Xywav® (calcium, magnesium, potassium, and sodium oxybates) Oral Solution: Executive Summary for Medicaid (Idiopathic Hypersomnia)

Xywav Overview

Xywav® (calcium, magnesium, potassium, and sodium oxybates; lower sodium oxybate [LXB]) oral solution is a central nervous system (CNS) depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years and older with narcolepsy, and idiopathic hypersomnia in adults.[1] Although the mechanism of action of Xywav in the treatment of idiopathic hypersomnia is unknown, it is hypothesized that its therapeutic effects are mediated through $GABA_B$ actions during sleep at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.[1]

In adult patients with idiopathic hypersomnia, Xywav can be administered as a twice-nightly or once-nightly regimen.[1] For twice nightly, Xywav is initiated at 4.5 g or less per night, divided into 2 doses, and titrated to effect in increments of up to 1.5 g per night per week, up to 9 g total nightly dose.[1] For once nightly, Xywav is initiated at 3 g or less per night and titrated to effect in increments of up to 1.5 g per night per week, up to 6 g total nightly dose.[1] The safety and effectiveness of Xywav for the treatment of idiopathic hypersomnia in pediatric patients have not been established.

Xywav is a Schedule III controlled substance and has a black box warning associated with CNS depression and abuse and misuse.[1] Xywav is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Xywav and Xyrem REMS.[1]

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and ABUSE AND MISUSE.

See full prescribing information for complete boxed warning.

Central Nervous System Depression

- **XYWAV is a CNS depressant, and respiratory depression can occur with XYWAV use (5.1, 5.4)**

Abuse and Misuse

- **The active moiety of XYWAV is oxybate or gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death (5.2, 9.2)**

XYWAV is available only through a restricted program called the XYWAV and XYREM REMS (5.3)

Idiopathic Hypersomnia Overview

Idiopathic hypersomnia is a central disorder of hypersomnolence.[2] The primary symptom of idiopathic hypersomnia is EDS, which is characterized by "daily periods of irrepressible need to sleep or daytime lapses into sleep."[3] People with idiopathic hypersomnia may also experience sleep inertia (defined as prolonged difficulty waking, with repeated lapses into sleep, irritability, and confusion), cognitive disfunction (also called "brain fog"), prolonged nighttime sleep, and long, unrefreshing naps.[2,3] The *International Classification of Sleep Disorders, 2nd Edition* (ICSD-2) described 2 subtypes of idiopathic hypersomnia: with long sleep time (≥10 hours) and without long sleep time (>6 hours to <10 hours).[4] However, the *International Classification of Sleep Disorders*, 3rd edition (ICSD-3) discontinued this distinction, noting that idiopathic hypersomnia "is likely a heterogeneous condition."[3] A recent claims analysis reported that at least two-thirds of patients with newly diagnosed idiopathic hypersomnia slept >11 hours per night.[5]

Idiopathic hypersomnia is listed in both the ICSD-3[3] and the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5; in which it is classified under the term "hypersomnolence disorder").[6] In both sets of diagnostic criteria, EDS (present for at least 3 months) is considered the cardinal symptom of idiopathic hypersomnia, with other clinical symptoms as supportive features.[3,6] The ICSD-3 additionally requires findings on formal sleep testing (multiple sleep latency test [MSLT], polysomnography, or actigraphy) for diagnosis.[3] Other potential causes of hypersomnolence must be ruled out.[3,6]

The etiology and pathophysiology of idiopathic hypersomnia are unknown.[3] A genetic component likely exists, as an estimated 34% to 38% of people with idiopathic hypersomnia have a family history of excessive sleepiness, idiopathic hypersomnia, or another central hypersomnolence disorder.[2] The true prevalence of idiopathic hypersomnia is also unknown, but idiopathic hypersomnia may be more common in women.[7] Use of sleep testing for an idiopathic hypersomnia diagnosis is uncommon in clinical practice, which likely impacts estimates of idiopathic hypersomnia prevalence.[8] Symptoms of idiopathic hypersomnia typically first appear during adolescence.[7]

The impact of idiopathic hypersomnia on quality of life can be significant.[9] People with idiopathic hypersomnia experience severe sleep inertia and often do not hear an alarm clock, need to set several alarms, or need to have someone else wake them up. They also may have trouble focusing, a greater risk of accidents while driving, impaired functioning at school or work, and an overall reduced quality of life.[7,10-12]

Until the approval of Xywav, there were no US Food and Drug Administration–approved therapeutic options for treating idiopathic hypersomnia in the United States.[13] People with idiopathic hypersomnia are often treated off-label with wake-promoting agents and stimulants used to treat EDS in narcolepsy, such as modafinil, methylphenidate, amphetamine, and dextroamphetamine.[2,7] Nonpharmacologic methods are also used to manage symptoms, such as daytime naps or caffeine.[2] Many stimulants contain warnings regarding the increased risk of

cardiovascular events associated with their use, such as elevated blood pressure and rapid heart rate.[14,15]

