PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

XYREM®

Sodium Oxybate Solution

Solution, 500 mg/mL, Oral

Must be diluted before use

Central Nervous System Depressant

Jazz Pharmaceuticals Ireland Limited
5th Floor- Waterloo Exchange
Waterloo Road
Ireland- Dublin 4

Date of Authorization:
2025-01-23

Importer and Distributor: Innomar Strategies Inc.
3470 Superior Court, Oakville, Ontario L6L 0C4
Canada

Submission Control Number: 289933

RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations	01/2025
4 DOSAGE AND ADMINISTRATION, 4.2.2 Dosing in Special Populations and Conditions	01/2025
7 WARNINGS AND PRECAUTIONS	01/2025

TABLE OF CONTENTS

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

XYREM (sodium oxybate) oral solution is indicated for:

- 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.

Distribution restrictions:

XYREM is only available through a controlled distribution program. Under this program, only prescribers and pharmacists registered with the program are able to prescribe and dispense the product. In addition, XYREM can only be dispensed to patients who are registered and meet all the conditions of the program. Please call 1-866-599-7365 or write to XSP@innomar-strategies.com to obtain information about the program (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 4.1 Dosing Considerations and 7 WARNINGS AND PRECAUTIONS, Controlled Distribution Program).

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.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): There is limited experience with XYREM in the geriatric population (see 4.2.2 Dosing in Special Populations and Conditions, Geriatrics (≥ 65 years of age); 7.1.4 Special Populations, Geriatrics (≥ 65 years)).

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 (see 7 WARNINGS AND PRECAUTIONS, Neurologic; 9 DRUG INTERACTIONS).
- with concomitant use of alcohol (see 7 WARNINGS AND PRECAUTIONS, Neurologic; 9 DRUG INTERACTIONS).
- in patients with succinic semialdehyde dehydrogenase deficiency (see 10.3 Pharmacokinetics). This rare disorder is an inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

- **XYREM is a central nervous system (CNS) depressant with abuse potential and should not be used with alcohol, other CNS depressants, or for the treatment of indications other than cataplexy in patients with narcolepsy.**

- Clinically significant respiratory depression and obtundation, confusion, depression and other neuropsychiatric events may occur in patients treated with XYREM at recommended doses (see 7 WARNINGS AND PRECAUTIONS, Neurologic and 7 WARNINGS AND PRECAUTIONS, Psychiatric).

- The active moiety of XYREM is oxybate or gamma-hydroxybutyrate (GHB), a substance with known abuse potential. Abuse or misuse of GHB, either alone or in combination with other CNS depressants, is associated with important CNS adverse reactions, including seizure, respiratory depression, profound decreases in level of consciousness, coma, and death (see 7 WARNINGS AND PRECAUTIONS, Abuse and Misuse).

- Due to the risks of CNS depression and abuse and misuse, XYREM is available only through a controlled distribution program (see 7 WARNINGS AND PRECAUTIONS, Controlled Distribution Program).

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) Enrollment in Controlled Distribution Program.

- Oxybate, the active ingredient in XYREM, is also known as gamma-hydroxybutyrate (GHB). Due to the known abuse potential of GHB, physicians should evaluate patients for their history of drug use (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7 WARNINGS AND PRECAUTIONS, Abuse and Misuse).
- Patients should be advised not to consume alcohol in combination with XYREM (see 2 CONTRAINDICATIONS; 9.3 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, Special Populations and Conditions).
- Concomitant use of XYREM with divalproex sodium may result in higher exposures of GHB. An initial dose reduction of at least 20% of XYREM is recommended when used concomitantly with divalproex sodium (see 4.2.2 Dosing in Special Populations and Conditions, Co-administration with Divalproex Sodium; 9.4 Drug-Drug Interactions).
- XYREM is an oral liquid that must be diluted prior to ingestion (see 4.3 Reconstitution).
- High Sodium Content

  Each mL of XYREM oral solution contains 91 mg of sodium, resulting in a high sodium load at effective doses (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING, Table 3). Sodium content should be considered when prescribing XYREM, especially for patients with conditions requiring salt restrictions such as hypertension, congestive heart failure, or compromised renal function. It is recommended to assess blood pressure before initiating treatment with XYREM, monitor blood pressure regularly during treatment, and if deemed appropriate, instruct patients to limit their sodium intake (see 7 WARNINGS AND PRECAUTIONS, High Sodium Content).

4.2 Recommended Dose and Dosage Adjustment

4.2.1 Initiating Treatment

- **Adults (≥ 18 years of age)**

XYREM should be titrated to effect. The recommended nightly oral starting dose is 4.5 grams (g), 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 dosages of 6 to 9 g/night. The efficacy and safety of XYREM at dosages higher than 9 g/night have not been investigated, and dosages 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).

XYREM must be diluted before administration (see 4.3 Reconstitution).

4.2.2 Dosing in Special Populations and Conditions

- **Pediatrics (< 18 years of age)**

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

- **Geriatrics (≥ 65 years of age)**

There is 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 Impairment**

Patients with compromised liver function will have a longer elimination half-life and greater systemic exposure, along with reduced clearance (see 10.3 Pharmacokinetics, Special Populations and Conditions and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic). The starting dose should be decreased by one-half (½) and dose increments should be titrated to effect, while closely monitoring potential adverse events.

