CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-196

APPROVED LABELING

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.

- 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

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

the prescriber in this assessment, evaluation forms are included with the physician Xyrem Success Program[SM], 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[SM]

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[SM]

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.

R_x only

CIII

Xyrem® (sodium oxybate) oral solution

!WARNING: Central nervous system depressant with abuse potential. Should not be used with alcohol or other CNS depressants.

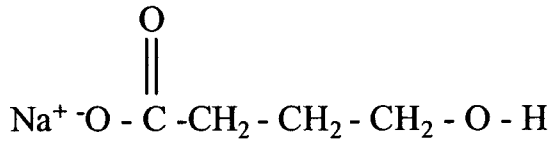
Sodium oxybate is GHB, a known drug of abuse. Abuse has been associated with some important central nervous system (CNS) adverse events (including death). Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Reports of respiratory depression occurred in clinical trials. Almost all of the patients who received sodium oxybate during clinical trials were receiving CNS stimulants; whether this affected respiration during the night is unknown. Xyrem® is available only through restricted distribution, the Xyrem Success Program℠, by calling 1-877-67-XYREM (1-877-679-9736).

Important CNS adverse events associated with abuse of GHB include seizure, respiratory depression and profound decreases in level of consciousness, with instances of coma and death. For events that occurred outside of clinical trials, in people taking GHB for recreational purposes, the circumstances surrounding the events are often unclear (e.g., dose of GHB taken, the nature and amount of alcohol or any concomitant drugs).

Under the Xyrem Success Program℠, Xyrem® is made available to prescribers through a single centralized pharmacy and with the following procedures: 1) The prescriber must contact the centralized pharmacy (1-877-67-XYREM℠), which will provide the prescriber with educational materials explaining the risks and proper use of sodium oxybate, and the details of the program. 2) Once the prescriber has read the materials and returned the necessary form, the pharmacy will ship educational materials to the patient. 3) Once it is documented that the patient has read the materials, the drug will be shipped to the patient. The Xyrem Success Program℠ also includes provisions for detailed surveillance of the patients (patients are to be seen no less frequently than every 3 months and physicians are expected to report all serious adverse events to the manufacturer) and information to help minimize the risks of inadvertent use by others. (See WARNINGS)

DESCRIPTION

Xyrem® (sodium oxybate) is a central nervous system depressant with anti-cataplectic activity in patients with narcolepsy. Sodium oxybate is intended for oral administration. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $C_4H_7NaO_3$ and the molecular weight is 126.09 grams/mole. The chemical structure is:



Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. Xyrem® oral solution contains 500 mg of sodium oxybate per milliliter of USP purified water, neutralized to pH 7.5 with malic acid.

CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism by which sodium oxybate produces an effect on cataplexy is unknown.

Pharmacokinetics

Sodium oxybate is rapidly but incompletely absorbed after oral administration; absorption is delayed and decreased by a high fat meal. It is eliminated mainly by metabolism with a half-life of 0.5-1 hour. Pharmacokinetics are nonlinear with blood levels increasing 3.7-fold as dose is doubled from 4.5 to 9 grams. The pharmacokinetics are not altered with repeat dosing.

Absorption

Sodium oxybate is absorbed rapidly following oral administration with an absolute bioavailability of about 25%. The average peak plasma concentrations (1st and 2nd peak) following administration of a 9 g daily dose divided into two equivalent doses given four hours apart were 78 and 142 mcg/ml, respectively. The average time to peak plasma concentration (T_{max}) ranged from 0.5 to 1.25 hours in eight pharmacokinetic studies. Following oral administration, the plasma levels of sodium oxybate increase more than proportionally with increasing dose. Single doses greater than 4.5 grams have not been studied. Administration of sodium oxybate immediately after a high fat meal resulted in delayed absorption (average T_{max} increased from 0.75 hr to 2.0 hr) and a reduction in peak plasma level (C_{max}) by a mean of 58% and of systemic exposure (AUC) by 37%.

Distribution

Sodium oxybate is a hydrophilic compound with an apparent volume of distribution averaging 190-384 ml/kg. At sodium oxybate concentrations ranging from 3 to 300 mcg/ml, less than 1% is bound to plasma proteins.

Metabolism

Animal studies indicate that metabolism is the major elimination pathway for sodium oxybate, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. The primary pathway involves a cytosolic $NADP^+$-linked enzyme, GHB dehydrogenase, that catalyses the conversion of sodium oxybate to succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle where it is metabolized to carbon dioxide and water. A second mitochondrial oxidoreductase enzyme, a transhydrogenase, also catalyses the conversion to succinic semialdehyde in the presence of α-ketoglutarate. An alternate pathway of biotransformation involves β-oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

Studies *in vitro* with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A up to the concentration of 3 mM (378 micrograms/ml). These levels are considerably higher than levels achieved with therapeutic doses.

Elimination

The clearance of sodium oxybate is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible.

Special Populations

Geriatric

The pharmacokinetics of sodium oxybate in patients greater than the age of 65 years have not been studied.

Pediatric

The pharmacokinetics of sodium oxybate in pediatric patients under the age of 18 years have not been studied.

Gender

In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of sodium oxybate following a single oral dose of 4.5 grams.

Race

There are insufficient data to evaluate any pharmacokinetic differences among races.

Renal Disease

Because the kidney does not have a significant role in the excretion of sodium oxybate, no pharmacokinetic study in patients with renal dysfunction has been conducted; no effect of renal function on sodium oxybate pharmacokinetics would be expected.

Hepatic Disease

Sodium oxybate undergoes significant presystemic (hepatic first-pass) metabolism. The kinetics of sodium oxybate in 16 cirrhotic patients, half without ascites, (Child's Class A) and half with ascites (Child's Class C) were compared to the kinetics in 8 healthy adults after a single oral dose of 25 mg/kg. AUC values were double in the cirrhotic patients, with apparent oral clearance reduced from 9.1 in healthy adults to 4.5 and 4.1 ml/min/kg in Class A and Class C patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control subjects (mean $t_{1/2}$ of 59 and 32 versus 22 minutes). It is prudent to reduce the starting dose of sodium oxybate by one-half in patients with liver dysfunction (see Dosage and Administration).

Drug-Drug Interaction

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. However, pharmacodynamic interactions with these drugs cannot be ruled out.

CLINICAL TRIALS

The effectiveness of sodium oxybate as an anti-cataplectic agent was established in 2 randomized, double-blind, placebo-controlled trials (Trials 1 and 2) in patients with narcolepsy, 85% and 80%, respectively, of whom were also being treated with CNS stimulants. The high percentages of concomitant stimulant use make it impossible to assess the efficacy and safety of Xyrem® independent of stimulant use. In each trial, the treatment period was 4 weeks and the total daily doses ranged from 3 to 9 grams, with the daily dose divided into 2 equal doses. The first dose each night was taken at bedtime and the second dose was taken 2.5 to 4 hours later. There were no restrictions on the time between food consumption and dosing.

Trial 1 was a multi-center, double-blind, placebo-controlled, parallel-group trial that enrolled 136 narcoleptic patients with moderate to severe cataplexy (median of 21 cataplexy attacks per week) at baseline. Prior to randomization, medications with possible effects on cataplexy were withdrawn, but stimulants were continued at stable doses. Patients were randomized to receive placebo, sodium oxybate 3gms/day, sodium oxybate 6gms/day, or sodium oxybate 9gms/day.

Trial 2 was a multi-center, double-blind, placebo-controlled, parallel-group, randomized withdrawal trial that enrolled 55 narcoleptic patients who had been taking open-label sodium oxybate for 7 to 44 months. To be included, patients were required to have a history of at least 5 cataplexy attacks per

week prior to any treatment for cataplexy. Patients were randomized to continued treatment with sodium oxybate at their stable dose or to placebo. Trial 2 was designed specifically to evaluate the continued efficacy of sodium oxybate after long-term use.

