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/distributer 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