- **Patients with Renal Impairment**

Because less than 5% of unchanged drug 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.

Healthcare providers may consider advising patients with impaired renal function to reduce their sodium intake (see 7 WARNINGS AND PRECAUTIONS, High Sodium Content).

- **Co-administration with Divalproex Sodium**

When initiating divalproex sodium in patients taking a stable dosage of XYREM, a reduction of the XYREM dosage by at least 20% is recommended with initial concomitant use (see 9.4 Drug-Drug Interactions). When initiating XYREM in patients already taking divalproex sodium, a lower starting dosage of XYREM is recommended. Subsequently, the dosage of XYREM can be adjusted based on individual clinical response and tolerability.

4.2.3 Discontinuing Treatment

The discontinuation effects of XYREM have not been systematically evaluated in controlled clinical trials (see 14 CLINICAL TRIALS). Abrupt discontinuation in clinical trials resulted in symptoms consistent with re-emerging narcolepsy. In some patients, cataplexy may return at a higher frequency upon cessation. This may be due to the normal variability of the disease.

Although the clinical trial experience with XYREM at therapeutic doses does not show clear evidence of a withdrawal syndrome, events such as insomnia, restlessness, headache, anxiety, dizziness, rebound fatigue and sleepiness, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, confusion, hallucination, and psychotic disorders were observed following discontinuation of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the recommended dosage range (see 7 WARNINGS AND PRECAUTIONS, Withdrawal).

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, Instructions for use for a complete description.

Prior to ingestion, each dose of XYREM must be diluted with approximately 60 mL (2 oz or ¼ cup) of water or enough to fill ¾ 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

Total Nightly Dose (g)	Total Nightly Dose (mL)	Single Dose (taken twice nightly) (g)	Single Dose (taken twice nightly) (mL)
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.

Prepare all doses of XYREM prior to bedtime. Prior to ingestion, each dose of XYREM must be diluted with approximately ¼ cup (approximately 60 mL) of water in the empty pharmacy-provided containers (see 4.2 Recommended Dose and Dosage Adjustment; 4.3 Reconstitution and PATIENT MEDICATION INFORMATION, Instructions for use). Solutions prepared following dilution should be sealed with a child-resistant cap until use and consumed within 24 hours.

Patients should take each dose of XYREM while in bed and lie down immediately after dosing and remain in bed following ingestion of each dose. XYREM may cause patients to fall asleep abruptly without first feeling drowsy (see 7 WARNINGS AND PRECAUTIONS, Falls).

Patients will often fall asleep within 5 minutes of taking XYREM, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night.

Patients may need to set an alarm to awaken for the second dose. If the second dose is missed or delayed, see section 4.5 Missed Dose. Two XYREM doses should never be taken at one time.

4.5 Missed Dose

Two XYREM doses should never be taken at one time.

If the initial bedtime dose is missed or delayed, take it as soon as it is remembered. A second dose may be taken 2.5 to 4 hours later only if there is sufficient sleep time prior to waking, otherwise, the second dose should be skipped.

If the second dose is missed or delayed, it should only be taken if there is sufficient sleep time prior to waking, otherwise, that dose should be skipped.

If insufficient sleep time has passed since the last dose has been taken, patients should be cautioned not to engage in hazardous activities or activities requiring complete mental alertness (see

7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery).

5 OVERDOSAGE

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 regarding overdose with sodium oxybate is primarily extrapolated from literature reports of toxicity from illicit use of GHB. In these circumstances the co-ingestion of other drugs and alcohol is common, and this, together with the dose ingested, the time since ingestion, the co-ingestion of other drugs and alcohol, and the fed or fasted state may influence the presentation and severity of clinical manifestations of overdose.

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.

Recommended Treatment of Overdose

General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid- sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with GHB overdose has been responsive to 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 or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Solution 500 mg/mL sodium oxybate	malic acid purified water, USP

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 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 and a patient medication information leaflet.

Sodium Content in XYREM

XYREM contributes to the patient's total daily sodium intake. The sodium content per total nightly dose of XYREM is presented in **Table 3** for reference.

While Health Canada's Chronic Disease Risk Reduction Intakes (CDRR) value for sodium is 2,300 mg/day for healthy adults, this limit may not apply to all individuals (see 7 WARNINGS AND PRECAUTIONS, High Sodium Content).

Table 3 - Sodium Content per Total Nightly XYREM Dose

Total Nightly Dose* (g)	Total Nightly Dose (mL)	Sodium Content/Total Nightly Dose	Contribution to the Recommended Maximum Daily Intake in Healthy Adults (2,300 mg)
3	6	546 mg	24%
4.5	9	819 mg	36%
6	12	1092 mg	47%
7.5	15	1365 mg	59%
9	18	1638 mg	71%

*The effective dose range is 6 g to 9 g per night.
Note: Sodium guidelines are subject to change. Healthcare providers should consult the most up-to-date recommendations.

7 WARNINGS AND PRECAUTIONS

See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Controlled Distribution Program

XYREM is available only through a controlled distribution program because of the risks of central

nervous system (CNS) depression, abuse, and misuse.

Healthcare professionals who prescribe XYREM should be educated and enrolled in the controlled distribution program.

