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

For adult patients with idiopathic hypersomnia (IH),

THE ENDLESS PULL BACK TO BED

starts first thing in the morning[1-5]

That's why there's XYWAV—

the treatment taken each night to help manage multiple daily symptoms of IH.[6]

Find out why XYWAV may be the right treatment choice for your adult patients with IH.[6]

INDICATION AND USAGE

XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL total salts (equivalent to 0.413 g/mL of oxybate) is indicated for the treatment of idiopathic hypersomnia (IH) in adults.

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 idiopathic hypersomnia (IH) 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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

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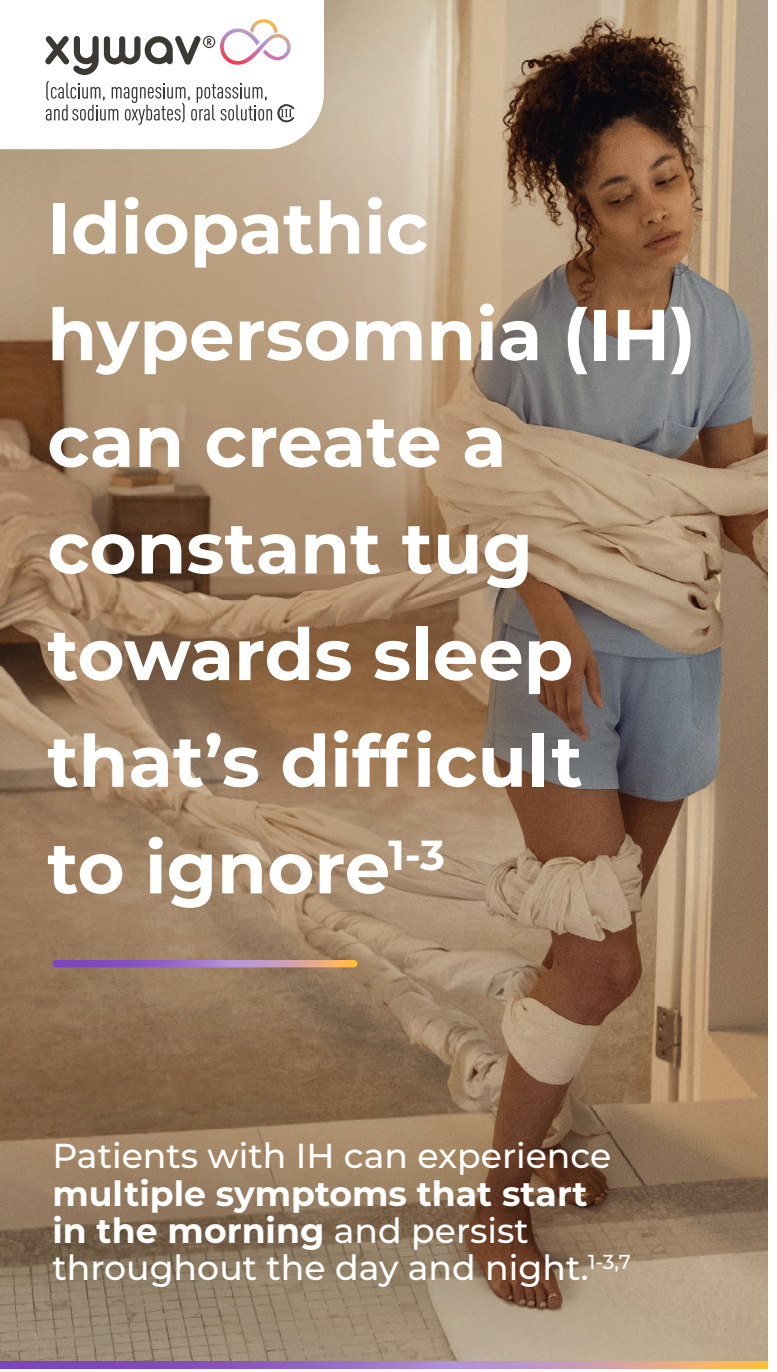


Idiopathic hypersomnia (IH) can create a constant tug towards sleep that's difficult to ignore[1-3]

Patients with IH can experience **multiple symptoms that start in the morning** and persist throughout the day and night.[1-3,7]

IMPORTANT SAFETY INFORMATION (cont'd)

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 throughout and full Prescribing Information, including BOXED Warning.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings 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.