The primary efficacy measure in each clinical trial was the frequency of cataplexy attacks.

Table 1
Summary of Outcomes in Clinical Trials Supporting the Efficacy of Sodium Oxybate

Trial/ Dosage Group (n)	Baseline	Median Change From Baseline	Comparison to Placebo p-value
CATAPLEXY ATTACKS			
	Trial 1		
		(median attacks/wk)	
Placebo (33)	20.5	-4	—
3.0 g/d (33)	20.0	-7	0.5541
6.0 g/d (31)	23.0	-10	0.0451
9.0 g/d (33)	23.5	-16	0.0016
	Trial 2		
		(median attacks/two weeks)	
Placebo (29)	4.0	21.0	-
Sodium oxybate (26)	1.9	0	<0.001

In Trial 1, both the 6 gm/day and 9 gm/day doses gave statistically significant reductions in the frequency of cataplexy attacks. The 3 gms/day dose had little effect. In Trial 2, following the discontinuation of long-term open-label sodium oxybate therapy, patients randomized to placebo experienced a significant increase in cataplexy ($p<0.001$), providing evidence of long-term efficacy of sodium oxybate. In Trial 2, the response was numerically similar for patients treated with doses of 6-9 gms/day, but there was no effect seen in patients treated with doses less than 6 gms/day, suggesting little effect at these doses.

INDICATIONS AND USAGE

Xyrem® (sodium oxybate) oral solution is indicated for the treatment of cataplexy in patients with narcolepsy.

In Xyrem® clinical trials, approximately 80% of patients maintained concomitant stimulant use (see BLACK BOX WARNINGS).

CONTRAINDICATIONS

Sodium oxybate is contraindicated in patients being treated with sedative hypnotic agents.

Sodium oxybate is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency. This rare disorder is an inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.

WARNINGS

SEE BOXED WARNING

Due to the rapid onset of its CNS depressant effects, sodium oxybate should only be ingested at bedtime, and while in bed. For at least 6 hours after ingesting Sodium oxybate, patients must not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery, driving a motor vehicle, or flying an airplane. When patients first start taking Xyrem® or any other sleep medicine, until they know whether the medicine will still have some carryover effect on them the next day, they should use extreme care while driving a car, operating heavy machinery, or performing any other task that could be dangerous or requires full mental alertness.

The combined use of alcohol (ethanol) with sodium oxybate may result in potentiation of the central nervous system-depressant effects of sodium oxybate and alcohol. Therefore, patients should be warned strongly against the use of any alcoholic beverages in conjunction with sodium oxybate. Sodium oxybate should not be used in combination with sedative hypnotics or other CNS depressants.

Central Nervous System Depression/Respiratory Depression

Sodium oxybate is a CNS depressant with the potential to impair respiratory drive, especially in patients with already-compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported (see OVERDOSAGE). In clinical trials 2 subjects had profound CNS depression. A 39 year-old woman, a healthy volunteer received a single 4.5gm dose of sodium oxybate after fasting for 10 hours. An hour later, while asleep, she developed decreased respiration and was treated with an oxygen mask. An hour later, this event recurred. She also vomited and had fecal incontinence. In another case, a 64 year-old narcoleptic man was found unresponsive on the floor on day 170 of treatment with Sodium oxybate at a total daily dose of 4.5gms/day. He was taken to an emergency room where he was intubated. He improved and was able to return home later the same day. Two other patients discontinued sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea.

The respiratory depressant effects of Xyrem®, at recommended doses, were assessed in 21 patients with narcolepsy, and no dose-related changes in oxygen saturation were demonstrated in the group as a whole. One of these patients had significant concomitant pulmonary illness, and 4 of the 21 had

moderate-to-severe sleep apnea. One of the 4 patients with sleep apnea had significant worsening of the apnea/hypopnea index during treatment, but worsening did not increase at higher doses. Another patient discontinued treatment because of a perceived increase in clinical apnea events. Caution should be observed if Xyrem® is prescribed to patients with compromised respiratory function. Prescribers should be aware that sleep apnea has been reported with a high incidence (even 50%) in some cohorts of narcoleptic patients.

Confusion/Neuropsychiatric Adverse Events

During clinical trials, 7% of patients treated with sodium oxybate experienced confusion. Fewer than 1% of patients discontinued the drug because of confusion. Confusion was reported at all recommended doses from 6-9gms/day. In a controlled trial where patients were randomized to fixed total daily doses of 3, 6, and 9g/day or placebo, a dose-response relationship for confusion was demonstrated with 17% of patients at 9g/day experiencing confusion. In all cases, the confusion resolved soon after termination of treatment. In the majority of cases, confusion resolved with continued treatment. However, patients treated with Xyrem® who become confused should be evaluated fully, and appropriate intervention considered on an individual basis.

Other neuropsychiatric events included psychosis, paranoia, hallucinations, and agitation. The emergence of thought disorders and/or behavior abnormalities when patients are treated with sodium oxybate requires careful and immediate evaluation.

Depression

In clinical trials, 6% of patients treated with sodium oxybate reported depressive symptoms. In the majority of cases, no change in sodium oxybate treatment was required. Three patients (<1%) discontinued because of depressive symptoms. In the controlled clinical trial, where patients were randomized to fixed doses of 3, 6, 9g/day or placebo, there was a single event of depression at the 3g/day dose.

Among patients with a previous history of depressive psychiatric disorder, there were 2 suicides and 1 attempted suicide recorded in the 448 patient dataset. Of the 2 suicides, one patient used sodium oxybate in conjunction with other drugs. Sodium oxybate was not involved in the second suicide. Sodium oxybate was the only drug involved in the attempted suicide. A fourth patient without a previous history of depression attempted suicide by taking an overdose of a drug other than sodium oxybate.

The emergence of depression when patients are treated with Xyrem® requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored especially carefully for the emergence of depressive symptoms while taking Xyrem®.

Usage in the Elderly

There is very limited experience with sodium oxybate in the elderly. Therefore, elderly patients should be monitored closely for impaired motor and/or cognitive function when taking sodium oxybate.

PRECAUTIONS

Incontinence

During clinical trials, 9% of narcoleptic patients treated with sodium oxybate experienced either a single episode or sporadic nocturnal urinary incontinence and <1% experienced a single episode of nocturnal fecal incontinence. Less than 1% of patients discontinued as a result of incontinence. Incontinence has been reported at all doses tested.

In a controlled trial where patients were randomized to fixed total daily doses of 3, 6, and 9g/day or placebo, a dose-response relationship for urinary incontinence was demonstrated with 14% of patients at 9g/day experiencing urinary incontinence. In the same trial, one patient experienced fecal incontinence at a dose of 9g/day and discontinued treatment as a result.

If a patient experiences urinary or fecal incontinence during Xyrem® therapy, the prescriber should consider pursuing investigations to rule out underlying etiologies, including worsening sleep apnea or nocturnal seizures, although there is no evidence to suggest that incontinence has been associated with seizures in patients being treated with Xyrem®.

Sleepwalking

The term "sleepwalking" in this section refers to confused behavior occurring at night and, at times, associated with wandering. It is unclear if some or all of these episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Sleepwalking was reported in 7% of 448 patients treated in clinical trials with sodium oxybate. In sodium oxybate-treated patients <1% discontinued due to sleepwalking. In controlled trials of up to 4 weeks duration, the incidence of sleepwalking was 1% in both placebo and sodium oxybate-treated patients. Sleepwalking was reported by 32% of patients treated with sodium oxybate for periods up to 16 years in one independent uncontrolled trial. Fewer than 1% of the patients discontinued due to sleepwalking. Five instances of significant injury or potential injury were associated with sleepwalking during a clinical trial of sodium oxybate including a fall, clothing set on fire while attempting to smoke, attempted ingestion of nail polish remover, and overdose of oxybate. Therefore, episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

Sodium Intake

Daily sodium intake in patients taking sodium oxybate ranges from 0.5 g (for a 3 g sodium oxybate dose) to 1.6 g (for a 9 g sodium oxybate dose). This should be considered in patients with heart failure, hypertension or compromised renal function.

