R_x only

Xyrem® (sodium oxybate) oral solution

CIII

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

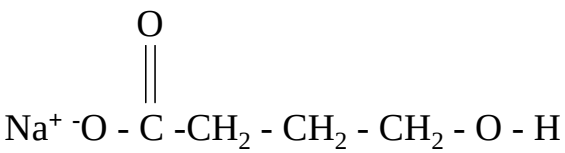
Sodium oxybate is GHB, a known drug of abuse. Abuse has been associated with some important central nervous system (CNS) adverse events (including death). Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Reports of respiratory depression occurred in clinical trials. Almost all of the patients who received sodium oxybate during clinical trials were receiving CNS stimulants.

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).

Xyrem is available through the Xyrem Success Program, using a centralized pharmacy 1-866-XYREM88® (1-866-997-3688). The Success Program provides educational materials to the prescriber and the patient explaining the risks and proper use of sodium oxybate, and the required prescription form. Once it is documented that the patient has read and/or understood the materials, the drug will be shipped to the patient. The Xyrem Success Program also recommends patient follow-up every 3 months. Physicians are expected to report all serious adverse events to the manufacturer. (See WARNINGS).

DESCRIPTION

Xyrem (sodium oxybate) is a central nervous system depressant that reduces excessive daytime sleepiness and cataplexy 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 to 1 hour. Pharmacokinetics are nonlinear with blood levels increasing 3.7-fold as dose is doubled from 4.5 to 9 grams (g). 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 (1^{st} and 2^{nd} peak) following administration of a 9 g daily dose divided into two equivalent doses given four hours apart were 78 and 142 micrograms/milliliter (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 g 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 mcg/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 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 g.

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. Alteration of gastric pH with omeprazole produced no significant change in the oxybate kinetics.

CLINICAL TRIALS

Cataplexy

The effectiveness of sodium oxybate in the treatment of cataplexy was established in two 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 g, with the daily dose divided into two 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 3 g/night, sodium oxybate 6 g/night, or sodium oxybate 9 g/night.

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 Trials 1 and 2 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/week)	
Placebo (33)	20.5	-4	—
6.0 g/night (31)	23.0	-10	0.0451
9.0 g/night (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 g/night and 9 g/night doses gave statistically significant reductions in the frequency of cataplexy attacks. The 3 g/night 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 to 9 g/night, but there was no effect seen in patients treated with doses less than 6 g/night, suggesting little effect at these doses.

Excessive Daytime Sleepiness

The effectiveness of sodium oxybate in the treatment of excessive daytime sleepiness in narcolepsy was established in two randomized, double-blind, placebo-controlled trials (Trials 3 and 4) in patients with narcolepsy. Seventy-eight percent of patients in Trial 3 were also being treated with CNS stimulants.

Trial 3 was a multi-center randomized, double-blind, placebo-controlled, parallel-arm trial that evaluated 228 patients with moderate to severe symptoms at entry into the study including a median Epworth Sleepiness Scale (see below) score of 18, and Maintenance of Wakefulness Test (see below) score of 8.25 minutes. These patients were randomized to one of 4 treatment groups: placebo; sodium oxybate 4.5 g/night; sodium oxybate 6 g/night; and sodium oxybate 9 g/night. The period of double-blind treatment in this trial was 8 weeks. Antidepressants were withdrawn prior to randomization; stimulants were continued at stable doses.

The primary efficacy measures in Trial 3 were the Epworth Sleepiness Scale and the Clinical Global Impression of Change. The Epworth Sleepiness Scale is intended to evaluate the extent of sleepiness in everyday situations by asking the patient a series of questions. In these questions, patients are asked to rate their chances of dozing during each of 8 activities on a scale from 0-3 (0=never; 1=slight; 2=moderate; 3=high). Higher total scores indicate a greater tendency to sleepiness. The Clinical Global Impression of Change is a 7-point scale, centered at *No Change*, and ranging from *Very Much Worse* to *Very Much Improved* . In Trial 3, patients were rated by evaluators who based their assessments on the severity of narcolepsy at baseline.

Trial 4 was a multi-center randomized, double-blind, double-dummy placebo-controlled, parallel-arm trial that evaluated 222 patients with moderate to severe symptoms at entry into the study including a median Epworth Sleepiness Scale score of 15, and Maintenance of Wakefulness Test (see below) score of 10.25 minutes. At entry, patients had to be taking modafinil for ≥ 1 month and at stable doses of 200, 400, or 600 mg daily for at least 1 month prior to randomization. The patients enrolled in the study were randomized to one of 4 treatment groups: placebo; sodium oxybate; modafinil; and sodium oxybate plus modafinil. Sodium oxybate was administered in a dose of 6 g/night for 4 weeks, followed by 9 g/night for 4 weeks. Modafinil was continued at the prior dose. Patients taking antidepressants could continue these medications at stable doses.

The only primary efficacy measure in Trial 4 was the Maintenance of Wakefulness Test. The Maintenance of Wakefulness Test measures latency (in minutes) to sleep onset averaged over 4 sessions at 2 hour intervals following nocturnal polysomnography. For each test session, the subject is asked to remain awake without using extraordinary measures. Each test session is terminated after 20 minutes if no sleep occurs, or after 10 minutes, if sleep occurs. The overall score is the mean sleep latency for the 4 sessions.

In Trial 3, statistically significant improvements were seen on the Epworth Sleepiness Scale and on the Clinical Global Impression of Change at the 6 g/night and 9 g/night doses of sodium oxybate.

Table 2
Daytime Sleepiness in Trial 3

Epworth Sleepiness Scale (Range 0-24)				
Dose Group [g/night (n)]	Baseline	Endpoint	Median Change from Baseline	Change from Baseline Compared to Placebo **(p-value)**
Placebo (59)	17.5	17.0	-0.5	-
6 (58)	19.0	16.0	-2.0	< **0.001**
9 (47)	19.0	12.0	-5.0	< **0.001**

Table 3

Clinical Global Impression of Change in Day and Nighttime Symptoms (Responder Analysis) in Trial 3

Dose Group [g/night (n)]	Percent Responders (Very Much Improved or Much Improved)	Significance Compared to Placebo (p-value)
		Change from Baseline
Placebo (59)	22%	-
6 (58)	52%	**<0.001**
9 (47)	64%	**<0.001**

In Trial 4, a statistically significant improvement on the Maintenance of Wakefulness Test score was seen in the sodium oxybate and sodium oxybate plus modafinil groups.

Table 4
Daytime Sleepiness as Evaluated in Trial 4

Maintenance of Wakefulness Test (minutes)				
Dose Group (n)	Baseline	Endpoint	Mean Change from Baseline	Endpoint Compared to Placebo
Placebo (55)	9.7	6.9	-2.7	-
Sodium Oxybate (50)	11.3	12.0	0.6	**<0.001**
Sodium Oxybate plus Modafinil (54)	10.4	13.2	2.7	<0.001

This trial was not capable by design of comparing the effects of sodium oxybate to modafinil, because patients receiving modafinil were not titrated to a maximally effective dose.

INDICATIONS AND USAGE

Xyrem (sodium oxybate) oral solution is indicated for the treatment of excessive daytime sleepiness and 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 performing any 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 two subjects had profound CNS depression. A 39 year-old woman, a healthy volunteer received a single 4.5 g 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 4.5 g/night. 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. In the randomized controlled Trials 3 and 4, a total of 40 narcolepsy patients were included with a baseline apnea/hypopnea index of 16 to 67 events per hour

indicative of mild to severe sleep disordered breathing. None of the 40 patients had a clinically significant worsening of their respiratory function as measured by apnea/hypopnea index and pulse oximetry while receiving sodium oxybate at dosages of 4.5 to 9 g/night in divided dosages. Nevertheless, 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, 2.6% 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 to 9 g/night. In a controlled trial where patients were randomized to fixed total daily doses of 3, 6, and 9 g/night or placebo, a dose-response relationship for confusion was demonstrated with 17% of patients at 9 g/night experiencing confusion. In all cases in that controlled trial, the confusion resolved soon after termination of treatment. In Trial 3 where sodium oxybate was titrated from an initial 4.5 g/night dose, there was a single event of confusion in one patient at the 9 g/night dose. In the majority of cases in all clinical trials, confusion resolved either soon after termination of dosing or 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, 3.2% of patients treated with sodium oxybate reported depressive symptoms. In the majority of cases, no change in sodium oxybate treatment was required. Four patients (<1%) discontinued because of depressive symptoms. In the controlled clinical trial where patients were randomized to fixed doses of 3, 6, 9 g/night or placebo, there was a single event of depression at the 3 g/night dose. In Trial 3, where patients were titrated from an initial 4.5 g/night starting dose, the incidence of depression was 1 (1.7%), 1 (1.5%), 2 (3.2%), and 2 (3.6%) for the placebo, 4.5g, 6 g, and 9 g/night doses respectively.

