Xywav (calcium oxybate, magnesium oxybate, potassium oxybate, sodium oxybate)

New Indication Review

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Introduction

- **Brand name:** Xywav
- **Generic name:** Calcium oxybate, magnesium oxybate, potassium oxybate, sodium oxybate
- **Pharmacologic class:** CNS depressant
- **Strength and Formulation:** 234/96/130/40mg; per mL; oral solution
- **Manufacturer:** Jazz Pharmaceuticals
- **How supplied:** Solution (0.5g/mL)—180mL
- **Legal Classification:** CIII

New Indication

- Treatment of **idiopathic hypersomnia** in adults.

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Other Indication(s)

- Treatment of **cataplexy** or **excessive daytime sleepiness** in patients 7 years of age and older with narcolepsy.

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Mechanism of Action

- Exact mechanism of action is unknown.
- Gamma-hydroxybutyrate (GHB) is an endogenous compound and metabolite of the neurotransmitter GABA.
- Therapeutic effects may be mediated through $GABA_B$ actions during sleep at noradrenergic, dopaminergic, and thalamocortical neurons.

Dosage & Administration: Idiopathic Hypersomnia

- Dilute each dose with 60mL of water.
- Administer at least 2 hours after eating.

Dosing Regimen	Initial Dose	Titration Increments	Maximum Dose
Twice nightly	≤4.5g/night divided in 2 doses; once at bedtime and once 2.5–4hrs later	≤1.5g/night per week	9g/night divided in 2 doses
Once nightly	≤3g/night	≤1.5g/night per week	6g/night

Dosage & Administration: Idiopathic Hypersomnia

- May change between twice and once nightly regimens during titration based on efficacy and tolerability.
- If second dose is missed, the dose should be skipped and Xywav should not be taken again until the next night.
- If transitioning from Xyrem to Xywav:
  - On first night of Xywav, initiate treatment at same dose and regimen as Xyrem.
  - Titrate as needed based on efficacy and tolerability.

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Clinical Trial: Idiopathic Hypersomnia

- Approval was based on a double-blind, placebo-controlled, randomized-withdrawal study (ClinicalTrials.gov Identifier: NCT03533114).
- Of the 154 patients enrolled, only 115 were evaluable for efficacy data and randomly assigned 1:1 to receive Xywav or placebo in the 2-week double-blind, randomized withdrawal period (DB RWP).
- At baseline, patients were:
  - Receiving Xyrem only: 2%
  - Receiving Xyrem + additional stimulant or alerting agent: 4%
  - Receiving a stimulant or alerting agent, but not Xyrem: 54%
  - Treatment naïve: 41%

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Clinical Trial: Idiopathic Hypersomnia

- Approximately 57% of patients continued to take a stable dose of stimulant during the stable dose period (SDP) and DB RWP.
- Patients were considered for once nightly regimen if they reported difficulty awakening as a result of sleep inertia or long sleep time.
- Patients were considered for twice nightly regimen if they reported disrupted nighttime sleep or difficulty with sleep maintenance.
- At start of DB RWP:
  - Xywav once nightly: 23% (27/115) of patients; median nightly dose: 4.5g
  - Xywav twice nightly: 77% (88/115) of patients; median nightly dose: 7.5g

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Clinical Trial: Idiopathic Hypersomnia

- **Primary efficacy endpoint:** Change in Epworth Sleepiness Scale (ESS) score, a measure of reduction in excessive daytime sleepiness from the end of the SDP to the end of the DB RWP.
  - 8-item self-reported questionnaire by which patients rate their perceived likelihood of falling asleep during usual daily life activities (0-3; never doze to high chance of dozing).
- **Secondary efficacy endpoints:** Patient global impression of change (PGIc) and the Idiopathic Hypersomnia Severity Scale (IHSS), both assessed as a change from the end of the SDP to the end of the DB RWP.
  - IHSS: 14-item self-reported questionnaire assessing the severity of idiopathic hypersomnia symptoms of excessive sleepiness, prolonged sleep duration, cognitive impairment, and sleep inertia (0-50; higher scores indicate greater severity/frequency of symptoms).

