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

# XYWAV Is the First and Only Low-Sodium Oxybate[a] Studied Across Narcolepsy and Idiopathic Hypersomnia (IH)[1-4]

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 IH in adults.



## Quality sleep tonight. Wakefulness tomorrow.

Change your members' nights and days with XYWAV, a cardiovascular-conscious oxybate.[1,4,5,a]

[a]XYWAV was developed with a unique composition of cations so that it contains 131 mg of sodium at the 9g nightly dose, which is 9% of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines recommendation of <1500 mg per day for the ideal sodium intake limit; XYWAV contains 92% less sodium than high-sodium oxybates.[4,6]

## 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.**

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

# Use this resource to:

**Review pivotal trial**
study designs, efficacy data, and safety data[1]

**See data from DUET, an open-label, single-arm, Phase 4 trial**
evaluating nighttime sleep and daytime symptoms in patients with narcolepsy and IH[2,3]

**Learn about risks and comorbidities**
in narcolepsy and IH patient populations[7]

## Table of contents


3 | Disease Overview

4 | Clinical Trials

8 | Safety Profiles

10 | Comorbidities

10 | FDA Superiority Findings in Narcolepsy

12 | Key Takeaways


DUET=Develop hypersomnia Understanding by Evaluating low-sodium oxybate Treatment.

### IMPORTANT SAFETY INFORMATION (cont.)

**Contraindications**

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

**Warnings and Precautions**

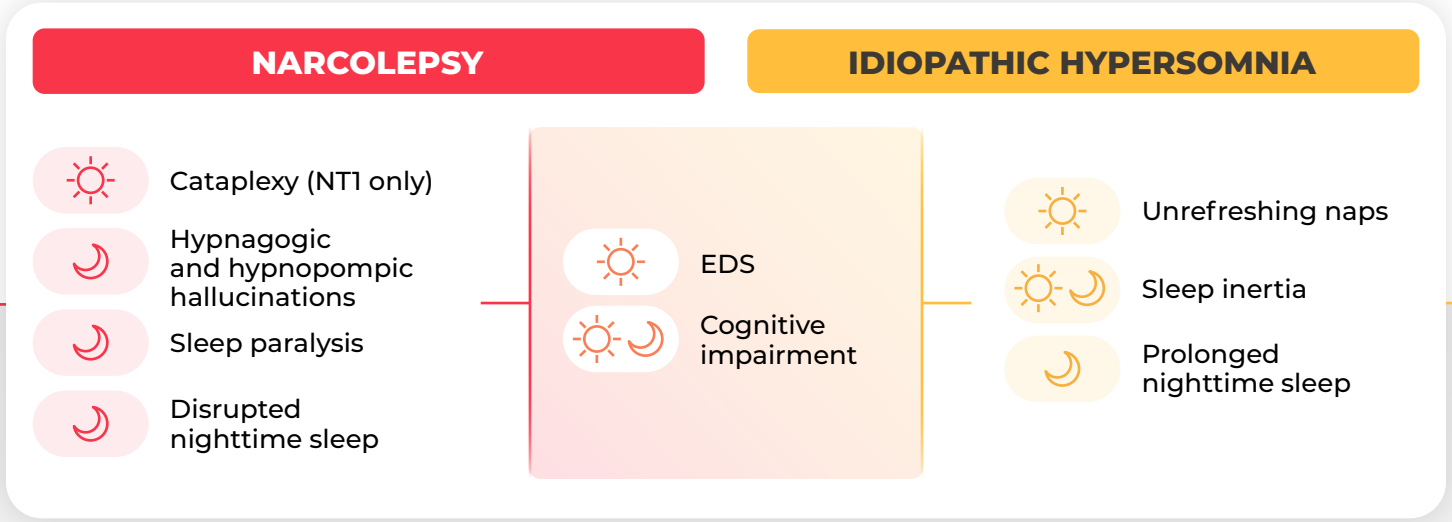
**Central Nervous System Depression**

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.