In the 717 patient dataset, there were two suicides and one attempted suicide recorded in patients with a previous history of depressive psychiatric disorder. Of the two 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, 7% 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 9 g/night or placebo, a dose-response relationship for urinary incontinence was demonstrated with 14% of patients initiated at 9 g/night experiencing urinary incontinence. In the same trial, one patient experienced fecal incontinence when initiated at a dose of 9 g/night 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 4% of 717 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 in that trial 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 is provided below and should be considered in patients with heart failure, hypertension or compromised renal function.

Table 5
Sodium Content per Total Nightly Dose

Xyrem Dose (g)	Xyrem (mL)	Sodium Content/Dose
3	6	546 mg
4.5	9	819 mg
6	12	1092 mg
7.5	15	1365 mg
9	18	1638 mg

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® 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 read and/or understand the materials before initiating therapy. Prescribers will discuss dosing (including the procedure for preparing the dose to be administered) prior to the initiation of treatment. Patients should also be informed that they should be seen by the prescriber frequently during the course of their treatment to review dose titration, symptom response and adverse reactions. 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. As a safety precaution, 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 to 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 one patient was clearly diagnosed with rheumatoid arthritis at the time of the first recorded positive ANA test. No instances of systemic lupus erythematosus have been reported in patients taking sodium oxybate.

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). However, pharmacodynamic interactions cannot be ruled out. Nonetheless, sodium oxybate should not be used in combination with sedative hypnotics or other CNS depressants. Alteration of gastric pH with omeprazole produced no significant change in the oxybate kinetics.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Sodium oxybate was not carcinogenic in rats administered oral doses of up to 1000 mg/kg/day (2 times the exposure in humans receiving the maximum recommended dose (MRHD) of 9 g/day, on an AUC basis) for 83 weeks in the male rats and for 104 weeks in female rats. The results of 2-year carcinogenicity studies in mouse and rat with gamma-butyrolactone, a compound that is metabolized to sodium oxybate *in vivo*, showed no clear evidence of carcinogenic activity. The plasma AUCs of sodium oxybate achieved at the high doses in these studies were 1/2 (mice and female rats) and 1/10 (male rats) the plasma AUCs at the MRHD.

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 717 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 (22%), nausea (21%), dizziness (17%), nasopharyngitis (8%), somnolence (8%) vomiting (8%), and urinary incontinence (7%).

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.

In these clinical trials, **10**% of patients discontinued because of adverse events. **The most frequent reasons for discontinuation (>1%) were nausea (2%), dizziness (2%) and vomiting (1%).**

Approximately 9% of patients receiving sodium oxybate in 5 placebo-controlled clinical trials (n=443) withdrew due to an adverse event, compared to 1% receiving placebo (n=79). The reasons for discontinuation that occurred more frequently in sodium oxybate-treated patients than placebo-treated patients were: nausea (2%), dizziness (2%) vomiting (1%); as well as urinary incontinence, confusional state, dyspnea, hypesthesia, paresthesia, somnolence, tremor, vertigo, and blurred vision, all occurring in <1% of patients.

Incidence in Controlled Clinical Trials

Most Commonly Reported Adverse Events in Controlled Clinical Trials

The most commonly reported adverse events (≥ 5%) in placebo controlled clinical trials associated with the use of sodium oxybate and occurring more frequently than seen in placebo-treated patients were: nausea (19%), dizziness (18%), headache (18%), vomiting (8%), somnolence (6%), urinary incontinence (6%), and nasopharyngitis (6%). These incidences are based on combined data from Trial 1, Trial 2, Trial 3, and two smaller randomized, double-blind, placebo-controlled, cross-over trials (n=655).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating incidence rates.

The data presented below come from two placebo-controlled clinical trials, Trial 1 and Trial 3.

Tables 6 and 7 list the incidence of treatment-emergent adverse events in Trials 1 and 3, respectively, for which there was an incidence of ≥ 5% and the incidence in at least one dosage group on sodium oxybate was greater than placebo. The number of patients in each dosage group represents the total number of patients treated at each dose. Treatment was initiated at assigned doses of 3, 6, and 9 g in Trial 1.

Table 6
Incidence (%) of Treatment-Emergent Adverse Events in Trial 1

System Organ Class	Placebo	Sodium Oxybate Dosage (g/night) at Onset		
MedDRA Preferred Term	N = 34	3 N = 34	6 N = 33	9 N = 35
Ear and labyrinth disorders				
Tinnitus	0	2 (5.9%)	0	0
Eye disorders				
Vision blurred	1 (2.9%)	2 (5.9%)	0	0
Gastrointestinal disorders				
Abdominal Pain Upper	0	0	1 (3.0%)	4 (11.4%)
Diarrhea	0	0	2 (6.1%)	3 (8.6%)
Dyspepsia	2 (5.9%)	1 (2.9%)	3 (9.1%)	3 (8.6%)
Nausea	2 (5.9%)	3 (8.8%)	8 (24.2%)	14 (40.0%)
Vomiting	0	0	3 (9.1%)	8 (22.9%)
General disorders and administration site conditions				
Feeling Drunk	0	0	0	3 (8.6%)
Lethargy	0	2 (5.9%)	0	0
Pain	1 (2.9%)	1 (2.9%)	1 (3.0%)	2 (5.7%)
Infections and infestations				
Gastroenteritis viral	0	0	2 (6.1%)	0
Nasopharyngitis	1 (2.9%)	1 (2.9%)	2 (6.1%)	2 (5.7%)
Upper respiratory tract infection	1 (2.9%)	1 (2.9%)	2 (6.1%)	0
Injury, poisoning and procedural complications				
Post procedural pain	0	0	0	2 (5.7%)
Investigations				
Blood pressure increased	1 (2.9%)	0	2 (6.1%)	0
Musculoskeletal and connective tissue disorders				
Back Pain	2 (5.9%)	0	2 (6.1%)	2 (5.7%)
Cataplexy	0	0	0	3 (8.6%)
Muscular weakness	0	2 (5.9%)	1 (3.0%)	0

Nervous system disorders				
Disturbance in attention	0	1 (2.9%)	0	3 (8.6%)
Dizziness	2 (5.9%)	8 (23.5%)	10 (30.3%)	13 (37.1%)
Headache	8 (23.5%)	3 (8.8%)	7 (21.2%)	13 (37.1%)
Hypoaesthesia	0	2 (5.9%)	0	0
Sleep Paralysis	1 (2.9%)	1 (2.9%)	2 (6.1%)	5 (14.3%)
Somnolence	3 (8.8%)	4 (11.8%)	4 (12.1%)	5 (14.3%)
Psychiatric disorders				
Confusional state	0	2 (5.9%)	1 (3.0%)	2 (5.7%)
Depression	0	2 (5.9%)	0	0
Disorientation	1 (2.9%)	1 (2.9%)	0	3 (8.6%)
Nightmare	0	1 (2.9%)	2 (6.1%)	0
Sleep disorder	0	0	2 (6.1%)	1 (2.9%)
Sleep walking	0	0	0	2 (5.7%)
Renal and urinary disorders				
Enuresis	0	0	1 (3.0%)	6 (17.1%)
Respiratory, thoracic and mediastinal disorders				
Pharyngolaryngeal pain	2 (5.9%)	0	3 (9.1%)	1 (2.9%)
Skin and subcutaneous tissue disorders				
Hyperhidrosis	0	1 (2.9%)	1 (3.0%)	2 (5.7%)

