

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 ABUSE AND MISUSE.**

See full prescribing information for complete boxed warning.

Central Nervous System Depression

- Xyrem is a CNS depressant, and respiratory depression can occur with Xyrem use (5.1, 5.4)

Abuse and Misuse

- Xyrem is the sodium salt of gamma-hydroxybutyrate (GHB). 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)

Xyrem is available only through a restricted program called the XYWAV and XYREM REMS (5.3)

INDICATIONS AND USAGE

Xyrem is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy (1)

DOSAGE AND ADMINISTRATION

Dosage for Adult Patients

- Initiate dosage at 4.5 g per night orally, divided into two doses (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 dosage 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

Dosage for Pediatric Patients (7 years of Age and Older)

- The recommended starting dosage, titration regimen, and maximum total nightly dosage are based on body weight (2.2).

Important Administration Information

- Prepare both doses prior to bedtime; dilute each dose with approximately ¼ cup of water in pharmacy-provided containers (2.3).
- Allow 2 hours after eating before dosing (2.3).
- Take each dose while in bed and lie down after dosing (2.3).

Patients with Hepatic Impairment

Recommended starting dosage is one-half of the original dosage per night administered orally, divided into two doses (2.4).

DOSAGE FORMS AND STRENGTHS

Oral solution, 0.5 g per mL (3)

CONTRAINDICATIONS

- In combination with sedative hypnotics or alcohol (4)
- Succinic semialdehyde dehydrogenase deficiency (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 (5.5).
- Confusion/Anxiety: Monitor for impaired motor/cognitive function (5.6).
- Parasomnias: Evaluate episodes of sleepwalking (5.7).
- High sodium content in Xyrem: Monitor patients with heart failure, hypertension, or impaired renal function (5.8).

ADVERSE REACTIONS

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

Most common adverse reactions in pediatric patients (≥5%) were nausea, enuresis, vomiting, headache, weight decreased, decreased appetite, dizziness, and sleepwalking (6.1).

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

DRUG INTERACTIONS

- Concomitant use with divalproex sodium: An initial reduction in Xyrem dose of at least 20% is recommended (2.5, 7.2).

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).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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DEPRESSION and ABUSE AND MISUSE

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FULL PRESCRIBING INFORMATION

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

- **Central Nervous System Depression**
Xyrem (sodium oxybate) is a CNS depressant. In clinical trials at recommended doses, obtundation and clinically significant respiratory depression occurred in adult patients treated with Xyrem [see *Warnings and Precautions (5.1)*]. Many patients who received Xyrem during clinical trials in narcolepsy were receiving central nervous system stimulants [see *Clinical Trials (14)*].
- **Abuse and Misuse**
Xyrem® (sodium oxybate) is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse 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 [see *Warnings and Precautions (5.2)*].

Because of the risks of CNS depression and abuse and misuse, Xyrem is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XYWAV and XYREM REMS [see *Warnings and Precautions (5.3)*].

1 INDICATIONS AND USAGE

Xyrem is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosing Information

The recommended starting dosage is 4.5 grams (g) per night administered orally, divided into two doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (see Table 1). Increase the dosage 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 dosage range of 6 g to 9 g per night orally. The dosage may be gradually titrated based on efficacy and tolerability. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

Table 1: Recommended Adult 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 Pediatric Dosing Information

Xyrem is administered orally twice nightly. The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight, as specified in Table 2. The dosage may be gradually titrated based on efficacy and tolerability.

Table 2: Recommended Pediatric Xyrem Dosage for Patients 7 Years of Age and Older*

Patient Weight	Initial Dosage		Maximum Weekly Dosage Increase		Maximum Recommended Dosage	
	Take at Bedtime:	Take 2.5 to 4 Hours Later:	Take at Bedtime:	Take 2.5 to 4 Hours Later:	Take at Bedtime:	Take 2.5 to 4 Hours Later:
<20 kg**	There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.					
20 kg to <30 kg	≤1 g	≤1 g	0.5 g	0.5 g	3 g	3 g
30 kg to <45 kg	≤1.5 g	≤1.5 g	0.5 g	0.5 g	3.75 g	3.75 g
≥45 kg	≤2.25 g	≤2.25 g	0.75 g	0.75 g	4.5 g	4.5 g

* For patients who sleep more than 8 hours per night, the first dose of Xyrem may be given at bedtime or after an initial period of sleep.

**If Xyrem is used in patients 7 years of age and older who weigh less than 20 kg, a lower starting dosage, lower maximum weekly dosage increases, and lower total maximum nightly dosage should be considered.

Note: Some patients may achieve better responses with unequal doses at bedtime and 2.5 to 4 hours later.

2.3 Important Administration Instructions for All Patients

The total nightly dosage of Xyrem is divided into two doses. Prepare both doses of Xyrem prior to bedtime. Prior to ingestion, each dose of Xyrem should be diluted with approximately ¼ cup (approximately 60 mL) of water in the empty pharmacy containers provided.

Take the first nightly dose of Xyrem at least 2 hours after eating [see *Clinical Pharmacology* (12.3)]. Take the second nightly dose 2.5 to 4 hours after the first dose.

Patients should take both doses 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 *Adverse Reactions* (6.2)]. 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. Rarely, patients may take up to 2 hours to fall asleep.

If the second dose is missed, that dose should be skipped and Xyrem should not be taken again until the next night. Both Xyrem doses should never be taken at one time.

2.4 Dosage Modification in Patients with Hepatic Impairment

The recommended starting dosage in patients with hepatic impairment is one-half of the original dosage per night, administered orally divided into two doses [see *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)].

2.5 Dosage Adjustment with Co-administration of 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 *Drug Interactions (7.2) and Clinical Pharmacology (12.3)*]. 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.

3 DOSAGE FORMS AND STRENGTHS

Xyrem is a clear to slightly opalescent oral solution, in a concentration of 0.5 g per mL (0.5 g/mL of sodium oxybate equivalent to 0.413 g/mL of oxybate).

4 CONTRAINDICATIONS

Xyrem is contraindicated for use in:

- combination with sedative hypnotics [see *Warnings and Precautions (5.1)*].
- combination with alcohol [see *Warnings and Precautions (5.1)*].
- patients with succinic semialdehyde dehydrogenase deficiency [see *Clinical Pharmacology (12.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Depression

Xyrem is a central nervous system (CNS) depressant. In adult clinical trials at recommended doses, obtundation and clinically significant respiratory depression occurred in patients treated with Xyrem. Xyrem is contraindicated in combination with alcohol and sedative hypnotics. 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. 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 Xyrem. Patients should be queried about CNS depression-related events upon initiation of Xyrem therapy and periodically thereafter.

Xyrem is available only through a restricted program under a REMS [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

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