Hepatic Insufficiency

Patients with compromised liver function will have an increased elimination half-life and systemic exposure to sodium oxybate. (see **Pharmacokinetics**). The starting dose should therefore be decreased by one-half in such patients, and response to dose increments monitored closely (see Dosage and Administration).

Renal Insufficiency

No studies have been conducted in patients with renal failure. Because less than 5% of sodium oxybate is excreted via the kidney, no dose adjustment should be necessary in patients with renal impairment. The sodium load associated with administration of sodium oxybate should be considered in patients with renal insufficiency.

Information for Patients

The Xyrem Patient Success Program[SM] includes detailed information about the safe and proper use of sodium oxybate, as well as information to help the patient prevent accidental use or abuse of sodium oxybate by others. Patients must confirm that they have read the materials before the first prescription will be filled. Prescribers will discuss the details of the program and the treatment (including the procedure for preparing the dose to be administered) prior to the initiation of treatment. Patients should also be informed that they must be seen by the prescriber frequently during the course of their treatment, and that a detailed account of the adverse reactions they may have experienced will be taken. Food significantly decreases the bioavailability of sodium oxybate (see Pharmacokinetics). Whether sodium oxybate is taken in the fed or fasted state may affect both the efficacy and safety of sodium oxybate for a given patient. Patients should be made aware of this and try to take the first dose several hours after a meal. Patients should be informed that sodium oxybate is associated with urinary and, less frequently, fecal incontinence. Patients should be instructed to lie down and sleep after each dose of sodium oxybate, and not to take sodium oxybate at any time other than at night, immediately before bedtime and again 2.5-4 hours later. Patients should be instructed that they should not take alcohol or other sedative hypnotics with sodium oxybate.

For additional information, patients should see the Medication Guide for Xyrem®.

Laboratory Tests

Laboratory tests are not required to monitor patient response or adverse events resulting from sodium oxybate administration.

In an open-label trial of long term exposure to sodium oxybate, which extended as long as 16 years for some patients, 30% (26/87) of patients tested had at least one positive anti-nuclear antibody (ANA) test. Of the 26, 17 patients had multiple positive ANA tests over time. The clinical course of these

patients was not always clearly recorded, but 1 patient was clearly diagnosed with rheumatoid arthritis at the time of the first recorded positive ANA test.

Drug Interactions

Interactions between sodium oxybate and three drugs commonly used in patients with narcolepsy (zolpidem tartrate, protriptyline HCL, and modafinil) have been evaluated in formal studies. Sodium oxybate, in combination with these drugs, produced no significant pharmacokinetic changes for either drug (see **Pharmacokinetics and Metabolism**). However, pharmacodynamic interactions cannot be ruled out. Nonetheless, sodium oxybate should not be used in combination with sedative hypnotics or other CNS depressants.

In animal models, sodium oxybate and depressant drug combinations generally gave greater central depressant effects than did either drug alone. Concomitant administration to animals of sodium oxybate and benzodiazepines, barbiturates, or ethanol increases sleep duration. In primates, sodium oxybate blood levels were elevated with phenytoin pretreatment and reduced with L-Dopa, ethosuximide, and trimethadione.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Oral carcinogenicity studies have been conducted in rats and mice with gamma-butyrolactone, a compound that is metabolized to sodium oxybate *in vivo,* with no clear evidence of carcinogenic potential. Plasma levels (AUC) of sodium oxybate achieved in these studies were estimated to be approximately 1/2 (mice and female rats) and 1/10 (male rats) those seen in humans receiving the maximum recommended daily dose of sodium oxybate.

Sodium oxybate was negative in the Ames microbial mutagen test, an *in vitro* chromosomal aberration assay in CHO cells, and an *in vivo* rat micronucleus assay.

Sodium oxybate did not impair fertility in rats at doses up to 1000 mg/kg (approximately equal to the maximum recommended human daily dose on a mg/m^2 basis).

Pregnancy

Pregnancy Category B: Reproduction studies conducted in pregnant rats at doses up to 1000 mg/kg (approximately equal to the maximum recommended human daily dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 1200 mg/kg (approximately 3 times the maximum recommended human daily dose on a mg/m^2 basis) revealed no evidence of teratogenicity. In a study in which rats were given sodium oxybate from day 6 of gestation through day 21 post-partum, slight decreases in pup and maternal weight gains were seen at 1000 mg/kg; there were no drug effects on other developmental parameters. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Sodium oxybate has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid, but umbilical vein levels of sodium oxybate were no more than 25% of the maternal concentration. No sodium oxybate was detected in the infant's blood 30 minutes after delivery. Elimination curves of sodium oxybate between a 2-day old infant and a 15-year old patient were similar. Subsequent effects of sodium oxybate on later growth, development and maturation in humans are unknown.

Nursing Mothers

It is not known whether sodium oxybate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sodium oxybate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in patients under 16 years of age have not been established.

Race and Gender Effects

There were too few non-Caucasian patients to permit evaluation of racial effects on safety or efficacy. More than 90% of the subjects in clinical trials were Caucasian.

The database was 58% female. No important differences in safety or efficacy of Xyrem® were noted between men and women. The overall percentage of patients with at least one adverse event was slightly higher in women (80%) than in men (69%). The incidence of serious adverse events and discontinuations due to adverse events were similar in both men and women.

ADVERSE REACTIONS

A total of 448 narcoleptic patients were exposed to sodium oxybate in clinical trials. The most commonly observed adverse events associated with the use of sodium oxybate were:

Headache 25%, nausea 21%, dizziness 17%, pain 16%, somnolence 13%, pharyngitis 11%, infection 10%, viral infection 10%, flu syndrome 9%, accidental injury 9%, diarrhea 8%, urinary incontinence 8%, vomiting 8%, rhinitis 8%, asthenia 8%, sinusitis 7%, nervousness 7%, back pain 7%, confusion 7%, sleepwalking 7%, depression 6%, dyspepsia 6%, abdominal pain 6%, abnormal dreams 6%, insomnia 5%.

Two deaths occurred in these clinical trials, both from drug overdoses. Both of these deaths resulted from ingestion of multiple drugs, including sodium oxybate in one patient.

Table 2

Incidence (%) of Treatment-Emergent Adverse Events in Trial 1

Body System Preferred Term	Placebo (n=34)	Sodium Oxybate Dose 3g (n=34)	 6g (n=33)	 9g (n=35)
Body as a Whole				
Asthenia	1 (3%)	0 (0%)	2 (6%)	0 (0%)
Flu Syndrome	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Headache	7 (21%)	3 (9%)	5 (15%)	11 (31%)
Infection	1 (3%)	3 (9%)	5 (15%)	0 (0%)
Infection Viral	1 (3%)	1 (3%)	3 (9%)	0 (0%)
Pain	2 (6%)	3 (9%)	4 (12%)	7 (20%)
Digestive System				
Diarrhea	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Dyspepsia	2 (6%)	0 (0%)	3 (9%)	2 (6%)
Nausea	2 (6%)	2 (6%)	5 (15%)	12 (34%)
Nausea and Vomiting	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Vomiting	0 (0%)	0 (0%)	2 (6%)	4 (11%)
Musculoskeletal System				
Myasthenia	0 (0%)	2 (6%)	1 (3%)	0 (0%)
Nervous System				
Amnesia	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Anxiety	1 (3%)	1 (3%)	0 (0%)	2 (6%)
Confusion	1 (3%)	3 (9%)	1 (3%)	5 (14%)
Dizziness	2 (6%)	8 (24%)	10 (30%)	12 (34%)
Dream Abnormal	0 (0%)	0 (0%)	3 (9%)	1 (3%)
Hypertension	1 (3%)	0 (0%)	2 (6%)	0 (0%)
Hypesthesia	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Sleep Disorder	1 (3%)	2 (6%)	4 (12%)	5 (14%)
Somnolence	4 (12%)	5 (15%)	4 (12%)	5 (14%)
Thinking Abnormal	0 (0%)	1 (3%)	0 (0%)	2 (6%)