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

# Narcolepsy and IH Are 24-Hour Sleep Disorders That Affect Patients Night and Day[8-10]

## Symptoms characteristic of narcolepsy and IH[8,9,11-13]




Daytime symptoms | Nighttime symptoms

## Patients should be assessed regularly as they may still experience symptoms[11,14,15]

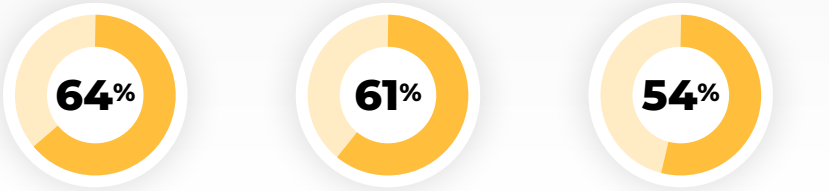
### IN NARCOLEPSY

Treatments, such as stimulants and WPAs, may help with EDS, but they are not approved for symptoms of narcolepsy other than EDS, and some patients experience residual symptoms despite treatment.[14]

### IN IDIOPATHIC HYPERSOMNIA

**There has been a lack of effective treatment options for IH. Registry data suggest patients experience multiple symptoms, despite medications.[11]**

In an online registry,[a] patients with IH experienced improvement with medications, but continued to report daily symptoms, including:




[a]Data from 563 respondents to the Hypersomnia Foundation's online patient registry questionnaire. Of the patients with IH, 82% (n=379) had taken medication for sleepiness within 30 days prior to completing the questionnaire.
[b]Difficulty awakening, requiring multiple alarms, or difficulty functioning with normal alertness upon awakening.

NT1=narcolepsy type 1; WPA=wake-promoting agent.

## 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.

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

# Two Phase 3 Trials Evaluated the Efficacy and Safety of XYWAV in Patients With Narcolepsy or IH

## NARCOLEPSY STUDY DESIGN[1]

### Phase 3, double-blind, placebo-controlled, randomized-withdrawal study in the treatment of cataplexy and EDS in 201 adults with narcolepsy type 1[a]

Following an open-label optimized treatment and titration period and 2-week stable dose period, patients entered a 2-week, double-blind, randomized withdrawal period, during which they either continued XYWAV (n=69) or were switched to placebo (n=65)

#### EFFICACY RESULTS

**PRIMARY ENDPOINT**

**Significant worsening (+2.4)** in median number of cataplexy attacks per week with **placebo** vs **no change (+0.0)** in median number of cataplexy attacks per week with **XYWAV** (*P*<0.0001)[1]

**SECONDARY ENDPOINT**

**Significant worsening (+2.0)** in median ESS score with **placebo** vs **no change (+0.0)** in median ESS score with **XYWAV** (*P*<0.0001)[1]

## IH STUDY DESIGN[1]

### Phase 3, double-blind, placebo-controlled, randomized-withdrawal study in 154 adults with IH[b]

Following an open-label optimized treatment and titration period and 2-week stable dose period, patients entered a 2-week, double-blind, randomized withdrawal period (n=115), during which they either continued XYWAV (n=56) or were switched to placebo (n=59)

#### EFFICACY RESULTS

**PRIMARY ENDPOINT**

**Significant worsening (+8.0)** in median ESS score with **placebo** vs **no change (+0.0)** in median ESS score with **XYWAV** (*P*<0.0001)[1]

**SECONDARY ENDPOINT**

**Significant worsening (+ 14.0)** in median IHSS score with **placebo** vs **no change (+0.0)** in median IHSS score with **XYWAV** (*P*<0.0001)[1]

[a]The safety population consisted of patients who took ≥1 dose of study medication (N=201), and the efficacy population consisted of randomized patients who took ≥1 dose of study medication and had 1 postrandomization efficacy assessment (n=134).[16]
[b]The safety population consisted of patients who took ≥1 dose of study medication (N=154), and the efficacy population consisted of randomized patients who took ≥1 dose of study medication and had 1 post-randomization efficacy assessment (n=115; XYWAV n=56; placebo n=59).[17]
ESS=Epworth Sleepiness Scale; IHSS=Idiopathic Hypersomnia Severity Scale.

## IMPORTANT SAFETY INFORMATION (cont.)

**Warnings and Precautions (cont.)**

**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.

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

# The Phase 4 DUET Trial Evaluated Nighttime Sleep and Daytime Symptoms in Patients With Narcolepsy[2]

## Narcolepsy cohort endpoints from DUET, a prospective, single-arm, open-label, multiple-cohort study in adults with narcolepsy type 1 or type 2 taking XYWAV (N=55)[2,a]

If taking an alerting agent or anticataplectic other than oxybate, patients had to be on a stable dosage for ≥1 month prior to enrollment and make no adjustments during the study period. The completer set included all participants who enrolled, took XYWAV for ≥1 night after the BL period, completed the SDP, and completed the PSG EOT visit. Changes described below are between BL period and EOT. [2]

### Primary Endpoint[2]

**ESS score[b]**

**-7.7**

LS mean change in ESS score

Mean ESS score (SE) (n=34) changed from 16.3 (0.5) at BL to 8.6 (1.0) at EOT

LS mean change from BL to EOT (SE) = −7.7 (0.9), 95% CI: −9.6 to −5.8

### Select Secondary Endpoints[2]

**N3 sleep (deep sleep) duration in minutes[b]**

**+45.0**

LS mean change in N3 sleep duration

Mean N3 sleep duration in minutes (SE) (n=34) changed from 61.1 (6.0) at BL to 106.1 (11.9) at EOT

