Sample Letter of Medical Necessity for XYWAV

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

A health plan may request a Letter of Medical Necessity to support coverage of XYWAV. A Letter of Medical Necessity helps explain your rationale and clinical decision-making in choosing therapy for a specific patient and may include supporting documentation.

The letter may be submitted as part of the prior authorization (PA) process with the claim form as part of an appeal or in response to a health plan's request for additional documentation.

Criteria may vary by health plan. Be sure to understand the specific health plan requirements for your patient.

Attached, please find a sample Letter of Medical Necessity for XYWAV, which highlights information that may be required by payers. Also included are optional statements and links to documents that may help support your request for coverage of XYWAV for your patient.

INDICATIONS AND USAGE
XYWAV 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.

Contraindications
XYWAV is contraindicated
- in combination with sedative hypnotics or alcohol
- 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.

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

Important Safety Information (cont.)

Warnings and Precautions (cont.)

Central Nervous System Depression (cont.)

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

Abuse and Misuse

XYWAV is a Schedule Ill 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.

Respiratory Depression and Sleep-Disordered Breathing

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

Depression and Suicidality

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

In Study 2, the 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.

Other Behavioral or Psychiatric Adverse Reactions

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

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

Important Safety Information (cont.)

Warnings and Precautions (cont.)

Other Behavioral or Psychiatric Adverse Reactions (cont.)

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

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

Parasomnias

Parasomnias can occur in patients taking XYWAV.

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

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

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

Most Common Adverse Reactions

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

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

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TO: **[Medical Director]**
[Insurance company]
[Address]
[City, State]
[ZIP code]

RE: **[Patient name]**
[Patient member ID number]
[Patient policy or group number]
[Patient date of birth]
[Case ID number, if applicable]
[Standard review OR Expedited review]

Dear Dr **[Last Name]**,

I am writing this letter on behalf of my patient, **[patient name]**, to request authorization for XYWAV® (calcium, magnesium, potassium, and sodium oxybates), oral solution, 0.5 g/mL total salts (equivalent to 0.413 g/mL of oxybate), to treat **[diagnosis and associated ICD-10 code (ie, idiopathic hypersomnia, G47.11 or G47.12; narcolepsy, G47.411 or G47.419)]**.[1,2]

[XYWAV is the first and only FDA-approved low-sodium oxybate indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.] [XYWAV is the first and only FDA-approved medication indicated to treat idiopathic hypersomnia (IH) in adults.][1,3]

Treatment of **[patient name]** with XYWAV is medically appropriate and necessary. This letter outlines the patient's clinical/medical history, prognosis, and treatment rationale.

1) **Patient's clinical/medical history:**
   - Summary of diagnosis:
     - ICD-10-CM code
     - Date symptoms started
     - Date of diagnosis
   - Labs and test results associated with [diagnosis]
   - Current symptoms and complications (eg, patient has had [X number of] cataplexy events)
   - Previous treatments [tried/failed/contraindicated] for [diagnosis]
   - Any relevant comorbidities

2) **Rationale for treatment:**
   - Plan of treatment (eg, dosage, frequency of therapy, length of treatment)
   - Clinical rationale (ie, summary of why, based on your clinical judgment, your patient requires treatment with XYWAV)

Please call me at [phone number] if I can provide you with any additional information. I look forward to receiving your timely response and approval so my patient can receive treatment for their condition.

Sincerely,

[Physician name and signature]
[Physician address]
[Physician phone number]

Enclosed are the following documents to support my clinical decision:
- Prescribing Information
- Prior authorization form
- Clinical notes/medical records
- Diagnostic test results (eg, polysomnography, Multiple Sleep Latency Test, actigraphy, and/or sleep log)
- Clinical questionnaire scores (eg, Epworth Sleepiness Scale, Idiopathic Hypersomnia Severity Scale)
- Documentation of prior medication history
- Relevant peer-reviewed literature

ICD-10-CM=International Classification of Diseases, Tenth Revision, Clinical Modification.

All of the following statements and links are also options for you to consider including in your Letter of Medical Necessity. You can choose to include one or more of the statements below.

1. **If you are submitting an appeal for a denial, consider including the following optional language:**

   I also request that my appeal be reviewed by a board-certified sleep medicine physician.

2. **If your letter is for narcolepsy patients 7 years of age or older with cataplexy or EDS, consider the following optional statements and links:**

   The **FDA has determined XYWAV to be clinically superior** to XYREM® (sodium oxybate) oral solution, 0.5 g/mL, indicating in their summary[4,a]:

   - XYWAV is clinically superior to XYREM by means of greater safety because XYWAV provides a greatly reduced chronic sodium burden
   - The differences in the sodium content between XYWAV and XYREM at the recommended doses will be clinically meaningful in reducing CV morbidity in a substantial proportion of patients for whom the drug is indicated

   For most adults in the general population, the **AHA recommends an optimal sodium intake goal** of less than 1,500 mg/day. If this goal cannot be attained, the AHA currently recommends reducing intake of dietary sodium by at least 1,000 mg/day.[5]

   The **scientific rationale for the AHA recommendation** was documented in an AHA presidential advisory published in 2011. The principal basis for the recommendation was the strength of evidence relating excess sodium to blood pressure, CV disease, and stroke.[6]