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.

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.

XYWAV and XYREM REMS

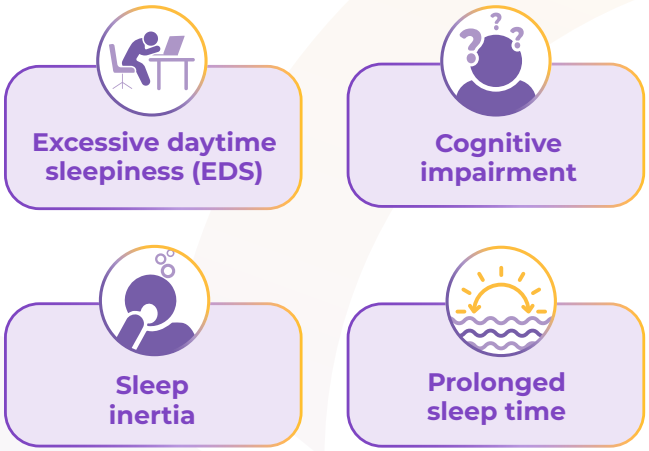
- Because of the risks of central nervous system depression and abuse and misuse, XYWAV is available only through a restricted distribution program called the XYWAV and XYREM REMS

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.

XYWAV has been evaluated across multiple symptoms of IH, including[6]:



With XYWAV, treatment doesn't have to wait until they've woken up in the morning.[6]

- XYWAV offers twice- or once-nightly dosing options for adult patients with IH.[6]
- For twice-nightly regimens, the first dose should be taken at bedtime and the second dose taken 2.5 to 4 hours later.[6]
- See full Prescribing Information for dosing information.

IMPORTANT SAFETY INFORMATION (cont'd)

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 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.

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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

Other Behavioral or Psychiatric Adverse Reactions
In Study 2, confusion and anxiety occurred in 3% and 16% of patients with idiopathic hypersomnia, respectively. One patient in Study 2 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 2, parasomnias including sleepwalking were reported in 5% of adult patients with idiopathic hypersomnia treated with XYWAV.

Parasomnias, including sleepwalking, have been reported in postmarketing experience with sodium oxybate (same active moiety as XYWAV).

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

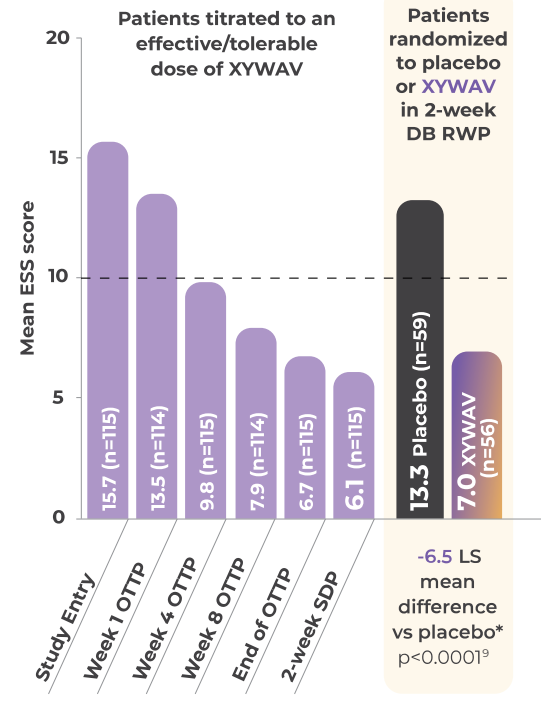
Most Common Adverse Reactions
In Study 2, the most common adverse reactions occurring in ≥5% of XYWAV-treated patients were nausea, headache, anxiety, dizziness, insomnia, decreased appetite, hyperhidrosis, vomiting, dry mouth, diarrhea, fatigue, somnolence, parasomnia, and tremor.

