xywav®

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

Dosing and Titration Guide

Including EMR integration and e-Prescribing

INDICATIONS 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 cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy, and 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 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.

How to get started

We've provided you with this guide to help facilitate the steps involved in prescribing, dosing, and titrating XYWAV. Use the tabs above to navigate through the contents of this guide.

XYWAV is the first and only FDA-approved treatment for both narcolepsy and idiopathic hypersomnia[1-3]

INDICATIONS AND USAGE
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Important Safety Information (cont'd)

Contraindications

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

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.

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Dosing for Patients With Narcolepsy

Adult patients new to oxybate therapy: Starting and titrating XYWAV

- XYWAV is taken at night divided into 2 doses[1]
- The recommended starting dosage 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[1]
- 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[1]
- Some patients may achieve better responses with unequal nightly doses at bedtime and 2.5 to 4 hours later[1]
- Doses higher than 9 g per night have not been studied and ordinarily should not be administered[1]
- Patients should be queried about CNS depression-related events upon initiation of XYWAV therapy and periodically thereafter[1]

Recommended Adult XYWAV Dosing Regimen[1]

Start at 4.5 g per night	>	Increase based on efficacy and tolerability by up to 1.5 g per night per week (eg, add 0.75 g to dose 1 and 0.75 g to dose 2)					
4.5 g per night		6.0 g per night		7.5 g per night		9.0 g per night	
Dose 1 2.25 g	Dose 2 2.25 g	Dose 1 3.0 g	Dose 2 3.0 g	Dose 1 3.75 g	Dose 2 3.75 g	Dose 1 4.5 g	Dose 2 4.5 g
		Recommended Dosage Range					

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

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.

Continued on next page

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Pediatric patients (ages 7 and up) new to oxybate therapy: Starting and titrating XYWAV

The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight.[1]

- XYWAV is taken at night divided into 2 doses[1]
- The first dose is taken at bedtime, and the second dose is taken 2.5 to 4 hours later[1]
  - Some patients may achieve better responses with unequal nightly doses at bedtime and 2.5 to 4 hours later[1]
- Total nightly doses higher than 9 g have not been studied and should not ordinarily be administered[1]
- The dosage may be gradually titrated based on efficacy and tolerability[1]

Recommended Initial XYWAV Dosage for Patients 7 Years of Age and Older[1]*

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.[1]

†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.[1]

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

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.

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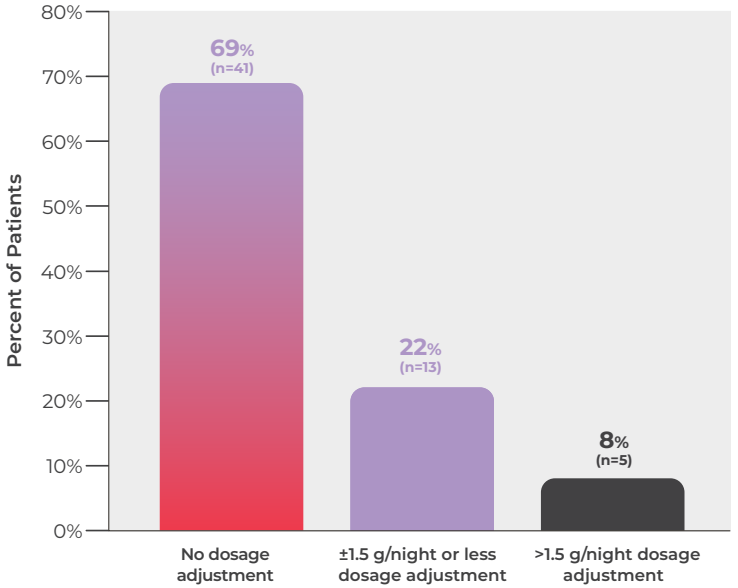
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Patients transitioning from XYREM® (sodium oxybate) oral solution

- On the first night of dosing with XYWAV, initiate treatment at the same dose (gram for gram) and regimen as XYREM[1]
  - Titrate as needed based on efficacy and tolerability[1]
- Because XYWAV contains other cations, inform patients that it will taste different than XYREM

In the clinical trial with XYWAV in adult patients with narcolepsy, 59 patients who were taking XYREM at study entry were switched from XYREM to XYWAV. The figure on the right indicates the outcome related to changes in XYWAV dosage from study entry to the stable-dose period in patients who switched from XYREM to XYWAV.[1,4]

Dose Changes During Transition From XYREM to XYWAV in the Clinical Trial (n=59)[1,4]



Dosage changes of ≤1.5 g/night were considered within 1 titration step in the clinical trial.[1]



Smaller bottle. Same amount of medicine.