LS mean change from BL to EOT (SE) = 45.0 minutes (8.8), 95% CI: 27.0 to 63.0

**Number of nocturnal awakenings[b]**

**-3.2**

LS mean change in nocturnal awakenings

Mean number of awakenings (SE) (n=34) changed from 13.9 (1.6) at BL to 10.8 at EOT

LS mean change from BL to EOT (SE) = −3.2 (0.9), 95% CI: −5.0 to −1.3

**Total number of stage transitions[b,c]**

**-13.1**

LS mean change in sleep stage transitions to N1 or wake

Mean total number of sleep stage transitions (SE) (n=34) changed from 54.6 (4.8) at BL to 41.6 (4.4) at EOT

LS mean change from BL to EOT (SE) = −13.1 (2.9), 95% CI: -19.0 to −7.1

**XYWAV is not indicated for the treatment of disrupted nighttime sleep in narcolepsy.**[1]

**Limitations: Open-label design and the lack of a control cohort restrict the ability to attribute the findings solely to XYWAV. Results shown are descriptive in nature.**[2]

[a]If not currently taking an oxybate medication, ESS score >10 at screening (visit 1); if currently taking an oxybate medication, had ESS score >10 at baseline (visit 2, after washout period).[2]
[b]LS mean and 95% CI were provided at the EOT visit using an analysis of covariance model adjusted for baseline value.[2]
[c]Number of stage transitions from N1, N2, N3, or REM to wake and from N2, N3, or REM to N1.[2]

BL=baseline; CI=confidence interval; EOT=end of treatment; LS=least squares; N1=non-REM sleep stage 1; N2=non-REM sleep stage 2; N3=non-REM sleep stage 3; NT2=narcolepsy type 2; PSG=polysomnography; REM=rapid eye movement; SDP=stable-dose period; SE=standard error.

## IMPORTANT SAFETY INFORMATION (cont.)

**Warnings and Precautions (cont.)**

**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.

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

# The Phase 4 DUET Trial Evaluated Nighttime Sleep and Daytime Symptoms in Patients With IH[3]

## IH cohort endpoints from DUET, a prospective, single-arm, open-label, multiple-cohort study in adults with IH (N=46)[3,a]

If taking an alerting agent, patients had to be on a stable dosage for ≥1 month prior to enrollment and make no adjustments during the study period. The completer set included all participants who enrolled, took XYWAV for ≥1 night after the BL period, completed the SDP, and completed the PSG EOT visit. Changes described below are between BL period and EOT. [3]

### Primary Endpoint[3]

**ESS score[b]**

**-8.4**

LS mean change **in ESS score**

Mean ESS score (SE) (n=40) changed from 16.5 (0.4) at BL to 8.1 (0.7) at EOT

LS mean change from BL to EOT (SE) = −8.4 (0.7), 95% CI: −9.8 to −7.0

### Select Secondary Endpoint[3]

**IHSS score[b]**

**-15.5**

LS mean change **in IHSS score**

LS mean IHSS score (SE) (n=36) changed from 33.2 (1.2) at BL to 17.7 (1.6) at EOT

LS mean change from BL to EOT (SE): −15.5 (1.5), 95% CI: −18.6 to −12.5

### Select Exploratory Endpoints[18]

**Total sleep time in minutes[b]**

**-54.1**

LS mean change **in total sleep time**

Mean total sleep time in minutes (SE) (n=40) changed from 467.5 (17.7) at BL to 413.4 (15.5) at EOT

LS mean change from BL to EOT (SE) = −54.1 (13.4), 95% CI = −81.3 to −26.9

**N3 sleep (deep sleep) duration in minutes[b]**

**+40.6**

LS mean change **in N3 sleep duration**

Mean N3 sleep duration in minutes (SE) (n=40) changed from 51.9 (5.6) at BL to 92.5 (8.5) at EOT

LS mean change from BL to EOT (SE) = 40.6 (7.3), 95% CI: 25.8 to 55.4

**Total number of stage transitions[b,c]**

**-17.1**

LS mean change **in sleep stage transitions** to N1 or wake

Mean total number of sleep stage transitions (SE) (n=40) changed from 60.9 (4.8) at BL to 43.7 (4.3) at EOT

LS mean change from BL to EOT (SE) = −17.1 (3.3), 95 CI: −23.8 to −10.5

**Limitations: Open-label design and the lack of a control cohort restrict the ability to attribute the findings solely to XYWAV. Results shown are descriptive in nature.[3]**

