xywav®
(calcium, magnesium, potassium, and sodium oxybates) oral solution

XYWAV is the first and only FDA-approved low-sodium[a] oxybate[1,2]

Indicated for the treatment of cataplexy[b] and/or EDS in patients 7 years of age and older with narcolepsy[1]

The only FDA-approved treatment indicated for adults with idiopathic hypersomnia[1,3]

[a]XYWAV has 131 mg of sodium at the maximum recommended nightly dose.[2]
[b]Cataplexy is the sudden, generally brief (<2 minutes), loss of muscle tone with retained consciousness.

EDS=excessive daytime sleepiness; FDA=Food and Drug Administration.

Important Safety 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. Many patients who received XYWAV during clinical trials in narcolepsy and idiopathic hypersomnia were receiving CNS stimulants.
- **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.

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.

Contraindications

XYWAV is contraindicated
- in combination with sedative hypnotics or alcohol and
- in patients with succinic semialdehyde dehydrogenase deficiency.

Please see additional Important Safety Information on next page and full Prescribing Information, including BOXED Warning.

A growing body of evidence indicates that members living with narcolepsy have an increased risk of CVD and events[4-7]

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The 2023 Cardiovascular Burden of Narcolepsy Disease (CV-BOND) was the first study to demonstrate higher rates of new-onset CV events after a diagnosis of narcolepsy[6]

People with narcolepsy had higher incidence rates of new-onset CV events than those without narcolepsy[6,a,b]:

1.7x
greater risk of any stroke

1.4x
greater risk of heart failure

1.5x
greater risk of MACE

1.3x
greater risk of CVD

[a]CV-BOND was a retrospective medical claims analysis including 12,816 adults with narcolepsy and 38,441 matched controls. Controls were matched 3:1 on cohort entry date, age, sex, region, and insurance type. Evaluated post-narcolepsy diagnosis for CV events. Excluded patients in each analysis with a history of that CV event in the 6 months prior to cohort entry. Patients remained eligible for inclusion in other CV event analyses, eg, a patient with a history of stroke could still be included in the HF and MACE analyses.[6] [b]HR: **any stroke** (95% CI) 1.71 (1.24, 2.34); *P*-value<0.05; **heart failure** (95% CI) 1.35 (1.03, 1.76); *P*-value<0.05; **MACE** 1.45 (1.20, 1.74); *P*-value<0.05; **CVD** (95% CI) 1.30 (1.08, 1.56).[6]

CV=cardiovascular; CVD=cardiovascular disease; HF=heart failure; HR=hazard ratio; MACE=major adverse cardiovascular events.

Important Safety Information (cont.)

Warning and Precautions

Central Nervous System Depression

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 (eg, post- or perioperative) is required, interruption of treatment with XYWAV should be considered.

Please see additional Important Safety Information on next page and full Prescribing Information, including BOXED Warning.

CV risk is an important consideration in managing members with narcolepsy

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An expert consensus panel developed recommendations for reducing the risk of CV and CM comorbidities in people with narcolepsy[8]

In 2024, the *Journal of the American Heart Association* published recommendations from a consensus panel of sleep medicine and cardiology experts.[8]

Consensus panel recommendations[8]

- **Recognize the risk of hypertension and CV/CM disease in patients with narcolepsy**
- **Reduce the risk of hypertension and CV/CM disease in patients with narcolepsy**
- **Reduce sodium intake to lower the risk of hypertension and CV disease in patients with narcolepsy**

According to a study in the *New England Journal of Medicine*, increase in sodium excretion leads to a rise in CV risk[9]

A meta-analysis of 10,709 participants from 6 studies showed that higher 24-hour sodium excretion was associated with higher CV risk in analyses that controlled for confounding factors.[10,a,b]

A 1,000-mg increase in urinary sodium excretion, an accurate way to measure sodium intake, was directly associated with an 18% increase in CV risk[9,c]

- The study assessed 24-hour urinary sodium excretion in 10,709 participants with an 8.8-year follow-up

Early monitoring for, and prevention of, CV risks in the narcolepsy population is critical[8]

[a]Primary outcome was a CV event, defined as a composite of coronary revascularization (coronary-artery bypass grafting or percutaneous coronary intervention), fatal or nonfatal myocardial infarction, or fatal or nonfatal stroke. [b]Multiple 24-hour urine samples, the most accurate method for assessing sodium intake, were obtained for each participant.[9] [c]Adjusted hazard ratio (95% CI) 1.18 (1.08-1.29).[9]

CM=cardiometabolic.