XYREM will be dispensed only by enrolled pharmacies in the controlled distribution program.

XYREM will be dispensed only to patients who are enrolled in the controlled distribution program with documentation of their knowledge of safe use. Enrollment ensures there is documentation the patient has been educated on XYREM preparation, dosing, and scheduling.

Abuse and Misuse

XYREM is classified as a Schedule I controlled substance.

Sodium oxybate, also known as gamma-hydroxybutyrate (GHB), is a CNS depressant with a risk for abuse and misuse. Sodium oxybate is a psychoactive drug that produces a wide range of pharmacological effects. It is a sedative-hypnotic that produces dose-dependent CNS effects. The onset of effect is rapid, enhancing its potential for 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 some commonalties 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, abuse and diversion of GHB have been reported, healthcare professionals should carefully evaluate patients for a history of drug use and monitor patients closely. Evidence of concerning use may include, but not be limited to, increase in size or frequency of dosing, drug-seeking behaviour, or feigned cataplexy. If inappropriate use is suspected, treatment with XYREM should be discontinued.

Falls

Patients will often fall asleep within 5 minutes of taking XYREM. 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 be advised to remain in bed following ingestion of XYREM.

High Sodium Content

XYREM contains a high amount of sodium with each mL of the oral solution containing 91 mg of sodium, contributing 1,638 mg of sodium for a maximum recommended nightly dosage (see 4.1 Dosing Considerations; 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING, Table 3). Exercise caution when using XYREM due to high sodium content. Evidence linking the sodium content of XYREM to increased cardiovascular risks in narcoleptic patients is limited. However, in the general population, high sodium intake is linked to elevated blood pressure which is associated with an increased risk of hypertension and major adverse cardiovascular events (MACE). Patients with narcolepsy frequently have multiple risk factors for MACE, including hypertension, diabetes, obstructive sleep apnea, hyperlipidemia and high body mass index (BMI). Patients with renal impairment, older adults, and those with preexisting cardiovascular conditions are at particular risk from excess sodium intake.

Sodium content should be taken into account when prescribing XYREM, especially for patients with preexisting conditions requiring salt restrictions such as hypertension, congestive heart failure, or compromised renal function. It is recommended for healthcare providers to assess blood pressure

before initiating treatment with XYREM, monitor blood pressure regularly during treatment, and if deemed appropriate, instruct patients to limit their sodium intake.

Dependence/Tolerance

Dependence

Cases of severe dependence and craving for GHB have been reported when the drug is taken around the clock. Patterns of use indicative of dependence include: 1) use of increasing doses, 2) increased frequency of use, and 3) continued use despite adverse consequences.

There have been case reports of dependence after illicit use of GHB at frequent repeated doses in excess of the therapeutic dose range.

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 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.

Withdrawal

There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 to 250 g/day) in excess of the recommended dosage range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal visual hallucinations, agitation and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required.

In XYREM clinical trial in adult narcolepsy/cataplexy patients at recommended doses, 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 at the same time.

Driving and Operating Machinery

Healthcare professionals should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that XYREM does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking XYREM.

Patients should be asked about CNS depression-related events upon initiation of XYREM therapy and periodically thereafter.

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 including Respiratory Depression

XYREM is a CNS depressant. Clinically significant obtundation and respiratory depression has occurred in clinical trials in adult patients taking XYREM at recommended doses. XYREM is contraindicated in combination with alcohol and sedative hypnotics. See also 7 WARNINGS AND PRECAUTIONS, Respiratory.

XYREM may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses of oxybate and illicit use of GHB, life-threatening respiratory depression, profound decreases in level of consciousness, with instances of seizure, coma and death have been reported (see 5 OVERDOSAGE).

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 BOX; 9.3 Drug-Behavioural Interactions; 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.

Many patients who received XYREM during the clinical trial to assess cataplexy in patients with narcolepsy were also receiving CNS stimulants (see 14 CLINICAL TRIALS).

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.

The emergence or increase in the occurrence of behavioural of psychiatric events in patients taking XYREM should be carefully monitored.

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

Parasomnia can occur with patients taking XYREM, including sleepwalking, abnormal dreams, sleep-related eating disorder, abnormal sleep-related event, nightmare, abnormal rapid eye movements sleep, sleep talking and sleep terror.

Parasomnias, including sleepwalking can be associated with significant injury. 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 4.1 Dosing Considerations, High Sodium Content and 7 WARNINGS AND PRECAUTIONS, High Sodium Content).

Reproductive Health

- **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^2) basis (see 16 NON-CLINICAL TOXICOLOGY,

Reproductive and Developmental Toxicology).

Respiratory

XYREM may impair respiratory drive. Caution should be observed when prescribing XYREM to patients with compromised respiratory function (see 7 WARNINGS AND PRECAUTIONS, Neurologic). Respiratory depression has been observed in clinical trial with sodium oxybate.

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. In a dedicated study assessing the respiratory depressant effects of XYREM, at recommended doses, in 21 patients with narcolepsy, 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.

Sleep apnea has been reported with a high incidence (even 50%) in some cohorts of narcoleptic patients. Increase apnea and reduced oxygenation may occur with XYREM administration. A significant increase in the number of central apneas and clinically significant oxygen desaturation may also occur in patients with obstructive sleep apnea treated with XYREM.