Skin				
Increased Sweating	0 (0%)	1 (3%)	1 (3%)	4 (11%)
Special Senses				
Amblyopia	1 (3%)	2 (6%)	0 (0%)	0 (0%)
Tinnitus	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Urogenital System				
Dysmenorrhea	1 (3%)	1 (3%)	0 (0%)	2 (6%)
Incontinence Urine	0 (0%)	0 (0%)	2 (6%)	5 (14%)

Other Adverse Events Observed During All Clinical Trials

During clinical trials sodium oxybate was administered to 448 patients with narcolepsy, and 125 healthy volunteers. A total of 150 patients received 9g/day, the maximum recommended dose. A total of 223 patients received sodium oxybate for at least one year. To establish the rate of adverse events, data from all subjects receiving any dose of sodium oxybate were pooled. All adverse events reported by at least two people are included except for those already listed elsewhere in the labeling, terms too general to be informative, or events unlikely to be drug induced. Events are classified by body system and listed under the following definitions: frequent adverse events (those occurring in at least 1/100 people); infrequent events (those occurring in 1/100 – 1/1000 people). These events are not necessarily related to sodium oxybate treatment.

Body As A Whole

Frequent: Allergic reaction, chills; **Infrequent:** Abdomen enlarged, hangover effect, neck rigidity.

Cardiovascular system

Infrequent: syncope,.

Digestive system

Frequent: Anorexia, constipation; **Infrequent:** mouth ulceration, stomatitis.

Hemic and lymphatic system

Infrequent: Anemia, ecchymosis, leukocytosis, lymphadenopathy, polycythemia.

Metabolic and nutritional

Frequent: Alkaline phosphatase increased, edema, hypercholesteremia, hypocalcemia, weight gain; **Infrequent:** Bilirubinemia, creatinine increased, dehydration, hyperglycemia, hypernatremia, hyperuricemia, SGOT increased, SGPT increased, thirst.

Musculoskeletal system

Frequent: Arthritis, leg cramps, myalgia

Nervous system

Frequent: Agitation, ataxia, convulsion, stupor, tremor; **Infrequent:** Akathisia, apathy, coma, depersonalization, euphoria, hypertonia, libido decreased, myoclonus, neuralgia, paralysis.

Respiratory system

Frequent: Dyspnea; **Infrequent:** Apnea, epistaxis, hiccup

Skin and appendages

Frequent: Acne, alopecia, rash; **Infrequent:** Contact dermatitis, urticaria.

Special senses

Infrequent: Taste loss.

Urogenital system

Frequent: Albuminuria, cystitis, hematuria, metrorrhagia, urinary frequency **Infrequent:** Urinary urgency.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Xyrem® is classified as a Schedule III controlled substance by Federal law. The active ingredient, sodium oxybate or gamma hydroxybutyrate (GHB), is listed in the most restrictive schedule of the Controlled Substances Act (Schedule I). Thus, non-medical uses of sodium oxybate (Xyrem® or GHB) are classified under Schedule I.

Abuse, Dependence, and Tolerance

Abuse

See applicable directions for use under **HANDLING AND DISPOSAL** below. Although sodium oxybate (also known as GHB) has not been systematically studied in clinical trials for its potential for abuse, illicit use and abuse have been reported. Sodium oxybate is a psychoactive drug that produces a wide range of pharmacological effects. It is a sedative-hypnotic that produces dose and concentration dependent central nervous system effects in humans. The onset of effect is rapid, enhancing its desirability as a drug of abuse or misuse.

The rapid onset of sedation, coupled with the amnestic features of sodium oxybate, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary (assault victim) user.

GHB is abused in social settings primarily by young adults. GHB has some commonalties with ethanol over a limited dose range and some cross tolerance with ethanol has been reported as well. Cases of severe dependence and craving for GHB have been reported. Dependence is indicated by the use of increasingly large doses, increased frequency of use, and continued use despite adverse consequences. Some of the doses reported abused in the "rave" setting have been similar to the dose range studied for therapeutic treatment of cataplexy.

Hospital emergency department reports increased 100-fold from 1992 to 1999 (source: Substance Abuse Mental Health Services Administration, Drug Abuse Warning Network [DAWN]). Sixty percent of the ED reports involved individuals 25 years and younger. Numerous deaths have been reported, typically involving GHB in combination with alcohol and other drugs, including five in the DAWN system in which GHB was the only drug that could be identified.

Dependence

There have been case reports of dependence after illicit use of GHB at frequent repeated doses (18 to 250 g/d), in excess of the therapeutic dose range. In these cases, the signs and symptoms of abrupt discontinuation included an abstinence syndrome consisting of insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, and tachycardia. These symptoms generally abated in 3 to 14 days. The discontinuation effects of sodium oxybate have not been systematically evaluated in controlled clinical trials. An abstinence syndrome has not been reported in clinical investigations. Although the clinical trial experience with sodium oxybate in narcolepsy/cataplexy patients at therapeutic doses does not show clear evidence of a withdrawal syndrome, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time.

Tolerance

Tolerance to sodium oxybate has not been systematically studied in controlled clinical trials. Open-label, long-term (≥6 months) clinical trials did not demonstrate development of tolerance. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended Xyrem® dosage regimen. Clinical studies of sodium oxybate in the treatment of alcohol withdrawal suggest a potential cross-tolerance with alcohol. Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g. increase in size or frequency of dosing, drug-seeking behavior). Physicians should document the diagnosis and indication for Xyrem®, being alert to drug-seeking behavior and/or feigned cataplexy.

OVERDOSAGE

Human Experience

Information regarding overdose with sodium oxybate is derived from reports in the medical literature that describe symptoms and signs in individuals who have ingested the drug illicitly or for medically-unapproved purposes. In these circumstances the co-ingestion of other drugs and alcohol is common, and may influence the presentation and severity of clinical manifestations of overdose.

In clinical trials two cases of overdose with Xyrem® were reported. In the first case, an estimated dose of 150 grams, more than 15 times the maximum recommended dose, caused a patient to be unresponsive with brief periods of apnea and to be incontinent of urine and feces. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of Xyrem® and numerous other drugs.

Signs and Symptoms

Information about signs and symptoms associated with overdosage with sodium oxybate derives from reports of its illicit use. Patient presentation following overdose is influenced by the dose ingested, the time since ingestion, the co-ingestion of other drugs and alcohol, and the fed or fasted state. Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even when obtunded), diaphoresis, headache, and impaired psychomotor skills may be observed. No typical pupillary changes have been described to assist in diagnosis; pupillary reactivity to light is maintained. Blurred vision has been reported. An increasing depth of coma has been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported. Respiration may be unaffected or compromised in rate and depth. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact.

Recommended Treatment of Overdose

General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of

obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with sodium oxybate overdose has been responsive to atropine intravenous administration. No reversal of the central depressant effects of sodium oxybate can be expected from naloxone or flumazenil administration. The use of hemodialysis and other forms of extracorporeal drug removal have not been studied in GHB overdose. However, due to the rapid metabolism of sodium oxybate, these measures are not warranted.

Poison Control Center

As with the management of all cases of drug overdosage, the possibility of multiple drug ingestion should be considered. The physician is encouraged to collect urine and blood samples for routine toxicologic screening, and to consult with a regional poison control center (1-800-222-1222) for current treatment recommendations.