XYWAV is the only FDA-approved treatment for adults with idiopathic hypersomnia (IH)[6,8]

Primary efficacy endpoint: Efficacy in excessive daytime sleepiness (as measured by ESS)

Significant worsening of daytime sleepiness in patients randomized to placebo compared to patients randomized to continue treatment with XYWAV during the DB RWP[6,9]

Mean ESS score remained stable from the end of the SDP through the end of the 2-week DB RWP with XYWAV—but worsened with placebo.[6,9]



ESS scores higher than 10 are indicative of excessive daytime sleepiness.[10]

XYWAV Placebo

Limitations: Trial was not designed to demonstrate efficacy during the OTTP; all patients were taking active drug while dose was being titrated to individual optimized dose; no conclusions can be drawn about the effect of XYWAV during this period.

Are any of your patients still experiencing symptoms of IH despite treating with WPAs or stimulants?

XYWAV was evaluated across a range of adult patients[6,9]

Click to see more clinical trial data.

XYWAV was evaluated in adult patients with varying degrees of baseline disease severity[6,9]

PRIMARY EFFICACY ENDPOINT[6,9]:

Epworth Sleepiness Scale (ESS)

ESS — Assesses excessive daytime sleepiness (EDS) or patient perceptions of likelihood they will fall asleep during usual daily activities

KEY SECONDARY ENDPOINTS[6,9]:

Patient Global Impression of Change (PGIc)

PGIc — Assesses patient perceptions of symptom change from “very much improved” to “very much worse”

Idiopathic Hypersomnia Severity Scale (IHSS)

IHSS — Assesses the severity of IH symptoms, including excessive sleepiness, sleep inertia, prolonged sleep time, and cognitive impairment

*LS mean difference between XYWAV and placebo in the change in ESS score from end of 2-week SDP to end of 2-week DB RWP.[9]

DB RWP=double-blind, randomized withdrawal period; ESS=Epworth Sleepiness Scale; IHSS=Idiopathic Hypersomnia Severity Scale; LS=least squares; OLE=open-label safety extension period; OTTP=open-label treatment titration and optimization period; PGIc=Patient Global Impression of Change; SDP=stable-dose period.

Study Design: The efficacy and safety of XYWAV was evaluated in a double-blind, placebo-controlled, randomized-withdrawal clinical trial. The trial consisted of a minimum of 10-week OTTP (up to 14 weeks), followed by a 2-week SDP, a 2-week DB RWP, and a 24-week OLE. A total of 154 patients aged 19 to 75 (median age 39) were included in the study (safety population). The primary endpoint was the change in the ESS score from the end of the SDP to the end of the DB RWP.[6]

The adverse reactions in the study (incidence ≥2% of XYWAV-treated patients in the OTTP and SDP): nausea, headache, anxiety, dizziness, insomnia, hyperhidrosis, decreased appetite, vomiting, dry mouth, diarrhea, fatigue, somnolence, tremor, parasomnia, balance disorder, muscle spasms, fall, paresthesia, snoring, weight decreased, bruxism, confusional state, depressed mood, feeling drunk, and irritability.[6]

IMPORTANT SAFETY INFORMATION (cont’d)

Additional Adverse Reactions

Additional adverse reactions that occurred in ≥2% of adult patients with idiopathic hypersomnia treated with XYWAV in the Open-Label Titration and Stable Dose periods of Study 2 were balance disorder, muscle spasms, fall, paresthesia, snoring, weight decreased, bruxism, confusional state, depressed mood, feeling drunk, and irritability.

Adverse reactions that occurred in ≥2% of patients in clinical studies with oxybate (but not in Study 2) and which may be relevant for XYWAV, were pain, pain in extremity, disturbance in attention, sleep paralysis, and disorientation.