Whereas XYREM was dispensed in an 8-oz bottle, XYWAV is dispensed in a 6-oz bottle. Although bottle size differs, you can inform your patients that both bottles contain the same amount of medicine—180 mL.[1,5]

69% of patients who transitioned from XYREM to XYWAV in Study 1 had no change in dosage[1,4]

Important Safety Information (cont'd)

Warnings and Precautions (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.

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Dosing for Patients With Idiopathic Hypersomnia (IH)

XYWAV offers individualized dosing so you can tailor optimal treatment for each IH patient[1]

XYWAV is an oral solution administered as a twice- or once-nightly dosing regimen[1]

Instruct your patients:

- On twice-nightly dosing to take their first nightly dose at bedtime, and the second dose should be taken 2.5 to 4 hours later. XYWAV should be administered at least 2 hours after eating[1]
- On once-nightly dosing to take their only nightly dose at bedtime and at least 2 hours after eating[1]
- To prepare XYWAV prior to bedtime and dilute it with approximately ¼ cup of water in the pharmacy-provided containers[1]
- To take XYWAV while in bed and to lie down after dosing. Patients should remain in bed after taking the first and second doses of XYWAV[1]

During titration, the dosing regimen may be changed as needed based on efficacy and tolerability.[1] Be sure to follow up with your XYWAV patients so they get an optimally tailored dose.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Depression and Suicidality

In Study 1, the 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.

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XYWAV offers individualized dosing so you can tailor optimal treatment for each Idiopathic Hypersomnia (IH) patient[1]

EXAMPLE DOSING SCHEDULE

Twice-Nightly Dosing With XYWAV[1]

	Twice-nightly dosing* start at ≤4.5 g per night	Titrate to effect in increments of ≤1.5 g per night per week (divided into 2 doses)		
Total Nightly Dosage	**4.5 g/night**	**6 g/night**	**7.5 g/night**	**9 g/night** (maximum total nightly dose)
Dose 1 (at bedtime)	**2.25 g**	**3 g**	**3.75 g**	**4.5 g**
Dose 2 (2.5-4 hours later)	**2.25 g**	**3 g**	**3.75 g**	**4.5 g**

*For twice-nightly regimens, doses can be divided equally or unequally. Some patients may achieve better responses with unequal doses at bedtime and 2.5 to 4 hours later.[1]

EXAMPLE DOSING SCHEDULE

Once-Nightly Dosing With XYWAV[1]

	Once-nightly dosing start at ≤3 g per night	Titrate to effect in increments of ≤1.5 g per night per week	
Total Nightly Dosage	**3 g/night** (total)	**4.5 g/night** (total)	**6 g/night** (maximum total nightly dose)

Important dosing considerations

- Patients should take the first nightly dose of XYWAV at bedtime and at least 2 hours after eating[1]
- The increase in the total nightly dose should NOT exceed 1.5 g per week[1]
- Total doses >9 g per night or single doses >6 g per night have not been studied and ordinarily should not be administered[1]
- During titration, the dosing regimen may be changed as needed based on efficacy and tolerability[1]
  - In the clinical study, when patients were switched from twice- to once-nightly dosing, the total nightly dose was initially the same as the first dose of the twice-nightly dosing regimen. When patients were switched from once- to twice-nightly dosing, the total nightly dose was no more than 1.5 g higher than the current dose, divided into two doses

Important Safety Information (cont'd)
Warnings and Precautions (cont'd)
Depression and Suicidality (cont'd)
In Study 2, the 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.