Clinical Burden Associated With Idiopathic Hypersomnia

Studies have shown that people diagnosed with idiopathic hypersomnia have an increased prevalence of cardiovascular comorbidities, autonomic nervous system dysfunction, sleep apnea, and psychiatric disorders such as anxiety and depression.[5,10] In a real-world study of a claims database, greater proportions of patients newly diagnosed with idiopathic hypersomnia, compared with patients without idiopathic hypersomnia, had hyperlipidemia (30.1% vs 19.8%), diabetes (19.8% vs 12.1%), anxiety (30.7% and 8.8%), depressive disorders (31.0% vs 7.0%), headache/migraine (23.9% vs 6.9%), heart failure (1.4% vs 0.6%), stroke (0.9% vs 0.4%), and history of cardiovascular disease (14.3% vs 7.8%).[5] People with idiopathic hypersomnia also commonly report symptoms of autonomic dysregulation such as fainting, cold extremities, and excessive sweating.[10,16]

Unmet Treatment Need in Idiopathic Hypersomnia

There is an unmet need for approved treatments for idiopathic hypersomnia. Recommendations in treatment guidelines are based on very low to moderate levels of supporting evidence.[17,18] Further, there is a lack of evidence for efficacy for idiopathic hypersomnia symptoms beyond EDS, such as sleep inertia.[19] Despite using off-label treatments, symptoms of idiopathic hypersomnia often persist in many people.[20]

Xywav: Efficacy and Safety in Adult Patients Diagnosed With Idiopathic Hypersomnia

The efficacy and safety of Xywav for the treatment of idiopathic hypersomnia in adults were established in a double-blind, placebo-controlled, randomized withdrawal, multicenter study.[1] This study consisted of a minimum 10-week open-label titration and optimization period (with up to 4 additional weeks), followed by a 2-week stable-dose period, a 2-week double-blind, randomized withdrawal period, and a 24-week open-label extension.[1] One hundred fifty-four patients were enrolled, and 115 patients were evaluable for efficacy data and were randomized 1:1 to continue treatment with Xywav or to switch to placebo during the double-blind randomized withdrawal period.[1]

This study enrolled patients diagnosed with idiopathic hypersomnia, 19 to 75 years of age.[1] Sodium oxybate and/or CNS stimulants were allowed at study entry. Participants were allowed to continue taking CNS stimulants as long as they had been taking a stable dose for at least 2 months prior to study entry and remained on the same dose and regimen throughout the study.[12] Approximately 57% of patients continued taking a stable dose of stimulant throughout the study.[1] The Xywav dosing regimen (once or twice nightly) was initiated at the discretion of the investigator according to clinical presentation.[1] Based on clinical response during the open-label titration and optimization period, investigators were permitted to switch patients between twice-nightly and once-nightly dosing regimens.[1] At the start of the double-blind

randomized withdrawal period, 23% (27/115) of patients were taking Xywav once nightly (median nightly dose, 4.5 g), and 77% (88/115) of patients were taking Xywav twice nightly (median nightly dose, 7.5 g). There were no meaningful differences in demographics, baseline characteristics, or disease severity between patients receiving Xywav once nightly vs twice nightly.[1]

The primary endpoint was change in Epworth Sleepiness Scale (ESS) score, as a measure of reduction in EDS from the end of the stable-dose period to the end of the randomized withdrawal period.[1] Key secondary endpoints included Patient Global Impression of change (PGIc) and the Idiopathic Hypersomnia Severity Scale (IHSS), a 14-item self-assessment questionnaire that measures the severity, frequency, and functional impact of the 3 key idiopathic hypersomnia symptoms (EDS, sleep inertia, and prolonged nighttime sleep).[21] Both the PGIc and IHSS were administered during the same period as the primary endpoint.[1] Other secondary and exploratory endpoints were the Functional Outcomes of Sleep Questionnaire, short version (FOSQ-10) and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP), respectively.[12]