Table 7
Incidence (%) of Treatment-Emergent Adverse Events in Trial 3 where dose titration from 4.5 to 9 grams occurred in weekly intervals

System Organ Class	**Placebo**	**Sodium Oxybate Dosage (g/night) at Onset**		
MedDRA Preferred Term	**N = 60**	**4.5 N = 185**	**6 N = 114**	**9 N = 46**
Gastrointestinal disorders				
Nausea	2 (3.3%)	14 (7.6%)	12 (10.5%)	9 (19.6%)
Vomiting	1 (1.7%)	3 (1.6%)	4 (3.5%)	4 (8.7%)
Nervous system disorders				
Disturbance in Attention	0	2 (1.1%)	0	3 (6.5%)
Dizziness	1 (1.7%)	17 (9.2%)	9 (7.9%)	4 (8.7%)
Somnolence	0	2 (1.1%)	0	5 (10.9%)
Renal and urinary disorders				
Enuresis	1 (1.7%)	6 (3.2%)	4 (3.5%)	6 (13.0%)

Dose Response Information

Discontinuations of treatment due to adverse events were most common at the highest dose of sodium oxybate. A dose-response relationship was observed for nausea, vomiting, paresthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking and enuresis. The incidence of all these events was notably higher at 9 g/d. Dizziness was most common at 3 and 9 g/night.

Less Common Adverse Events

During clinical trials sodium oxybate was administered to 717 patients with narcolepsy, and 182 healthy volunteers. A total of 283 patients and 25 healthy volunteers received 9 g/night, the maximum recommended dose. A total of 334 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 to 1/1000 people). These events are not necessarily related to sodium oxybate treatment.

Blood and lymphatic system disorders

Frequent: none; **Infrequent:** leukopenia, lymphadenopathy.

Cardiac disorders

Frequent: none; **Infrequent:** tachycardia.

Ear and labyrinth disorders

Frequent: ear pain, vertigo; **Infrequent:** ear discomfort**,** tinnitus.

Eye disorders

Frequent: vision blurred; **Infrequent:** conjunctivitis, eye irritation, eye pain, eye redness, eye swelling, keratoconjunctivitis sicca, miosis.

Gastrointestinal disorders

Frequent: constipation, dyspepsia, toothache; **Infrequent:** abdominal distension, dysphagia, eructation, fecal incontinence, flatulence, gastroesophageal reflux disease, oral pain, retching, salivary hypersecretion, stomach discomfort.

General disorders and administration site conditions

Frequent: asthenia, chest pain, fatigue, influenza like illness, malaise, pyrexia; **Infrequent:** chest discomfort, discomfort, edema, feeling abnormal, feeling cold, feeling hot, feeling hot and cold, feeling jittery, gait abnormal, hangover, lethargy, sensation of foreign body, sluggishness.

Immune system disorders

Frequent: none; **Infrequent:** hypersensitivity, multiple allergies.

Infections and infestations

Frequent: bronchitis, gastroenteritis viral, influenza, nasopharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection; **Infrequent:** bladder infection, bronchial infection, cellulitis, dental caries, ear infection, fungal infection, gastroenteritis, herpes simplex, herpes zoster, laryngitis, localized infection, otitis externa, pharyngitis, pneumonia, tinea pedis, tooth abscess, tooth infection, vaginal infection, vaginal mycosis.

Injury, poisoning and procedural complications

Frequent: contusion, fall, pain trauma activated; **Infrequent:** ankle fracture, back injury, concussion, head injury, joint sprain, limb injury, muscle strain, post procedural pain, road traffic accident, skin laceration, tooth injury.

Investigations

Frequent: weight decreased; **Infrequent:** alanine aminotransferase increased, blood alkaline phosphatase increased, blood calcium decreased, blood cholesterol increased, blood glucose increased, blood uric acid increased, blood urine, electrocardiogram abnormal, heart rate increased, liver function test abnormal, protein urine, respiratory rate increased, urine analysis abnormal.

Metabolism and nutrition disorders

Frequent: anorexia; **Infrequent:** decreased appetite, hypernatremia, hypocalcemia, increased appetite.

Musculoskeletal and connective tissue disorders

Frequent: arthralgia, back pain, myalgia, neck pain; **Infrequent:** arthritis, chest wall pain, joint stiffness, joint swelling, muscle tightness, muscle twitching, muscular weakness, musculoskeletal discomfort, musculoskeletal stiffness, polyarthritis, sensation of heaviness, tendonitis.

Neoplasms benign, malignant and unspecified

Frequent: none; **Infrequent:** cyst.

Nervous system disorders

Frequent: balance disorder, headache, hypoesthesia, memory impairment; **Infrequent:** coordination abnormal, depressed level of consciousness, dizziness postural, dysarthria, dysgeusia, dyskinesia, dysstasia, head discomfort, hyperaesthesia, mental impairment, migraine, myoclonus, paralysis, psychomotor hyperactivity, restless leg syndrome, sedation, sinus headache, sleep talking, sudden onset of sleep, syncope, tension headache.

Psychiatric disorders

Frequent: abnormal dreams, confusional state, depression, insomnia, nervousness, nightmare, sleep disorder; **Infrequent:** affect lability, crying, emotional disorder, euphoric mood, fear, hallucination-auditory, hypnagogic hallucination, initial insomnia, libido increased, middle insomnia, mood altered, panic disorder, paranoia, restlessness, sleep attacks, stress symptoms.

Renal and urinary disorders

Frequent: none; **Infrequent:** chromaturia, hematuria, incontinence, micturition urgency, nocturia, pollakiuria, proteinuria, urinary incontinence.

Reproductive system and breast disorders

Frequent: none; **Infrequent:** ovarian cyst, vaginal hemorrhage.

Respiratory, thoracic and mediastinal disorders

Frequent: cough, dyspnea, nasal congestion, pharyngolaryngeal pain, sinus congestion; **Infrequent:** allergic sinusitis, apnea, asthma, dry throat, hiccups, hyperventilation, nocturnal dyspnea, oropharyngeal swelling, respiratory disorder, rhinitis, rhinitis allergic, sinus disorder, snoring, throat secretion increased, upper respiratory tract congestion.

Skin and subcutaneous tissue disorders

Frequent: pruritis; **Infrequent:** acne, alopecia, cold sweat, dermatitis contact, night sweats, rosacea, skin irritation, urticaria.

Surgical and medical procedures

Frequent: none; **Infrequent:** endodontic procedure.

Vascular disorders

Frequent: hypertension; **Infrequent:** hypotension, peripheral coldness.

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 had been reported over that period of time, 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. However, the incidence of hospital emergency department reports of events involving GHB and GHB-related analogs has decreased by about 33% since 2000, and reports to the American Association of Poison Control Centers of GHB exposures has decreased from 1916 (involving 6 deaths) in 2001 to 800 (without any deaths) in

2003.

Dependence

There have been case reports of dependence after illicit use of GHB at frequent repeated doses (18 to 250 g/day), 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 largely from reports in the medical literature that describe symptoms and signs in individuals who have ingested GHB illicitly. 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 addition, overdose with GHB may be indistinguishable from overdose with other drugs, or from several other medical conditions that result in similar symptoms

In clinical trials two cases of overdose with Xyrem were reported. In the first case, an estimated dose of 150 g, 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 GHB 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 to 4 hours later. The dose of Xyrem should be titrated to effect. The recommended starting dose is 4.5 g/night divided into

two equal doses of 2.25 g. The starting dosage can then be increased to a maximum of 9 g/night in increments of 1.5 g/night (0.75 g per dose). One to two weeks are recommended between dosage increases to evaluate clinical response and minimize adverse effects. The effective dose range of Xyrem is 6 to 9 g/night. The efficacy and safety of Xyrem at doses higher than 9 g/night have not been investigated, and doses greater than 9 g/night ordinarily should not be administered.

Prepare both doses of Xyrem prior to bedtime. Each dose of Xyrem must be diluted with two ounces (60 mL, 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 and the second taken 2.5 to 4 hours later; both doses should be taken while seated 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 allow at least 2 hours after eating before 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). 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. The pharmacy provides two dosing cups with child-resistant caps with each Xyrem shipment.

