HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) 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
- **XYWAV is a CNS depressant, and respiratory depression can occur with XYWAV use (5.1, 5.4)**

Abuse and Misuse
- **The active moiety of XYWAV is oxybate or 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)**

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

----------INDICATIONS AND USAGE----------

XYWAV 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 up to 1.5 g per night per week (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
• Some patients may achieve better responses with unequal doses at bedtime and 2.5 to 4 hours later.		

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).
- Take the first nightly dose of XYWAV at least 2 hours after eating (2.3).
- Take each dose while in bed and lie down after dosing (2.3).

For Patients Transitioning from Xyrem to XYWAV: Initiate at the same dose and regimen as Xyrem (gram for gram). Titrate as needed based on efficacy and tolerability. (2.4).

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/mL total salts (equivalent to 0.413 g/mL of oxybate) (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 XYWAV 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 XYWAV 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).

----------ADVERSE REACTIONS----------

Most common adverse reactions in adults (≥5%) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting (6.1).

In a pediatric study with sodium oxybate, (same active moiety as XYWAV), the most common adverse reactions (≥5%) were enuresis, nausea, headache, vomiting, weight decreased, decreased appetite, and dizziness (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 XYWAV dose of at least 20% is recommended (2.6, 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 XYWAV (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 7/2020

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17 PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

- **Central Nervous System Depression**
  XYWAV is a CNS depressant. Clinically significant respiratory depression and obtundation may occur in patients treated with XYWAV at recommended doses *[see Warnings and Precautions (5.1, 5.4)]*. Many patients who received XYWAV during clinical trials in narcolepsy were receiving central nervous system stimulants *[see Clinical Trials (14.1)]*.

- **Abuse and Misuse**
  The active moiety of XYWAV is oxybate or 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, XYWAV 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

XYWAV 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 up to 1.5 g per night per week (e.g., 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later), to the recommended dosage range of 6 g to 9 g per night. The dosage may be gradually titrated based on efficacy and tolerability. Some patients may achieve better responses with unequal doses at bedtime and 2.5 to 4 hours later. Doses higher than 9 g per night have not been studied and ordinarily should not be administered.

Table 1: Recommended Adult XYWAV Dosage Regimen (g = grams)

If a Patient's Total Nightly Dosage 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

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

2.2 Pediatric Dosing Information

For pediatric patients 7 years of age and older, XYWAV is administered orally twice per night. 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. Doses higher than 9 g per night have not been studied and ordinarily should not be administered.

Table 2: Recommended Initial XYWAV 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 nightly dose of XYWAV may be given at bedtime or after an initial period of sleep.

**If XYWAV 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 nightly doses at bedtime and 2.5 to 4 hours later.

2.3 Important Administration Instructions for All Patients

The total nightly dosage of XYWAV is divided into two doses. Prepare both doses of XYWAV prior to bedtime. Prior to ingestion, each dose of XYWAV should be diluted with approximately ¼ cup (approximately 60 mL) of water in the empty pharmacy containers provided. Solutions prepared following dilution should be consumed within 24 hours.

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

Patients should take each dose of XYWAV while in bed and lie down immediately after dosing, and remain in bed following ingestion of each dose. XYWAV 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 XYWAV, 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, that dose should be skipped and XYWAV should not be taken again until the next night. Two XYWAV doses should never be taken at one time.

2.4 Patients Transitioning from Xyrem to XYWAV

On the first night of dosing with XYWAV, initiate treatment at the same dose (gram for gram) and regimen as Xyrem. Titrate as needed based on efficacy and tolerability *[see Dosage and Administration (2.1)]*.

2.5 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)]*.

2.6 Dose Adjustment with Co-administration of Divalproex Sodium

When initiating divalproex sodium in patients taking a stable dosage of XYWAV, a reduction of the XYWAV dosage by at least 20% is recommended with initial concomitant use *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. When initiating XYWAV in patients already taking divalproex sodium, a lower starting dosage of XYWAV is recommended. Subsequently, the dosage of XYWAV can be adjusted based on individual clinical response and tolerability.

3 DOSAGE FORMS AND STRENGTHS

XYWAV is a clear to slightly opalescent oral solution at a total salt concentration of 0.5 g per mL. Each mL contains 0.5 g of total salts present as 0.234 g calcium oxybate, 0.096 g magnesium oxybate, 0.13 g potassium oxybate, and 0.04 g sodium oxybate (equivalent to 0.413 g total oxybate).

4 CONTRAINDICATIONS

XYWAV 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

XYWAV is a central nervous system (CNS) depressant. Clinically significant respiratory depression and obtundation has occurred in adult patients taking sodium oxybate (same active moiety as XYWAV) at recommended doses in clinical trials and may occur in patients treated with XYWAV at recommended doses. XYWAV is contraindicated in combination with alcohol and sedative hypnotics. The concurrent use of XYWAV 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 XYWAV is required, dose reduction or discontinuation of one or more CNS depressants (including XYWAV) should be considered. In addition, if short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with XYWAV should be considered.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that XYWAV does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring

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