Important Safety Information (cont.)

Warning and Precautions (cont.)

Central Nervous System Depression (cont.)

After first initiating treatment and until certain that XYWAV does not affect them adversely (eg, impair judgment, thinking, or motor skills), caution patients against hazardous activities requiring complete mental alertness or motor coordination such as operating hazardous machinery, including automobiles or airplanes. Also caution patients against these hazardous activities for at least 6 hours after taking XYWAV. Patients should be queried about CNS depression-related events upon initiation of XYWAV therapy and periodically thereafter.

Please see additional Important Safety Information on next page and full Prescribing Information, including BOXED Warning.

Taking XYWAV instead of a high-sodium oxybate reduces sodium burden, a CV risk factor, for your members with narcolepsy[10,11]

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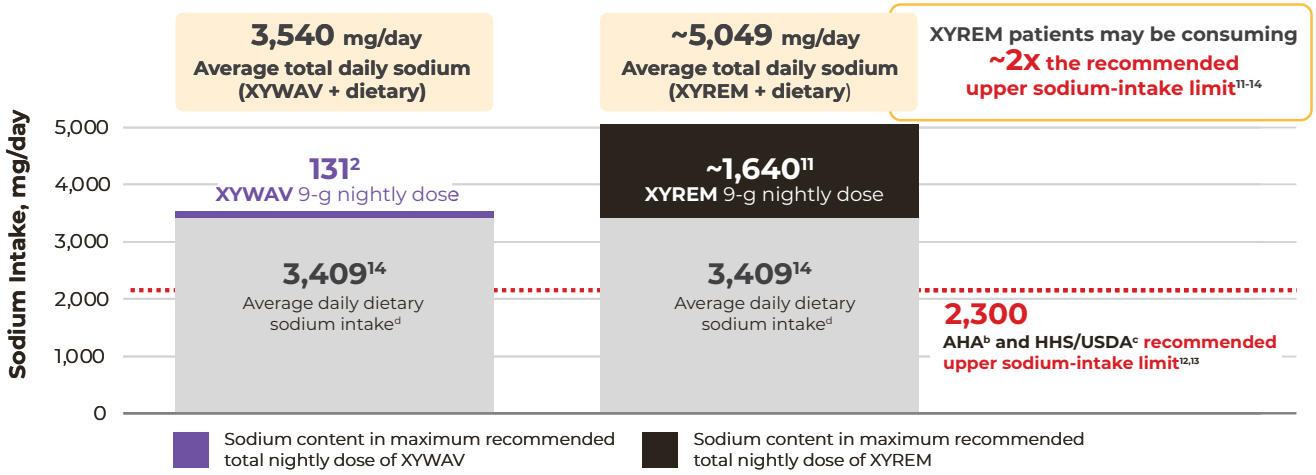
The FDA determined XYWAV to be clinically superior[a] to XYREM® (sodium oxybate) oral solution, 0.5 g/mL, a high-sodium oxybate, by means of greater CV safety[10]

As part of their findings, the FDA states that

XYWAV is **clinically superior** to XYREM by means of greater safety because XYWAV provides **a greatly reduced chronic sodium burden**[10]

The differences in the sodium content between **XYWAV and XYREM** at the recommended doses will be **clinically meaningful in reducing CV morbidity** in a substantial proportion of patients for whom the drug is **indicated**[10]

XYWAV has 131 mg of sodium per maximum recommended 9-g nightly dose vs ~1,640 mg per maximum recommended 9-g nightly dose for XYREM, which is ~1,500 mg less per night[2,11]



The AHA recommends no more than 2,300 mg of sodium per day with an ideal limit of <1,500 mg for most adults.[12]

[a]The decision of the FDA OOPD is based on findings that XYWAV provides a greatly reduced chronic sodium burden compared to XYREM. There are no head-to-head data for XYWAV and XYREM.[10] [b]For most adults.[12] [c]For people ages ≥14 years.[13] [d]For Americans aged ≥2.[14]
AHA=American Heart Association; HHS=US Department of Health and Human Services; OOPD=Office of Orphan Products Development; USDA=US Department of Agriculture.

Important Safety Information (cont.)

Warning and Precautions (cont.)

Abuse and Misuse

XYWAV is a Schedule III controlled substance. The active moiety of XYWAV is oxybate, also known as gamma-hydroxybutyrate (GHB), 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 amnestic features of GHB particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (eg, assault victim). Physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

Please see additional Important Safety Information on next page and full Prescribing Information, including BOXED Warning.