Patients taking stable doses of Xywav who were withdrawn from Xywav treatment and randomized to placebo during the double-blind randomized withdrawal period experienced significant worsening in ESS score at the end of the double-blind randomized withdrawal period relative to the end of the stable-dose period (mean [SD], 5.8 [3.7] to 13.3 [4.1]), compared with patients randomized to continue treatment with Xywav (6.3 [4.3] to 7.0 [5.0]) across all dosing regimens (least squares mean difference in change [95% confidence interval], −6.5 [−8.0, −5.0]; $P<0.0001$).[1,12] PGIc ratings showed that patients randomized to placebo experienced a significant worsening of symptoms of idiopathic hypersomnia overall compared with patients randomized to Xywav.[1,12] The percentage of patients with worsening PGIc scores for idiopathic hypersomnia overall (defined as scores of minimally, much worse, or very much worse) was greater for patients receiving placebo (88.1%) compared with patients receiving Xywav (21.4%; $P<0.0001$).[1,12] At the end of the randomized withdrawal period relative to the end of the stable-dose period, patients randomized to placebo experienced a significant worsening in IHSS total score (mean [SD], 15.2 [7.8] to 28.5 [9.0]), compared with patients randomized to Xywav (15.5 [9.2] to 16.9 [8.1]; estimated median difference in change, −12.0 [−15.0, −8.0]; $P<0.0001$).[1,12] FOSQ-10 total scores worsened from the end of the stable-dose period to the end of the randomized withdrawal period in patients randomized to placebo compared with those who continued Xywav treatment ($P<0.0001$; nominal P value), indicating reduced quality of life and functioning.[12] Work time missed (absenteeism), impairment while working (presenteeism), overall work impairment (absenteeism + presenteeism), and activity impairment, as assessed by the WPAI:SHP, were reduced during this period in patients randomized to placebo vs those who continued Xywav treatment ($P=0.0092$; $P<0.0001$; $P<0.0001$; $P<0.0001$, respectively; all nominal P values).[12]

The most common adverse reactions occurring in the open-label titration and optimization period were nausea (21%), headache (16%), anxiety (12%), dizziness (12%), insomnia (9%), hyperhidrosis (8%), decreased appetite (8%), vomiting (7%), dry mouth (6%), diarrhea (5%),

fatigue (5%), somnolence (5%), tremor (5%) and parasomnia (5%).[1] Of these, insomnia, dry mouth, fatigue, somnolence, and tremor were less common (<5%) in the study of Xywav in patients with narcolepsy.[1,22] Across all study periods (excluding placebo during the double-blind randomized withdrawal period; up to 42 weeks), 17 of 154 patients (11%) 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).[1] The most common adverse reaction leading to discontinuation was anxiety (3.2%).[1] The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.[1]

Xywav – Important Safety Information[1]

Contraindications
Xywav is contraindicated in combination with sedative hypnotics or alcohol and in patients with succinic semi-aldehyde dehydrogenase deficiency.[1]

Warnings and Precautions

- CNS Depression: Use caution when considering the concurrent use with other CNS depressants. If concurrent use is required, consider dose reduction or discontinuation of one or more CNS depressants (including Xywav). Consider interrupting Xywav treatment if short-term opioid use is required. After first initiating treatment and until certain that Xywav does not affect them adversely, 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.[1]

- Abuse and Misuse: Xywav is a Schedule III controlled substance. The rapid onset of sedation, coupled with the amnestic features of gamma-hydroxybutyrate (GHB, the active moiety of Xywav), particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (eg, assault victim).

- 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 clinical trials in adult patients with narcolepsy and idiopathic hypersomnia, depression and depressed mood were reported in patients treated with Xywav. In most cases, no change in Xywav treatment was required. Two suicides and 2 attempted suicides occurred in adult clinical trials with oxybate (same active moiety as Xywav). One patient experienced suicidal ideation and 2 patients reported depression in a pediatric clinical trial with oxybate. **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: Monitor patients for impaired motor/cognitive function or the emergence of or increase in anxiety and/or confusion. The emergence or increase in the occurrence of behavioral or psychiatric events in patients taking Xywav should be carefully monitored.

- Parasomnias: In clinical trials, parasomnias, including sleepwalking, were reported in adult patients treated with Xywav. Parasomnias, including sleepwalking, also 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 idiopathic hypersomnia) were nausea, headache, dizziness, anxiety, insomnia, decreased appetite, hyperhidrosis, vomiting, diarrhea, dry mouth, parasomnia, somnolence, fatigue, and tremor.

Summary

Idiopathic hypersomnia is a central disorder of hypersomnolence that is associated with increased risk of comorbidities and impaired quality of life and functioning.[3,8,10] Xywav is approved for treating idiopathic hypersomnia in adults[1] and is the only approved therapeutic option available for treating idiopathic hypersomnia.[13] The results of one phase 3 clinical trial demonstrated the efficacy of Xywav in treating EDS in adult patients with idiopathic hypersomnia and improving other symptoms of idiopathic hypersomnia, based on reductions in the Idiopathic Hypersomnia Severity Scale scores and improvements in the patients' ratings of global impression of change in their symptoms.[1,12] Measures of quality of life, functioning, work productivity, and activity impairment also improved in patients treated with Xywav in the phase 3 clinical study.[12] The safety profile of Xywav observed in patients with idiopathic hypersomnia was similar to that observed in patients with narcolepsy.[1] Xywav allows patients with idiopathic hypersomnia to benefit from oxybate therapy with a lower-sodium formulation without cardiovascular warnings or precautions in the label.[1,23,24]

References

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