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Clinical Trial: Idiopathic Hypersomnia

- Patients taking stable doses of Xywav who were withdrawn from Xywav treatment and randomly assigned to placebo during DB RWP experienced significant worsening in ESS score compared with patients randomly assigned to continue treatment with Xywav (*P* <.0001) across all dosing regimens.

Clinical Trial: Idiopathic Hypersomnia

Median Change in ESS Score		
	Placebo (n=59)	**Xywav (n=56)**
Baseline End of 2-Week SDP		
Median	5.0	6.5
End of 2-Week DB RWP		
Median	14.0	7.0
Median Change from End of 2-Week SDP to End of 2-Week DB RWP		
Median	8.0	0.0
P-value	<.0001	

Clinical Trial: Idiopathic Hypersomnia

- Patients randomly assigned to placebo experienced a worsening of symptoms of idiopathic hypersomnia overall based on PGIc compared with those who received Xywav.
  - The % of patients with worsening PGIc scores for idiopathic hypersomnia overall was greater for patients receiving placebo (88.1%) vs those receiving Xywav (21.4%) (*P* <.0001).
- At the end of DB RWP, patients randomly assigned to placebo experienced a worsening in IHSS total score compared with those assigned to Xywav (*P* <.0001).

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Clinical Trial: Idiopathic Hypersomnia

Median Changes in IHSS Total Score

	Placebo (n=59)	Xywav (n=56)
Baseline End of 2-Week SDP		
Median	14.0	14.0
End of 2-Week DB RWP		
Median	29.0	16.0
Median Change from End of 2-Week SDP to End of 2-Week DB RWP		
Median	14.0	0.0
P-value	<.0001	

PGIc at End of DB RWP

Worsened, %	Placebo (n=59)	Xywav (n=56)
Proportion Worsened (minimally, much, or very much worse)	52 (88.1%)	12 (21.4%)
P-value	<.0001	n/a

Considerations for Specific Populations

- **Pregnancy:** No adequate or well-controlled studies in pregnant women; may cause fetal harm based on animal studies.
- **Nursing mothers:** Excreted in human milk; consider benefits of breastfeeding along with mother's clinical need for Xywav and any potential adverse effects.
- **Pediatric:** Idiopathic hypersomnia: not established; Narcolepsy <7 years: not established.
- **Geriatric:** Cautious dosage selection; initiate at low end of dosing range.
- **Renal impairment:** Not studied.
- **Hepatic impairment:** Initiate at one-half of original dosage per night, divided into 2 doses.

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Contraindications

- Concomitant sedative hypnotics or alcohol.
- Succinic semialdehyde dehydrogenase deficiency.

Warnings and Precautions

- Risk of CNS depression.
- Increased abuse potential; monitor for signs of abuse.
- Respiratory dysfunction.
- Sleep-related breathing disorders, especially in men, postmenopausal women not on hormone replacement therapy, obese, or patients with narcolepsy.
- History of depression, suicidal ideation, and other behavioral/psychiatric events; monitor for emergence of depressive symptoms.
- Parasomnias, including sleepwalking.

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Xywav and Xyrem REMS

- Xywav is available only through a restricted distribution program because of the risks of CNS depression, and abuse and misuse.
- Requirements:
  - Health care 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 REMS program with documentation of safe use.
  - More information: www.XywavXyremREMS.com or call (866) 997-3688.

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Interactions

- **See Contraindications.**
- CNS depression potentiated by concomitant other CNS depressants (eg, opioids, benzodiazepines, sedating antidepressants or antipsychotics, sedating antiepileptic drugs, general anesthetics, muscle relaxants, illicit CNS drugs).
- Potentiated by divalproex sodium; monitor closely and adjust accordingly.

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Adverse Reactions

- **Adults: Most common (≥5%)**
  - Nausea, headache, dizziness, anxiety, insomnia, decreased appetite, hyperhidrosis, vomiting, diarrhea, dry mouth, parasomnia, somnolence, fatigue, and tremor.

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Product Monograph

- For more information view the product monograph available at:

https://www.empr.com/drug/xywav/