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 and a professional insert. The pharmacy provides two 90 mL dosing cups with child-resistant caps with each Xyrem shipment. 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 62161-008-18: Each tamper evident single unit carton contains one 180 mL bottle (500 mg/mL) of Xyrem, one press-in-bottle-adaptor and one oral dispensing syringe.

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 bacterial 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:

Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

For questions of a medical nature or to order Xyrem call the Xyrem Success Program® at 1-866-XYREM88 (1-866-997-3688).

Protected by US Patent Numbers 6780889, 6472431; Additional US Patents Pending

MEDICATION GUIDE

Xyrem® (ZĪE-rem) oral solution
(sodium oxybate)
C III

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 with each refill. 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 or being familiar with the other patient education materials. Your doctor must instruct you about the safe and effective use of Xyrem. If you have any questions about Xyrem, ask your doctor or call the central pharmacy at the toll free number 1-866-XYREM88® (1-866-997-3688). 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 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.**
- It is very important to keep Xyrem out of the reach of children and pets. Get emergency medical help right away if a child drinks your Xyrem.
- 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 of Xyrem is gamma-hydroxybutyrate (GHB). GHB is a chemical that has been abused and misused. Abuse and misuse of Xyrem can cause serious medical problems, including seizures, loss of consciousness, coma, and death. Abuse of Xyrem can lead to dependence, craving for the medicine, and severe withdrawal symptoms.
- Xyrem can cause 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 performing these activities.
- You should not drink alcohol or take other medicines that cause sleepiness. You could have serious side effects.
- You can get Xyrem only by prescription. You must get it through the central pharmacy. Before you first receive Xyrem, your doctor or the central pharmacy will confirm that you understand how to use the drug safely and effectively.

What is Xyrem?

Xyrem is a prescription medicine used for the treatment of narcolepsy, to:

- reduce too much daytime sleepiness
- reduce cataplexy (weak or paralyzed muscles) attacks

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:

- **have or had depression or tried to harm yourself.** You should be watched carefully for new symptoms of depression.
- **have liver problems.** Your dose may need to be adjusted.
- **have sleep apnea, snoring, breathing, or lung problems.** You may have a higher chance of serious breathing problems with Xyrem.
- **are on a salt-restricted diet, have high blood pressure, heart failure, or kidney problems.** Xyrem contains a lot of sodium (salt) and may not be right for you.
- **are pregnant or plan to become pregnant.** It is not known if Xyrem can harm your unborn baby.
- **are breastfeeding.** It is not known if Xyrem can pass through your milk. Talk to your doctor about the best way to feed your baby if you take Xyrem.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and supplements. Especially, tell your doctor if you take other medicines to help you sleep (sedatives). Sedatives should not be used with Xyrem.

How should I take Xyrem?

See "Directions for using Xyrem" at the end of this Medication Guide for detailed information about taking Xyrem.

- Take Xyrem exactly as prescribed by your doctor.
- Take Xyrem two times each night or as directed by your doctor. Follow the "Directions for Use" at the end of this Medication Guide and prepare your Xyrem doses before going

to bed. Take the first dose at bedtime while in bed. Take your second dose 2 ½ (2.5) to 4 hours after the first dose. You should set an alarm clock to make sure you wake up to take the second dose. If you miss the second dose, skip that dose and do not take Xyrem again until the next night. Never take two Xyrem doses at once.

- Allow at least 2 hours after eating before taking Xyrem. Food will lower the amount of Xyrem that passes into your body.
- **In case of accidental overdose, call 911.**
- You should see your doctor every 3 months for a check-up while taking Xyrem. Your doctor should check your response to Xyrem treatment, including improvement in your symptoms and if you are having any side effects.

What are the possible side effects with Xyrem?

Xyrem can cause serious side effects, including:

- **breathing problems.** These can include decreased breathing, trouble breathing and sleep apnea (short periods of no breathing while sleeping). Patients that already have breathing or lung problems have a higher chance for breathing problems with Xyrem.

- **mental health problems.** Call your doctor right away if you have:
  - **confusion**
  - **psychosis** (seeing or hearing things that are not real)
  - **abnormal thinking**
  - **agitation**
  - **depression**
  - **thoughts of killing yourself or try to kill yourself**

- **bedwetting.** Call your doctor if you get this side effect. Your doctor should check you.

- **sleepwalking.** Sleepwalking can cause injuries. Call your doctor if you start sleepwalking. Your doctor should check you.

The most common side effects with Xyrem are nausea, dizziness, and headache, vomiting, sleepiness and bed-wetting. An increase in side effects may happen with higher doses.

These are not the only possible side effects with Xyrem. If you are concerned about any possible side effects with Xyrem, talk with your doctor.

How should I store Xyrem?

- **Always store Xyrem in the original bottle in a safe and secure place, out of the reach of children and pets.**

- Keep Xyrem at room temperature, between 59° and 86° F.
- When you have completed using a bottle of Xyrem, pour any unused Xyrem down the drain, cross out the label with a marker, and place the empty bottle in the trash.
- **Always place your nightly doses of Xyrem safely out of the reach of children and pets.**

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 1-866-XYREM88 (1-866-997-3688).

How is my Xyrem prescription filled?

All Xyrem prescriptions are processed by a central, mail order pharmacy. The pharmacy staff provides several important services, including the following:

- Work with your insurance plan to help you get coverage for Xyrem
- Counsel you on the proper use of Xyrem
- Ship Xyrem to you
- Provide answers to your questions about Xyrem at 1-866-XYREM88 (1-866-997-3688)

Directions for Using Xyrem

Never leave your Xyrem in a place where children or pets can get to it.

Your Xyrem shipment will contain 1 or more bottles of medicine, 2 dosing cups with child-resistant caps, a liquid measuring device and this medication guide.

Step 1

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

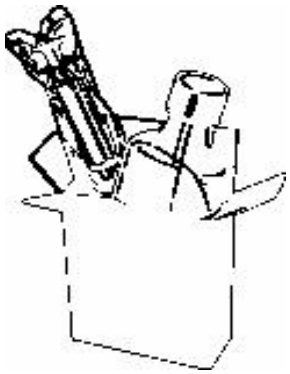


Figure 1

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).

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

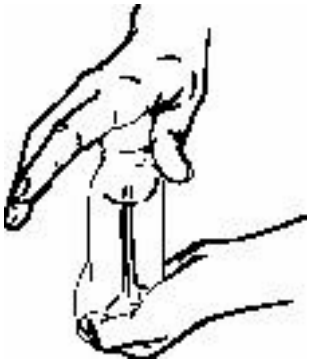


Figure 3

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).

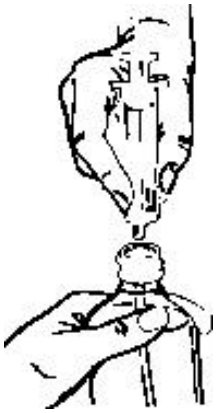


Figure 4

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).

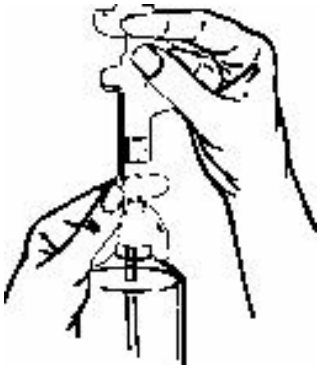


Figure 5

Step 6

Remove the measuring device from the center opening of the bottle. Empty each Xyrem dose into a dosing cup, then add about 2 ounces of water (60 mL, ¼ cup, or 4 tablespoons) to each cup (See Figure 6).