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. Animal reproduction studies are not always predictive of human response. 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^2) basis (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental 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^2 basis (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental 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 (< 18 years)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics (≥ 65 years)

There is 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

Adverse Event COSTART Term	Placebo (n=79)	Sodium Oxybate (n=147)
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

Body System COSTART Term	Placebo (n=34)	Sodium Oxybate Dose		
		3 g (n=34)	6 g (n=33)	9 g (n=35)
Body as a Whole				
Asthenia	1 (3%)	0 (0%)	2 (6%)	0 (0%)
Flu Syndrome	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Headache	7 (21%)	3 (9%)	5 (15%)	11 (31%)
Infection	1 (3%)	3 (9%)	5 (15%)	0 (0%)
Infection Viral	1 (3%)	1 (3%)	3 (9%)	0 (0%)
Pain	2 (6%)	3 (9%)	4 (12%)	7 (20%)
Digestive System				
Diarrhea	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Dyspepsia	2 (6%)	0 (0%)	3 (9%)	2 (6%)
Nausea	2 (6%)	2 (6%)	5 (15%)	12 (34%)
Nausea and Vomiting	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Vomiting	0 (0%)	0 (0%)	2 (6%)	4 (11%)
Musculoskeletal System				
Myasthenia	0 (0%)	2 (6%)	1 (3%)	0 (0%)
Nervous System				
Amnesia	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Anxiety	1 (3%)	1 (3%)	0 (0%)	2 (6%)
Confusion	1 (3%)	3 (9%)	1 (3%)	5 (14%)
Dizziness	2 (6%)	8 (24%)	10 (30%)	12 (34%)
Dream Abnormal	0 (0%)	0 (0%)	3 (9%)	1 (3%)
Hypertension	1 (3%)	0 (0%)	2 (6%)	0 (0%)
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%)
Skin				
Increased Sweating	0 (0%)	1 (3%)	1 (3%)	4 (11%)
Special Senses				
Amblyopia	1 (3%)	2 (6%)	0 (0%)	0 (0%)
Tinnitus	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Urogenital System				
Dysmenorrhea	1 (3%)	1 (3%)	0 (0%)	2 (6%)

Body System COSTART Term	Placebo (n=34)	Sodium Oxybate Dose		
		3 g (n=34)	6 g (n=33)	9 g (n=35)
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, hostility, hypersensitivity, increased libido, memory impairment, nightmare, nocturia, paranoia, psychosis, panic attack, vision blurred, and weight decreased.

*The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization (see 7 WARNINGS AND PRECAUTIONS, Falls).

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; 9.3 Drug-Behavioural Interactions; 9.4 Drug-Drug Interactions).

9.2 Drug Interactions Overview

Interactions between sodium oxybate and three drugs commonly used in patients with narcolepsy (zolpidem tartrate, protriptyline hydrochloride, and modafinil) have been evaluated in formal studies in healthy adults. Drug-drug interaction studies in healthy adults (18 to 50 years of age) were also conducted with sodium oxybate and divalproex sodium, diclofenac and ibuprofen.

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), a level considerably higher than levels achieved with recommended doses.

9.3 Drug-Behavioural Interactions

The combined use of alcohol (ethanol) with XYREM may result in potentiation of the CNS-depressant effects of XYREM. Therefore, patients should be warned to avoid the use of any alcoholic beverage in conjunction with sodium oxybate (see 2 CONTRAINDICATIONS).

The concurrent use of XYREM with other CNS depressants, including but not limited to opioids, benzodiazepines, barbiturates, ketamine, muscle relaxants, cannabis, and other sedatives, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. Patients should be warned to avoid the use of other CNS depressants in conjunction with XYREM.

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, barbiturates, 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 should not be used in combination with sedative hypnotics or other CNS depressants, including alcohol (see 2 CONTRAINDICATIONS; 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7 WARNINGS AND PRECAUTIONS, Neurologic).
divalproex sodium (anticonvulsant)	CT	25% increase in mean systemic exposure (AUC); C_{max} 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-administration with sodium oxybate inhibits metabolism. Sodium oxybate exposure is increased.	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. In addition, drug interaction studies in healthy adults demonstrated no pharmacokinetic or clinically significant pharmacodynamic interactions between sodium oxybate and duloxetine HCl.

No clinically significant pharmacokinetic interactions were observed when sodium oxybate 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

	C_{max} (mcg/mL)	T_{max} (hr)	$t_{½}$ (hr)	$AUC_{0-\infty}$ (mcg*hr/mL)	CL/F (mL/min/kg)	Vd/F (mL/Kg)
Single dose (4.5g) Mean (±SD)	90 (30.8)	0.75*	0.67 (0.17)	226 (74.6)	4.0 (1.1)	226 (65.4)

*Median is reported for T_{max}

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+-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.

Elimination:

The clearance of GHB 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. GHB has an elimination half-life of 0.66 hours.

Special Populations and Conditions

- **Pediatrics:** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.
- **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 t½ of 59 and 32 versus 22 minutes). The starting dose of XYREM should be reduced by half in patients with hepatic 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

XYREM should be stored between 15°C and 30°C.

