

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

<sup>c</sup> **XYREM**<sup>®</sup>

sodium oxybate solution

solution, 500 mg/mL, oral

Central Nervous System Depressant

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**RECENT MAJOR LABEL CHANGES**

Not applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

XYREM® (sodium oxybate) oral solution is a Schedule I controlled substance indicated for the treatment of cataplexy in patients with narcolepsy.

XYREM is not recommended for use in other indications, as safety and efficacy have not been established outside of cataplexy.

#### 1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see [7.1.3 WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics](#)).

#### 1.2 Geriatrics

Geriatrics: There is very limited experience with sodium oxybate in the geriatric population (see [4.2 Recommended Dose and Dosage Adjustment](#) and [7.1.4 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics](#)).

### 2 CONTRAINDICATIONS

XYREM is contraindicated:

- in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).
- with concomitant use of sedative hypnotic agents or alcohol (see [9.4 DRUG INTERACTIONS, Drug-Drug Interactions](#)).
- in patients with succinic semialdehyde dehydrogenase deficiency (see [10.3 CLINICAL PHARMACOLOGY, Pharmacokinetics](#)). This rare disorder is an inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.

### 3 SERIOUS WARNINGS AND PRECAUTIONS

- **WARNING: XYREM is a central nervous system (CNS) depressant with abuse potential and should not be used with alcohol or other CNS depressants.**
- Sodium oxybate is gamma-hydroxybutyrate (GHB), a known drug of abuse that has been associated with some important CNS adverse events, including death in abuse situations. Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Reports of respiratory depression occurred in clinical trials. Most patients receiving sodium oxybate during clinical trials maintained

concomitant stimulant use (see [8.2 Clinical Trial Adverse Reactions](#)).

- 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) (see [5 OVERDOSAGE](#) and [7 WARNINGS AND PRECAUTIONS](#)).
- Due to the risks of CNS depression and abuse and misuse, XYREM is available only through a patient safety program (see [4.1 Dosing Considerations](#) and [7 WARNINGS AND PRECAUTIONS](#)).
- XYREM is approved for use only in the treatment of cataplexy in patients with narcolepsy.

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

XYREM should only be prescribed by healthcare professionals who meet the following requirements: i) Experience in treating cataplexy in patients with narcolepsy; ii) Completion of the XYREM Physician Success Program.

- The XYREM Success Program is a Risk Management Program founded on the following core components that provide for the safe and effective use of the drug, and limit the potential for drug diversion and abuse:
  - Implementation of a program to educate healthcare professionals, pharmacists, and patients about the risks and benefits of XYREM, including critical information necessary for the safe use, storage, and handling of the drug.
  - The XYREM Success Program includes recommendations for educating patients and information to help minimize the risks of inadvertent use by others. These recommendations encourage healthcare professionals to see their patients every 3 months during the course of therapy and to report all serious adverse events to the manufacturer.
  - Implementation of a restricted distribution program for XYREM through a single wholesale distribution company that will ship the drug directly to pharmacies on an as-needed basis after patients have presented with an initial legitimate prescription.
  - Filling of the initial prescription only after the healthcare professional, pharmacist, and patient have received and read the educational materials.
  - Maintenance of a registry of XYREM Success Program trained healthcare professionals, pharmacies, and patients.

- Healthcare professionals may obtain more information about the XYREM Success Program by calling the following toll-free phone number: 1-866-5XYREM5 (1-866-599-7365).
- Treatment should be initiated by and remain under the guidance of a physician. Oxybate, the active ingredient, is also known as gamma-hydroxybutyrate (GHB). Due to the potential for abuse and misuse of illicit GHB, physicians should evaluate patients for a history of drug abuse (see [3 SERIOUS WARNINGS AND PRECAUTIONS](#); [7 WARNINGS AND PRECAUTIONS](#)).
- Patients should be advised not to consume alcohol in combination with XYREM (see [2 CONTRAINDICATIONS](#); [9.3 DRUG INTERACTIONS, Drug-Behavioural Interactions](#)).
- XYREM should be titrated to effect (see [4.2 Recommended Dose and Dosage Adjustment](#)).
- XYREM has twice nightly dosing: the first dose is taken at bedtime and the second 2.5 to 4 hours later (see [4.2 Recommended Dose and Dosage Adjustment](#)).
- XYREM is rapidly absorbed. Therefore, XYREM should be taken only at bedtime, and patients should not walk around after taking their dose of XYREM.
- Food significantly decreases the bioavailability of sodium oxybate. Whether XYREM is taken in the fed or fasted state may affect both the efficacy and safety of XYREM for a given patient. Patients should be made aware of this and take the first dose at least two hours after their last meal, prior to bedtime (see [4.4 Administration](#); [9.5 Drug-Food Interactions](#)).
- Patients with hepatic impairment are started on XYREM at one-half (½) of the original dosage per night, divided into two doses (see [10.3 Pharmacokinetics](#)).
- Concomitant use of XYREM with divalproex sodium may result in higher exposures of sodium oxybate, an initial dose reduction of at least 20% of XYREM is recommended if divalproex sodium is prescribed to patients already taking XYREM (see [9.4 Drug-Drug Interactions](#)).

#### 4.2 Recommended Dose and Dosage Adjustment

- **Adults (≥ 18 years of age):**

XYREM should be titrated to effect. The recommended starting dose is 4.5 g/night divided into two equal doses of 2.25 grams. The first dose should be taken at bedtime and the second dose should be taken 2.5 to 4 hours later. The starting dosage can be increased or decreased in increments of 1.5 g/night (0.75 g per dose), to a maximum of 9 g/night, while evaluating clinical response and adverse effects. Two-week intervals are recommended between dose titration.

XYREM is effective at doses of 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 are not recommended.

Eight to 10 weeks of therapy may be necessary before a maximal cataplexy response to sodium oxybate is seen (see [14 CLINICAL TRIALS](#)).

- **Pediatrics (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. The use of XYREM is not recommended in children under the age of 18, unless clearly needed.
- **Geriatrics:** There is very limited experience with sodium oxybate in patients 65 years of age and older. Caution should be exercised when using XYREM in elderly patients. In general, dose selection for elderly patients should start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concurrent disease or concomitant medications. Elderly patients should be monitored closely for impaired motor and/or cognitive function when taking XYREM.
- **Patients with Hepatic Insufficiency:** Patients with compromised liver function will have a longer elimination half-life and greater systemic exposure, along with reduced clearance (see [10.3 Pharmacokinetics](#) and [7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic](#)). The starting dose should be decreased by one-half and dose increments should be titrated to effect, while closely monitoring potential adverse events.
- **Patients with Renal Insufficiency:** Because less than 5% of sodium oxybate is excreted via the kidney, no dose adjustment should be necessary in patients with renal impairment. No studies have been conducted in patients with renal failure.

### 4.3 Reconstitution

XYREM is an oral solution with a concentration of 500 mg/mL sodium oxybate. Each bottle of XYREM is closed with a child-resistant cap. The pharmacist will also provide the patient with an oral dosing syringe and two pharmacy containers, with child-resistant caps. See [PATIENT MEDICATION INFORMATION](#) for a complete description.

Prior to ingestion, each dose of XYREM must be diluted with approximately 60 mL (2 oz) of water or enough to fill  $\frac{3}{4}$  of the supplied pharmacy containers. Containers should then be sealed with the child-resistant cap.

For measuring doses of XYREM, patients should only use the dosing syringe (graduated in grams) that is provided. However, if needed, Table 1 provides a conversion scale of total nightly XYREM dose(s) from grams to mL.

**Table 1 - Total Nightly Dose: Conversion Scale**

<b>Total Nightly Dose (g)</b>	<b>Total Nightly Dose (mL)</b>	<b>Single Dose (taken twice nightly) (g)</b>	<b>Single Dose (taken twice nightly) (mL)</b>
3 g	6 mL	1.5 g	3 mL
4.5 g	9 mL	2.25 g	4.5 mL
6 g	12 mL	3 g	6 mL
7.5 g	15 mL	3.75 g	7.5 mL
9 g	18 mL	4.5 g	9 mL

#### **4.4 Administration**

Food significantly reduces the bioavailability of sodium oxybate (see [9.5 Drug-Food Interactions](#) and [10.3 Pharmacokinetics](#)). Patients should stop eating at least 2 hours prior to taking the first dose of XYREM, at bedtime. A regular evening routine should be established, with regard to the content and timing of meals, in order to ensure consistent efficacy and safety.

Patients should prepare both doses of XYREM prior to bedtime (see [4.3 Reconstitution](#)). The first dose is to be taken at bedtime, and the second dose is to be taken 2.5 to 4 hours later, while sitting in bed. Patients may 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, the patient should lie down and remain in bed.

