

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XYREM safely and effectively. See full prescribing information for XYREM.

Xyrem® (sodium oxybate) oral solution CIII
Initial U.S. Approval: 2002

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and MISUSE AND ABUSE.

See full prescribing information for complete boxed warning.

- Respiratory depression can occur with Xyrem use (5.4)
- Xyrem is a Schedule III controlled substance and is the sodium salt of gamma hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma and death (5.2, 9.2)
- Because of the risks of CNS depression, abuse, and misuse, Xyrem is available only through a restricted distribution program called the Xyrem Success Program® using a centralized pharmacy. Prescribers and patients must enroll in the program. (5.3)

RECENT MAJOR CHANGES

Contraindications, concomitant use with alcohol (4) -----2/2012

INDICATIONS AND USAGE

Xyrem is a central nervous system depressant indicated for the treatment of:

- Cataplexy in narcolepsy (1.1).
- Excessive daytime sleepiness (EDS) in narcolepsy (1.2).

Xyrem may only be dispensed to patients enrolled in the Xyrem Success Program (1).

DOSAGE AND ADMINISTRATION

- Initiate dose at 4.5 grams (g) per night administered orally in two equal, divided doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (2.1)
- Titrate to effect in increments of 1.5 g per night at weekly intervals (0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) (2.1).
- Recommended dose range: 6 g to 9 g per night orally (2.1).

Total Nightly Dose	Take at Bedtime	Take 2.5 to 4 Hours Later
4.5 g per night	2.25 g	2.25 g
6 g per night	3 g	3 g
7.5 g per night	3.75 g	3.75 g
9 g per night	4.5 g	4.5 g

- Take each dose while in bed and lie down after dosing (2.2).

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WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and MISUSE AND ABUSE

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- Allow 2 hours after eating before dosing (2.2).
- Prepare both doses prior to bedtime; dilute each dose with approximately ¼ cup of water in pharmacy-provided vials (2.2).
- Patients with Hepatic Impairment: starting dose is 2.25 g per night administered orally in two equal, divided doses of approximately 1.13 g at bedtime and approximately 1.13 g taken 2.5 to 4 hours later (2.3).

DOSAGE FORMS AND STRENGTHS

Oral solution, 0.5 g per mL (3)

CONTRAINDICATIONS

- Succinic semialdehyde dehydrogenase deficiency (4).
- In combination with sedative hypnotics or alcohol (4).

WARNINGS AND PRECAUTIONS

- CNS depression: Use caution when considering the concurrent use of Xyrem with other CNS depressants (5.1).
- Caution patients against hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that Xyrem does not affect them adversely (5.1).
- Depression and suicidality: Monitor patients for emergent or increased depression and suicidality (5.4).
- Confusion/Anxiety: Monitor for impaired motor/cognitive function (5.5).
- Parasomnias: evaluate episodes of sleepwalking (5.7).
- High sodium content in Xyrem: Monitor patients with heart failure, hypertension, or impaired renal function (5.7).

ADVERSE REACTIONS

Most common adverse reactions (≥ 5% and at least twice the incidence with placebo) were nausea, dizziness, vomiting, somnolence, enuresis, and tremor (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals at 1-800-520-5568, or FDA at 1-800-FDA-1088 or www.fda.gov/Medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Geriatric patients: Monitor for impaired motor and/or cognitive function when taking Xyrem (8.5).

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Revised: 12/2012

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FULL PRESCRIBING INFORMATION

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and MISUSE AND ABUSE.

Xyrem (sodium oxybate) is a CNS depressant. In clinical trials at recommended doses obtundation and clinically significant respiratory depression occurred in Xyrem-treated patients. Almost all of the patients who received Xyrem during clinical trials in narcolepsy were receiving central nervous system stimulants [see Warnings and Precautions (5.1)].

Xyrem[®] (sodium oxybate) is the sodium salt of gamma hydroxybutyrate (GHB). Abuse of GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death [see Warnings and Precautions (5.2)].

Because of the risks of CNS depression, abuse, and misuse, Xyrem is available only through a restricted distribution program called the Xyrem Success Program[®], using a centralized pharmacy. Prescribers and patients must enroll in the program. For further information go to www.XYREM.com or call 1-866-XYREM88[®] (1-866-997-3688). [see Warnings and Precautions (5.3)].

1 INDICATIONS AND USAGE

Limitations of Use

Xyrem may only be dispensed to patients enrolled in the Xyrem Success Program [see Warnings and Precautions (5.3)].

1.1 Cataplexy in Narcolepsy

Xyrem (sodium oxybate) oral solution is indicated for the treatment of cataplexy in narcolepsy [see Clinical Studies (14.1)].

1.2 Excessive Daytime Sleepiness in Narcolepsy

Xyrem (sodium oxybate) oral solution is indicated for the treatment of excessive daytime sleepiness (EDS) in narcolepsy [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe Xyrem must enroll in the Xyrem Success Program and must comply with the requirements to ensure safe use of Xyrem [see Warnings and Precautions (5.3)].

2.1 Dosing Information

The recommended starting dose is 4.5 grams (g) per night administered orally in two equal, divided doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (see Table 1). Increase the dose by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dose range of 6 g to 9 g per night orally. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

Table 1: Xyrem Dose Regimen (g = grams)

If A Patient's Total Nightly Dose is:	Take at Bedtime:	Take 2.5 to 4 Hours Later:
4.5 g per night	2.25 g	2.25 g
6 g per night	3 g	3 g
7.5 g per night	3.75 g	3.75 g
9 g per night	4.5 g	4.5 g

2.2 Important Administration Instructions

Take the first dose of Xyrem at least 2 hours after eating because food significantly reduces the bioavailability of sodium oxybate.