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Choosing the right dosing regimen

Patient dosing considerations during the clinical trial[1]*:

XYWAV twice nightly[1]	XYWAV once nightly[1]
Patients were considered for twice-nightly dosing **if they reported disrupted nighttime sleep or difficulty with sleep maintenance**	Patients were considered for once-nightly dosing **if they reported difficulty awakening from nighttime sleep or long sleep time**

*Dose selection in clinical trials was at the clinician's discretion.[1]

There were no meaningful differences in demographics, baseline characteristics, or disease severity between patients receiving XYWAV once nightly vs twice nightly.

In the clinical study, when patients were switched from once- to twice-nightly dosing, the total combined twice-nightly dose was no more than 1.5 g higher than the single dose.[1]

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Depression and Suicidality (cont'd)

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.

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Choosing the right dosing regimen

Dose adjustments were made during the open-label titration and optimization period of the clinical trial

- **48%** of patients that started on once-nightly XYWAV during the OTTP* ended up on a twice-nightly regimen at the end of the SDP[6]*

77% of Idiopathic Hypersomnia (IH) patients concluded the double-blind, randomized-withdrawal period of the clinical trial on twice-nightly XYWAV.[1,7]

Not all IH patients are the same. That's why XYWAV dosing can be individualized for optimal efficacy and tolerability.

Study Design: The efficacy and safety of XYWAV in adults with idiopathic hypersomnia were evaluated in a double-blind, placebo-controlled, randomized-withdrawal clinical trial. The trial consisted of a minimum of 10-week open-label treatment titration and optimization period (up to 14 weeks), followed by a 2-week SDP, a 2-week DB RWP,† and a 24-week open-label safety extension period. 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 Epworth Sleepiness Scale (ESS) score from the end of the SDP to the end of the DB RWP.

*OTTP = optimized treatment and titration period; SDP = stable-dose period; DB RWP = double-blind, randomized-withdrawal period.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Other Behavioral or Psychiatric Adverse Reactions

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

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Dosage Calculation for Both Indications

How to complete the XYWAV Prescription Form

- When filling out the section for the initial 30-day prescription, complete EITHER the titrated dosing OR fixed dosing section (both are completed in the example below)
- The XYWAV Prescription Form is available online at XYWAVXYREMREMS.com

Example as Shown in Prescribing Information

2 times a night dosing (for narcolepsy and Idiopathic Hypersomnia [IH])*	OR	1 time a night dosing (IH patients only)	Number of days (at each titration step)
Starting dose: First dose: 2.25 g + second dose: 2.25 g = **4.5 g total nightly dose**		Starting dose: Dose: 3 g	Dose for 7 days
1st titration: First dose: 3 g + second dose: 3 g = **6 g total nightly dose**		1st titration: Dose: 4.5 g	Dose for 7 days
2nd titration: First dose: 3.75 g + second dose: 3.75 g = **7.5 g total nightly dose**		2nd titration: Dose: 6 g	Dose for 7 days
3rd titration: First dose: 4.5 g + second dose: 4.5 g = **9 g total nightly dose** (maximum dose for twice-nightly dosing)		*6 g is the recommended maximum for once-nightly dosing*	Dose for 7 days

*Doses may be divided equally or unequally and the first dose taken at bedtime and the second dose taken 2.5 to 4 hours later.

Important Safety Information (cont'd)
Warnings and Precautions (cont'd)
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 experienced visual hallucinations, which led to discontinuation of XYWAV.

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Dosage Calculation for Both Indications

How to convert XYWAV dosages from g to mL

- XYWAV is dispensed by the Certified Pharmacy in a maximum 30-day supply for the initial fill, and a maximum 90-day supply for each refill[1,7]
- Insurance plans, electronic medical record (EMR) systems, or e-Prescribe platforms may require conversion of XYWAV from grams to milliliters
- The recommended dosage for XYWAV per the full Prescribing Information equates to the total monthly quantities below[1]
- XYWAV is packaged in 6-oz bottles (180 mL) with a concentration of 0.5 g/mL[1]

Example of How to Calculate Amount of XYWAV Needed (in mL) for a 30-Day Supply[1]