Following dilution in the pharmacy containers, the preparation should be used 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 and to persons to whom it is not prescribed.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions required.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

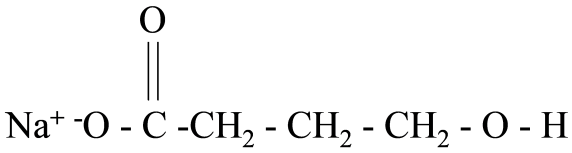
Drug Substance

Proper name: Sodium oxybate

Chemical name: Sodium 4-hydroxybutyrate

Molecular formula and molecular mass: $C_4H_7NaO_3$, 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 for the treatment of cataplexy 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

Trial/Dosage Group g/night (n)	Baseline	Median Change From Baseline	Comparison to Placebo p-value
CATAPLEXY ATTACKS			
Trial 1		(median attacks/week)	
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
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.

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 ≥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 ≥ 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 (< 18 years)).**

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:

The main active component of XYREM is oxybate, or gamma-hydroxybutyrate (GHB), a known drug of abuse. Abuse or misuse of GHB, either alone or when taken with other central nervous system (CNS) depressants may cause serious medical problems, including seizures, difficulty breathing (respiratory depression), decreases in the level of consciousness, coma, and death. **Do NOT take XYREM with alcohol or other CNS depressants.** This includes the following examples of CNS depressants:

- opioids,
- benzodiazepines,
- barbiturates,
- ketamine,
- muscle relaxants,
- cannabis, and
- other sedatives.

Due to these risks, you must be enrolled in a 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 program at 1-866-599-7365.

XYREM can also cause serious side effects when taken as prescribed, including:

- **CNS depression:**
  XYREM is a CNS depressant. CNS depressants slow your brain down, relax your muscles, and can slow breathing. Taking XYREM may lead to difficulty breathing (respiratory depression) and a reduced level of alertness (obtundation).
- **mental depression, confusion and other mental health problems.**

See the **Serious side effects and what to do about them** table for more information on this and other serious side effects.

What is XYREM used for?

XYREM is used to treat cataplexy (suddenly weak or paralyzed muscles) in adults with narcolepsy (a type of sleep disorder).

How does XYREM work?

The exact way XYREM works to reduce the number of cataplexy attacks 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 to any of the other ingredients in 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 because your dosage of XYREM may need to be reduced.
- 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.
- have high blood pressure.
- have diabetes.
- have high cholesterol (hyperlipidemia).
- think you are overweight.
- have heart problems.
- have kidney problems.
- are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. XYREM can pass through your milk and may harm the baby.
- have a history of substance use problems.
- have had previous thoughts or attempts of suicide.
- have or had behaviour or other psychiatric problems such as:
  - seeing or hearing things that are not real (hallucinations)
  - feeling more suspicious (paranoia)
  - being out of touch with reality (psychosis)
  - acting aggressive
  - agitation
  - anxiety

Other warnings you should know about:

Dependence and addiction: The active ingredient in XYREM, GHB, has been used illegally for its sedating effects. When GHB is used illegally (usually at higher doses and frequencies), dependence and craving for GHB have been reported. Acute withdrawal symptoms have also been reported after

repeated illicit use. It is important that you talk to your healthcare professional if you have questions or concerns about abuse, addiction, or dependence. Always use XYREM as prescribed.

Driving and using machines: XYREM can affect your mental alertness, judgment, thinking, and movement. 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.

Unusual behaviours during sleep: XYREM can cause unwanted events or experiences that occur during sleep, including walking while being asleep. Tell your healthcare professional if you develop any abnormal movements or behaviours while sleeping.

High sodium (salt) content: XYREM contains a high amount of sodium (salt). High amounts of salt can increase the risk of high blood pressure and major heart problems (such as heart attack, heart failure, stroke or death). It is important to talk about your salt intake with your healthcare professional. Your healthcare professional may check blood pressure before starting and during treatment with 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/or 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. These include:

- sedating antidepressants used to treat depression;
- sedating antiepileptic drugs used to prevent seizures;
- sedating antipsychotics used to treat mental health disorders (e.g., ketamine);
- general anesthetics used during surgery;
- illicit CNS depressants;
- muscle relaxants used to treat muscle spasms and back pain;
- medicines used to help with sleep (e.g., zopiclone, eszopiclone, and lemborexant);
- cannabis (marijuana);
- opioid analgesics used to relieve pain.

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

The following may also interact with XYREM:

- a high fat meal.
- anticonvulsants used to prevent or treat certain types of seizures (e.g., divalproex sodium, ethosuximide, phenytoin, topiramate, and valproate).
- herbal products such as sleep-aids (e.g., melatonin, valerian, and kava) or St. John's Wort.

How to take XYREM:

- The program will teach you about the safe and proper use of 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 both 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 (¼) cup (approximately 60 mL) of water or enough to fill ¾ (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:

CAUTION: Be very careful not to leave your XYREM in a place where children, pets, or people whom this product is not prescribed can get to it.

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 (¼) cup (approximately 60 mL) of water.

