Dosing and Titration Guide

Including EMR integration and e-Prescribing

GET STARTED

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.

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 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.

How to get started

We've provided you with this guide to help facilitate the steps involved in prescribing, dosing, and titrating XYWAV. To get started, use the bar at the top to navigate through the sections of this guide.

First and only FDA-approved lower-sodium oxybate for treating cataplexy or EDS in patients with narcolepsy[1-3]

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.

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

Initiate dose at 1:1 conversion from XYREM® (sodium oxybate) oral solution[1]

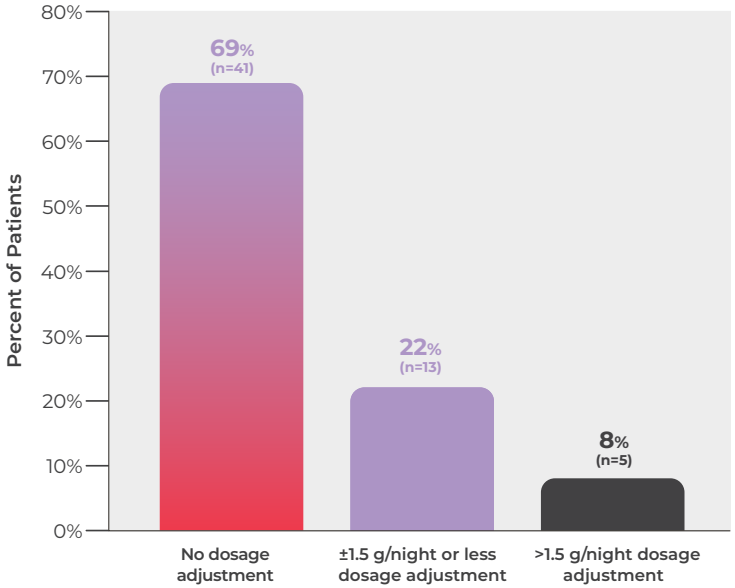
- On the first night of dosing with XYWAV, initiate treatment at the same dose (gram for gram) and regimen as XYREM[1]
  - Titrate as needed based on efficacy and tolerability[1]

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]

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]

Dosage 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]

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)

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

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 Dosage 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					

Because XYWAV contains other cations, inform patients that it will taste different than XYREM.[1,5,6]

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

XYWAV and XYREM REMS Program

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 Program.

Notable requirements of the Xywav and Xyrem REMS Program 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 Program with documentation of safe use

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

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.

†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.

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.

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

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 ePrescribe 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	x 30 Days =	270
6	3	6		3	6		12		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)

Depression and Suicidality

In a 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 clinical trials of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy (n=781), adverse reactions of depression were reported by 7% of 781 patients treated with Xyrem, with four patients (<1%) discontinuing because of depression. In most cases, no change in Xyrem treatment was required. In clinical trials of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy (n=781), there were two suicides and two attempted suicides in patients treated with Xyrem, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used Xyrem in conjunction with other drugs. Xyrem was not involved in the second suicide.

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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
- XYWAV should be taken at night divided into 2 doses, taken 2.5 to 4 hours apart[1]
- Both doses should be prepared 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]
- Both doses should be taken each night, and 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]
- 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)

Warnings and Precautions (cont'd)

Depression and Suicidality (cont'd)

In the pediatric clinical trial with Xyrem (same active moiety as XYWAV) in patients with narcolepsy (n=104), one patient experienced suicidal ideation while taking Xyrem and two patients reported depression. 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, which require careful and immediate evaluation.

Other Behavioral or Psychiatric Adverse Reactions

In a randomized-withdrawal clinical trial in adult patients, confusion occurred in 1% of patients treated with XYWAV and anxiety occurred in 5% of patients treated with XYWAV. One patient experienced visual hallucinations and confusion after ingesting approximately 9 grams of XYWAV. Other neuropsychiatric reactions reported in clinical trials of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy and in the postmarketing setting included hallucinations, paranoia, psychosis, aggression, and agitation.

In a pediatric clinical trial with Xyrem (same active moiety as XYWAV) in patients with narcolepsy, neuropsychiatric reactions, including acute psychosis, confusion, and anxiety, were reported while taking Xyrem. The emergence or increase in the occurrence of behavioral or psychiatric events in patients taking XYWAV should be carefully monitored.

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The XYWAV and XYREM REMS*

- XYWAV is exclusively distributed via the XYWAV and XYREM REMS and is available from the Certified Pharmacy
- 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 or XYREM for your patient:
  - The XYWAV Prescription Form or XYREM Prescription Form is provided through Jazz Pharmaceuticals and is available to download online at XYWAVXYREMREMS.com
- 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 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

*Risk Evaluation and Mitigation Strategy.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Parasomnias

Parasomnias can occur in patients taking XYWAV.

In a randomized-withdrawal clinical trial, parasomnias, including sleepwalking were reported in 6% of adult patients treated with XYWAV. 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

In the adult clinical trial, in patients with narcolepsy, the most common adverse reactions (incidence ≥5% of XYWAV-treated patients) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting.