Total nightly dosage	Dose 1			Dose 2			Total per night		Total per month
g	g	mL		g	mL		mL		mL
≤2	≤1	≤2		≤1	≤2		≤4		≤120
3	1.5	3		1.5	3		6		180
4.5	2.25	4.5		2.25	4.5		9		270
6	3	6	+	3	6	=	12	x 30 Days =	360
7.5	3.75	7.5		3.75	7.5		15		450
9	4.5	9		4.5	9		18		540

Note: Initial prescription fill cannot exceed 1 month of therapy. Refills cannot exceed 3 months' supply.[7]

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Other Behavioral or Psychiatric Adverse Reactions (cont'd)

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.

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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. 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.[1]

Studies in vitro with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A up to the concentration of 3 mM (378 mcg/mL).[1]

XYWAV is contraindicated for use in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of XYWAV.[1]

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and[1]:

- Protriptyline hydrochloride
- Zolpidem tartrate—Please note that this medication is on the REMS Sedating Drug List. The Certified Pharmacy is required to call the prescriber of this medication if the patient taking this medication is prescribed XYWAV
- Modafinil
- The alcohol dehydrogenase inhibitor fomepizole

However, pharmacodynamic interactions with these drugs cannot be ruled out.

In addition[1]:

- Drug interaction studies in healthy adults demonstrated no pharmacokinetic or clinically significant pharmacodynamic interactions between sodium oxybate and duloxetine HCl
- Diclofenac: Co-administration of sodium oxybate (6 g per day as 2 equal doses of 3 grams dosed 4 hours apart) with diclofenac (50 mg/dose twice per day) showed no significant differences in systemic exposure to GHB. Co-administration did not appear to affect the pharmacokinetics of diclofenac
- Ibuprofen: Co-administration of sodium oxybate (6 g per day as 2 equal doses of 3 grams dosed 4 hours apart) with ibuprofen (800 mg/dose 4 times per day also dosed 4 hours apart) resulted in comparable systemic exposure to GHB as shown by plasma C_{max} and AUC values. Co-administration did not affect the pharmacokinetics of ibuprofen
- Alteration of gastric pH with omeprazole produced no significant change in the pharmacokinetics of GHB

Dosage modifications and adjustments[1]

- Patients taking divalproex sodium: 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
- Patients with hepatic impairment: The starting dose should be reduced by half in these patients because of an increase in exposure to XYWAV

Important Safety Information (cont'd)
Warnings and Precautions (cont'd)
Parasomnias
Parasomnias can occur in patients taking XYWAV.

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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 is exclusively distributed via the XYWAV and XYREM REMS and will be dispensed only by the Certified Pharmacy
  - XYWAV will be dispensed and shipped only to patients who are enrolled in the XYWAV and XYREM REMS with documentation of safe use
- Prescribers and patients who are already actively enrolled in the XYREM REMS are not required to re-enroll in the XYWAV and XYREM REMS
- To prescribe XYWAV for your patient:
  - The XYWAV Prescription Form is provided through Jazz Pharmaceuticals
- Download the Prescription Form via XYWAVXYREMREMS.com, and print, sign, and:
  - Fax to the XYWAV and XYREM REMS: 1-866-470-1744 (toll-free)
  - OR mail to the XYWAV and XYREM REMS, PO Box 66589, St. Louis, MO 63166-6589
- At no time can the patient be prescribed or take XYWAV and XYREM® (sodium oxybate) oral solution at the same time
- Submit any individual state requirements for prescribing controlled substances
  - For more information, call the XYWAV and XYREM REMS at 1-866-997-3688 (toll-free) or go to XYWAVXYREMREMS.com

*REMS = Risk Evaluation and Mitigation Strategy.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Parasomnias (cont'd)

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.

Continued on next page

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Guidance for electronic prescribing

eRx requirements

eRx submissions are received at the Certified Pharmacy. Follow the process below to help prevent prescribing errors.