DOSAGE AND ADMINISTRATION

Xyrem® is required to be taken at bedtime while in bed and again 2.5-4 hours later. The recommended starting dose is 4.5 g/day divided into 2 equal doses of 2.25 grams. The starting dosage can then be increased to a maximum of 9 g/day in increments of 1.5 g/d (0.75 g per dose). Two weeks are recommended between dosage increases to evaluate clinical response and minimize adverse effects. Xyrem® is effective at doses of 6-9 g/day. The efficacy and safety of Xyrem® at doses higher than 9 g/day have not been investigated, and doses greater than 9 g/day ordinarily should not be administered.

Prepare both doses of Xyrem® prior to bedtime. Each dose of Xyrem® must be diluted with 2 ounces (60mL, ¼ cup, or 4 tablespoons) of water in the child resistant dosing cups provided prior to ingestion. The first dose is to be taken at bedtime while in bed and the second taken 2.5-4 hours later while sitting in bed. Patients will probably need to set an alarm to awaken for the second dose. The second dose must be prepared prior to ingesting the first dose, and should be placed in close proximity to the patient's bed. After ingesting each dose patients should then lie down and remain in bed.

Because food significantly reduces the bioavailability of sodium oxybate, the patient should try to eat well before (several hours) going to sleep and taking the first dose of sodium oxybate. Patients should try to minimize variability in the timing of dosing in relation to meals.

Hepatic Insufficiency

Patients with compromised liver function will have increased elimination half-life and systemic exposure along with reduced clearance (see Pharmacokinetics and Metabolism). As a result, the starting dose should be decreased by one-half and dose increments should be titrated to effect while closely monitoring potential adverse events.

Preparation and Administration Precautions

Each bottle of Xyrem® is provided with a child resistant cap and two dosing cups with child resistant caps.

Care should be taken to prevent access to this medication by children and pets.

See the Medication Guide for a complete description.

HOW SUPPLIED

Xyrem® (sodium oxybate) is a clear to slightly opalescent oral solution. It is supplied in kits containing one bottle of Xyrem®, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide, a professional insert, and two 90 mL dosing cups with child resistant caps. Each amber oval PET bottle contains 180 mL of Xyrem® oral solution at a concentration of 500 mg/mL and is sealed with a child resistant cap.

NDC 62161-008-20: Each tamper evident single unit carton contains one 180 mL bottle (500 mg/mL) of Xyrem®, one press-in-bottle-adaptor, one oral syringe, and two dosing cups with child resistant cap.

STORAGE

Store at 25°C (77°F); excursions permitted up to 15°-30°C (59°-86° F) [see USP Controlled Room Temperature].

Solutions prepared following dilution should be consumed within 24 hours to minimize bacteria growth and contamination.

HANDLING AND DISPOSAL

Xyrem® is a Schedule III drug under the Controlled Substances Act. Xyrem® should be handled according to state and federal regulations. It is safe to dispose of Xyrem® oral solution down the sanitary sewer.

Rx only

CAUTION

Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

Distributed By

Orphan Medical Inc.
Minnetonka, Minnesota 55305

For questions of a medical nature or to order Xyrem® call the Xyrem Success Program℠ at 1-877-67-XYREM℠ (877-679-9736)

US Patents Pending

Rev. May 2002
Part No.

File: xyrem/approval/21196draftlabel17julrev.doc

MEDICATION GUIDE

Xyrem® (ZÎE-rem) oral solution
(sodium oxybate)

It is very important that you carefully read and follow all instructions before using Xyrem®. Read this information carefully before you begin treatment. Read the information you get whenever you get refills. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment. Your doctor must instruct you in the safe and effective use of Xyrem®. If you have any questions about Xyrem®, ask your doctor or call the central pharmacy that sent you the medicine at the toll free number 1-877-67-XYREM℠ (1-877-679-9736). Do not throw away this Medication Guide. You may need to refer to it again later.

What is the most important information I should know about Xyrem®?

- Xyrem® is a Schedule III, federally controlled substance. This means that **if you sell, distribute, or give your Xyrem® to anyone else, or if you use your Xyrem® for purposes other than what it was prescribed for, you may be punished under federal and state law by jail and fines.** Your Xyrem® should be used only by you, as prescribed.
- It is critical to keep Xyrem® out of the reach of children.
- Xyrem® can cause serious side effects including trouble breathing while asleep, confusion, abnormal thinking, depression, and loss of consciousness. Tell your doctor if you have any of these problems while taking Xyrem®.
- The active ingredient in Xyrem® is gamma hydroxybutyrate (GHB), a chemical that has been abused (misused). Abuse can cause serious medical problems, including trouble breathing, seizures (convulsions), loss of consciousness, coma, and death. Abuse of Xyrem® could also lead to dependence, craving for the medicine, and severe withdrawal symptoms.
- Xyrem® causes sleep very quickly. Therefore, take Xyrem® only at bedtime and while in bed.
- Do not drive a car, operate heavy machinery, or perform any activity that is dangerous or that requires mental alertness for at least 6 hours after taking Xyrem®. When you first start taking Xyrem®,until you know whether it makes you sleepy the next day, use extreme care while driving a car, operating heavy machinery or doing anything else that could be dangerous or needs you to be fully mentally alert.
- You can get Xyrem® only by prescription. You must get it from one central pharmacy. Before you use Xyrem®, your doctor should teach you about the safe and effective use of this medicine. You cannot get the medicine until you have read the information the pharmacy will send you about Xyrem®.

What is Xyrem®?

Xyrem® is a brand of medicine used to reduce the number of cataplexy (weak or paralyzed muscles) attacks in patients with narcolepsy. Xyrem® is a controlled drug. This means anyone who misuses, sells, or distributes it may be prosecuted under federal and state law. You must not share it with anyone else.

Who should not take Xyrem®?

- Do not take Xyrem® if you
  - take other sleep medicines or sedatives (medicines that cause sleepiness),
  - have a rare condition called succinic semialdehyde dehydrogenase deficiency
- Tell your doctor if you
  - are pregnant or plan to become pregnant or are breastfeeding. It is not known whether Xyrem® can pass through your milk and harm the baby.
  - have had depression. You may be more likely to get depressed taking Xyrem®.
  - have liver problems. Your dose may need to be adjusted.
  - have sleep apnea, snoring, or breathing or lung problems. You may be more likely to get serious side effects.
  - are on a salt restricted diet, have high blood pressure, or heart failure. Xyrem® contains a lot of sodium (salt) and may not be right for you.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and supplements.

How should I take Xyrem®?

- Take Xyrem® exactly as prescribed by your doctor.
- Xyrem® works very fast. Take it only while in bed when you are ready to fall asleep.
- Take Xyrem® 2 times each night. Take the first dose right at bedtime and the second dose 2½ to 4 hours later. You will probably need to set an alarm clock to make sure you wake up to take the second dose. To get the most benefit from Xyrem®, it is important that you take both doses each night, exactly as prescribed by your doctor.
- Food will decrease the amount of Xyrem® that is absorbed by your body. Therefore, it is best to take Xyrem well after a meal (several hours).You need to take your second dose 2 ½-4 hours after that first dose. If you miss the second dose, skip that dose and do not take Xyrem® again until the next night. Never take 2 Xyrem® doses at once.
- **If you take more Xyrem® than prescribed or take it by accident, get emergency medical help right away**.
- To take Xyrem®, you must first mix it with water. **See "Directions for using Xyrem®" at the end of this Medication Guide for detailed information about taking Xyrem®.**
- Your doctor will want to see you often to check your response to Xyrem® therapy, including any side effects you may be experiencing.

What should I avoid while taking Xyrem®?