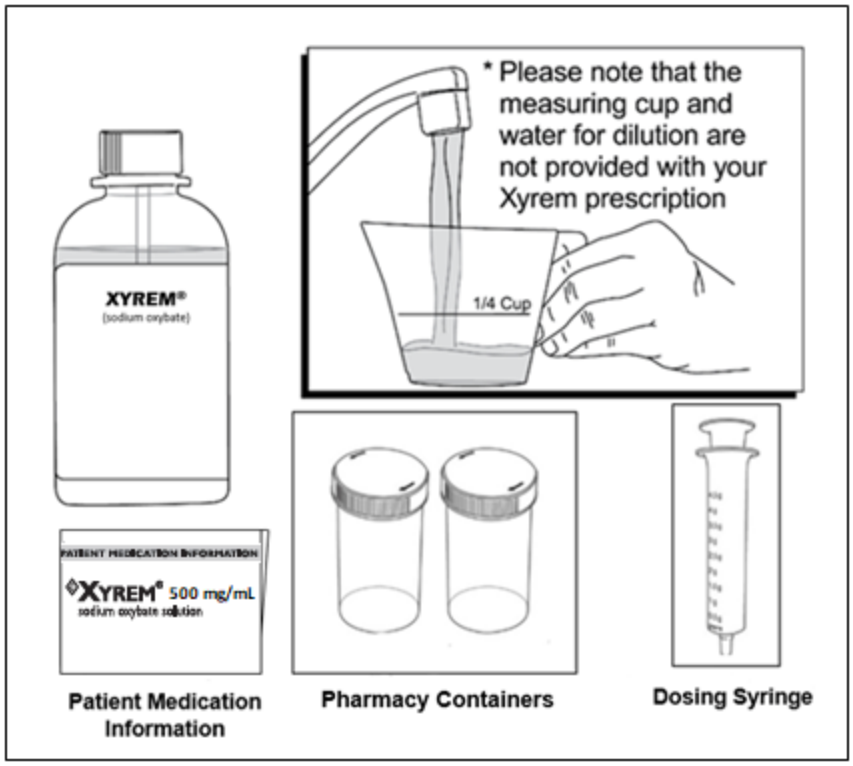


Figure A

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 (¼) 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.**

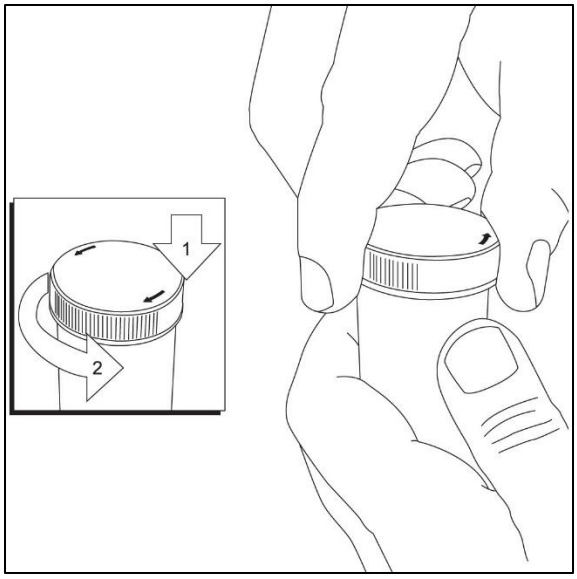


Figure B

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**).

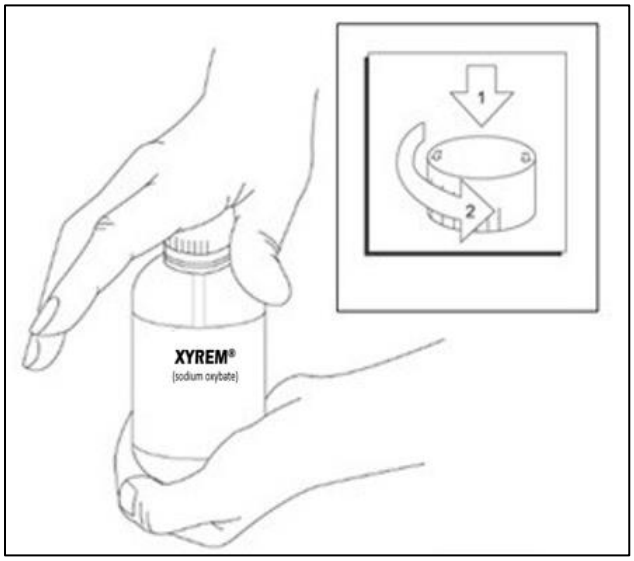


Figure C

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

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

The two doses of XYREM are prepared separately. To prepare the first dose:

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**).