[a]If not currently taking an oxybate medication, ESS score >10 at screening (visit 1); if currently taking an oxybate medication, had ESS score >10 at baseline (visit 2, after washout period).[3]
[b]LS mean and 95% CI were provided at the EOT visit using an analysis of covariance model adjusted for baseline value.[3,18]
[c]Number of stage transitions from N1, N2, N3, or REM to wake and from N2, N3, or REM to N1.[2]

## IMPORTANT SAFETY INFORMATION (cont.)

**Warnings and Precautions (cont.)**

**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.

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

# The Safety Profile of XYWAV Across Pivotal Phase 3 and DUET Phase 4 Trials

## The safety profile of XYWAV in patients with narcolepsy

### Adverse Reactions Occurring in ≥5% of Patients Treated With XYWAV in the OL OTTP and SDP in the Pivotal Phase 3 Trial[1,a]

| Adverse reaction | OL OTTP + SDP, % (14 weeks, N=201) |
|---|---|
| Headache | 20 |
| Nausea | 13 |
| Dizziness | 10 |
| Decreased appetite | 8 |
| Parasomnia[b] | 6 |
| Diarrhea | 6 |
| Hyperhidrosis[c] | 6 |
| Anxiety[d] | 5 |
| Vomiting | 5 |

**Additional adverse reactions occurring in ≥2% but <5% of adult patients treated with XYWAV** included fatigue,[e] dry mouth, depressed mood, and enuresis in 4% of patients; irritability, paresthesia, depression, and tremor in 3% of patients; somnolence and muscle spasms in 2% of patients[1]

In patients who remained on treatment, **adverse reactions tended to occur early and diminish over time**[1]

### TEAEs Occurring in ≥5% of Patients Treated With XYWAV in DUET[2]

| TEAE | Participants, % (N=55) |
|---|---|
| Nausea | 23.6 |
| Dizziness | 14.5 |
| Headache | 12.7 |
| Somnolence | 10.9 |
| Vomiting | 10.9 |
| Anxiety | 7.3 |
| Nasal congestion | 7.3 |
| Oropharyngeal pain | 7.3 |
| Brain fog | 5.5 |
| Cough | 5.5 |
| Decreased appetite | 5.5 |
| Enuresis | 5.5 |
| Hypoesthesia | 5.5 |

Thirty-four participants (61.8%) reported a TEAE; 4 participants discontinued treatment due to a TEAE; TEAEs that led to discontinuation included nausea (n=1), anxiety (n=1), dysphoria (n=1), and irritability (n=1); there were no serious TEAEs reported in this cohort[2]

[a]In Study 1, adverse reactions related to XYWAV were reported less frequently, as an overall incidence, in patients on XYREM at study entry than in XYREM-naive patients.[1]
[b]Includes abnormal dreams, abnormal sleep-related event, rapid eye movements, sleep abnormal, sleep paralysis, sleep talking, sleep terror, sleep-related eating disorder, somnambulism.[1]
[c]Includes hyperhidrosis and night sweats.[1]
[d]Includes anxiety, agitation, panic attack, tension.[1]
[e]Includes fatigue and asthenia.[1]

OL=open label; OTTP=optimized treatment and titration period; TEAE=treatment-emergent adverse event.

## IMPORTANT SAFETY INFORMATION (cont.)

**Warnings and Precautions (cont.)**

**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.

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

# The Safety Profile of XYWAV Across Pivotal Phase 3 and DUET Phase 4 Trials

## The safety profile of XYWAV in patients with IH

### Adverse Reactions Occurring in ≥6% of Patients Treated With XYWAV in the OTTP and SDP in the Pivotal Phase 3 Trial[1,3]

| Adverse reaction | OL OTTP + SDP, % (up to 16 weeks, N=154) |
|---|---|
| Nausea | 21 |
| Headache | 16 |
| Anxiety[a] | 12 |
| Dizziness | 12 |
| Insomnia[b] | 9 |
| Hyperhidrosis[c] | 8 |
| Decreased appetite | 8 |
| Vomiting | 7 |
| Dry mouth | 6 |

**Adverse reactions occurring in ≥2% but <6% of adult patients treated with XYWAV in the OTTP and SDP (up to 16 weeks, N=154) in Study 2:**

Diarrhea, fatigue,[d] somnolence,[e] tremor, and parasomnia[f] in 5% of patients; balance disorder,[g] muscle spasms, falls, paresthesia, snoring, decreased weight, bruxism, confusional state, depressed mood, feeling drunk, and irritability in 3% of patients[1]