XYWAV enables healthcare providers to individualize their patients' dosing[1]

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All patients should take the first nightly dose of XYWAV in bed at night and at least 2 hours after eating[1]

2x

Twice-nightly dosing for adults with narcolepsy with cataplexy or EDS and/or adults with idiopathic hypersomnia (IH)[1]

- For patients new to oxybates, the recommended starting dose is 4.5 g per night orally, divided into 2 doses:
  - 2.25 g taken at bedtime and 2.25 g taken 2.5 to 4 hours later
  - Increase the dosage by up to 1.5 g per night per week to the recommended dosage range of 6 g to 9 g per night
- Doses higher than 9 g per night have not been studied and ordinarily should not be administered
- Some patients may achieve better responses with unequal doses at bedtime and 2.5 to 4 hours later

1x

Once-nightly dosing option for adults with IH[1]

- For patients new to oxybates, the recommended starting dose is 3 g/night
- Increase the dosage by up to 1.5 g per night per week to the recommended dosage range of 6 g/night
- Single doses >6 g/night have not been studied and ordinarily should not be administered

For more information on XYWAV dosing, click here

Important Safety Information (cont.)

Warning and Precautions (cont.)

XYWAV and XYREM REMS

- Because of the risks of central nervous system depression and abuse and misuse, XYWAV is available only through a restricted distribution program called the XYWAV and XYREM REMS.

Notable requirements of the XYWAV and XYREM REMS include the following:

- Healthcare Providers who prescribe XYWAV are specially certified
- XYWAV will be dispensed only by the central pharmacy that is specially certified
- XYWAV will be dispensed and shipped only to patients who are enrolled in the XYWAV and XYREM REMS with documentation of safe use

Further information is available at www.XYWAVXYREMREMS.com or 1-866-997-3688.

Respiratory Depression and Sleep-Disordered Breathing

XYWAV may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses of oxybate and with illicit use of GHB, life-threatening respiratory depression has been reported. Increased apnea and reduced oxygenation may occur with XYWAV administration in adult and pediatric patients. A significant increase in the number of central apneas and clinically significant oxygen desaturation may occur in patients with obstructive sleep apnea treated with XYWAV. Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not on hormone replacement therapy, and among patients with narcolepsy.

Depression and Suicidality

In Study 1, the pivotal randomized-withdrawal clinical trial in adult patients with narcolepsy (n=201), depression and depressed mood were reported in 3% and 4%, respectively, of patients treated with XYWAV. Two patients (1%) discontinued XYWAV because of depression. In most cases, no change in XYWAV treatment was required.

In Study 2, the pivotal randomized-withdrawal clinical trial in adult patients with idiopathic hypersomnia (n=154), depression and depressed mood were reported in 1% and 3%, respectively, of patients treated with XYWAV. All patients continued XYWAV treatment.

Please see additional Important Safety Information on next page and full Prescribing Information, including BOXED Warning.

Consider XYWAV, the only low-sodium[a] oxybate for your members 7 years of age and older with narcolepsy with cataplexy and/or EDS or adults with idiopathic hypersomnia[1-3]

[a]XYWAV has 131 mg of sodium at the maximum recommended nightly dose.[2]

Important Safety Information (cont.)

Warning and Precautions (cont.)

Depression and Suicidality (cont.)

Two suicides and two attempted suicides occurred in adult clinical trials with oxybate (same active moiety as XYWAV). One patient experienced suicidal ideation and two patients reported depression in a pediatric clinical trial with oxybate. These events occurred in patients with and without previous histories of depressive disorders. The emergence of depression in patients treated with XYWAV requires careful and immediate evaluation. Monitor patients for the emergence of increased depressive symptoms and/or suicidality while taking XYWAV.

Other Behavioral or Psychiatric Adverse Reactions

In Study 1, confusion and anxiety occurred in 1% and 5% of patients treated with XYWAV, respectively. One patient experienced visual hallucinations and confusion after ingesting approximately 9 grams of XYWAV.

In Study 2, confusion and anxiety occurred in 3% and 15% of patients, respectively. One patient experienced visual hallucinations which led to discontinuation of XYWAV.

Other neuropsychiatric reactions reported with oxybate (same active moiety as XYWAV) in adult or pediatric clinical trials and in the postmarketing setting include hallucinations, paranoia, psychosis, aggression, agitation, confusion and anxiety. The emergence or increase in the occurrence of behavioral or psychiatric events in patients taking XYWAV should be carefully monitored.