STEP 1: Enter the Certified Pharmacy information

- Under mail-order pharmacies, search by Pharmacy Name (SDS Pharmacy) or NCPDP #2633611
  - Address: Specialty Distribution Services, Inc 4600 N Hanley Dr Suite B, St. Louis, MO 63134
  - Phone: 1-866-997-3688

STEP 2: Specify indication

- Narcolepsy or Idiopathic Hypersomnia (IH)

STEP 3: Select Fixed-dose entry or Titrated-dosing entry

Fixed-dose entry

- Enter a fixed dose by selecting the dose from the dropdown menu or by entering it manually
- For manual entry of a twice-nightly dosage, enter only the first of the 2 nightly doses and specify a twice-nightly frequency
- For manual entry of a once-nightly dosage for a patient with IH, enter the nightly dose and specify a once-nightly frequency

Titrated-dosing entry

- The titration schedule must be entered manually in the pharmacy notes section

When prescribing XYWAV for patients with narcolepsy younger than 18 years old, you must enter the patient's weight on the XYWAV Prescription Form where indicated.

STEP 4: Enter quantity in days and units of measure

- e-Prescribing platforms, EMR systems, or insurance plans may require conversion from grams to milliliters

STEP 5: Enter refills

- The XYWAV prescription is valid for 6 months from the date written, and up to 5 refills are allowed on a XYWAV prescription[7]
- The XYWAV Prescription Form is used for the initial prescription and for patients who are restarting treatment after the 6 months[7]

STEP 6: Enter maximum daily dosage

- Maximum 9 g total nightly dose for 2x/night dosing
- Maximum 6 g total nightly dose for 1x/night dosing (for adult patients with IH only)



Additional steps for New York prescribers

- **Verify I-STOP**
- **Enter dual authentication code**

STEP 7: Submit

Important Safety Information (cont'd)
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.

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Using the electronic medical record (EMR) to order refills

There may be a restriction to the number of characters allowable when utilizing EMR systems or when e-prescribing. See below for an example of a simple way to enter the XYWAV titration schedule in an electronic database.

Adult narcolepsy patient sample electronic titration entry
2.25 g 2x/night x7d
3.0 g 2x/night x7d
3.75 g 2x/night x7d
4.5 g 2x/night x30d

Pediatric narcolepsy patient sample electronic titration entry
1.5 g 2x/night x7d
2.0 g 2x/night x7d
2.5 g 2x/night x7d
3.0 g 2x/night x30d

Adult Idiopathic Hypersomnia (IH) patient sample once-nightly electronic titration entry
3.0 g 1x/night x7d
4.5 g 1x/night x7d
6.0 g 1x/night x30d

Adult IH patient sample twice-nightly electronic titration entry
2.25 g 2x/night x7d
3.0 g 2x/night x7d
3.75 g 2x/night x7d
4.5 g 2x/night x30d

The XYWAV Prescription Form is used for initial prescriptions and for patients who are reinstating XYWAV after a lapse in therapy of 6 months or longer.[8]

Important Safety Information (cont'd)

Most Common Adverse Reactions (cont'd)

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.

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

Help your patients integrate their treatment regimen into their routine

Advise them on a consistent nighttime routine for preparing and taking XYWAV properly

- A bedtime routine consistent with XYWAV dosing and administration requirements should be established
- Patients with narcolepsy should take XYWAV at night divided into 2 doses[1]
- Patients with Idiopathic Hypersomnia (IH) can take XYWAV twice- or once-nightly, depending on clinical evaluation
- For patients on twice-nightly dosing regimens:
  - Both doses should be taken each night[1]
  - Patients should never take 2 XYWAV doses at the same time[1]
  - If the second dose is missed, that dose should be skipped and XYWAV should not be taken again until the next night[1]
  - Doses should be taken 2.5 to 4 hours apart
- Patients should prepare their dose(s) prior to bedtime[1]
- Patients should wait at least 2 hours after eating before taking their first nightly dose of XYWAV[1]
- Patients should take each dose while in bed and lie down immediately after dosing[1]
- XYWAV can cause sleep very quickly without first feeling drowsy[1]
- Patients should not do anything that requires them to be fully awake or is dangerous for at least 6 hours after taking XYWAV[1]