#### **4.5 Missed Dose**

In the event a dose is missed, that dose should be skipped. If the first dose is missed, that dose should be skipped and the second dose taken. Two XYREM doses should never be taken at one time. If a first dose is taken and the second dose is missed, that dose should be skipped and XYREM should not be taken again until the next night.

### **5 OVERDOSAGE**

#### Signs and Symptoms

Information regarding overdose with sodium oxybate is extrapolated from literature reports of toxicity from illicit GHB. The co-ingestion of other drugs and alcohol is common and may influence the presentation and severity of clinical manifestations of overdose. Therefore, literature reports of GHB overdose must be interpreted cautiously because overdose may be indistinguishable from other drug overdoses or medical conditions.

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. Acidosis and an increasing depth of coma have 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.

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 experience urinary and fecal incontinence. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of XYREM and numerous other drugs.

### Management

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) or 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 intravenous atropine 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, but have been reported in cases of acidosis associated with GHB ingestions of 125 g or greater; however, due to the rapid metabolism of sodium oxybate, these measures may not be warranted.

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 centre for current treatment recommendations.

For management of a suspected drug overdose, contact your regional poison control centre.

## **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**

**Table 2 – Dosage Forms, Strengths, Composition and Packaging**

<b>Route of Administration</b>	<b>Dosage Form / Strength/Composition</b>	<b>Non-medicinal Ingredients</b>
oral	solution	malic acid

	500 mg/mL	purified water, USP
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XYREM is a clear to slightly opalescent oral solution. It is supplied in a tamper evident single unit carton containing one bottle of XYREM, a press-in-bottle-adapter (PIBA), a 10 mL oral measuring device (plastic syringe), and a patient medication information leaflet. 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. The pharmacist places the PIBA in the bottle prior to dispensing XYREM to the patient and provides two pharmacy containers, with child-resistant caps.

## 7 WARNINGS AND PRECAUTIONS

See [3 SERIOUS WARNINGS AND PRECAUTIONS](#).

### General

XYREM (sodium oxybate or gamma-hydroxybutyrate (GHB)), is classified as a Schedule I controlled substance.

### Abuse and Misuse

While sodium oxybate has not been systematically studied in clinical trials for its potential for abuse, illicit use and abuse of GHB 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 CNS 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.

Illicit GHB has been abused in social settings primarily by young adults. Illicit GHB has some commonalities with ethanol over a limited dose range and some cross-tolerance with ethanol has been reported. Some of the doses reported during abuse may have been similar to the dose range studied for therapeutic treatment of cataplexy.

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 sodium oxybate (e.g., increase in size or frequency of dosing, drug-seeking behaviour). Physicians should document the diagnosis and indication for XYREM, being alert to drug-seeking behaviour and/or feigned cataplexy.

### Patient Safety Program

XYREM is available only through a patient safety program due to the risks of CNS depression, abuse, and misuse. See [4.1 Dosing Considerations](#) for more details on the patient safety program.

Requirements of the patient safety program include the following:

- Healthcare professionals who prescribe XYREM are educated and enrolled in the patient

safety program.

- XYREM will be dispensed only by pharmacies enrolled in the patient safety program.
- XYREM will be dispensed only to patients who are enrolled in the patient safety program, with documentation of safe use.

### Sodium Intake

Each mL of XYREM (sodium oxybate) oral solution contains 91 mg of sodium (refer to Table 3, below). Sodium content should be considered when prescribing XYREM for patients with salt restrictions such as hypertension, congestive heart failure, or compromised renal function.

**Table 3 - Sodium Content per Total Nightly XYREM Dose**

<b>Total Nightly Dose (g)</b>	<b>Total Nightly Dose (mL)</b>	<b>Sodium Content/Total Nightly Dose</b>
3	6	546 mg
4.5	9	819 mg
6	12	1092 mg
7.5	15	1365 mg
9	18	1638 mg

### **Dependence/Tolerance**

#### Dependence

There have been case reports of dependence after illicit use of GHB at frequent repeated doses in excess of the therapeutic dose range (18 to 250 g/day). In these cases, the discontinuation resulted in an abstinence syndrome consisting of insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, and tachycardia, generally abating in 3 to 14 days. The effects of sodium oxybate discontinuation have not been systematically evaluated in controlled clinical trials. Neither a withdrawal nor an abstinence syndrome has been reported during clinical investigations, although, 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 markedly increased.

#### Tolerance

Tolerance to sodium oxybate has not been systematically studied in controlled clinical trials. Open-label, long-term ( $\geq 6$  months) clinical trials did not demonstrate development of tolerance. There have been some case reports of symptoms of tolerance developing after illicit GHB 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.

### **Driving and Operating Machinery**

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

XYREM produces a rapid onset of sedation and should only be ingested at bedtime. 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 caution while performing any task that could be dangerous or requires full mental alertness.

The combined use of XYREM with alcohol may result in potentiation of the CNS-depressant effects of sodium oxybate. Therefore, patients should be warned to avoid the ingestion of any alcohol in conjunction with XYREM (see [2 CONTRAINDICATIONS](#) and [9.3 Drug-Behavioural Interactions](#)).

XYREM should not be used in combination with sedative hypnotic or other CNS depressants, including sedating anti-epileptic drugs (AEDs) (see [9.4 Drug-Drug Interactions](#)).

### **Genitourinary**

#### Incontinence

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

In a controlled clinical 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 at 9 g/night experiencing urinary incontinence. In the same trial, one patient experienced fecal incontinence 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.

### **Hepatic/Biliary/Pancreatic**

#### Hepatic Insufficiency

Patients with compromised liver function will have an increased elimination half-life and systemic exposure to sodium oxybate (see [10.3 Pharmacokinetics](#)). Decrease the starting dose

by one-half in such patients, and closely monitor the response to any dose increments (see [4.2 Recommended Dose and Dosage Adjustment](#)).

## **Neurologic**

### Central Nervous System (CNS) Depression

XYREM is a CNS depressant with potential for obtundation and respiratory depression. CNS adverse events associated with abuse include seizure, respiratory depression and profound decreases in level of consciousness, with instances of coma and death (see [3 SERIOUS WARNINGS AND PRECAUTIONS](#)).

Patients should be warned against the use of sodium oxybate in conjunction with other CNS depressants. The concurrent use of XYREM with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death (see [2 CONTRAINDICATIONS](#); [3 SERIOUS WARNINGS AND PRECAUTIONS](#); [9.4 Drug-Drug Interactions](#); [9.3 Drug-Behavioural Interactions](#)). In addition, there have been clinical observations of coma and increased plasma GHB concentration after co-administration of sodium oxybate with topiramate (see [9.4 Drug-Drug Interactions](#)).

If use of these CNS depressants in combination with XYREM is required, dose reduction or discontinuation of one or more CNS depressants (including XYREM) should be considered. In addition, if short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with XYREM should be considered.

The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls complicated by injuries, and in some cases requiring hospitalization. Patients should remain in bed following ingestion of the first and second doses.

## **Psychiatric**

### Confusion/Neuropsychiatric Adverse Events

During clinical trials, 7% of patients treated with sodium oxybate experienced confusion. Fewer than 1% of patients discontinued the drug because of confusion. In all cases, the confusion resolved soon after termination of treatment. In the majority of cases, confusion resolved with continued treatment. Patients treated with XYREM who become confused should be evaluated fully, and appropriate intervention considered on an individual basis.

Other neuropsychiatric events reported in clinical trials and during post-approval use included psychosis, paranoia, hallucinations, anxiety, irritability, hostility, aggression, and agitation. The emergence of thought disorders and/or behaviour abnormalities when patients are treated with sodium oxybate requires careful and immediate evaluation, including during dose titration.

### Depression and Suicidality

In clinical trials, 6% of patients treated with sodium oxybate reported adverse events of

depressive symptoms. In the majority of cases, no change in sodium oxybate treatment was required. Three patients (< 1%) discontinued because of depressive symptoms. There was no dose relationship in depression reported during clinical trials.

Among patients with a previous history of depressive psychiatric disorder, there were two suicides and one attempted suicide recorded in the 448 patient dataset. Of the two suicides, one patient used multiple drugs, including sodium oxybate. 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. XYREM is not recommended in patients with major depression.

### Parasomnias

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

## **Renal**

### Renal Insufficiency

The sodium load associated with administration of sodium oxybate should be considered in patients with renal insufficiency (see [7 WARNINGS AND PRECAUTIONS, Sodium Intake](#)).

## **Reproductive Health: Female and Male Potential**

- **Fertility**

Effects of XYREM on fertility in humans have not been studied. In animals, oral administration of sodium oxybate (0, 150, 350, or 1000 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females through early gestation resulted in no adverse

effects on fertility. The highest dose tested is approximately equal to the maximum recommended human dose (MRHD) of 9 g per night XYREM on a body surface area (mg/m<sup>2</sup>) basis (see [16 NON-CLINICAL TOXICOLOGY](#)).

