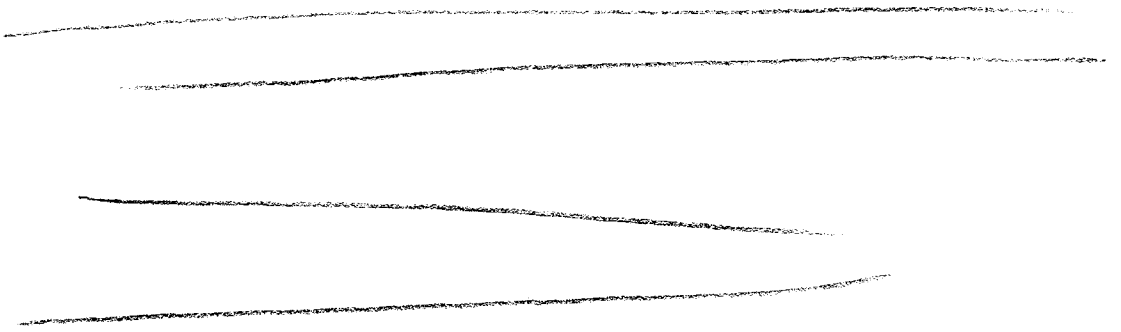
As you know, the size of the safety database in your application is, and remains, with the Safety Update, small by the usual standard. The number of patients who reached the highest daily dose, 9gms/day, did not change appreciably with the Safety Update and is only 141, 74 of whom were treated for at least 6 months.

Given this small experience, we are particularly concerned about the results of a recent site audit, which have raised questions about the acceptablity of the data generated at this site. As a result of this audit, we now believe that one or more additional site audits will be needed prior to approval. The next site audit is planned within a month.

Once the above issues are adequately addressed, we are prepared to approve Xyrem for the treatment of cataplexy in narcolepsy under Subpart H as requested in your March 12, 2002 letter. Upon initial marketing under Subpart H, the distribution of Xyrem will be regulated as described in 21 CFR 314.520. Attached to this letter are proposed labeling and an outline of a proposed risk management program that is acceptable to us. The primary component of the risk management program is a central pharmacy.

Also attached to this letter are marked up versions of the documents you plan to send to doctors and patients as part of your Physician and Patient Success Programs, including draft product labeling and a draft Medication Guide for distribution with Xyrem. All of these documents, and the specific details of the risk management program, are subject to change pending your response to this Approvable Letter, and therefore should be considered provisional at this time.

___/___ page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.



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Sincerely,

{See appended electronic signature page}

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

Enclosures:
Labeling
Medguide
Risk Management Program