Prepare both doses of Xyrem prior to bedtime. Prior to ingestion, each dose of Xyrem should be diluted with approximately $\frac{1}{4}$ cup (approximately 60 mL) of water in the empty pharmacy vials provided. Patients should take Xyrem while in bed and lie down immediately after dosing as Xyrem may cause them to fall asleep abruptly without first feeling drowsy. 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. Rarely, patients may take up to 2 hours to fall asleep. Therefore, patients should remain in bed following ingestion of the first dose, and should not take the second dose until 2.5 to 4 hours later. Patients may need to set an alarm to awaken for the second dose.

2.3 Dose Modification in Patients with Hepatic Impairment

The recommended starting dose in patients with hepatic impairment is 2.25 g per night administered orally in two equal, divided doses: approximately 1.13 g at bedtime and approximately 1.13 g taken 2.5 to 4 hours later [*see Use in Specific Populations (8.6); Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Xyrem is a clear to slightly opalescent oral solution, in a concentration of 0.5 g per mL.

4 CONTRAINDICATIONS

Xyrem is contraindicated in patients being treated with sedative hypnotic agents.

Patients should not drink alcohol when using Xyrem.

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

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Depression

Xyrem is a central nervous system (CNS) depressant. Alcohol and sedative hypnotics are contraindicated in patients who are using Xyrem. The concurrent use of Xyrem with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. 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.

Healthcare providers 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 the second nightly dose of Xyrem. Patients should be queried about CNS depression-related events upon initiation of Xyrem therapy and periodically thereafter [*See Warnings and Precautions (5.3)*].

5.2 Abuse and Misuse

Xyrem is a Schedule III controlled substance. The active ingredient of Xyrem, sodium oxybate or gamma-hydroxybutyrate (GHB), is a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with the amnesic features of Xyrem, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim). Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g. increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy) [*see Warnings and Precautions (5.3); Drug Abuse and Dependence (9.2)*].

5.3 Xyrem Success Program

Because of the risks of central nervous system depression and abuse/misuse, Xyrem is available only through a restricted distribution program called the Xyrem Success Program.

Required components of the Xyrem Success Program are:

- Use of a centralized pharmacy
- Healthcare Providers who prescribe Xyrem must complete the enrollment forms and comply with the requirements.
- To receive Xyrem, patients must understand the risks and benefits of Xyrem.

Further information is available at www.XYREM.com or 1-866-XYREM88[®] (1-866-997-3688).

5.4 Respiratory Depression and Sleep-Disordered Breathing

Xyrem may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported [*see Overdosage (10)*].

In a study assessing the respiratory-depressant effects of Xyrem at doses up to 9 g per night in 21 patients with narcolepsy, no dose-related changes in oxygen saturation were demonstrated

in the group as a whole. One of the four patients with preexisting, moderate-to-severe sleep apnea had significant worsening of the apnea/hypopnea index during treatment.

In a study assessing the effects of Xyrem 9 g per night in 50 patients with obstructive sleep apnea, Xyrem did not increase the severity of sleep-disordered breathing and did not adversely affect the average duration and severity of oxygen desaturation overall. However, there was a significant increase in the number of central apneas in patients taking Xyrem, and clinically significant oxygen desaturation ($\leq 55\%$) was measured in three patients (6%) after Xyrem administration, with one patient withdrawing from the study and two continuing after single brief instances of desaturation. Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with Xyrem administration.

In clinical trials in 128 patients with narcolepsy, two subjects had profound CNS depression, which resolved after supportive respiratory intervention. Two other patients discontinued sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea. In two controlled trials assessing polysomnographic (PSG) measures in patients with narcolepsy, 40 of 477 patients were included with a baseline apnea/hypopnea index of 16 to 67 events per hour, indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a clinically significant worsening of respiratory function as measured by apnea/hypopnea index and pulse oximetry at doses of 4.5 g to 9 g per night.

Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients and in postmenopausal women not on hormone replacement therapy as well as among patients with narcolepsy.

5.5 Depression and Suicidality

In clinical trials in patients with narcolepsy (n=781), there were two suicides and two attempted suicides in Xyrem-treated patients, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used Xyrem in conjunction with other drugs. Xyrem was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 Xyrem-treated patients, with four patients (< 1%) discontinuing because of depression. In most cases, no change in Xyrem treatment was required.

In a controlled trial, with patients randomized to fixed doses of 3 g, 6 g, or 9 g per night Xyrem or placebo, there was a single event of depression at the 3 g per night dose. In another controlled trial, with patients titrated from an initial 4.5 g per night starting dose, the incidences of depression were 1 (1.7%), 1 (1.5%), 2 (3.2%), and 2 (3.6%) for the placebo, 4.5 g, 6 g, and 9 g per night doses, respectively.

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

5.6 Other Behavioral or Psychiatric Adverse Reactions

During clinical trials in narcolepsy, 3% of 781 patients treated with Xyrem experienced confusion, with incidence generally increasing with dose.

Less than 1% of patients discontinued the drug because of confusion. Confusion was reported at all recommended doses from 6 g to 9 g per night. In a controlled trial where patients were randomized to fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose-response relationship for confusion was demonstrated, with 17% of patients at 9 g per night experiencing confusion. In all cases in that controlled trial, the confusion resolved soon after termination of treatment. In Trial 3 where sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in one patient at the 9 g per night dose. In the majority of

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