## **Respiratory**

### **Respiratory Depression**

Caution should be observed when prescribing XYREM to patients with compromised respiratory function. 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 [5 OVERDOSAGE](#)).

Prescribers should be aware that sleep apnea has been reported with a high incidence (even 50%) in some cohorts of narcoleptic patients.

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. Two other patients discontinued sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea.

Respiratory depression has been reported in clinical trials. 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.

The concomitant use of XYREM with other CNS depressants, including alcohol, opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating antiepileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression (see [2 CONTRAINDICATIONS](#); [3 SERIOUS WARNINGS AND PRECAUTIONS](#); [9.4 Drug-Drug Interactions](#); [9.3 Drug-Behavioural Interactions](#)).

## **7.1 Special Populations**

### **7.1.1 Pregnant Women**

#### **Pregnancy**

There are no adequate and well-controlled studies in pregnant women to establish the safe use of sodium oxybate during pregnancy or identify potential developmental risks associated

with the use of XYREM in pregnant women. Therefore, XYREM should only be used during pregnancy if the potential benefit outweighs the potential risk to the fetus.

In animal studies, oral administration of sodium oxybate to pregnant rats (0, 150, 350, or 1000 mg/kg/day) or rabbits (0, 300, 600, or 1200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity. The highest doses of sodium oxybate tested in rats and rabbits were approximately 1 and 3 times, respectively, the MRHD of 9 g per night on a body surface area (mg/m<sup>2</sup>) basis (see [16 NON-CLINICAL TOXICOLOGY](#)).

However, oral administration of sodium oxybate (0, 150, 350, or 1000 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring post-natal viability and body weight gain at the highest dose tested. The no-effect dose for pre- and post-natal developmental toxicity in rats is less than the MRHD on a mg/m<sup>2</sup> basis (see [16 NON-CLINICAL TOXICOLOGY](#)).

### Labour and Delivery

The use of XYREM during labour and delivery is not recommended unless clearly needed.

XYREM has not been studied in labour or delivery.

Placental transfer is rapid and gamma-hydroxybutyrate (GHB) has been detected in newborns at delivery after intravenous administration of GHB to mothers.

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.

Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

### **7.1.2 Breast-feeding**

GHB is excreted in human milk after oral administration of sodium oxybate. Caution should be exercised when XYREM is administered to a nursing woman.

There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XYREM and any potential adverse effects on the breastfed infant from XYREM or from the underlying maternal condition.

### **7.1.3 Pediatrics**

**Pediatrics (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. The effects of sodium oxybate on early growth, development, and maturation in children are not known. The use of XYREM is, therefore, not recommended in children under the age of 18, unless clearly needed.



#### 7.1.4 Geriatrics

There is very limited experience with sodium oxybate in patients greater than 65 years of age. In general, dose selection for elderly patients should start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concurrent disease or concomitant medications (see [4.2 Recommended Dose and Dosage Adjustment](#)). Elderly patients should be monitored closely for impaired motor and/or cognitive function when taking XYREM.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

A total of 448 narcoleptic patients were exposed to sodium oxybate in clinical trials. The most commonly observed adverse events associated with the use of sodium oxybate were: Headache 25%, nausea 21%, dizziness 17%, pain (unspecified) 16%, somnolence 13%, pharyngitis 11%, infection 10%, viral infection 10%, flu syndrome 9%, accidental injury 9%, diarrhea 8%, urinary incontinence 8%, vomiting 8%, rhinitis 8%, asthenia 8%, sinusitis 7%, nervousness 7%, back pain 7%, confusion 7%, sleepwalking 7%, depression 6%, dyspepsia 6%, abdominal pain 6%, abnormal dreams 6%, and insomnia 5%.

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

In these clinical trials, 13% of patients discontinued because of adverse events. The most frequent reasons for discontinuation (> 1%) were nausea (2%) and headache (1%).

Approximately 6% of patients receiving sodium oxybate in 3 controlled clinical trials (n=147) 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 in placebo-treated patients were: nausea (3%), somnolence (2%) and confusion (1%). Amnesia, asthenia, chest pain, dizziness, dyspnea, fecal incontinence, hallucinations, headache, hyperkinesia, paranoid reaction, thinking abnormal, vertigo, and vomiting, caused discontinuation in a single patient each.

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 4 lists the most commonly reported adverse events from controlled clinical trials associated with the use of sodium oxybate.

**Table 4 - Most Common Adverse Events Occurring at ≥ 5% in Controlled Clinical Trials**

<b>Adverse Event COSTART Term</b>	<b>Placebo (n=79)</b>	<b>Sodium Oxybate (n=147)</b>
Dizziness	3%	23%
Headache	15%	20%
Nausea	5%	16%
Somnolence	9%	12%
Pain (unspecified)	4%	12%
Sleep disorder	3%	9%
Confusion	1%	7%
Infection	1%	7%
Dyspepsia	6%	6%
Vomiting	1%	6%
Urinary incontinence	0%	5%
Nervousness	8%	5%

Table 5 lists the incidence of treatment-emergent adverse events in Trial 1 (see [14 CLINICAL TRIALS](#)). Events have been included for which there are at least two episodes in the considered drug group and for which the incidence in at least one dosage group is greater on drug than placebo.

**Table 5 - Incidence (%) of Treatment-Emergent Adverse Events in Trial 1**

<b>Body System COSTART Term</b>	<b>Placebo (n=34)</b>	<b>Sodium Oxybate Dose</b>		
		<b>3 g (n=34)</b>	<b>6 g (n=33)</b>	<b>9 g (n=35)</b>
<b><i>Body as a Whole</i></b>				
Asthenia	1 (3%)	0 (0%)	2 (6%)	0 (0%)
Flu Syndrome	0 (0%)	1 (3%)	0 (0%)	2 (6%)

Body System COSTART Term	Placebo (n=34)	Sodium Oxybate Dose		
		3 g (n=34)	6 g (n=33)	9 g (n=35)
Headache	7 (21%)	3 (9%)	5 (15%)	11 (31%)
Infection	1 (3%)	3 (9%)	5 (15%)	0 (0%)
Infection Viral	1 (3%)	1 (3%)	3 (9%)	0 (0%)
Pain	2 (6%)	3 (9%)	4 (12%)	7 (20%)
<b><i>Digestive System</i></b>				
Diarrhea	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Dyspepsia	2 (6%)	0 (0%)	3 (9%)	2 (6%)
Nausea	2 (6%)	2 (6%)	5 (15%)	12 (34%)
Nausea and Vomiting	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Vomiting	0 (0%)	0 (0%)	2 (6%)	4 (11%)
<b><i>Musculoskeletal System</i></b>				
Myasthenia	0 (0%)	2 (6%)	1 (3%)	0 (0%)
<b><i>Nervous System</i></b>				
Amnesia	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Anxiety	1 (3%)	1 (3%)	0 (0%)	2 (6%)
Confusion	1 (3%)	3 (9%)	1 (3%)	5 (14%)
Dizziness	2 (6%)	8 (24%)	10 (30%)	12 (34%)
Dream Abnormal	0 (0%)	0 (0%)	3 (9%)	1 (3%)
Hypertension	1 (3%)	0 (0%)	2 (6%)	0 (0%)
Hypoesthesia	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Sleep Disorder	1 (3%)	2 (6%)	4 (12%)	5 (14%)
Somnolence	4 (12%)	5 (15%)	4 (12%)	5 (14%)
Thinking Abnormal	0 (0%)	1 (3%)	0 (0%)	2 (6%)
<b><i>Skin</i></b>				
Increased Sweating	0 (0%)	1 (3%)	1 (3%)	4 (11%)

Body System COSTART Term	Placebo (n=34)	Sodium Oxybate Dose		
		3 g (n=34)	6 g (n=33)	9 g (n=35)
<b><i>Special Senses</i></b>				
Amblyopia	1 (3%)	2 (6%)	0 (0%)	0 (0%)
Tinnitus	0 (0%)	2 (6%)	0 (0%)	0 (0%)
<b><i>Urogenital System</i></b>				
Dysmenorrhea	1 (3%)	1 (3%)	0 (0%)	2 (6%)
Incontinence Urine	0 (0%)	0 (0%)	2 (6%)	5 (14%)

### 8.3 Less Common Clinical Trial Adverse Reactions

During clinical trials, sodium oxybate was administered to 448 patients with narcolepsy and 125 healthy volunteers. A total of 150 patients received 9 g/night, the maximum recommended dose. A total of 223 patients received sodium oxybate for at least one year. To establish the rate of adverse events, data from all subjects receiving any dose of sodium oxybate were pooled. All adverse events reported by at least two people are included except for those already listed elsewhere in the labeling, terms too general to be informative, or events unlikely to be drug-induced. These events are not necessarily related to sodium oxybate treatment.