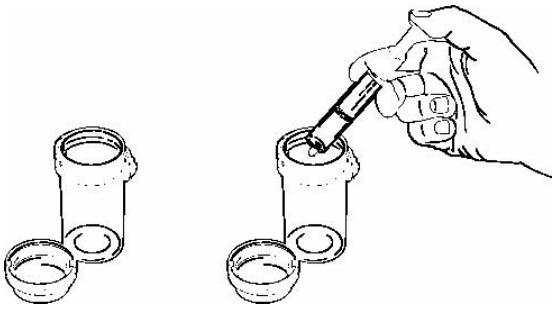


Figure 6

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

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

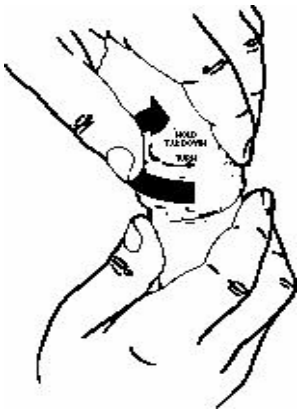


Figure 7

Step 7

Right before going to sleep, place your second dose in a secure location near your bed. Set an alarm to go off 4 hours after your first dose to wake you up for your second dose. If you wake up before the alarm and it has been at least 2 ½ (2.5) hours, turn off your alarm and take your second 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).

Figure 8

Drink all of the first dose right before bedtime (See Figure 9).

Figure 9

Step 8

When you wake up 2 ½ (2.5) 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 62161-008-18

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

Distributed By:
Jazz Pharmaceuticals, Inc
Palo Alto, CA 94304

For questions of a medical nature or to order Xyrem call the Xyrem Patient Success Program at 1-866-XYREM88 (1-866-997-3688).

Protected by US Patent Numbers 6780889, 6472431; additional patents pending.

Rev. November 2005

Part No. 604966

This Medication Guide has been approved by the US Food and Drug Administration.

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 has received and read the educational materials
- Upon receipt of the initial prescription, the pharmacy will verify that patient education and materials have been provided by the physician. If not, the pharmacy will provide verbal education and supply patient education material with the first prescription.
- Maintain patient and prescribing physician registries

II. YOU HAVE ALSO AGREED TO THE FOLLOWING:

- The bulk drug will be manufactured only at FDA-approved site(s).
- The drug product will be manufactured only at FDA-approved site(s).
- Following manufacture the drug product will be stored at facilities compliant with Schedule III regulations, where a consignment inventory will be maintained.
- Xyrem will be distributed and dispensed through a central pharmacy contracted to fulfill this function. There may also be 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, and DEA and state license numbers
    - Verify the prescription

- Obtain patient insurance information

- The central pharmacy will then verify that the physician is eligible to prescribe Xyrem by validation of DEA registration via an appropriate database, including confirmation that the physician has an active DEA number, and determine whether any actions are pending against the physician.
- The central pharmacy will ship the Xyrem Physician Success Program® materials to first time prescribers when needed.
- If a patient has prescription drug coverage, the central pharmacy will then contact the patient's insurance company to determine coverage, and 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 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 either in advance of or with the first shipment.
- Prior to an initial Xyrem shipment to a patient, the central pharmacy will do one of the following:
  - 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 pharmacy; or
  - Review the educational materials with the patient by telephone to complete the required education. Education over the phone will be documented by the central pharmacy.
- 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 courier's own tracking service for shipments. If the courier tracking service were to indicate a discrepancy from either the patient's or designee's name, the pharmacy will contact the patient directly by phone to ensure delivery
- 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.
- If a shipment is lost, an investigation will be launched to find it.
- 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.

- 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 shipment 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.
    - Physicians are urged to rewrite prescriptions for Xyrem 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 patient name
    - Prescriptions by volume (frequency)
    - Prescriptions by dose

C. Drug Product Shipments to Patients

Every prescription 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 or has been manufactured with the PIBA in place.
- An Exacta-Med Dispenser® which allows the patient to withdraw the appropriate dose of drug.
- Two dosing cups with child-resistant caps per shipment, one for each of two nightly doses.
- A Medication Guide.

E. Education Materials

1. Xyrem Physician Success Program

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

2. Xyrem Patient Success Program

This program consists of a videotape and printed educational material, which patients will receive from their physician or the pharmacy, prior to or together with the first shipment of drug. In addition, patients will be educated by either their physician or the pharmacy staff. The pharmacy will confirm that the patient has read and/or understood the educational materials.

<Logo on each page>
Xyrem® (sodium oxybate) CIII oral solution
SUCCESS PROGRAM® for physicians

<cover>

<Picture of Xyrem bottle and carton>

TABLE OF CONTENTS

Package Insert and Medication Guide also included.

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

PRESCRIBING XYREM – A BRIEF GUIDE

The procedure for writing and dispensing Xyrem prescriptions is outlined below. The central pharmacy with the Xyrem Success Program is always available at 1-866-XYREM88 (1-866-997-3688) to support you, your staff and your patients, and to answer any questions you might have.

Before Prescribing Xyrem

- Prescribing Xyrem requires entry into a physician registry.
- To do so, complete the enclosed Physician Registration Form and return it to the pharmacy.

Prescribing Requirements

- Confirm that each patient for whom you prescribe Xyrem has been educated with respect to Xyrem preparation, dosing and scheduling, and whether you have given the patient a copy of the patient education materials.
- Since optimal patient response often requires dose titration, you should evaluate your patients frequently during the early stages of treatment.

- The recommended starting dose is 4.5 grams nightly taken in equally-divided doses of 2.25 grams. Each patient's dose may be titrated within the effective dose range of 6 to 9 grams/night.
- Once stable dosage is established, patients should be evaluated and prescriptions rewritten every 3 months

Prescription Form

- Fax the completed Xyrem Patient Prescription and Enrollment Form and all subsequent prescriptions to the pharmacy at 1-866-470-1744.
- Patients are entered in a registry maintained at the pharmacy

Central Pharmacy's Role

Following receipt of your prescription, the pharmacy will:

- Send confirmation of each prescription received to your office.
- Request additional information or clarification if necessary.
- Contact the patient's insurance provider to verify benefits and eligibility.
- Contact the patient to:
  - confirm that you have educated the patient regarding the Xyrem Patient Success Program, and given the patient a copy of the education materials. If not, the pharmacy will educate the patient.
  - confirm Xyrem delivery details.
  - review preparation, administration and storage instructions.
- Dispense and ship Xyrem by overnight courier to the patient or his/her designee.
- Send Xyrem Patient Success Program materials to the patient with the first Xyrem shipment, if you have not already provided them.
- Maintain a patient and prescriber registry.

If you have any questions please call the Xyrem Physician Success Program at 1-866-XYREM88 (1-866-997-3688)

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

PHYSICIAN REGISTRATION FORM

XYREM® SUCCESS PROGRAM PHYSICIAN REGISTRATION

Please check each box:

☐ I have read the materials in the Xyrem Physician Success Program®.

☐ I understand that Xyrem® (sodium oxybate) oral solution is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy, and that safety or efficacy has not been established for any other indication.

☐ I understand that the safety of doses greater than 9 g/day has not been established.

Please print clearly and fill out completely.

Prescriber's Name Prof. Designation (MD, DO, etc.)

Street Address 1

Street Address 2

City State Zip

Phone Fax

DEA Number Office Contact

Jazz Pharmaceuticals, Inc.

Rev 11/05

<Logo> Xyrem® (sodium oxybate) oral solution CIII
SUCCESS PROGRAM®
Patient Prescription and Enrollment Form

Prescriber Information

Prescriber's Name: _____ Office Contact: _____
Street Address: _____
City: _____ State: _____ Zip: _____
Phone: _____ Fax: _____
License Number: _____ DEA Number: _____

Prescription Form

Patient Name: _____ SS#: _____ DOB: _____ Sex: M/F
Address: _____
City: _____ State: _____ Zip: _____
Rx: Xyrem® Oral Solution (500 mg/mL) Quantity: _____ months supply
Total Nightly Dose: _____ gms
Sig: Take _____ mLs (_____ gms) p.o. diluted in 60 mL water at h.s. and then take _____ mLs (_____ gms) p.o. diluted in 60 mL water again 2 ½ to 4 hours later.
Conversion Table: 4.5 g = 4.5 mL twice nightly, 6 g = 6 mL twice nightly, etc.
Xyrem is medically appropriate for this patient.
Refills (circle one): 0 1 2 3 4 5

_____ Date: _____ / _____ / _____
Prescriber's Signature

Please check each box — To be completed at initial prescription only

☐ I verify that the patient has been educated with respect to Xyrem preparation, dosing and scheduling.
☐ I verify that the patient has received his/her own copy of the Patient Success Program materials (optional).