- Do not drive a car, operate heavy machinery, or perform any activity that is dangerous or that requires mental alertness for at least 6 hours after taking Xyrem®. When you first start taking Xyrem® or any other sleep medicine until you know whether the medicine will still have some carryover effect in you the next day, use extreme care while undertaking similar activities the next day..
- Do not drink alcohol or take sedatives. Alcohol and certain medicines can increase the chance of dangerous side effects. Tell your doctor about all the medicines you take including non-prescription medicines and supplements.

What are the possible side effects of Xyrem®?

- The most common side effects of Xyrem® are nausea, dizziness, headache, sleep problems, confusion, vomiting, and bed-wetting. **Tell your doctor** if you develop these less common but possibly serious side effects: sleepwalking (confused behavior during the night that may include walking around and doing other activities while not aware of what you are doing), increased sleepiness during the day, snoring, you stop breathing for a short time while you sleep (sleep apnea), breathing problems, depression, and abnormal thinking.

These are not all of the side effects of Xyrem®. If you are concerned about any possible side effects consult your doctor.

Effects of abusing (misusing) Xyrem (GHB)

- Some people who repeatedly abuse GHB become addicted to it. People who repeatedly abuse GHB can develop withdrawal symptoms. These symptoms include the need to continue taking the drug, anxiety, trouble sleeping, and abnormal thinking.

How should I store Xyrem®?

Always store Xyrem® in the original bottle in a safe and secure place (locked up if appropriate), out of the reach of children. Pour any unused Xyrem® down the drain. Destroy the drug name on the label with a marker. Place the empty bottle in the trash so it is not used for illegal purposes. **Always place your nightly doses of Xyrem® safely out of the reach of children.**

General advice about Xyrem®

Medicines are sometimes prescribed for purposes not mentioned in Medication Guides. Do not use Xyrem® for a condition for which it was not prescribed. Do not give Xyrem® to other people. It may harm them, and it is against the law. This Medication Guide summarizes the most important information about Xyrem®. If you want more information, talk with your doctor. You can ask your doctor for information about Xyrem® that is written for health professionals. Also, you can call the central pharmacy at the toll free number 1-877-67-XYREM℠ (1-877-679-9736).

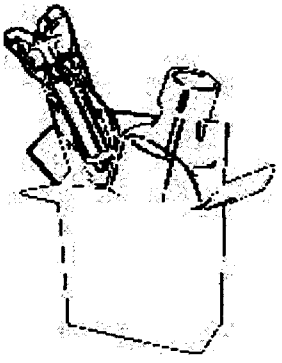
Directions for Using Xyrem®

CAUTION: Be very careful not to leave your Xyrem® in a place where children or pets can get to it.

The Xyrem® carton contains 1 bottle of medicine, 2 dosing cups with child-resistant caps, 1 liquid measuring device and printed product information.

Step 1

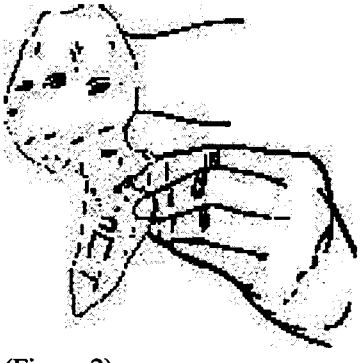
Remove the Xyrem® bottle and the measuring device from the box (See Figure 1).



(Figure 1)

Step 2

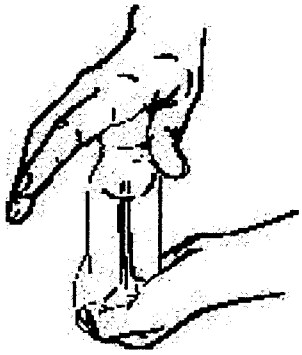
Remove the measuring device from the wrapper (See Figure 2).



(Figure 2)

Step 3

Remove the bottle cap by pushing down while turning the cap counterclockwise (to the left). (See Figure 3).

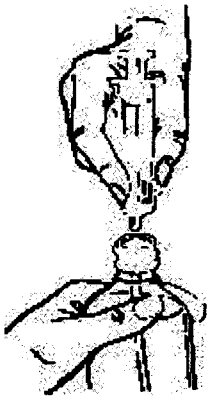


(Figure 3)

After removing the cap, set the bottle upright on a tabletop.

Step 4

While holding the bottle in its upright position, insert the tip of the measuring device into the center opening on top of the bottle and press down firmly (See Figure 4).

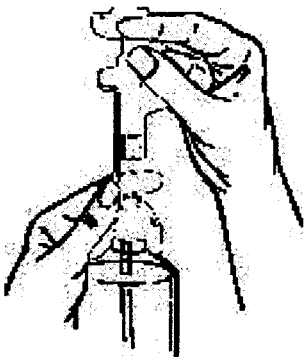


(Figure 4)

Step 5

While holding the bottle and measuring device down with one hand, draw up the prescribed dose with the other hand by pulling on the plunger.

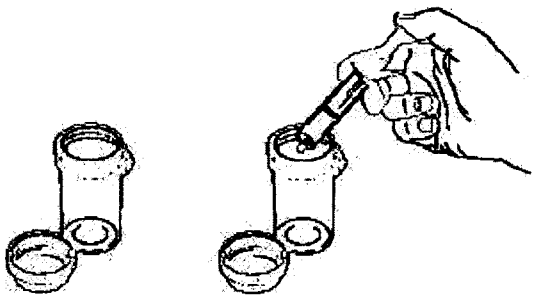
Note: Medicine will not flow into the measuring device unless you keep the bottle in its upright position (See Figure 5).



(Figure 5)

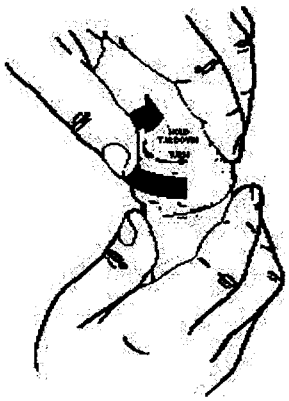
Step 6

Remove the measuring device from the center opening of the bottle. Empty the medicine from the measuring device into 1 of the dosing cups provided by pushing on the plunger, then add in 2 ounces (oz) of water to the cup. 2 oz is about 60 mL, 1/4 cup, or 4 tablespoons. (See Figure 6) Repeat this step for the second dosing cup.



(Figure 6)

Prepare both doses before bedtime. Place the caps provided on the dosing cups and turn the each cap clockwise (to the right) until it clicks and locks into its child resistant position. (See Figure 7.)



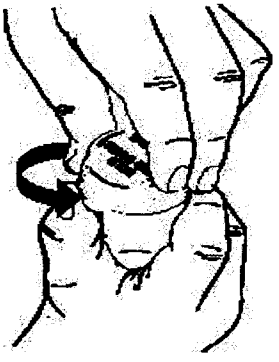
(Figure 7)

Recap the Xyrem® bottle and store it in a safe and secure place (locked up if appropriate), out of the reach of children. Rinse out the liquid measuring device with water.

Step 7

Right before going to sleep, place your second dose in a secure location (locked up if appropriate) near your bed. You may need to set an alarm so you wake up to take your second dose no earlier than 2 ½ hours and no later than 4 hours after your first dose.

Remove the cap from the first dosing cup by pressing down on the child resistant locking tab (See Figure 8) and turning the cap counterclockwise (to the left). Drink all of the first dose while sitting in bed, recap the cup, and then lie down right away. (See Figure 9).



(Figure 8)

(Figure 9)

Step 8

When you wake up 2½ to 4 hours later, remove the cap from the second dosing cup. While sitting in bed, drink all of the second dose right before lying down to continue sleeping. Recap the second cup.

Rx only NDC 62161-008-20

Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

Distributed By:
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Minnetonka, Minnesota 55305

For questions of a medical nature or to order Xyrem call the Xyrem Patient Success Program℠ at 1-877-67-XYREM℠ (1-877-679-9736).