**Body As A Whole:** >1%: allergic reaction, chills; 1% - 0.1%: abdomen enlarged, hangover effect, neck rigidity.

**Cardiovascular system:** 1% - 0.1%: syncope.

**Digestive system:** >1%: anorexia, constipation; 1% - 0.1%: mouth ulceration, stomatitis.

**Hemic and lymphatic system:** 1% - 0.1%: anemia, ecchymosis, leukocytosis, lymphadenopathy, polycythemia.

**Metabolic and nutritional:** >1%: alkaline phosphatase increased, edema, hypercholesterolemia, hypocalcemia, weight gain; 1% - 0.1%: bilirubinemia, creatinine increased, dehydration, hyperglycemia, hypernatremia, hyperuricemia, SGOT increased, SGPT increased, thirst.

**Musculoskeletal system:** >1%: arthritis, leg cramps, myalgia.

**Nervous system:** >1%: agitation, ataxia, convulsion, stupor, tremor; 1% - 0.1%: akathisia, apathy, coma, depersonalization, euphoria, hypertonia, libido decreased, myoclonus, neuralgia, paralysis.

**Respiratory system:** >1%: dyspnea; 1% - 0.1%: apnea, epistaxis, hiccup.

**Skin and appendages:** >1%: acne, alopecia, rash; 1% - 0.1%: contact dermatitis, urticaria.

**Special senses:** 1% - 0.1%: taste loss.

**Urogenital system:** >1%: albuminuria, cystitis, hematuria, metrorrhagia, urinary frequency; 1% - 0.1%: urinary urgency.

## 8.5 Post-Market Adverse Reactions

In addition to the adverse events reported during clinical studies and listed above, the following adverse reactions have been identified during post-approval use of XYREM (sodium oxybate) oral solution. Because these reactions are reported voluntarily from a population of uncertain size, reliable estimates of their frequency cannot be made. Adverse reactions that have been reported during post-marketing experience include: aggression, angioedema, arthralgia, decreased appetite, dry mouth, fall, fatigue, fluid retention, hypersensitivity, increased libido, memory impairment, nightmare, nocturia, panic attack, vision blurred, and weight decreased.

## 9 DRUG INTERACTIONS

### 9.1 Serious Drug Interactions

#### Serious Drug Interactions

- XYREM is contraindicated for use in combination with alcohol or sedative hypnotics.
- Use of other CNS depressants may potentiate the CNS-depressant effects of XYREM (see [2 CONTRAINDICATIONS](#); [9.4 Drug-Drug Interactions](#); [9.3 Drug-Behavioural Interactions](#)).

### 9.2 Drug Interactions Overview

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 µg/mL), a concentration that is considerably higher than the concentrations achieved with therapeutic doses.

The concomitant use of XYREM with other CNS depressants, including but not limited to alcohol, opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit central nervous system depressants, may potentiate the central nervous system depressant effects of sodium oxybate, increasing the risk of respiratory depression, hypotension, profound sedation, syncope, and death.

Anticonvulsants, such as divalproex sodium and topiramate may increase sodium oxybate exposure.

GHB dehydrogenase inhibitors, such as valproate and phenytoin, may reduce sodium oxybate metabolism and increase exposure.

Food may interfere with the absorption of sodium oxybate.

### 9.3 Drug-Behavioural Interactions

The combined use of alcohol (ethanol) or illicit CNS depressant drugs with sodium oxybate may result in potentiation of the CNS-depressant effects (respiratory depression, hypotension, profound sedation, syncope, and death) of sodium oxybate. Therefore, patients should be warned to avoid the consumption of any alcohol or use of illicit drugs in conjunction with sodium oxybate (see [2 CONTRAINDICATIONS](#); [3 SERIOUS WARNINGS AND PRECAUTIONS](#)).

### 9.4 Drug-Drug Interactions

**Table 6 – Established or Potential Drug-Drug Interactions**

Proper/Common name	Source of Evidence	Effect	Clinical comment
CNS depressants (e.g., benzodiazepines, barbituates, Z-drugs, GHB, opioid analgesics, sedating anti-depressants, sedating anti-psychotics, general anesthetics, muscle relaxants, alcohol)	C, T, CT	May potentiate CNS depressant effects of sodium oxybate.	XYREM is contraindicated for concomitant use with alcohol and sedative hypnotic agents (see <a href="#">2 CONTRAINDICATIONS</a> ).  XYREM should not be used in combination with sedative hypnotics or other CNS depressants, including alcohol (see <a href="#">2 CONTRAINDICATIONS</a> ; <a href="#">3 SERIOUS WARNINGS AND PRECAUTIONS</a> ).
divalproex sodium (anticonvulsant)	CT	25% increase in mean systemic exposure (AUC); C <sub>max</sub> was comparable; greater impairment in attention and working memory than either drug alone.	An initial dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking XYREM. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting XYREM dose when introducing XYREM.  Monitor patient response closely and adjust dose, accordingly, if concomitant use of XYREM and divalproex sodium is warranted.

topiramate (anticonvulsant)	C	Co-administration with sodium oxybate was associated with clinical observations of coma and elevated plasma GHB.	Monitor patient response closely and adjust dose, accordingly, if concomitant use of XYREM and topiramate is warranted.
GHB dehydrogenase inhibitors (e.g., phenytoin, valproate, ethosuximide)	T, CT	Co-administrations with sodium oxybate inhibits metabolism.  Sodium oxybate exposure is increased.	In patients taking phenytoin, enhanced sodium oxybate efficacy is expected. Use caution when considering the concomitant use of XYREM with GHB dehydrogenase inhibitors. Monitor patient response closely and adjust dose, accordingly.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

In drug-drug interaction studies in healthy adults, sodium oxybate, in combination with protriptyline hydrochloride, zolpidem tartrate, or modafinil, produced no significant pharmacokinetic changes for sodium oxybate or the other drugs. However, pharmacodynamic interactions cannot be excluded. Sodium oxybate should not be used in combination with sedative hypnotics or other CNS depressants, including alcohol (see [2 CONTRAINDICATIONS](#); [3 SERIOUS WARNINGS AND PRECAUTIONS](#)).

No clinically significant pharmacokinetic interactions were observed when XYREM was co-administered with diclofenac or ibuprofen.

### 9.5 Drug-Food Interactions

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%. Single doses greater than 4.5 g have not been studied. Patients should stop eating at least 2 hours prior to taking the first dose of XYREM, at bedtime (see [4.4 Administration](#)).

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established. Caution should be exercised when using XYREM in combination with herbal products thought to produce CNS depressant effects, such as those taken as sleep-aids (e.g., melatonin, valerian, kava) or anti-depressants (e.g., St. John's Wort).

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

The mechanism by which sodium oxybate (also known as gamma-hydroxybutyrate; GHB) produces its anti-cataplectic effects is unknown. Gamma hydroxybutyrate is a CNS depressant that produces dose-dependent sedation and anesthesia. GHB is also an endogenous compound that is widely found throughout the body although its function outside of the CNS is essentially unknown. Endogenous GHB appears to fulfill the criteria necessary to be considered a neurotransmitter or neuromodulator.

### 10.2 Pharmacodynamics

The pharmacodynamic response to sodium oxybate dosing (4.5 to 9 g/night) in terms of sleep architecture was characterized in 21 patients with narcolepsy. A dose-related increase in Stages 3 and 4 (slow-wave) sleep and delta power was noted, with improved sleep continuity represented by a dose-related decrease in the number of nighttime awakenings, without significant changes in total sleep time. Also noted were dose related decreases in total REM sleep and a decrease in Stage 1 sleep. No significant changes were seen in Stage 2 sleep nor the duration of wake after sleep onset. Measurement of daytime wakefulness utilizing the Maintenance of Wakefulness Test showed dose related increases in sleep latency and a dose related decrease in the percentage of patients with sleep-onset REM periods. A dose related decrease in the Epworth Sleepiness Score was also seen.

### 10.3 Pharmacokinetics

**Table 7 - Summary of XYREM Pharmacokinetic Parameters in Patients with Narcolepsy**

	<b>C<sub>max</sub></b> (µg/mL)	<b>T<sub>max</sub></b> (hr)	<b>t<sub>½</sub></b> (hr)	<b>AUC<sub>0-∞</sub></b> (µg*hr/mL)	<b>CL/F</b> (mL/min/kg)	<b>Vd/F</b> (mL/Kg)
<b>Single dose (4.5g) Mean (±SD)</b>	90 (30.8)	0.75*	0.67 (0.17)	226 (74.6)	4.0 (1.1)	226 (65.4)

\*Median is reported for T<sub>max</sub>

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 non-linear 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. The pharmacokinetics of XYREM in patients with narcolepsy is similar to the pharmacokinetics of XYREM in healthy participants.