Remember to counsel patients and caregivers about the serious risks associated with XYWAV, including its contraindication for use in combination with alcohol or sedative hypnotics, and the risks of concomitant use with other CNS depressants or other potentially interacting agents.[1]

Important Safety Information (cont'd)

Additional Adverse Reactions

Adverse reactions that occurred in 2-<5% of adult patients treated with XYWAV in the Open-Label Titration and Stable Dose Periods of the randomized-withdrawal study in adult patients with narcolepsy with cataplexy (Study 1) were fatigue, dry mouth, depressed mood, enuresis, irritability, paresthesia, depression, tremor, somnolence, and muscle spasms. Adverse reactions occurring in 2-<5% of patients treated with XYWAV in the IH study include 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 1) and which may be relevant for XYWAV, were pain, feeling drunk, pain in extremity, cataplexy, disturbance in attention, sleep paralysis, and disorientation.

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Comprehensive support in patients' hands throughout treatment

myWAV and the myWAV app

An easy-to-use online tool for patients to get treatment education and resources, anywhere and anytime.

Empowers patients and caregivers to find support during their treatment journey.

Patients can download the myWAV app to learn important information about creating a routine, plan their dosing schedules, set helpful reminder alerts and alarms, and track their progress.

myWAV™

BY THE MAKER OF xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution CIII

Encourage your XYWAV patients to enroll at myWAV.com

Important Safety Information (cont'd)

Additional Adverse Reactions (cont'd)

Discontinuation: In Study 1, 9 of 201 patients (4%) reported adverse reactions that led to withdrawal from the study (anxiety, decreased appetite, depressed mood, depression, fatigue, headache, irritability, nausea, pain in extremity, parasomnia, somnolence, and vomiting). The most common adverse reaction leading to discontinuation was nausea (1.5%). In Study 2, 17 of 154 (11%) patients across all study periods (excluding placebo during the DB RWP) (up to 42 weeks) reported adverse reactions that led to withdrawal from the study (anxiety, nausea, insomnia, vomiting, fatigue, feeling abnormal, fall, decreased appetite, dizziness, paresthesia, tremor, parasomnia, confusional state, hallucination visual, and irritability). The most common adverse reaction leading to discontinuation was anxiety (3.2%). In Study 1 and Study 2, the majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.

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

JazzCares® for XYWAV

Committed to helping you and your patients get access to support and resources throughout treatment

Jazz Pharmaceuticals, the leader in sleep medicine, is committed to helping remove barriers to access for appropriate patients who may benefit from XYWAV.

JazzCares
Making a difference in Patients' lives, one Patient at a time



Access and affordability*

Our teams work directly with your office to verify each patient's insurance coverage and support you and your staff through the insurance coverage process. Several financial assistance options are also available for eligible patients.



Nurse and pharmacy support

A JazzCares Nurse Case Manager will be there for your patients from the very beginning and will provide support throughout treatment. A pharmacist is also available 24/7 to answer patients' questions.



Personalized resources

JazzCares for XYWAV has the resources to help your patients by giving them personalized information and support throughout their treatment journey.

*Insurance coverage and plans may vary. The JazzCares program at Jazz Pharmaceuticals provides general information only and is not a guarantee of any coverage or reimbursement outcome. All treatment decisions rest solely with the treating physician or qualified healthcare professional.

Important Safety Information (cont'd)

Additional Adverse Reactions (cont'd)

In the pediatric clinical trial with XYREM (same active moiety as XYWAV), 7 of 104 patients reported adverse reactions that led to withdrawal from the study (hallucination, tactile; suicidal ideation; weight decreased; sleep apnea syndrome; affect lability; anger, anxiety, depression; and headache).

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

XYWAV financial assistance programs through JazzCares®

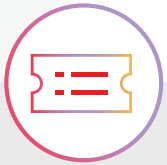
Jazz Pharmaceuticals is committed to supporting patient access for XYWAV.