Patient Information

Best time to contact patient: ☐ Day ☐ Evening
Day #: _____ Evening #: _____
Insurance Company Name: _____ Phone #: _____
Insured's Name: _____ Relationship to Patient: _____
Identification Number: _____ Policy/Group Number: _____
Prescription Card: ☐ No ☐ Yes If Yes, Carrier: _____ Policy #: _____ Group: _____

Please attach copies of patient's insurance cards

Fax completed form to Xyrem Success Program (toll-free) 1-866-470-1744

For information, call the Xyrem Team (toll-free) at 1-866-XYREM88 (1-866-997-3688)

PS-XYR 58
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SUGGESTED GUIDELINES FOR TITRATING XYREM

Xyrem (sodium oxybate) oral solution is indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.

Xyrem Dosing Considerations:

- It is a concentrated liquid that **must** be diluted with water (approximately 60 mL, 2 oz, ¼ cup, or 4 tablespoons).
- It is taken nightly in 2 equal doses.
- Both doses are prepared before bedtime in the provided dosing cups.
- Patients should be instructed to take their first Xyrem dose at bedtime.
- On awakening, 2½ – 4 hours later, the second dose of Xyrem is taken before continuing sleep.
- Both doses should be taken when seated in bed.

Recommended Xyrem Titration

- The recommended starting dose is 4.5 grams per night (4.5 g = 9 mL total dose = two nightly doses of 4.5 mL each).

- Clinical trials have determined that Xyrem is effective in the dose range of 6 to 9 grams per night. Xyrem should be titrated in increments of 1.5 grams per night at one to two week intervals. If adverse effects occur, decrease dose by 1.5 grams per night.

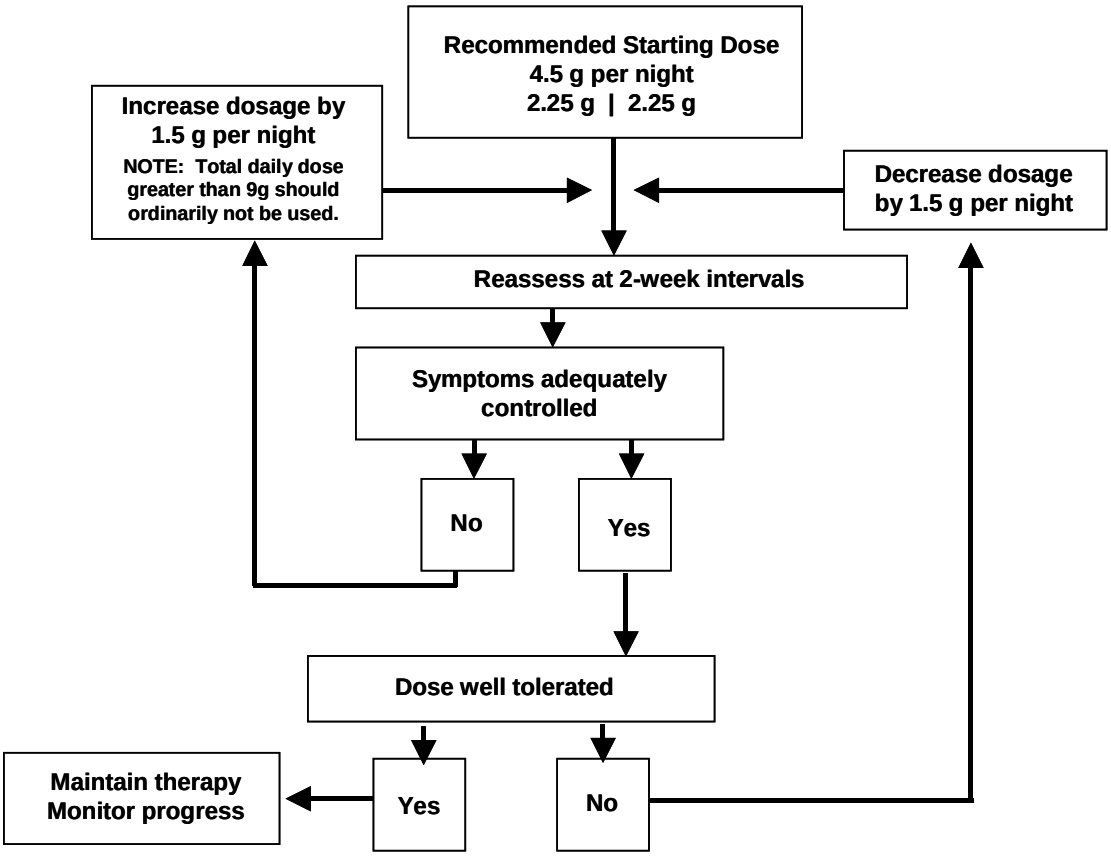
- Dose titration may be required up to 9 grams per night.

- It is recommended that each dose titration not exceed 1.5 grams per night.

- It is recommended that review of dose response take place at one to two-week intervals until a stable dose is achieved.

- The maximum approved dose is 9 grams per night.

- Improvement may be expected during the first weeks of therapy. Titration to optimal dose may take up to 8 weeks.



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

INFORMATION YOU NEED TO KNOW ABOUT XYREM

- Be diagnostically accurate. Confirm patient's diagnosis of narcolepsy with cataplexy and/or excessive daytime sleepiness, particularly those patients new to you and/or your practice.

- Be judicious when deciding to increase a dose. Make sure the indicators are there for increasing or altering a dose.

- Be suspicious of a pattern of excuses for refills or repeated requests for refills on an emergency basis.

- Be vigilant. Recognize that there is potential for patients to abuse Xyrem.

Xyrem has been placed in a bifurcated Federal schedule. Xyrem is a Schedule III controlled substance when used for legitimate medical purposes, as prescribed. However, like all forms of GHB, Xyrem is classified as a Schedule I controlled substance when used for any other reason or by anyone other than for whom it was prescribed. Your patients should be informed that Federal law prohibits the transfer of Xyrem to any persons other than the patient for whom it was prescribed. If you have questions about this, please call the pharmacy at 1-866-XYREM88 (1-866-997-3688).

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

SUCCESS PROGRAM CONTACT INFORMATION

1-866-XYREM88 (1-866-997-3688)
Fax prescriptions to 1-866-470-1744

<Phone contact card>
<Logo>
Xyrem® (sodium oxybate) oral solution CIII
SUCCESS PROGRAM® for physicians

Xyrem Success Program

For medical information, insurance reimbursement, prescription information, and any other questions, call the Xyrem Physician Success Program.

1-866-XYREM88®
(1-866-997-3688)

Rev Date 11/05

The above card can be found on the packaging that contained this booklet.

<Back cover>

<Logo> Jazz Pharmaceuticals, Inc

Rev Date 11/05

<Logo>
Xyrem® (sodium oxybate) CIII oral solution
SUCCESS PROGRAM® for physicians

Dear Doctor:

Enclosed please find information regarding Xyrem (sodium oxybate) oral solution and the Xyrem Success Program. These materials are necessary to initiate Xyrem therapy for your patients.

First approved in July 2002, Xyrem is now indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. The active ingredient in Xyrem, sodium oxybate, is the sodium salt of gamma hydroxybutyrate (GHB). The use of illicit 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 has been approved for marketing under a risk management program that was developed in agreement with the Food & Drug Administration; this program is intended to educate physicians and patients and to prevent diversion. The Xyrem Success Program includes:

Patient Support

- Pharmacy services are provided by a central pharmacy, which handles all insurance coverage, product dispensing, mail order delivery and patient counseling.
- Patients are entered in a registry maintained at the pharmacy.
- Patients are educated prior to receiving their first Xyrem shipment.

Physician Support

- If you are prescribing Xyrem for the first time, you need to register with the Success Program. On the enclosed Physician Registration Form, please confirm that: 1) you have read the enclosed materials; 2) you understand Xyrem is approved for the treatment excessive daytime sleepiness and cataplexy in patients with narcolepsy; and 3) you understand that the safety of doses greater than 9 g/day has not been established.
- Xyrem prescriptions for new patients are to be written on the enclosed prescription form. This form should be filled out completely to ensure timely fulfillment of your patient's prescription by the pharmacy.
- Be sure that you have provided Xyrem dosing, preparation, and administration counseling to each patient. You should also provide each patient with the Xyrem Patient Success Program® materials.