#### **Absorption:**

Sodium oxybate is absorbed rapidly following oral administration with an absolute bioavailability of about 88%. 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 µg/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 increased 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 to 384 mL/kg. At sodium oxybate concentrations ranging from 3 to 300 µg/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<sup>+</sup>-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  $\alpha$ -ketoglutarate. An alternate pathway of biotransformation involves  $\beta$ -oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

### **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 and Conditions**

- **Pediatrics:** The pharmacokinetics of sodium oxybate in patients under the age of 18 years have not been studied.
- **Geriatrics:** The pharmacokinetics of sodium oxybate in patients greater than the age of 65 years have not been studied.
- **Sex:** 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.

The overall clinical trial 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 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.

- **Ethnic Origin:** There were too few non-Caucasian subjects in clinical trials to evaluate the effects of race on pharmacokinetics, safety or efficacy. More than 90% of the subjects in clinical trials were Caucasian.
- **Hepatic Insufficiency:** Sodium oxybate undergoes significant presystemic (hepatic first-pass) metabolism. The pharmacokinetics 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 pharmacokinetics 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 mL/min/kg 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 XYREM by one-half in patients with liver impairment (see [4.2 Recommended Dose and Dosage Adjustment](#)).
- **Renal Insufficiency:** Because the kidney does not have a significant role in the excretion of sodium oxybate, no pharmacokinetic study in patients with renal impairment has been conducted; no effect of renal function on sodium oxybate pharmacokinetics would be expected.

## 11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C and 30°C.

Following dilution, solutions prepared should be consumed within 24 hours to minimize bacterial growth and contamination.

Any unused XYREM should be returned to the pharmacy for proper disposal. Do not pour it down the drain.

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

## 12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions required.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

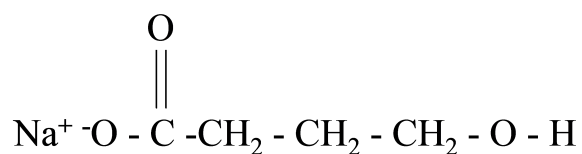
#### Drug Substance

Proper name: Sodium oxybate

Chemical name: Sodium 4-hydroxybutyrate

Molecular formula and molecular mass: C<sub>4</sub>H<sub>7</sub>NaO<sub>3</sub>, 126.09 grams/mole

Structural formula:



Physicochemical properties: Sodium oxybate is a white to off-white, crystalline powder. Freely soluble in water. Insoluble in acetone and ethanol. Melting point: 146°-149°C (after drying at 105°C for 45 min.)

### 14 CLINICAL TRIALS

#### 14.1 Clinical Trials by Indication

##### Treatment of Cataplexy in Patients with Narcolepsy

Table 8 - Summary of patient demographics for clinical trials in narcolepsy

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Trial 1	Multi-centre, double-blind, placebo-controlled, parallel-group trial	XYREM (3 g, 6 g, or 9 g) or placebo total daily doses for 4 weeks	136	43.06 years	Male: 57 Female: 79
Trial 2	Multi-centre, double-blind, placebo-controlled, parallel-group, randomized withdrawal trial	Continued treatment with XYREM at their stable dose or placebo	55	47.7 years	Male: 23 Female: 32

The effectiveness of sodium oxybate as an anti-cataplectic agent 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 central nervous system (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-centre, 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-centre, double-blind, placebo-controlled, parallel-group, randomized withdrawal trial that enrolled 55 narcoleptic patients who had been taking open-label sodium oxybate for 7 to 44 months. To be included, patients were required to have a history of at least 5 cataplexy attacks per week prior to any treatment for cataplexy. Patients were randomized to continued treatment with sodium oxybate at their stable dose or to placebo. Trial 2 was designed specifically to evaluate the continued efficacy of sodium oxybate after long-term use.

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

**Table 9 - Summary of Outcomes in Clinical Trials Supporting the Efficacy of Sodium Oxybate**

<b>Trial/Dosage Group g/night (n)</b>	<b>Baseline</b>	<b>Median Change From Baseline</b>	<b>Comparison to Placebo p-value</b>
<b>CATAPLEXY ATTACKS</b>			
<b>Trial 1</b>		<b>(median attacks/week)</b>	
Placebo (33)	20.5	-4	—
3.0 (33)	20.0	-7	0.5541
6.0 (31)	23.0	-10	0.0451
9.0 (33)	23.5	-16	0.0016
<b>Trial 2</b>		<b>(median attacks/two weeks)</b>	
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.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

**General Toxicology:** The acute toxicity of sodium oxybate has been studied in mice, rats, rabbits, and dogs primarily by parenteral routes of administration. Reported lethality (Lethal Dose of 50% [LD50]) ranges from 1700 mg/kg given intraperitoneally to 9990 mg/kg given orally in the rat.

In two repeat-dose toxicology studies, in rats orally administered sodium oxybate up to 26 weeks, transient hypoactivity, prostration, decreases in body weight and food consumption, and changes in serum chemistry (lower total protein and albumin) were noted at the highest dose tested (1000 mg/kg/day). The NOAEL was considered to be 350 mg/kg/day, associated with plasma exposures (AUC) of sodium oxybate less than that in humans at the maximum recommended human dose (MRHD) of XYREM (9 g/night).

In dogs, when orally dosed up to 52 weeks with sodium oxybate, clinical signs (emesis, soft feces, tremors, loss of appetite and thin appearance, hypoactivity, salivation, and prostration), decreased body weight and food consumptions, and atrophy/microscopic findings in the salivary and mucosal glands were noted at  $\geq 350$  mg/kg/day. The NOAEL was considered to be 150 mg/kg/day, associated with plasma exposures (AUC) of sodium oxybate less than that in humans at the MRHD.

**Genotoxicity:** Sodium oxybate was negative in the *in vitro* bacterial gene mutation assay, an *in vitro* chromosomal aberration assay in mammalian cells, and in an *in vivo* rat micronucleus assay.

**Carcinogenicity:** Administration of sodium oxybate to rats at oral doses of up to 1000 mg/kg/day for 83 (males) or 104 (females) weeks resulted in no increase in tumors. Decreased survival of males at 1000 mg/kg/day during the second half of the second year of the study resulted in discontinuance of test article administration in this sex group beginning in Week 83 of the study. Plasma exposure (AUC) at the highest dose tested was 2 times that in humans at the MRHD of 9 g per night.

The results of 2-year carcinogenicity studies in mouse and rat with gamma-butyrolactone, a prodrug that is rapidly and completely metabolized to sodium oxybate *in vivo*, showed no clear

evidence of carcinogenic activity. The plasma AUCs of sodium oxybate achieved at the highest doses tested in these studies were less than that in humans at the MRHD.

**Reproductive and Developmental Toxicology:** A Segment I fertility study was conducted in rats at doses of 150, 350, and 1000 mg/kg/day from 28 days (males) and 14 days (females) prior to mating. Females were treated through Day 7 of gestation. An effect on the overall reproductive performance was not observed in this study.

Segment II teratology studies, indicated that sodium oxybate was not teratogenic. In rats and rabbits no developmental toxicity was reported at dosages up to 1000 and 1200 mg/kg/day, respectively.

In a Segment III study of perinatal and postnatal effects, sodium oxybate was administered to pregnant rats at doses of 150, 350, and 1000 mg/kg/day from Day 6 of gestation through Day 20 of lactation. Pregnancy, implantation sites, and live birth indices were unaffected by treatment at any dose. There was an increase in postnatal mortality at 1000 mg/kg/day, and surviving pups showed lower rates of growth. Post-weaning behavioural and maturational assessments, including fertility, showed no drug-related effects. The no-effect dose in this study was 350 mg/kg/day.

**Juvenile Toxicity:** In a study in which sodium oxybate (0, 100, 300, or 900 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 21 through 90), mortality was observed at the two highest doses tested. Deaths occurred during the first week of dosing and were associated with clinical signs (including decreased activity and respiratory rate) consistent with the pharmacological effects of the drug. Administration of sodium oxybate had no adverse effects on sexual maturity, neurobehavioural assessments (acoustic startle habituation, spatial learning and memory, locomotor activity), estrous cycling, mating and fertility, ophthalmology, clinical pathology, ovarian and uterine examinations, sperm evaluations, organ weights, bone growth parameters (femur length and density), macro- and microscopic examinations, or neurohistopathology at doses up to 900 mg/kg/day. The NOAEL for general toxicity was considered to be 100 mg/kg/day while the NOAEL for growth and development was considered  $\geq$  900 mg/kg/day. **XYREM is not indicated for use in children under 18 years of age (see [1.1 Pediatrics](#); [7.1.3 Pediatrics](#)).**

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

XYREM®

#### Sodium Oxybate Solution

Read this carefully before you start taking **XYREM** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **XYREM**.