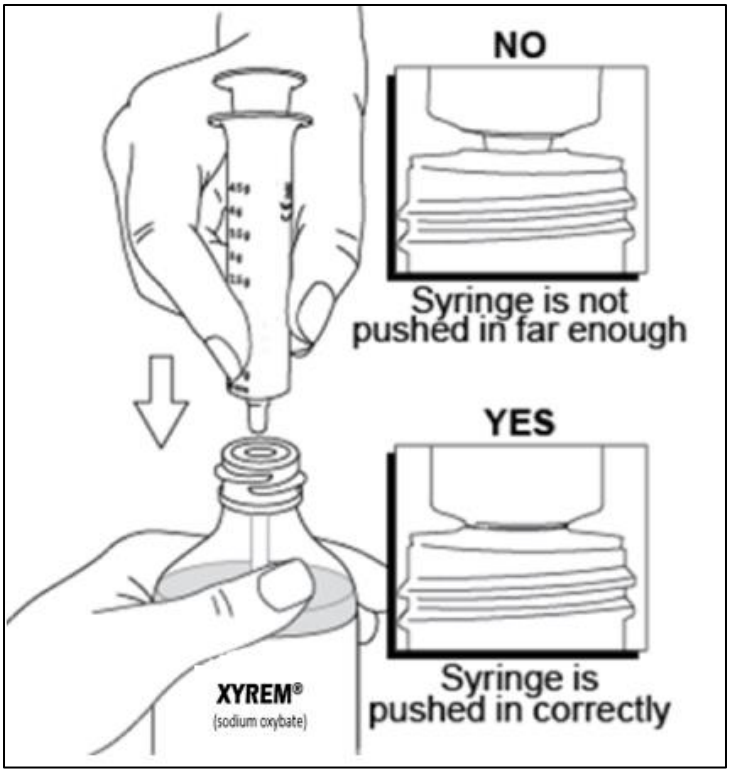


Figure D

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

The measuring device is a 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
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.

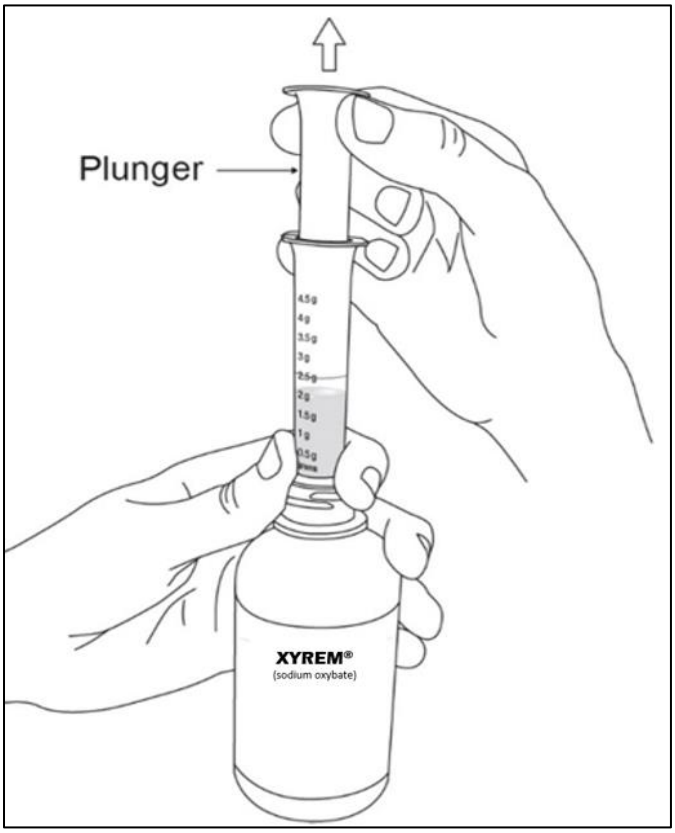


Figure E

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).

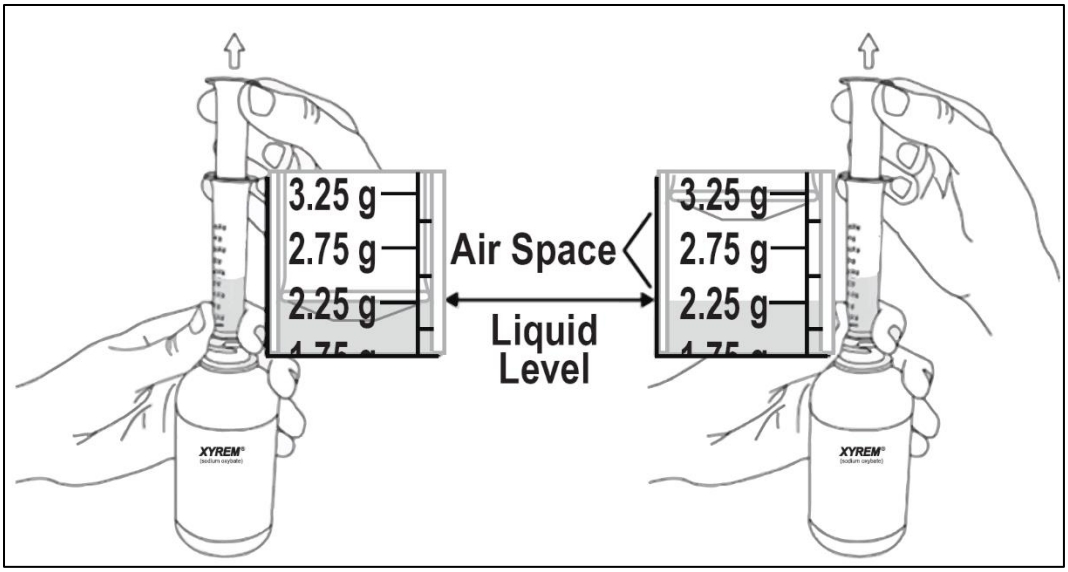


Figure F

e. After you draw up the first 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**).