US Patent Pending
Rev. May 2002
Part No. 542599

This medication guide has been approved by the US Food and Drug Administration.

File: Xyrem/approval/EdMedGuide17julrev.doc

Dear Doctor:

This letter is to inform you of the Xyrem® Post Marketing Evaluation Program, which is required as a condition of Xyrem's approval: *"Patients prescribed Xyrem® must be seen and evaluated by the prescriber with the issuance of every new prescription (every 3 months), at which time a detailed account of the patient's experience on treatment must be provided."* The Xyrem® Post Marketing Evaluation Program will provide data on the first 6 months of Xyrem® therapy for 1000 patients to the FDA.

To assist you in meeting this requirement, we enclose a supply of Xyrem® Post Marketing Evaluation forms that include an assessment of adverse events that may be observed in association with Xyrem® treatment. These forms should be completed at the 3 month and 6 month visits.. Completion of these forms is not required at the initiation of Xyrem® therapy. In addition to general adverse events, please query the patient specifically for reports of vomiting, incontinence, sleepwalking, confusion and convulsions. Elaboration of these events in the narrative portion of the evaluation form will allow us to clarify the nature of any relationship between these events and Xyrem® therapy. Please return the forms for each patient at month 3 and 6, respectively, even if there are no adverse events to report. In section 2 of the form, please describe any suspicions that Xyrem® may have been inappropriately used. Inappropriate use of Xyrem® could include, but is not necessarily limited to, the ingestion of excessive quantities by the patient, accidental or deliberate use by others in the patient's house or difficulty preparing the Xyrem® dose resulting in an uncertain quantity ingested. These forms should also be completed at any time an adverse event comes to your attention. Instructions for completing the forms are enclosed.

Additionally, we encourage you to report any adverse event, especially those serious in nature, to the FDA's Medwatch system (1-800-FDA-1088 or www.fda.gov/medwatch. If you have any queries about any aspect of the Xyrem® Post Marketing Evaluation Program please contact 1-XXX-XXX-XXXX.

We thank you in advance for your assistance in completing these forms.

Yours sincerely,

David Fuller, M.D.
Vice President of Medical Affairs
Orphan Medical

XYREM® POST MARKETING EVALUATION PROGRAM INSTRUCTIONS

Complete the enclosed form when each repeat Xyrem® prescription is written during the first 6 months of each patient's therapy, until the FDA requirements for data are met. Additionally, at any time during a patient's treatment with Xyrem®, we encourage you to report any adverse event, especially those serious in nature, to Orphan Medical, Inc., at 1-XXX-XXX-XXXX, and directly to the FDA's Medwatch system (1-800-FDA-1088 or www.fda.gov/medwatch).

A new Xyrem® prescription is required at least every 3 months. You will need to complete a Xyrem® Post-Marketing Evaluation Program form at the 3 month and 6 month visits. Completion of these forms is not required at the initiation of Xyrem® therapy.

Complete the form by printing legibly using black or blue ink.

Adverse Events

Ask the patient if they have experienced any of the following symptoms since the last visit, or over the last 3 months: vomiting, incontinence, sleepwalking, confusion, and convulsions. Elicit any other side effects not mentioned in this list. If the patient does not report any adverse events, complete the other parts of the form and return.

Use precise medical terminology when describing events (e.g., fatigue, not wiped-out).

Enter only one adverse event per line — for example nausea and vomiting should be entered on two separate lines as 1) nausea and 2) vomiting.

If more than 5 adverse events are reported, please use a separate form. For each of the adverse events listed, provide a brief narrative summary. Events that qualified as 'serious' (i.e., death; a life-threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; a congenital anomaly/birth defect; note that important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when they may jeopardize the patient and require medical or surgical intervention to prevent one of the outcomes listed previously) should be described in as much detail as possible.

Inappropriate use of Xyrem®

Examples of items that may need to be noted in this section are as follows:

- Premature requests for refills
- Requests for refills to make up for reportedly lost or stolen Xyrem® supplies
- Requests for adjustments in dose that are not appropriate for patient symptoms
- Use of Xyrem® at a frequency greater than the recommended two nightly doses
- Difficulty preparing the Xyrem® dose resulting in an uncertain quantity ingested

Finally, please ensure that all sections are completed, including your contact details and then return this form in the postage paid envelopes provided or fax to 1- XXX- XXX- XXXX. Enclosed are enough forms for at least 5 patients. You may photocopy blank forms or request additional forms and pre-paid envelopes by calling Orphan Medical at 1-XXX-XXX-XXXX.

Orphan Medical thanks you for your cooperation. You will be notified when this assessment is no longer required.

Outline of Xyrem® Post-Marketing Evaluation Program

Introduction & Rationale

In the approvable letter to Orphan Medical of 6th July 2001, the FDA made the following statement as a condition of approval of Xyrem®: "Patients must be seen and evaluated by the prescriber with the issuance of every 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 Orphan Medical every 3 months initially with the longer term reporting requirements to be negotiated with the Agency".

In particular, the FDA is interested in continued surveillance for reports of vomiting, incontinence, sleepwalking, confusion or convulsions that have been observed in association with Xyrem® treatment. The FDA also wishes to be informed of any evidence of inappropriate use of Xyrem® including ingestion of excessive quantities by the patient, accidental or deliberate use by others in the patient's household or difficulty preparing the Xyrem® dose resulting in an uncertain quantity ingested.

In order to satisfy this requirement, an outline of this program is provided below.

Target Exposure

It is intended that the Xyrem® Post-Marketing Evaluation Program will capture safety data resulting from the first 6 months of treatment for 1000 patients to be prescribed Xyrem®.

Parties Involved & Responsibilities

Party	Responsibilities
Orphan Medical	• overall program management • ongoing review & assessment of data produced • submission of reports to FDA
Physicians	• regular review of patients, completion of Post-Marketing Patient Evaluation forms: minimum 2 per patient (3 & 6 months)
Contract Research Organization	• data management and production of summary tables & reports
FDA	• review of safety data

Materials provided to Physicians

The materials to be used in the Xyrem® Post-Marketing Evaluation Program include:

- Letter to all Xyrem® prescribers
- Xyrem® Post-Marketing Evaluation form
- Instructions for competing the forms
- Pre-paid reply envelopes (and fax number)

Physician Notification

To support compliance with the Xyrem® Post-Marketing Evaluation Program, all prescribers will be notified of this program. The primary method for informing prescribers of this program, their obligations and providing them with Post-Marketing Evaluation Program materials, will be the Xyrem Physician Success Program℠. **All** prescribers will receive the Xyrem Success Program℠ folder prior to writing Xyrem® prescriptions.

The Xyrem® Post-Marketing Evaluation Program materials will be provided as a separate section within the Success Program folder. Materials sufficient for at least 5 patients completing 6 months will be provided to each physician. Specific reference to the Xyrem® Post-Marketing Evaluation Program is also made in the cover letter to the Physician Success Program under Physician Responsibilities and Requirements.

Additional Post-Marketing Evaluation Program forms will be available from Orphan Medical and may be mailed to prescribers identified by the Central Pharmacy as having greater than 5 patients on Xyrem®. These forms may also be copied.

Data Collection Process

- Following the initial Xyrem® prescription, patients must be seen by their physicians at least every 3 months
- At each visit after the initial prescription, prescribers are required to complete a Xyrem® Post-Marketing Evaluation Program form which includes assessment of:

    - Adverse events, in particular, if the patient has " experienced any of the following adverse events, in particular, new onset of vomiting, incontinence, sleepwalking, confusion or convulsions since the last visit."
    - Evidence of inappropriate use

- Physicians are required to complete the forms and either mail or fax them to Orphan Medical (or a contracted data management organization)
- Completed forms will be logged, queried (where appropriate) and the information transferred to a computer database.