#### Serious Warnings and Precautions

##### Abuse and Misuse:

XYREM is a central nervous system (CNS) depressant that contains sodium oxybate, also known as gamma-hydroxybutyrate (GHB). Due to XYREM's CNS effects, even when taken as prescribed, there is potential for abuse or misuse.

Taking XYREM with alcohol or other CNS depressants (e.g., sedatives, tranquilizers and hypnotics) may increase the risk of serious medical problems. This includes seizures, difficulty breathing (respiratory depression), confusion, CNS depression, loss of consciousness, coma, and death. **Do NOT take XYREM with alcohol or other CNS depressants.**

Due to these risks, you must be enrolled in a patient safety program to receive XYREM. During your treatment, your healthcare professional will also regularly monitor your health. However, if you notice any side effects tell your healthcare professional. If you have any questions about XYREM, ask your healthcare professional or call the patient safety program at 1-866-599-7365.

#### What is XYREM used for?

XYREM is used to treat cataplexy (suddenly weak or paralyzed muscles) in adults with narcolepsy (attacks of sleep that cannot be controlled).

#### How does XYREM work?

The exact way XYREM works to reduce the number of cataplexy is not known.

#### What are the ingredients in XYREM?

Medicinal ingredient: sodium oxybate.

Non-medicinal ingredients: malic acid and purified water.

#### XYREM comes in the following dosage forms:

Oral solution: 500 mg/mL sodium oxybate.

**Do not use XYREM if:**

- you are allergic to sodium oxybate or any of the other ingredients of XYREM.
- you are taking or plan to take medicines that can cause sleepiness (e.g., other sleep medicines or sedatives).
- you are drinking or plan to drink alcohol. Do **not** consume any alcohol while taking XYREM.
- you have a rare condition called succinic semialdehyde dehydrogenase deficiency.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take XYREM. Talk about any health conditions or problems you may have, including if you:**

- have past or current depression. You may be more likely to get depressed taking XYREM. XYREM should not be used if you have major depression.
- have liver problems.
- have breathing or lung problems.
- have snoring problems or sleep apnea (a sleep disorder which causes pauses in breathing or shallow breathing while sleeping). You may be more likely to get serious side effects.
- are on a salt restricted diet. XYREM contains significant levels of sodium (salt) and may not be right for you. This can include if you have:
  - high blood pressure;
  - heart problems;
  - kidney problems.
- are pregnant or plan to become pregnant.
- are breastfeeding. XYREM can pass through your milk and may harm the baby.
- have a history of illicit or prescription drug abuse.
- have had previous thoughts or attempts of suicide.

**Other warnings you should know about:**

**Dependence and addiction:** There are important differences between dependence and addiction. It is important that you talk to your healthcare professional if you have questions or concerns about abuse, addiction, or dependence.

**Driving and using machines:** XYREM can affect your mental alertness. Do **NOT** drive or do tasks that require special attention for at least 6 hours after taking XYREM. In addition, before you drive or do tasks that require special attention the next day, wait until you know how you respond to XYREM. This is especially important when you first start taking XYREM.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**



### Serious Drug Interactions

Serious drug interactions exist with XYREM and CNS depressants (used to slow your brain down, relax your muscles, and provide a sense of calm). Do **not** take XYREM with the following CNS depressants:

- alcohol or medicines with alcohol
- sleep medicines or sedatives used to help with sleeping and anxiety;
- barbiturates used to relax the body and help with sleeping;
- benzodiazepines used to help you sleep or that help reduce anxiety.

Other CNS depressants are not recommended for use with XYREM. This includes:

- sedating antidepressants used to treat depression;
- sedating antiepileptic drugs used to prevent seizures;
- sedating antipsychotics used to treat mental health disorders;
- general anesthetics used during surgery;
- illicit CNS depressants;
- muscle relaxants used to treat muscle spasms and back pain;
- opioid analgesics used to relieve pain.

Talk to your healthcare professional if you take or plan to take any CNS depressants.

### The following may interact with XYREM:

- a high fat meal;
- herbal products such as sleep-aids (e.g., melatonin, valerian, and kava) or St. John's Wort.

### How to take XYREM:

- Take XYREM two times each night exactly as prescribed by your healthcare professional. The first dose is taken at bedtime and the second dose is taken 2.5 to 4 hours later while sitting in bed. You may need to set an alarm to awaken for the second dose.
- Food will affect the amount of XYREM that your body absorbs. Make sure to eat your last meal at least 2 hours before you take your first dose and go to bed. You should try to wait the same amount of time after your last meal each night before taking XYREM to ensure the timing is the same for each dose.
- You should lie down and remain in bed after taking your first and second dose of XYREM. XYREM can cause you to fall asleep quickly. Falling asleep while standing or while rising from the bed has led to falls and injuries which has required hospitalization.
- Prepare both doses of XYREM before bedtime. Each dose of XYREM must be diluted with a quarter ( $\frac{1}{4}$ ) cup (approximately 60 mL) of water or enough to fill  $\frac{3}{4}$  (three-

quarters) of the supplied pharmacy containers provided prior to ingestion and sealed with the child-resistant cap. The second dose should be placed in close proximity to your bed.

### Instructions for use:

Before starting your treatment with XYREM, be certain that you are completely familiar with the supplies needed for mixing and taking XYREM and the steps for preparation and use of XYREM.

Supplies you will need for mixing and taking XYREM (also see **Figure A**):

- the XYREM bottle;
- a dosing syringe for measuring and dispensing the XYREM doses;
- two empty pharmacy containers with child-resistant caps for mixing, storing, and taking the XYREM doses;
- the Patient Medication Information leaflet;
- a measuring cup that can measure about a quarter ( $\frac{1}{4}$ ) cup (approximately 60 mL) of water.

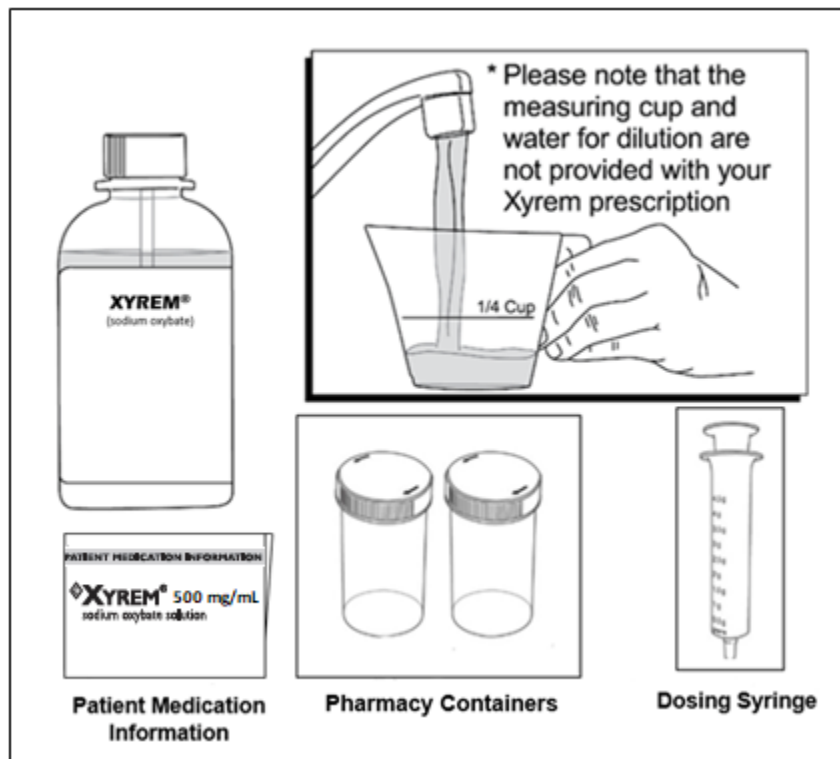
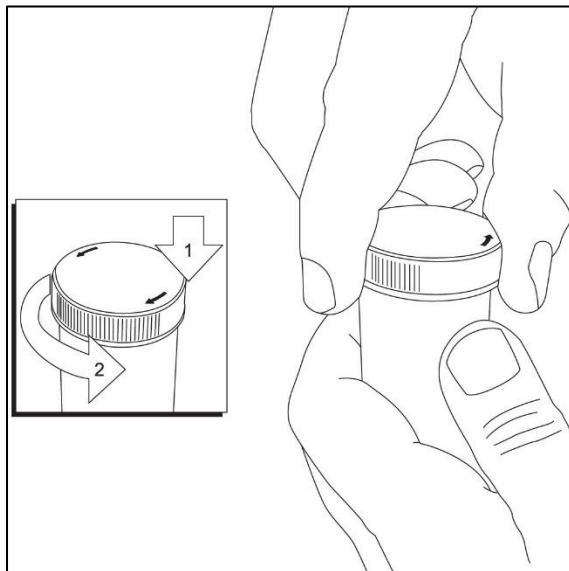