- It is also important for you to know that, just like all pharmacies that dispense controlled substances, the central pharmacy will maintain records about who is prescribing Xyrem. These records will be made available to any state or federal agency that requests them.
- Since optimal patient response often requires dose titration, we encourage you to evaluate your patients frequently during the early stages of treatment.
- Once stable dosage is established, we recommend patients be evaluated and prescriptions rewritten every 3 months. Note: the patient's first Xyrem shipment will be limited to a 1-month supply and future shipments a 3-month supply.
- As with all prescription medications, we urge you to submit reports of all serious adverse reactions to the company.

If you require any additional assistance, please call the Xyrem Physician Success Program at 1-866-XYREM88 (1-866-997-3688).

Sincerely,

Philip Perera, M.D.
Chief Medical Officer
Vice President Clinical Research and Medical Affairs
Jazz Pharmaceuticals, Inc.

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

<Logo>
Jazz Pharmaceuticals, Inc
Palo Alto, CA 94304

Rev Date **11/05**

PHYSICIAN REGISTRATION FORM

XYREM® SUCCESS PROGRAM PHYSICIAN REGISTRATION

Please check each box:

☐ I have read the materials in the Xyrem Physician Success Program®.

☐ I understand that Xyrem® (sodium oxybate) oral solution is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy, and that safety or efficacy has not been established for any other indication.

☐ I understand that the safety of doses greater than 9 g/day has not been established.

Please print clearly and fill out completely.

Prescriber's Name Prof. Designation (MD, DO, etc.)

Street Address 1

Street Address 2

City State Zip

Phone Fax

DEA Number Office Contact

Jazz Pharmaceuticals, Inc.

Rev 11/05

<Logo>
Xyrem® (sodium oxybate) CIII oral solution
SUCCESS PROGRAM for patients

<Bottom of each page
Any questions? Please call 1-866-XYREM88 (1-866-997-3688) Xyrem Patient Success Program

Please see FDA-approved medication guide for more detailed information.>

<cover>

Your doctor has prescribed Xyrem (sodium oxybate) oral solution.

<Picture of Xyrem bottle and carton>

Frequently asked questions about the use and safe handling of Xyrem

WHAT YOU WILL FIND IN THIS BOOKLET

Xyrem contains sodium oxybate, which has been shown to improve excessive daytime sleepiness and reduce the number of cataplexy attacks in patients with narcolepsy. This booklet answers important questions about obtaining, using, and storing Xyrem and precautions to be considered when doing so.

FILLING YOUR XYREM PRESCRIPTION

How is my prescription filled?

All Xyrem prescriptions are filled by a central, mail order pharmacy.

.What does the central pharmacy do?

- Your doctor sends the Xyrem prescription directly to the pharmacy.
- A team member from the pharmacy will contact you within 48 hours of receiving your prescription to review insurance information. For more information, see the section titled "Insurance Coverage."
- The pharmacy will confirm that you have received and/or understood this educational

booklet. If your physician did not provide these materials to you, the pharmacy will review them with you before sending your first shipment of Xyrem.

- The pharmacy will always confirm where and when you would like Xyrem delivered and who will sign for the shipment. Xyrem will be shipped via an overnight courier. When the courier arrives you, or someone you designate, must sign for your Xyrem delivery.

What will I receive with my shipment of Xyrem?

With each shipment you receive, there will be 1 or more bottles of Xyrem, a liquid measuring device, 2 dosing cups with child-resistant caps and a printed medication guide.

Can my local pharmacy provide Xyrem?

No, but in some cases, you may be able to have the courier deliver Xyrem to your local pharmacy for later pickup.

What does it mean that Xyrem is a controlled substance?

The active ingredient of Xyrem, known as GHB, has been a target for persons who abuse drugs. Because Xyrem is a controlled substance, it is illegal for you to sell or give your Xyrem to anyone else, or to use your Xyrem for purposes other than it was prescribed. As with all controlled substances, failure to adhere to these rules may result in penalties as defined in the Controlled Substances Act.

Therefore, your Xyrem must be:

- used only by you.
- used only as directed by your physician.
- stored in a safe and secure place.

INSURANCE COVERAGE

Will insurance pay for my Xyrem?

In most cases, YES. A team member from the pharmacy will contact you and your insurance plan to coordinate your coverage for Xyrem.

What is the pharmacy's role with my insurance?

An experienced Reimbursement Specialist will:

- call you to review your benefits and eligibility.

- inform you of your co-pay responsibility, if applicable.
- obtain prior authorization from your insurance company, if needed.
- file appropriate appeals on your behalf.
- assist with obtaining alternate funding that may be available to you.
- support you with all aspects of insurance.

The pharmacy's attempt to obtain coverage from a patient's third-party payer does not constitute or guarantee success.

HOW DO I TAKE XYREM?

Xyrem is to be taken only as directed by your doctor.

Xyrem should be taken twice nightly: the first dose is taken at bedtime and the second dose is taken 2½ to 4 hours later. Both doses should be taken while seated in bed.

Preparing your doses

Before going to bed, draw up each of your Xyrem doses with the provided measuring device and empty into the two dosing cups. Dilute each dose with about 2 oz of water (about 60mL, ¼ cup, or 4 tablespoons). Then place the child-resistant caps onto the dosing cups and put them in a safe place by your bed, out of the reach of children and pets.

Taking your doses

- Food will decrease the amount of Xyrem that is absorbed. Therefore, you should allow about two hours after a meal before taking your first dose of Xyrem.
- Xyrem is a medicine that produces sleepiness; therefore, as a safety precaution, it is best to be in bed when you take your first dose. As with any medicine that causes sleepiness, if you continue evening activities after taking your dose, such as watching television or walking around, you may experience light-headedness, dizziness, nausea, confusion or other unpleasant feelings.
- Set an alarm to go off 4 hours after your first dose to wake you up for your second dose. If you wake up before the alarm and it has been at least 2 ½ hours, turn off your alarm and take your second dose.

What do I do if I miss a Xyrem dose?

- Never take 2 doses of Xyrem at once to make up for a missed dose.
- Leave a minimum of 2½ hours between each nightly dose.
- Remember not to engage in activities requiring mental alertness within 6 hours of dosing.

How soon will I see a change in my symptoms?

You can expect to see some improvement in your symptoms shortly after beginning Xyrem therapy. If you are not experiencing any change in your symptoms, contact your doctor for assessment and possible dose adjustment. Individual symptom response may vary and it may take several weeks to achieve the maximum beneficial effect of Xyrem.

You and your doctor will discuss your response to treatment, and your doctor may increase or decrease your dose as a result. **NEVER CHANGE THE DOSE OF XYREM YOURSELF.**

Are there side effects with Xyrem?

The most common side effects reported with Xyrem are nausea, dizziness, headache, vomiting, sleepiness and bed-wetting. An increase in side effects may occur with higher doses.

If you experience the following side effects while using Xyrem, you should promptly call your doctor: confusion, vomiting, sleep walking, breathing problems (at night), depression or abnormal thinking.

These are not the only possible side effects with Xyrem. If you are concerned about any other possible side effects with Xyrem, please consult your doctor.

Are there any precautions I should take while on Xyrem?

- While taking Xyrem, you should not drink alcoholic beverages or take medications that cause drowsiness.
- Do not drive a car, operate heavy machinery or perform any activity that is dangerous or requires mental alertness, for at least 6 hours after taking Xyrem. When you first start taking Xyrem, use extreme care while performing these activities until you know whether it makes you sleepy the next day.
- Before starting Xyrem, tell your healthcare provider if you are pregnant, breast-feeding or plan to become pregnant. It is not known whether Xyrem can pass through your milk.
- Keep your Xyrem in a secure location, out of the reach of children. Xyrem does not require refrigeration.

Can I take other medications with Xyrem?

Xyrem should not be used in combination with alcohol or medications that can cause drowsiness. You should tell your doctors and pharmacist about any other medicines you are currently taking, including non-prescription medicines and any vitamins or herbal, nutritional or dietary supplements.