Commercially insured patients



The XYWAV Coupon Program

Did you know that >99% of all commercial patients **CAN PAY AS LITTLE AS $5 FOR XYWAV?**[a,b]



The XYWAV Quick Start Voucher

Waiting for your patients' coverage? Your patients **COULD RECEIVE A FREE 1-MONTH SUPPLY OF XYWAV WITH THE QUICK START VOUCHER.**[a]



The XYWAV Bridge Program

Your patient **MAY BE ELIGIBLE FOR UP TO 120 DAYS OF FREE XYWAV WHILE WAITING FOR COVERAGE APPROVAL.**[a]

The XYWAV Patient Assistance Program

The JazzCares Patient Assistance Program **MAY BE ABLE TO HELP PATIENTS WHO ARE UNINSURED OR WHOSE INSURANCE DOES NOT COVER XYWAV.**[c,d]

ADDITIONAL QUESTIONS?

Visit JazzCares.com/HCP to contact your Jazz Pharmaceuticals Access and Reimbursement Manager or call JazzCares at 1-866-997-3688, Monday – Friday, 7 AM – 8 PM, Central Time.

[a]Applies only to eligible, commercially insured patients enrolled in the XYWAV and XYREM REMS.
[b]Eligible patients pay as little as $5. Subject to monthly maximum benefit.
[c]Subject to financial and other eligibility criteria. Must be enrolled in the XYWAV and XYREM REMS.
[d]The Patient Assistance Program application is available online at www.JazzCares.com/XYWAV.
Jazz Pharmaceuticals reserves the right to terminate or modify this program at any time with or without notice. Other terms and conditions apply. Please see the terms and conditions at www.JazzCares.com/HCP/XYWAV.

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Important Safety Information (cont'd)

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

The safety and effectiveness of XYWAV for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy have been established. XYWAV has not been studied in a pediatric clinical trial for narcolepsy or IH. Use of XYWAV in pediatric patients 7 years of age and older with narcolepsy is supported by evidence from an adequate and well-controlled study of sodium oxybate in pediatric patients 7 to 17 years of age, a study in adults showing a treatment effect of XYWAV similar to that observed with sodium oxybate, pharmacokinetic data of sodium oxybate from adult and pediatric patients, and pharmacokinetic data of XYWAV from healthy adult volunteers.

Safety and effectiveness of XYWAV in pediatric patients below the age of 7 years with narcolepsy have not been established.

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

Important Safety Information (cont'd)

Dependence and Tolerance (cont'd)

In the clinical trial experience with XYREM in narcolepsy/cataplexy patients at recommended doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time. In the XYWAV clinical trial in adult narcolepsy/cataplexy patients at recommended doses, one patient reported insomnia following abrupt discontinuation of XYWAV. 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.

Learn more at XywavHCP.com

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

XYWAV is the first and only FDA-approved treatment for both narcolepsy and idiopathic hypersomnia[1-3]

INDICATIONS 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 cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy, and for the treatment of idiopathic hypersomnia (IH) in adults.

References: 1. XYWAV® (calcium, magnesium, potassium, and sodium oxybates). Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **2.** Thorpy MJ. Recently approved and upcoming treatments for narcolepsy. *CNS Drugs.* 2020;34(1):9-27. **3.** Bogan RK, Thorpy MJ, Dauvilliers Y, et al. Efficacy and safety of calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate [LXB]; JZP-258) in a placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy. *Sleep.* 2021;44(3):zsaa206. **4.** Data on File (JZP258-2020-016). Jazz Pharmaceuticals, Inc. **5.** XYREM® (sodium oxybate). Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **6.** Arnulf I, Morse AM, Chandler P, Parvataneni R, Chen D, Dauvilliers Y. Efficacy and safety of once- and twice-nightly dosing of lower-sodium oxybate in adults with idiopathic hypersomnia. Poster presented at: 35th Annual Meeting of the Associated Professional Sleep Societies (APSS) Virtual Meeting; June 10-13, 2021. **7.** Data on File (JZP080-301-20). Jazz Pharmaceuticals, Inc. **8.** XYWAV and XYREM REMS Document. NDA 21196; NDA 212690. XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) and XYREM® (sodium oxybate). Palo Alto, CA: Jazz Pharmaceuticals, Inc. Approved 02/2015. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=345. Accessed October 1, 2022.

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