Figure A

### Step 1: Setup

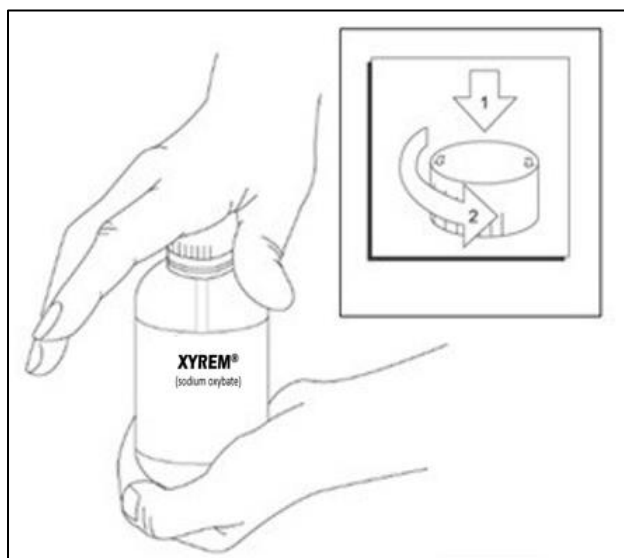
- a. Take the XYREM bottle and syringe out of the packaging.

- b. Remove the plastic wrapper from the syringe. Only use the syringe provided with your XYREM prescription.
- c. Fill a measuring cup with about a quarter ( $\frac{1}{4}$ ) cup (approximately 60 mL) of water.
- d. Open both pharmacy containers by pressing down on the child-resistant locking cap and turning the cap counterclockwise to the left (see **Figure B**). **Make sure the pharmacy containers are empty.**



**Figure B**

- e. Open the XYREM bottle by removing the child-resistant bottle cap by pushing down while turning the cap counterclockwise to the left (see **Figure C**).

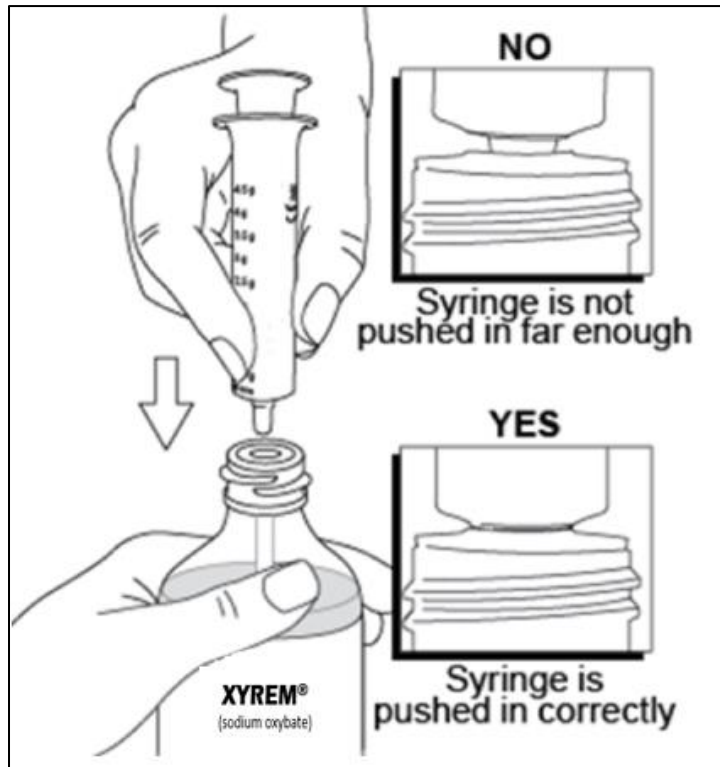


**Figure C**

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

**Step 2: Preparation of the First XYREM Dose** (prepare before bedtime)

- a. Place the XYREM bottle on a hard, flat surface and grip the bottle with one hand.
- b. Firmly press the syringe into the center opening of the bottle with your other hand (See **Figure D**).



**Figure D**

- c. On the syringe, identify the specific amount in grams (g) that matches your prescribed dose.

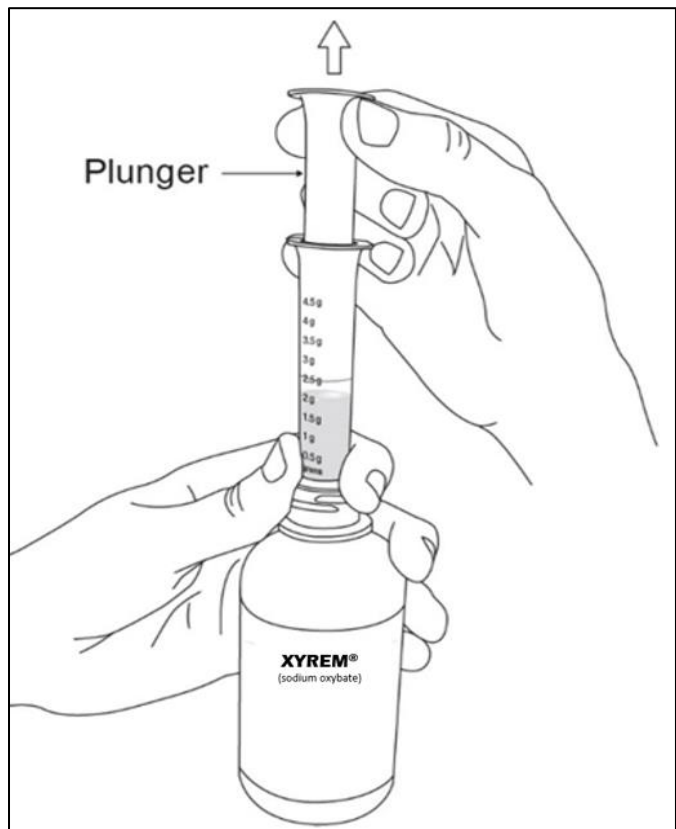
The measuring device is an oral syringe with markings only in grams. In case you need the dose in millilitres (mL), you can consult the conversion tables below:

Single dose in grams (to be taken twice per night)	Single dose in mL (to be taken twice per night)
1.5 grams	3 mL
2.25 grams	4.5 mL
3 grams	6 mL
3.75 grams	7.5 mL

Single dose in grams (to be taken twice per night)	Single dose in mL (to be taken twice per night)
4.5 grams	9 mL

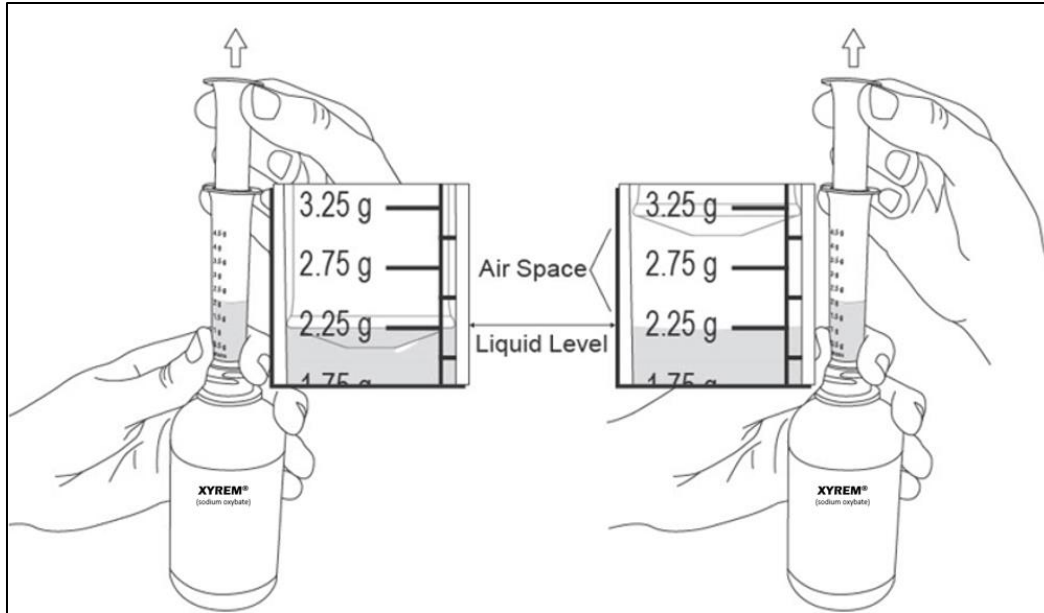
Total dose per night in grams	Total dose per night in mL
3 grams	6 mL
4.5 grams	9 mL
6 grams	12 mL
7.5 grams	15 mL
9 grams	18 mL

- d. Pull up on the plunger on the syringe until the medicine flows into the syringe and the liquid level is lined up with the marking on the syringe that matches your prescribed dose (see **Figure E**). Keep the bottle upright so that the XYREM medicine will flow into the syringe.