Report Date:

Month Day Year

Xyrem® Post-Marketing Evaluation

Serial No.

Patient Infor

Gender (✓ one ale ☐ Female

Initials:

F M L

Date of Birth:

Month Day Year

Weight: ☐ lb ☐ kg

List of pre-existing and co-existing medical conditions:

	Yes	No
Vomiting	☐	☐
Incontinence	☐	☐
alking	☐	☐
Confusion	☐	☐
Convulsions	☐	☐

Other:

Xyrem® Oral Solution:
Total nightly dose:

_____ gm.
_____ mL } **RECORD BOTH**

Lot # (If known):

____

Xyrem® Therapy Start Date:
(If unknown, give estimate)

Month Day Year

Expiration Date (If known):

Month Day Year

SECTION 1

Has the patient experienced any of the following symptoms since the last visit, and/or over the last 3 months: **vomiting, incontinence, sleepwalking, confusion** or **convulsions**. If the patient has experienced these or **any other** medical events or symptoms, please list them in the following table. Please also describe these events in A brief narrative in the space provided on page 2.

☐ Check if none.

Adverse Event *(Diagnosis or syndrome if known or signs/symptoms)*	**Is Event Serious?** *(See criteria below)* Yes	No	**Date of Onset** Day/Month/Year	**Time of Onset** 24-Hour Clock	**Stop Date** Day/Month/Year	**Nightly Dosage at Onset (Record both grams AND mls)** gm.	mL	Event abated after drug stopped or dose reduced Yes	No	Event reappeared after reintroduction Yes	No	**Frequency** 01=Isolated 02=Moderate 03=Continuous	**Severity** 01=Mild 02=Moderate 03=Severe	**Action Taken with Xyrem®** 01=No Change 02=Permanent Discontinuation 03=Temporarily Stopped 04=Dose Reduced
	☐	☐	___/___/___	☐☐:☐☐	___/___/___	___	___	☐	☐	☐	☐			
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	☐	☐	___/___/___	☐☐:☐☐	___/___/___	___	___	☐	☐	☐	☐			

IF *YES*, PLEASE INDICATE WHICH CRITERIA APPLY.

Serious Adverse Event Reporting Information: *All **SERIOUS** and **UNEXPECTED** events must be reported.* Call the Medical monitor at Orphan Medical at **888-867-7426** within 24 hours for **any** Adverse Event resulting in the following outcomes:

- ☐ Death
- ☐ Inpatient hospitalization or prolongation of existing hospitalization
- ☐ A congenital anomaly/birth defect
- ☐ A life-threatening adverse drug experience
- ☐ A persistent or significant disability/incapacity
- ☐ Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when they may jeopardize the patient and require medical or surgical intervention to prevent one of the outcomes listed previously.

If patient discontinued please state reason for discontinuation:

____

____

If stopped, date: _______________________

Month Day Year

Name/Address or Reporter: (please Print) ____

____

____

Phone number: (   )   -   **Ext.:** ____________

Signature: ____

– Please also complete reverse side of page. –
(When faxing, please include both sides.)

Report Date: ☐☐ Month ☐☐ Day ☐☐☐☐ Year

Xyrem® Post-Marketing Evaluation *(Continued)*

Serial No.

SECTION 2

Patient Initials: ☐☐☐ F M L

Continued narrative for AE's reported on page 1.

Please provide a brief narrative describing the adverse events listed earlier in this form. Use additional sheets if necessary.

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Evidence of Inappropriate Drug Use

Please indicate in this section whether there is any evidence that your patient may have used Xyrem® inappropriately such as premature requests for refills, reports of "theft or loss of the medication, or difficulty in using or preparing Xyrem® as prescribed.

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☐☐ ☐☐ ☐☐☐☐ *y.)*

Manufacturer report number: ____________________

Date rec'd by manufacturer: MONTH DAY YEAR

SECTION 3

CONCOMITANT MEDICATIONS

Medication *(Generic names preferred; use trade name for combination drugs)*	Indication	Dates Month/Day/Year	
________	________	Start Date	☐☐ ☐☐ ☐☐☐☐
		Stop Date	☐☐ ☐☐ ☐☐☐☐
________	________	Start Date	☐☐ ☐☐ ☐☐☐☐
		Stop Date	☐☐ ☐☐ ☐☐☐☐
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		Stop Date	☐☐ ☐☐ ☐☐☐☐
________	________	Start Date	☐☐ ☐☐ ☐☐☐☐
		Stop Date	☐☐ ☐☐ ☐☐☐☐

Report Type: ☐ Initial ☐ 15-day ☐ Periodic ☐ Follow-up # _____	

(When faxing, please include both sides.)

Dear Doctor:

I'd like to take this opportunity to introduce you to Xyrem® (sodium oxybate) oral solution and the Xyrem Success Program℠.

Xyrem is indicated for the treatment of cataplexy in patients with narcolepsy. The active ingredient in Xyrem, sodium oxybate, is the sodium salt of gamma hydroxybutyrate (GHB). The use of non-prescription GHB has been associated with a number of serious central nervous system adverse clinical events, including seizures, respiratory depression, decreases in level of consciousness, confusion, and psychotic events. Because of these events, Xyrem is approved for marketing under a restricted distribution program in agreement with the Food & Drug Administration. This program is called the Xyrem Success Program℠.

Under this program, both you and your patients have specific responsibilities and requirements that must be met before a prescription for Xyrem can be written or filled. These requirements are listed below:

Patient Responsibilities and Requirements

- One central pharmacy will distribute Xyrem directly to your patient(s) who must be part of a registry, which will be maintained at the pharmacy.
- Patients must be advised of, and comply with the requirements of this program in order to receive product.
- Each patient for whom you prescribe Xyrem must be seen and evaluated by you every 3 months. Prescriptions for Xyrem® must be rewritten at least every 3 months.

Physician Responsibilities and Requirements

- Xyrem prescriptions must be written on the enclosed special prescription forms. This form must be filled out completely before the central pharmacy can dispense the initial prescription.
- The required starting dose is 4.5 grams, with titration, if necessary, up to 9 grams.
- Prior to your very first Xyrem prescription being filled, you must confirm the following: 1) that you have read the enclosed materials; 2) that you understand Xyrem is approved for the treatment of cataplexy in patients with narcolepsy; and 3) that you have provided Xyrem dosing, preparation and administration counseling to your patient.
- It is also important for you to know that, just like any other pharmacy that dispenses controlled substances, the central pharmacy will be maintaining records about who is prescribing Xyrem. These records must be available to any state or federal agency that requests them.
- A new prescription must be written every three months. This requirement may change in the future and you will be notified accordingly.
- You must participate in the Xyrem® Post-Marketing Evaluation Program as described below.

Xyrem Post-Marketing Evaluation Program

- At each visit subsequent to the initial prescription visit, you are requested 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 you in this assessment, evaluation forms are included in these materials. This evaluation form should be completed at month 3 and month 6 of a patient's course of therapy. It is of utmost importance that you fill out this form as completely as possible. Please refer to the enclosed instruction sheet and/or contact Orphan Medical at 1-XXX-XXX-XXXX if you have any questions. You will be notified when this assessment is no longer required.

The enclosed materials in this binder provide specific details about all of the above requirements as well as important information about the dosing, preparation and administration, and use of Xyrem. The materials also provide you with information to help your patient(s) successfully obtain and use Xyrem.

Orphan Medical, the company that brings you Xyrem, is Dedicated to Patients with Uncommon Diseases®. If you require any additional assistance, please call the Xyrem Physician Success Program℠ at 1-877-67 XYREM℠ (1-877-679-9736).

Sincerely,

David Fuller, M.D.
Vice President of Medical Affairs
Orphan Medical Inc.

Please see full prescribing information for Xyrem® (sodium oxybate) oral solution.