Discontinuation: In Study 2, across all study periods (excluding placebo during the DB RWP) (up to 42 weeks), 17 of 154 (11%) patients withdrew from the trial due to adverse reactions, with anxiety the most common reason (3.2%). Other adverse reactions leading to study withdrawal included nausea, insomnia, vomiting, fatigue, feeling abnormal, fall, decreased appetite, dizziness, paresthesia, tremor, parasomnia, confusional state, hallucination visual, and irritability. The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.

Drug Interactions

XYWAV is contraindicated in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of XYWAV.

Concomitant use of sodium oxybate with divalproex sodium results in an increase in systemic exposure to GHB, which was shown to cause a greater impairment on some tests of attention and working memory in a clinical study.

A similar increase in exposure is expected with concomitant use of XYWAV and divalproex sodium; therefore, an initial dose reduction of XYWAV is recommended when used concomitantly with divalproex sodium. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of XYWAV and divalproex sodium is warranted.

Pregnancy and Lactation

There are no adequate data on the developmental risk associated with the use of XYWAV or sodium oxybate in pregnant women. XYWAV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. GHB is excreted in human milk after oral administration of sodium oxybate. 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 XYWAV and any potential adverse effects on the breastfed infant from XYWAV or from the underlying maternal condition.

Pediatric Use

Safety and effectiveness of XYWAV for the treatment of idiopathic hypersomnia in pediatric patients have not been established.

Geriatric Use

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

The starting dose of XYWAV should be reduced in patients with liver impairment.

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.

Dependence and Tolerance

There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per 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.

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Even if your patients with IH have started on certain other treatments, you can consider XYWAV.

Hear Jennie's story on her journey to finally being prescribed XYWAV

Click to hear her story.

References: 1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014. **2.** Trotti LM, Ong JC, Plante DT, Murray CF, King R, Bliwise DL. Disease symptomatology and response to treatment in people with idiopathic hypersomnia: initial data from the Hypersomnia Foundation registry. *Sleep Med*. 2020;75:343-349. **3.** Vernet C, Leu-Semenescu S, Buzare MA, Arnulf I. Subjective symptoms in idiopathic hypersomnia: beyond excessive sleepiness. *J Sleep Res*. 2010;19(4):525-534. **4.** Arnulf I, Leu-Semenescu S, Dodet P. Precision medicine for idiopathic hypersomnia. *Sleep Med Clin*. 2019;14(3):333-350. **5.** Trotti LM. Waking up is the hardest thing I do all day: sleep inertia and sleep drunkenness. *Sleep Med Rev*. 2017;35:76-84 **6.** XYWAV® (calcium, magnesium, potassium, and sodium oxybates). Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **7.** Dauvilliers Y, Bogan RK, Arnulf I, Scammell TE, St Louis EK, Thorpy MJ. Clinical considerations for the diagnosis of idiopathic hypersomnia. *Sleep Med Rev* 2022;66:101709 **8.** FDA grants first of its kind indication for chronic sleep disorder treatment. News release. U.S. Food and Drug Administration; August 12, 2021. Accessed March 18, 2024. https://www.fda.gov/news-events/press-announcements/fda-grants-first-its-kind-indication-chronic-sleep-disorder-treatment **9.** Dauvilliers Y, Arnulf I, Foldvary-Schaefer N, et al. Safety and efficacy of lower-sodium oxybate in adults with idiopathic hypersomnia: a phase 3, placebo-controlled, double-blind, randomised withdrawal study. *Lancet Neurol*. 2022;21(1):53-65. **10.** Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14(6):540-545.

IMPORTANT SAFETY INFORMATION (cont'd)

Dependence and Tolerance (cont'd)

In the XYWAV clinical trial in adult idiopathic hypersomnia patients at recommended doses, six patients reported insomnia, two patients reported early insomnia, and one patient reported visual and auditory hallucinations following abrupt discontinuation of XYWAV.

Tolerance to XYWAV has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended XYWAV dosage regimen.

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Jazz Pharmaceuticals