It is also important to tell other health care providers that you are taking Xyrem before starting or changing any medications.

How often should my doctor check my progress with Xyrem?

When you first start taking Xyrem, you may need to talk to your doctor frequently until he or she has determined the best dose for you. You can expect that your dose may need to be adjusted. After your dose has been established, your doctor should check your progress at least every 3 months while you are taking Xyrem.

STORAGE AND SAFETY TIPS AT HOME

Storage

- Always keep Xyrem in its original container.
- Xyrem can be stored at room temperature.
- Like all medications, Xyrem should be kept in a secure location out of the reach of children and pets. In case of accidental ingestion, call the poison center at 1-800-222-1222 or dial 911.

Disposal

- When you can no longer draw medication out of the bottle with the measuring device, it is time to throw the bottle away. Pour any unused Xyrem down the drain. Scribble over the label with a marker before putting it in the trash so someone else cannot use it for illegal purposes.

Refills

- Remember to reorder your Xyrem when you have only a 7-day supply remaining. Call the pharmacy at 1-866-997-3688 to request a refill.

Problems

- If your supply of Xyrem is lost or stolen, please report the incident immediately to the local police and the pharmacy.

- Use only as directed. Remember that use of your Xyrem by others is illegal.

- If you have questions, concerns, or need advice regarding Xyrem, call your doctor or the pharmacy.

TRAVELING TIPS…

Before your trip

- When packing for your trip, be sure to take enough Xyrem for the length of time you will be away.

- Always travel with Xyrem in its original container, with the pharmacy label on it.

- Take only the number of bottles of Xyrem needed for your stay away from home. Be sure that any Xyrem bottles left behind are in a secure place before you leave home.

During your trip

- Do not pack your Xyrem in a suitcase that will be checked baggage. Keep it in a secure location when it is not in your possession.

- Remember to take your dispensing device and the dosing cups with child-resistant caps when traveling. In an unfamiliar environment, it is especially important that your second nightly dose of Xyrem is not left in an unsecured place or within the reach of children or pets.

- When you pack to return home, do not forget your Xyrem.

- If you should forget your Xyrem while traveling within the United States or need more due to an extended stay, call the pharmacy at 1-866-997-3688.

- If traveling internationally, be aware that Xyrem may be subject to different regulations in other countries. Always travel with Xyrem in its original container, with the pharmacy label on it.

Problems

- If your supply of Xyrem is lost or stolen while traveling, please report the incident immediately to the local police and the pharmacy.

If you have questions, concerns, or need advice regarding Xyrem while traveling, call the pharmacy.

Xyrem Success Program Contact Information

1-866-XYREM88 (1-866-997-3688)

FAX 1-866-470-1744

For international access call the pharmacy at **+ 314-918-6600**

NOTES…

GETTING MORE INFORMATION…

Where can I get more information on Xyrem, narcolepsy, and other sleep disorders?

For more information on Xyrem, please call your help line at 1-866-XYREM88 (1-866-997-3688) or visit the Xyrem Web site at http://www.xyrem.info.

The following organizations offer information on a wide range of sleep disorders:

Jazz Pharmaceuticals, Inc.
3180 Porter Drive
Palo Alto, CA 94304
Phone: 1-866-XYREM88

www.advocatesforsleep.com
Advocates for Sleep
818 West 46th Street, Suite 203
Minneapolis, MN 55419
Phone: 1-800-823-8893

www.talkaboutsleep.com
Talk About Sleep, Inc.
818 West 46th Street, Suite 203
Minneapolis, MN 55419
Phone: 612-822-6896
Fax: 612-822-6875

www.rarediseases.org
NORD (National Organization for Rare Disorders)
55 Kenosia Avenue
P.O. Box 1968
Danbury, CT 06813-1968
Phone: 1-800-999-6673

www.sleepfoundation.org
National Sleep Foundation
1522 K Street NW, Suite 500
Washington, DC 20005
Phone: 202-347-3471

www.narcolepsynetwork.org
Narcolepsy Network, Inc.
79A Main Street
North Kingstown, RI 02852
Phone: 888-292-6522
Fax: 401-633-6567
E-mail: narnet@ narcolepsynetwork.org

Keep this booklet as a helpful reminder. If you have questions or need information, don't hesitate to contact the pharmacy with the Xyrem Success Program.

1-866-XYREM88 (1-866-997-3688)

FAX 1-866-470-1744

<Back cover>

<Logo> Jazz Pharmaceuticals, Inc

Rev Date 11/05

<Logo>
Xyrem® (sodium oxybate) CIII oral solution
SUCCESS PROGRAM® for patients

Dear Patient,

Welcome to the Xyrem Success Program. Your doctor recently prescribed Xyrem (sodium oxybate) oral solution for you. We have developed the Xyrem Patient Success Program to support you as you start your treatment. The program includes the enclosed Xyrem Patient Success Program booklet, other educational materials and a toll-free phone number: 1-866-XYREM88® (1-866-997-3688). The educational materials contain important information on obtaining, using and storing Xyrem.

Xyrem is a medication that has been approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. Important information about Xyrem includes the following:

- Twice nightly dosing: the first dose is taken at bedtime and the second dose 2½ - 4 hours later
- Both doses should be taken while sitting up in bed
- Xyrem should not be taken with alcohol or other medications that cause drowsiness
- Your Xyrem prescription is filled and sent by a central, mail order pharmacy
- The active ingredient of Xyrem, known as GHB, has been a target for persons who abuse drugs. Therefore your Xyrem must be used only by you, only as directed by your physician, and stored in a safe, secure place.

A team member from the pharmacy will call you within 48 hours of receiving your prescription to review your insurance information. **It is important that you take this call in order to receive your prescription.** A pharmacist is also available to discuss any questions you may have.

To support you in obtaining and using Xyrem, we have developed the Xyrem Patient Success Program which includes the enclosed educational materials. We hope that you will find this information helpful.

Yours sincerely,

Philip Perera, M.D.
Chief Medical Officer

Vice President Clinical Research and Medical Affairs
Jazz Pharmaceuticals, Inc.
<Logo
Jazz Pharmaceuticals, Inc
Palo Alto, CA 94304

Rev Date 11/05

NDA 21-196/S-005
FDA Approved Labeling Text dated 11/18/05

<Logo> Xyrem® (sodium oxybate) oral solution CIII
SUCCESS PROGRAM®
Patient Prescription and Enrollment Form

Prescriber Information

Prescriber's Name: _____ Office Contact: _____

Street Address: _____

City: _____ State: _____ Zip: _____

Phone: _____ Fax: _____

License Number: _____ DEA Number: _____

Prescription Form

Patient Name: _____ SS#: _____ DOB: _____ Sex: M/F

Address: _____

City: _____ State: _____ Zip: _____

Rx: Xyrem® Oral Solution (500 mg/mL) Quantity: _____ months supply

Total Nightly Dose: _____ gms

Sig: Take _____ mLs (_____ gms) p.o. diluted in 60 mL water at h.s. and then take _____ mLs (_____ gms) p.o. diluted in 60 mL water again 2 ½ to 4 hours later.

Conversion Table: 4.5 g = 4.5 mL twice nightly, 6 g = 6 mL twice nightly, etc.

Xyrem is medically appropriate for this patient.

Refills (circle one): 0 1 2 3 4 5

_____ Date: _____ / _____ / _____
Prescriber's Signature

Please check each box — To be completed at initial prescription only

☐ I verify that the patient has been educated with respect to Xyrem preparation, dosing and scheduling.

☐ I verify that the patient has received his/her own copy of the Patient Success Program materials (optional).

Patient Information

Best time to contact patient: ☐ Day ☐ Evening

Day #: _____ Evening #: _____

Insurance Company Name: _____ Phone #: _____

Insured's Name: _____ Relationship to Patient: _____

Identification Number: _____ Policy/Group Number: _____

Prescription Card: ☐ No ☐ Yes If Yes, Carrier: _____ Policy #: _____ Group: _____

Please attach copies of patient's insurance cards

Fax completed form to Xyrem Success Program (toll-free) 1-866-470-1744

For information, call the Xyrem® Team (toll-free) at 1-866-XYREM88® (1-866-997-3688)

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