   Per a **2021 publication from Chen et al**, XYWAV has only 131 mg of sodium per maximum 9-g nightly dose, compared to 1,640 mg of sodium in a 9-g dose of a high-sodium oxybate.[7]

   The **Cardiovascular Burden of Narcolepsy Disease (CV-BOND)** study, a retrospective medical claims analysis of 12,816 adults with narcolepsy that matched 38,441 individuals without narcolepsy, found that those with narcolepsy were at an increased risk for CV events. Events included stroke (1.7x increased risk), CV disease (1.3x increased risk), MACE (1.5x increased risk), and heart failure (1.4x increased risk).[8,b]

   [a]The decision of the FDA OOPD is based on findings that XYWAV provides a greatly reduced chronic sodium burden compared to XYREM.[4] There are no head-to-head data for XYWAV and XYREM.
   [b]Hazard ratio: **any stroke** (95% CI) 1.71 (1.24, 2.34); *P*-value<0.05; **heart failure** (95% CI) 1.35 (1.03, 1.76); *P*-value<0.05; **MACE** 1.45 (1.20, 1.74); *P*-value<0.05; **CV disease** (95% CI) 1.30 (1.08, 1.56).[8]

3. **If your letter is for adult patients diagnosed with idiopathic hypersomnia (IH), consider the following optional statements and links:**

   XYWAV is the **first and only FDA-approved** treatment for adults with IH.[3] IH is a rare sleep disorder characterized by multiple symptoms, including **EDS, sleep inertia, prolonged sleep time, and cognitive impairment**.[9,10] Efficacy and safety of XYWAV for the treatment of IH in adults as a once- or twice-nightly dosing regimen was established in a **Phase 3, double-blind, placebo-controlled, randomized-withdrawal study**. In this clinical trial, XYWAV was studied across multiple symptoms of IH.[10]

AHA=American Heart Association; CV=cardiovascular; EDS=excessive daytime sleepiness; FDA=Food and Drug Administration; MACE, major adverse cardiovascular events; OOPD=Office of Orphan Products Development.

3. If your letter is for adult patients diagnosed with idiopathic hypersomnia (IH), consider the following optional statements and links: (cont.)

*[**Note to prescriber**: While XYREM is not indicated for IH, a few health plans may require patients to step through XYREM or a high sodium oxybate before approving use of XYWAV.]*

For most adults in the general population, the **AHA recommends an optimal sodium intake goal** of less than 1,500 mg/day. If this goal cannot be attained, the AHA currently recommends reducing intake of dietary sodium by at least 1,000 mg/day.[5]

The **scientific rationale for the AHA recommendation** was documented in an AHA presidential advisory published in 2011. The principal basis for the recommendation was the strength of evidence relating excess sodium to blood pressure, CV disease, and stroke.[6]

Per a **2021 publication from Chen et al**, XYWAV has only 131 mg of sodium per maximum 9-g nightly dose, compared to 1,640 mg of sodium in a 9-g dose of XYREM, a high-sodium oxybate. This represents a >1,500-mg reduction in sodium per maximum recommended nightly dose of XYWAV compared with XYREM.[7]

In a **retrospective cohort study** utilizing medical claims data from over 32 million adults, 4,980 (0.015%) were newly diagnosed with IH. Among patients with newly diagnosed IH, common CV and metabolic comorbidities included hypertension (15.0%), history of CV disease (14.3%), hyperlipidemia (30.1%), and diabetes or use of diabetes/obesity medication (19.8%).[11]

References: 1. XYWAV® (calcium, magnesium, potassium, and sodium oxybates). Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **2.** ICD-10-CM tabular list of diseases and injuries. Centers for Medicare & Medicaid Services website. https://www.cms.gov/medicare/coding-billing/icd-10-codes/2024-icd-10-cm. Accessed November 27, 2024. **3.** FDA grants first of its kind indication for chronic sleep disorder treatment. News release. U.S. Food and Drug Administration; August 12, 2021. https://www.fda.gov/news-events/press-announcements/fda-grants-first-its-kind-indication-chronic-sleep-disorder-treatment. Accessed November 27, 2024. **4.** Clinical superiority findings. US Department of Health and Human Services. US Food and Drug Administration website. https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings. Updated October 17, 2024. Accessed November 27, 2024. **5.** Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e563-e595. **6.** Whelton PK, Appel LJ, Sacco RL, et al. Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations. *Circulation*. 2012;126(24):2880-9. doi: 10.1161/CIR.0b013e318279acbf. **7.** Chen C, Jenkins J, Zomorodi K, Skowronski R. Pharmacokinetics, bioavailability, and bioequivalence of lower-sodium oxybate in healthy participants in two open-label, randomized, crossover studies. *Clin Transl Sci*. 2021;14(6):2278-2287. **8.** Ben-Joseph RH, Saad R, Black J, et al. Cardiovascular burden of narcolepsy disease (CV-BOND): a real-world evidence study. *Sleep*. 2023:46(10):zsad161. **9.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders*, 3rd ed, Text Revision. 2023. **10.** 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. **11.** Saad R, Prince P, Taylor B, Ben-Joseph RH. Characteristics of adults newly diagnosed with idiopathic hypersomnia in the United States. *Sleep Epidemiology*. 2023;3(5):100059.

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