CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-196

APPROVED LABELING

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Xyrem® Risk Management Program

I. As a condition of approval, the requirements of your Risk Management Program include the following, with the details of the Program set out below in III.

- Implementation of a restricted distribution program for Xyrem
- Implementation of a program to educate physicians and patients about the risks and benefits of Xyrem, including support via ongoing contact with patients and a toll-free Helpline
- Filling of the initial prescription only after the prescriber and the patient have received and read the educational materials
- Maintain patient and prescribing physician registries

II. You have also agreed to the following:

- The bulk drug will be manufactured at a single site.
- The drug product will be manufactured at a single site.
- Following manufacture the drug product will be stored at a facility compliant with Schedule III regulations, where a consignment inventory will be maintained.
- The inventory will be owned by Orphan Medical, Inc., and the facility will be managed by a central pharmacy which will maintain the consignment inventory.
- Xyrem® will be distributed and dispensed through a primary and exclusive central pharmacy (which you have represented will contract with Orphan Medical to fulfill this function). Orphan Medical has a designated back-up distributor. Xyrem® will NOT be stocked in retail pharmacy outlets.

III. Risk Management Program Details

A. Dispensing

You will ensure that Xyrem is dispensed in the following manner:

- Prescriptions will be communicated by facsimile or other convenient method by the physician, or the physician's office, to the central pharmacy.
- Upon receipt of a prescription the central pharmacy will contact the prescribing physician and/or the physician's office and
  - Identify physician's name, license and DEA registration
  - Verify the prescription
  - Obtain patient insurance information
- The central pharmacy will then verify that the physician is eligible to prescribe Xyrem® by consulting the National Technical Information Services (NTIS). This stage of verification will include confirming that the physician has an active DEA number and will check on whether any actions are pending against the physician.

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- If the physician is a first-time prescriber of Xyrem® the pharmacy will then ship, if the physician does not already have them, comprehensive printed materials to that physician; these materials (see Xyrem Physician Success Program℠ below) also contain information regarding the proper handling of the drug with an outline of precautions to be taken against diversion.
- You have agreed that if a patient has prescription drug coverage, the central pharmacy will then contact the patient's insurance company to obtain coverage. The central pharmacy will notify the patient of his/her approval status.
- All patient registry information will be verified before the initial prescription can be filled.
- Comprehensive printed and video materials (see Xyrem Patient Success Program℠ below) that also contain information regarding the proper handling of the drug with an outline of precautions to be taken against diversion will be provided to the patient in advance of the shipment.
- Prior to Xyrem® being shipped to a patient for the first time, the central pharmacist will confirm with the patient by telephone that the patient has read the educational materials contained in the Xyrem Patient Success Program℠. That confirmation will be recorded by the central pharmacist.
- Once approval has been established, the central pharmacy will verify the patient's home address and availability for shipping, and arrange shipment through Federal Express or a similar carrier.
- The patient may provide the name of a designee to the central pharmacy who is authorized to accept shipment of Xyrem® when the patient is unable to do so. This designee must be 18 years of age or older.
- Receipt of the initial drug shipment will be ensured through the following:
    - A phone call by the pharmacy to the patient, no more than 1 business day after the shipment has been delivered, to verify that the medication has been received; and
    - The courier service's own tracking system for shipments
- The package will be sent under condition that if the patient, or his/her designee is unavailable to accept a shipment of Xyrem® and execute the required receipt after two delivery attempts, the package will be returned to the pharmacy.
- You have agreed that, if a shipment is lost, an investigation will be launched to find it.
- If required by the patient's insurance company, the product may be shipped by the central pharmacy to another pharmacy for patient pick-up. The sponsor anticipates that this will be an unusual occurrence, and has a mechanism for verifying the second pharmacy's ability to protect against diversion of sodium oxybate before shipping the drug there through NTIS and State Boards of Pharmacy.

- Prescription refills will be permitted in the number specified in the original prescription. In addition, you have agreed that:
    - If a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned by the pharmacist.
    - A lost, stolen, destroyed, or spilled prescription/supply will be documented and the prescription replaced to the extent necessary to honor the original prescription (e.g., a destroyed or spilled bottle will reduce the prescription refill amount). The pharmacist has the discretion to grant or not grant refill requests under those circumstances and at a

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minimum will contact the prescribing physician to determine if the physician has any special concerns in regard to that refill request. New supplies of Xyrem® will be sent to the patient only if the pharmacist and physician are in agreement.

- Repeat instances of lost, stolen, destroyed, or spilled prescriptions/supplies will be flagged for monitoring and future instances thoroughly questioned.
- The first prescription will be limited to a one month's supply of Xyrem®.
- Following further contact between the pharmacy and patient, and verification that the patient understands the material in the Xyrem Patient Success Program℠, supplies of Xyrem® that are intended to last longer than a month may be shipped.
- The quantity of drug shipped to the patient with each refill may also be regulated based on the requirements of the patient's health insurance plan and the terms of the prescription itself.
- It is anticipated that the majority of patients will receive only one month's shipment at a time.
- Patients will never receive more than 3 months' supply of Xyrem® per shipment.
- Prescriptions for Xyrem® will be rewritten at least every 3 months

B. Registries

- Every patient and prescribing physician will be registered with the central pharmacy in a secure database. The database will contain the physician's name, address, telephone and facsimile numbers, DEA and state license numbers and prescribing frequency. The database will be made available for review by federal and state agencies upon request. From this database it will be possible to obtain the following information:
  - Prescriptions by physician specialty
  - Prescriptions by patient name
  - Prescriptions by volume (frequency)
  - Prescriptions by dose

C. Xyrem Post-Marketing Evaluation Program

- You have agreed that that the prescriber will be urged to see and evaluate his or her patients every 3 months. In addition, you will urge prescribers to submit reports of all serious adverse reactions to Orphan Medical every 3 months initially with the longer term reporting requirements to be negotiated with the Agency.

- At each visit subsequent to the initial prescription visit, you have agreed that the prescriber will be urged to query the patient for potential adverse events associated with Xyrem use, as well as document any suggestion of inappropriate Xyrem use (e.g., premature requests for refills). To assist

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the prescriber in this assessment, evaluation forms are included with the physician Xyrem Success Program℠, which are to be completed by the prescriber at Month 3 and Month 6 of a patient's course of therapy. It is of utmost importance that the prescriber fill out this form as completely as possible.

D. Drug Product Kit

Every box of Xyrem® shipped to the patient will contain all the items below:.

- The drug product, a clear solution, in a 180 mL amber bottle with a closure mechanism that is child-resistant
- The Press-In-Bottle-Adapter (PIBA Well) which will be inserted into the bottle by the pharmacist
- An Exacta-Med Dispenser® which allows the patient to withdraw the appropriate dose of drug
- Two child-resistant dosing cups, one for each of 2 nightly doses.
- A package insert and Medication Guide

E. Education materials

1. Xyrem Physician Success Program℠

This program consists of printed material(s) to educate physicians about the features of Xyrem®. When a physician prescribes the drug for the first time, the physician must verify that he/she has read these materials before the medication will be sent to the patient.

2. Xyrem Patient Success Program℠

This program consists of a videotape and printed educational material. The patient will receive this material prior to the first shipment of drug. The central pharmacist will not ship the product unless the patient has confirmed to the pharmacist that he or she has read the educational materials.

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