Parasomnias

Parasomnias can occur in patients taking XYWAV.

In Study 1 and Study 2, parasomnias, including sleepwalking, were reported in 6% and 5% of adult patients treated with XYWAV, respectively.

In a clinical trial of XYREM (same active moiety as XYWAV) in adult patients with narcolepsy, five instances of sleepwalking with potential injury or significant injury were reported. Parasomnias, including sleepwalking, have been reported in a pediatric clinical trial with sodium oxybate (same active moiety as XYWAV) and in postmarketing experience with sodium oxybate.

Episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

Most Common Adverse Reactions

The most common adverse reactions (occurring in ≥5% of XYWAV-treated patients in adult clinical trials in either narcolepsy or IH) were nausea, headache, dizziness, anxiety, insomnia, decreased appetite, hyperhidrosis, vomiting, diarrhea, dry mouth, parasomnia, somnolence, fatigue, and tremor.

In the pediatric clinical trial with XYREM (same active moiety as XYWAV), that included pediatric patients 7 to 17 years of age with narcolepsy, the most common adverse reactions (≥5%) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%), and sleepwalking (6%). The overall adverse reaction profile of XYREM in the pediatric clinical trial was similar to that seen in the adult clinical trial program. The safety profile in pediatric patients with XYWAV is expected to be similar to that of adult patients treated with XYWAV and to that of pediatric patients treated with XYREM.

Please see full Prescribing Information, including BOXED Warning.

For more information on XYWAV, visit www.xywavhcp.com.

References: 1. XYWAV® (calcium, magnesium, potassium, and sodium oxybates). Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **2.** Chen C, Jenkins J, Zomorodi K, Skowronski R. Pharmacokinetics, bioavailability, and bioequivalence of lower-sodium oxybate in healthy participants in two open-label, randomized, crossover studies. *Clin Transl Sci*. 2021;14(6):2278-2287. **3.** FDA grants first of its kind indication for chronic sleep disorder treatment. News release. U.S. Food and Drug Administration; August 12, 2021. Accessed February 12, 2025. https://www.fda.gov/news-events/press-announcements/fda-grants-first-its-kind-indication-chronic-sleep-disorder-treatment. **4.** Ohayon MM. Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population. *Sleep Med*. 2013;14(6):488-492. **5.** Black J, Reaven NL, Funk SE, et al. Medical comorbidity in narcolepsy: findings from the Burden of Narcolepsy Disease (BOND) study. *Sleep Med*. 2017;33:13-18. **6.** Ben-Joseph RH, Saad R, Black J, et al. Cardiovascular Burden of Narcolepsy Disease (CV-BOND): a real-world evidence study. *Sleep*. 2023;46(10):zsad161. **7.** Kaufmann C, Riaz M, Park H, et al. Evidence for an independent association of cardiovascular disease in patients with narcolepsy. *Sleep*. 2024;47(suppl 1):A368. **8.** Kwon Y, Gami AS, Javaheri S, et al. Cardiovascular risks in people with narcolepsy: expert panel consensus recommendations. *J Am Heart Assoc*. 2024;13(16):e035168. **9.** Ma Y, He FJ, Sun Q, et al. 24-hour urinary sodium and potassium excretion and cardiovascular risk. *N Engl J Med*. 2022;386(3):252-263. **10.** US Department of Health and Human Services, US Food and Drug Administration website. Clinical superiority findings. Updated December 18, 2024. Accessed February 12, 2025. https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings. **11.** XYREM® (sodium oxybate). Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **12.** American Heart Association. Why should I limit sodium? Accessed February 12, 2025. https://www.heart.org/-/media/files/health-topics/answers-by-heart/why-should-i-limit-sodium.pdf?la=en. **13.** US Department of Health and Human Services and US Department of Agriculture. *Dietary Guidelines for Americans 2020-2025*. 9th edition. December 2020. Accessed February 12, 2025. https://www.dietaryguidelines.gov/sites/default/files/2021-03/Dietary_Guidelines_ for_Americans-2020-2025.pdf. **14.** Quader ZS, Zhao L, Gillespie C, et al. Sodium intake among persons aged ≥2 years — United States, 2013 – 2014. *MMWR Morb Mortal Wkly Rep*. 2017;66(12):324-328.

Jazz Pharmaceuticals

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