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: ESSDS Pharmacy, 8931 Springdale Ave, St. Louis, MO 63134
  - Phone: 1-866-997-3688 (toll-free)

STEP 2: 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, enter only the first of the 2 nightly doses and specify a twice-nightly frequency

Titrated-dosing entry

- The titration schedule must be entered manually in the pharmacy notes section
- At the right are examples of how to enter the XYWAV titration schedule for adults and pediatric patients, using a limited number of characters

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

ADULT Sample

Fixed-Dose Manual Entry	Electronic Titration Entry
2.25 g 2x nightly	**2.25 g** 2x nightly x7 days
	3.0 g 2x nightly x7 days
	3.75 g 2x nightly x7 days
	4.5 g 2x nightly fill up to 30-day supply

PEDIATRIC Sample

Fixed-Dose Manual Entry	Electronic Titration Entry
1.5 g 2x nightly	**1.5 g** 2x nightly x7 days
	2.0 g 2x nightly x7 days
	2.5 g 2x nightly x7 days
	3.0 g 2x nightly fill up to 30-day supply

Continued on next page

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.

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Guidance for electronic prescribing (cont'd)

eRx requirements (cont'd)

STEP 3: Enter quantity in days and units of measure

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

STEP 4: 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 5: Enter maximum daily dosage

- The maximum recommended daily dosage of XYWAV in adults and in pediatric patients 7 years of age and older weighing 45 kg or more is 9 g/night (18 mL).[1] Doses higher than 9 g/night have not been studied and should not ordinarily be administered[1]

Additional steps for New York prescribers

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

STEP 6: Submit

Important Safety Information (cont'd)

Additional Adverse Reactions

Additional adverse reactions that occurred in ≥2% 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.

Additional adverse reactions that occurred in ≥2% of patients in clinical studies with Xyrem (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.

Discontinuation: In a randomized-withdrawal clinical trial 9 of 201 adult 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%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.

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).

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Using the electronic medical record (EMR) to order refills

There may be a restriction to the number of characters allowed 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 Example Electronic Titration Entry
2.25 g 2x nightly x7 days
3.0 g 2x nightly x7 days
3.75 g 2x nightly x7 days
4.5 g 2x nightly fill up to 30-day supply

Pediatric Example Electronic Titration Entry
1.5 g 2x nightly x7 days
2.0 g 2x nightly x7 days
2.5 g 2x nightly x7 days
3.0 g 2x nightly fill up to 30-day supply

The XYWAV Prescription Form or XYREM Prescription Form is used for initial prescriptions and for patients who are reinstating XYWAV or XYREM after a lapse in therapy of 6 months or longer.[7]

Adult Example Unequal Dosing Electronic Entry
3.5 g at bedtime, **2.25 g** 2.5-4 hours later
3 g first dose at bedtime, **2.5 g** second dose 2.5-4 hours later
2.25 g 1x nightly + **3.5 g** 1x nightly 2.5-4 hours later

Important Safety Information (cont'd)

Drug Interactions

XYWAV should not be used 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.

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Drug interactions

- 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]:	In addition[1]:
• Protriptyline hydrochloride • Zolpidem tartrate • Modafinil • The alcohol dehydrogenase inhibitor fomepizole However, pharmacodynamic interactions with these drugs cannot be ruled out.	• 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 two equal doses of 3 grams dosed four 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 two equal doses of 3 grams dosed four hours apart) with ibuprofen (800 mg/dose four times per day also dosed four 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

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JazzCares® for XYWAV

Committed to helping get you and your patients 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*

The Certified Pharmacy will work directly with your office to verify patients' insurance coverage and offer support with the insurance coverage process. Jazz also provides financial assistance options for your patients.

Nurse and pharmacy support

The JazzCares Nurse Case Manager will be with patients throughout their treatment journey. A pharmacist will be available 24/7 through the Certified Pharmacy to answer questions patients may have about their prescription.

Personalized resources

JazzCares for XYWAV has the resources to help your patients by giving them personalized information so they can get the most out of their treatment.

Cost and Coverage

Patients with commercial prescription drug insurance may be eligible for the JazzCares for XYWAV Coupon Program, a savings program that lets your patients pay as little as $5 per prescription (subject to terms and conditions, including a monthly maximum amount).*

LEARN MORE AT XywavHCP.com
To speak with a JazzCares Nurse Case Manager, call 1-866-997-3688.
A Nurse Case Manager is available Monday – Friday, 7 AM – 8 PM, Central Time.
A pharmacist is available 24 hours a day, 7 days a week.

*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.

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Important Safety Information (cont'd)

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. 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 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. The discontinuation effects of XYWAV have not been systematically evaluated in controlled clinical trials.

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.

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.

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.* Published online October 14, 2020. doi.org/10.1093/sleep/zsaa206. **4.** Data on File (JZP258-2020-016). Jazz Pharmaceuticals, Inc. **5.** XYREM® (sodium oxybate). Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **6.** Lawless HT, Rapacki F, Horne J, Hayes A. The taste of calcium and magnesium salts and anionic modifications. *Food Qual Pref.* 2003;14(4):319-325. **7.** 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 September 15, 2020.

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

Jazz Pharmaceuticals