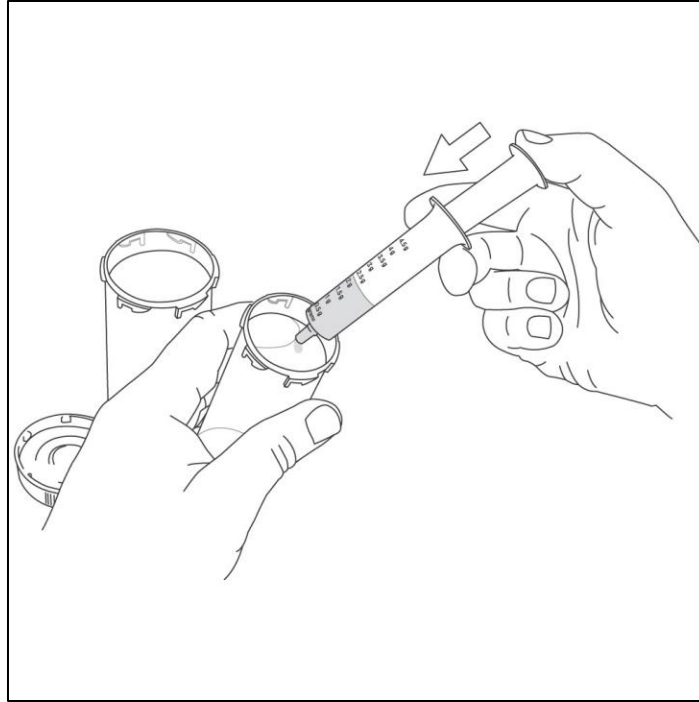
**Figure E**

**Note:** Make sure that the **liquid level** lines up with the marking on the syringe that matches your prescribed dose even if an air space forms between the plunger and the liquid (see **Figure F** for an example of drawing up 2.25 g).



**Figure F**

- e. After you draw up the first divided dose, remove the syringe from the opening of the XYREM bottle.
- f. Empty all of the medicine from the syringe into one of the provided **empty** pharmacy containers by pushing down on the plunger until it stops (see **Figure G**).



**Figure G**

- g. Using a measuring cup, pour about a quarter ( $\frac{1}{4}$ ) cup (approximately 60 mL) of water into the pharmacy container with the first dose of XYREM solution. **Be careful to add only water to the pharmacy container and not more XYREM.**
- h. Place the child-resistant cap on the pharmacy container and turn the cap clockwise to the right until it clicks and locks into its child-resistant position (see **Figure H**).



**Figure H**

### **Step 3: Preparation of the Second XYREM Dose** (prepare before bedtime)

- a. Repeat **Step 2** drawing up the amount of medicine prescribed for your second dose.
- b. Empty the syringe into the second pharmacy container.
- c. Add a quarter ( $\frac{1}{4}$ ) cup (approximately 60 mL) of water into the pharmacy container with the second dose of XYREM solution. **Be careful to add only water to the pharmacy container and not more XYREM.**
- d. Place the child-resistant cap on the pharmacy container and turn the cap clockwise to the right until it clicks and locks into its child-resistant position (see **Figure H**).

### **Step 4: Storing the Prepared XYREM Doses and Cleaning the Syringe**

- a. Put the cap back on the XYREM bottle and store the XYREM bottle and both prepared doses in a safe and secure place. Store in a locked place if needed.
- b. Keep the XYREM bottle and both prepared XYREM doses out of the reach of children and pets.
- c. Rinse the syringe out with water and squirt the liquid into the sink drain by pushing down on the plunger until it stops.

### **Step 5: Taking the First XYREM Dose**

- a. At bedtime, and before you take the first XYREM dose, put the second XYREM dose in a secure location (locked up if appropriate) near your bed. You may want to set an alarm clock for 2.5 to 4 hours later to make sure you wake up to take the second dose.
- b. When it is time to take the first XYREM dose, remove the cap from the pharmacy container by pressing down on the child-resistant locking cap and turning the cap counterclockwise to the left.
- c. Drink all of the first XYREM dose while sitting in bed. Put the cap back on the first pharmacy container and immediately lie down to sleep.
- d. You should fall asleep soon. Some people fall asleep within 5 minutes and most fall asleep within 15 minutes. Some patients take less time to fall asleep, and some take more time. The time it takes you to fall asleep might be different from night to night.

### **Step 6: Taking the Second XYREM Dose**

- a. When you wake up 2.5 to 4 hours later for your second dose of XYREM, take the cap off the second pharmacy container by pressing down on the child-resistant locking cap and turning the cap counterclockwise to the left.
- b. If you wake up before the alarm and it has been at least 2.5 hours since the first XYREM dose, turn off the alarm and take the second XYREM dose.
- c. Drink all of the second XYREM dose while sitting in bed. Put the cap back on the second pharmacy container and immediately lie down to continue sleeping.



**Usual dose:**

Your healthcare professional will decide the right dose of XYREM for you. This will depend on your condition, age, health, and if you take certain other medications.

You will discuss your response to XYREM with your healthcare professional and they may adjust your dose every two weeks. Never change the dose of XYREM yourself.

**Overdose:**

If you think you, or a person you are caring for, have taken too much XYREM, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

In the event a dose is missed, that dose should be skipped. If the first dose is missed, that dose should be skipped and the second dose taken. Two XYREM doses should never be taken at one time. If a first dose is taken and the second dose is missed, that dose should be skipped and XYREM should not be taken again until the next night.

**What are possible side effects from using XYREM?**

These are not all the possible side effects you may have when taking XYREM. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects of XYREM are:

- bed-wetting during the night. To help prevent bed-wetting, make sure you go to the bathroom before taking your first dose of XYREM.
- confusion.
- dizziness.
- frequent urination.
- headache.
- nausea.
- sleep problems.
- vomiting.

Other possible side effects from using XYREM may include:

- accidental injury and falls;
- acne;
- akathisia (a movement disorder that makes it hard to stay still);
- anorexia (an eating disorder characterized by low body weight);
- bleeding outside of the menstrual cycle;
- bruising;
- chills;

- complete or partial loss of feeling or sensation in an area of the body (hypoesthesia);
- dehydration or thirst;
- dry mouth;
- enlarged abdomen size;
- flu symptoms;
- hair loss;
- hangover effects;
- hiccups;
- increased sweating;
- infection, including viral infection;
- involuntary and rhythmic shaking;
- leg cramps;
- mouth ulcers or sores;
- muscle aches, pain, or weakness;
- neck rigidity;
- nervousness;
- panic attack;
- weight decreased.

### Effects of abusing (misusing) XYREM (GHB)

GHB (gamma-hydroxybutyrate) can be a drug of abuse if used improperly, and some people who repeatedly abuse GHB become addicted to it. People who repeatedly abuse GHB at high frequency and at high doses can develop withdrawal symptoms. These symptoms include the need to continue taking the drug, anxiety, trouble sleeping, and abnormal thinking.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>COMMON</b>			
<b>Allergic reaction:</b> difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives, rash, or swelling of the face, lips, tongue or throat.			✓
<b>Behavioural or mental changes:</b> psychosis, paranoia, hallucinations, anxiety, irritability, hostility,		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
aggression, agitation, memory impairment, or abnormal thinking.			
<b>Central nervous system (CNS) depression</b> (brain slows down): respiratory depression (slow, shallow or weak breathing), low blood pressure, drowsiness, loss of consciousness, or coma.			✓
<b>Depression</b> (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive), or thoughts of death or suicide.		✓	
<b>Eye problems:</b> vision blurred in one or both eyes, or vision changes.	✓		
<b>Hypertension</b> (high blood pressure)		✓	
<b>Seizures</b> (fit): loss of consciousness with uncontrollable shaking.			✓
<b>Sleeping problems:</b> abnormal dreams, nightmares, sleep walking, sleep apnea (stop breathing for short periods during your normal nightly sleep), insomnia (hard to fall asleep and hard to stay asleep), or confused behaviour occurring at night.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

## Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

## Storage:

- Always store XYREM at room temperature (15°C to 30°C), in the original bottle.
- Always keep XYREM and your nightly doses out of the reach and sight of children and pets in a safe and secure place (locked up if appropriate).
- Return any unused XYREM to your pharmacy for proper disposal. Do not pour it down the drain.

## If you want more information about XYREM:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website [www.jazzpharma.com](http://www.jazzpharma.com), or by calling the patient safety program at 1-866-599-7365.

This leaflet was prepared by Jazz Pharmaceuticals Ireland Limited.

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