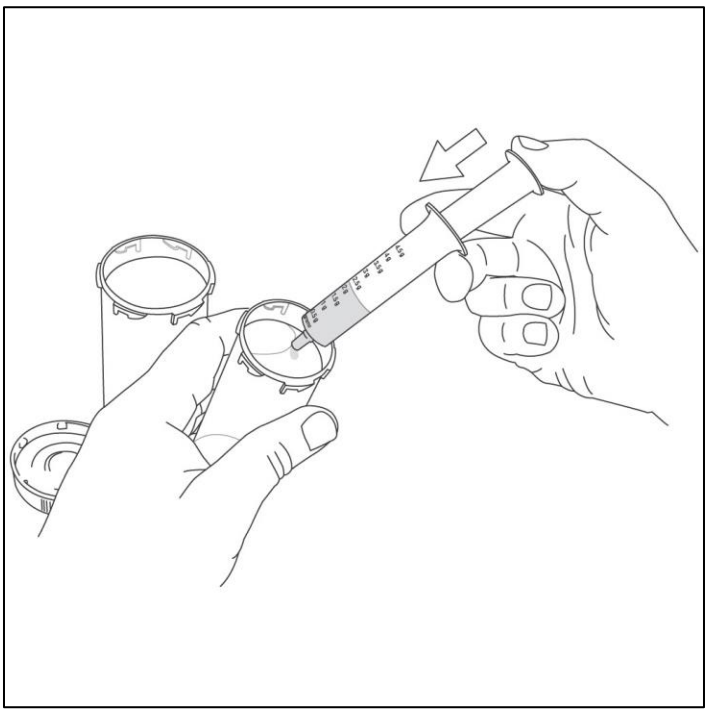


Figure G

g. Using a measuring cup, pour about a quarter (¼) 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**).

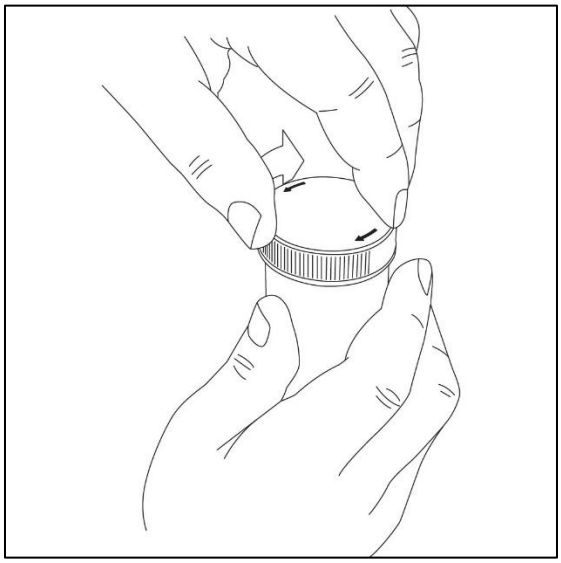


Figure H

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 (¼) 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. The prepared XYREM doses should be taken within 24 hours.
c. Keep the XYREM bottle and both prepared XYREM doses out of the reach of children and pets.
d. 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 or stop your 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, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you miss a dose, do not take two doses at one time.

- If the first dose is missed or delayed, take it as soon as you remember. A second dose may be taken 2.5 to 4 hours later only if there is sufficient sleep time prior to waking up, otherwise, the second dose should be skipped.
- If a first dose is taken and the second dose is missed or delayed, it should only be taken if there is sufficient sleep time prior to waking up. If there is insufficient sleep time prior to waking up, skip the second dose.

If insufficient sleep time has passed since the last dose has been taken, do NOT drive or engage in activities that require complete mental alertness.

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.

Side effects of 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);

- bed-wetting during the night. To help prevent bed-wetting, make sure you go to the bathroom before taking your first dose of XYREM;
- bleeding outside of the menstrual cycle;
- bruising;
- chills;
- complete or partial loss of feeling or sensation in an area of the body (hypoesthesia);
- confusion;
- dehydration or thirst;
- dizziness;
- dry mouth;
- enlarged abdomen size;
- flu symptoms;
- frequent urination;
- hair loss;
- hangover effects;
- headache;
- hiccups;
- increased sweating;
- infection, including viral infection;
- involuntary and rhythmic shaking;
- leg cramps;
- mouth ulcers or sores;
- muscle aches, pain, or weakness;
- nausea;
- neck rigidity;
- nervousness;
- panic attack;
- vomiting;
- weight decreased.

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**	
COMMON			
Allergic reaction: 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.			✓

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**	
Behavioural or mental changes: psychosis, paranoia, hallucinations, anxiety, irritability, hostility, aggression, agitation, memory impairment, or abnormal thinking.		✓	
Central nervous system (CNS) depression (brain slows down): respiratory depression (slow, shallow or weak breathing), low blood pressure, drowsiness, loss of consciousness, or coma.			✓
Depression (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.		✓	
Eye problems: vision blurred in one or both eyes, or vision changes.	✓		
Hypertension (high blood pressure)		✓	
Seizures (fit): loss of consciousness with uncontrollable shaking.			✓
Sleeping problems: 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.
- After preparing the XYREM solution in the provided containers, they should be taken within 24 hours as directed by your healthcare professional.
- 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, or by calling the program at 1-866-599-7365.

This leaflet was prepared by Jazz Pharmaceuticals Ireland Limited.

Date of Authorization 2025-01-23