In patients who remained on treatment, **adverse reactions tended to occur early and diminish over time**[1]

### TEAEs Occurring in ≥5% of Patients Treated With XYWAV in DUET[3]

| TEAE | Participants, % (N=46) |
|---|---|
| Nausea | 19.6 |
| Dizziness | 17.4 |
| Headache | 17.4 |
| Vomiting | 10.9 |
| Middle insomnia | 8.7 |
| Anxiety | 6.5 |
| Decreased appetite | 6.5 |
| Enuresis | 6.5 |
| Somnolence | 6.5 |

**Thirty-four patients (73.9%) reported a TEAE; 1 patient discontinued treatment due to a TEAE of depression**[3]

[a]Includes anxiety, nervousness, panic attack.[1]
[b]Includes middle insomnia, initial insomnia, insomnia, and terminal insomnia.[1]
[c]Includes hyperhidrosis and night sweats.
[d]Includes fatigue and asthenia.[1]
[e]Includes somnolence and sedation.[1]
[f]Includes confusional arousal, sleep paralysis, nightmare, sleep talking, somnambulism, and hypnopompic hallucination.[1]
[g]Includes balance disorder and ataxia.[1]

## IMPORTANT SAFETY INFORMATION (cont.)

**Warnings and Precautions (cont.)**

**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.

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.

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

# Among Patients With Narcolepsy or IH, ≥70% Had at Least 1 CV, CM, or Renal Comorbidity[7,a]

**A retrospective study analyzing EHR and claims data described the demographic and clinical characteristics of patients with narcolepsy or IH at treatment initiation[7]**




**of people with narcolepsy** had ≥1 comorbidity (n/N=34,783/47,518)




**of people with IH** had ≥1 comorbidity (n/N=18,409/23,392)




**of people across both cohorts had ≥2** CV, CM, or renal comorbidities

Comorbidities should be considered when selecting treatments to mitigate excess sodium intake and associated CV and CM risk.

[a]Defined as coronary revascularization, diabetes, CVD, hyperlipidemia, hypertension, MACE, obesity, sleep apnea, or renal impairment.[7]

# FDA Superiority Findings in Narcolepsy

**The FDA determined XYWAV to be clinically superior[b] to XYREM® (sodium oxybate) oral solution, 0.5 g/mL, a high-sodium oxybate, by means of greater CV safety[19]**

**As part of their findings, the FDA states that**

- **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

[b]The decision of the FDA OOPD is based on findings that XYWAV provides a greatly reduced chronic sodium burden compared to XYREM. There are no head-to-head data for XYWAV and XYREM.[19]

CM=cardiometabolic; CV=cardiovascular; CVD=cardiovascular disease; EHR=electronic health records; FDA=Food and Drug Administration; MACE=major adverse cardiovascular event; OOPD=Office of Orphan Products Development.

## IMPORTANT SAFETY INFORMATION (cont.)

**Warnings and Precautions (cont.)**

**Other Behavioral or Psychiatric Adverse Reactions (cont.)**

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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## IMPORTANT SAFETY INFORMATION (cont.)

**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**

See pages 6 and 7 for most common adverse reactions.

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.

**Additional Adverse Reactions**

See pages 6 and 7 for adverse reactions that occurred in 2-<5% in patients treated with XYWAV.

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.

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.

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).

**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.

# Key Takeaways

- **XYWAV is the first and only low-sodium oxybate**[a] for patients 7 and up with cataplexy or EDS in narcolepsy or adults with IH[1,7]
- Narcolepsy and IH are **24-hour sleep disorders** with symptoms that impact patients night and day[8-10]
- A majority of patients with narcolepsy or IH present with **at least 1 CV/CM/renal comorbidity** at treatment initiation[7]
- **CV/CM/renal comorbidities should be considered when selecting treatments** to mitigate excess sodium intake and associated CV and CM risk[7]

Serious adverse events have occurred with XYWAV treatment. Warnings and precautions for XYWAV include CNS depression, abuse and misuse, the XYWAV and XYREM REMS, respiratory depression and sleep-disordered breathing, depression and suicidality, other behavioral or psychiatric adverse reactions, and parasomnias.[1]

[a]XYWAV has 131 mg of sodium at the 9g nightly dose.[4]

## IMPORTANT SAFETY INFORMATION (cont.)

**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 wellcontrolled 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.

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

**For more information on XYWAV, contact your Jazz Account Manager and visit www.jazzmarketaccess.com**

## IMPORTANT SAFETY INFORMATION (cont.)

### Dependence and Tolerance (cont.)

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.

**Please see full Prescribing Information, including BOXED Warning.**

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