Rx 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.

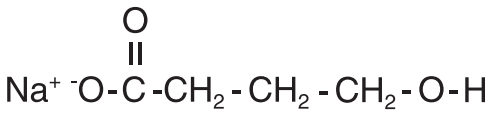
Sodium oxybate is GHB, a known drug of abuse. Abuse has been associated with some important central nervous system (CNS) adverse events (including death). Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Reports of respiratory depression 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 (1st and 2nd peak) following administration of a 9 g daily dose divided into two equivalent doses given four hours apart were 78 and 142 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, 4.5 g, 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; I**nfrequent:** 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 a 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, 1/4 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 68727-100-01: 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).

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