Xywav® (calcium, magnesium, potassium, and sodium oxybates) Oral Solution

Public Comment for Medicaid

Indications Xywav is approved for the treatment of cataplexy or excessive daytime sleepiness (abbreviated EDS) in patients 7 years of age and older with narcolepsy, and for the treatment of idiopathic hypersomnia (abbreviated IH) in adults.

Narcolepsy Narcolepsy is a chronic neurologic disorder that involves dysregulation of the sleep/wake cycle (Thorpy and Dauvilliers 2015). It is characterized by a pentad of symptoms, including EDS (which is present in all patients), cataplexy, disrupted nighttime sleep, sleep-related hallucinations, and sleep paralysis (ICSD-3 2014; Khan 2015; Zachariev 1999; Rosenthal 1990; Frauscher 2013).

Idiopathic hypersomnia IH is a distinct, chronic neurologic sleep disorder that is always characterized by EDS and often by sleep inertia (prolonged difficulty waking, with repeated lapses into sleep, irritability, and confusion) and long, unrefreshing naps (ICSD-3 2014; Billiard 2016).

Both narcolepsy and IH are associated with increased prevalence of cardiovascular and metabolic abnormalities, such as hypertension and diabetes (Thorpy 2014; Black 2017; Ohayon 2013; Cohen 2018; Jennum 2013; Saad 2021). Unlike sodium oxybate (Xyrem®), which is approved for treating cataplexy or EDS in patients 7 years of age and older with narcolepsy, Xywav does not have a warning regarding high sodium content or precautions around monitoring patients with heart failure, hypertension, or impaired renal function (Xywav [package insert] 2021). At the maximum recommended dosage of 9 g per night, sodium intake with Xywav is reduced by 1509 mg, which is 92% less than sodium oxybate. As a mixed-cation oxybate, the amount of each cation at the maximum recommended daily dose of Xywav (9 g/night) is below the adult recommended daily allowance (Xywav [package insert] 2021; HHS/USDA 2015). Xywav has been acknowledged by the FDA's Office of Orphan Products Development in the narcolepsy population for its significant chronic sodium burden reduction compared with sodium oxybate, which "will be clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated" (FDA 2021).

For patients with narcolepsy, Xywav is initiated twice nightly at 4.5 g per night, divided into 2 doses, which are taken at bedtime and 2.5 to 4 hours later (Xywav [package insert] 2021). For patients with narcolepsy transitioning from sodium oxybate, Xywav is initiated at the same gram-for-gram dose and regimen, with an option for additional titration to balance efficacy and tolerability (Xywav [package insert] 2021). For patients with IH, Xywav is initiated twice nightly at a total dose of up to 4.5 g divided into 2 doses, or once nightly up to 3 g, then can be titrated to a maximum total dose of 9 g for twice nightly or 6 g for once nightly (Xywav [package insert] 2021). Some patients with narcolepsy or IH may achieve better responses with the total nightly dose divided into 2 unequal nightly doses (Xywav [package insert] 2021).

Key clinical data

Narcolepsy Xywav was approved by the FDA for narcolepsy based on a phase 3 study of adult patients and on clinical experience in pediatric patients with sodium oxybate, which has the same active moiety as Xywav (Xywav [package insert] 2021). The adult study enrolled patients diagnosed with narcolepsy with cataplexy and included a 12-week titration and optimization period, followed by a 2-week stable dose period. In a 2-week double-blind randomized withdrawal period, 134 patients who completed the stable-dose period were randomized to continue treatment with Xywav or switch to placebo (Xywav [package insert] 2021). Patients randomized to discontinue Xywav and switch to placebo experienced a significant increase in the average weekly number of cataplexy attacks compared with patients randomized to continue treatment with Xywav (Xywav [package insert] 2021). In addition, the median number of cataplexy-free days per week decreased in participants randomized to placebo but remained stable in participants randomized to continue Xywav treatment (Bogan 2021). Participants who switched to placebo also had significantly worse scores on the Epworth Sleepiness Scale, a subjective measure of an individual's recent level of daytime sleepiness (Johns 1991; Littner 2005), from the end of the stable-dose period to the end of the randomized withdrawal period (Xywav [package insert] 2021). The most common adverse reactions in adults (≥10% incidence) were headache, nausea, and dizziness. In a pediatric study with sodium oxybate, the most common adverse reactions (≥10% incidence) were enuresis, nausea, vomiting, headache, and decreased weight (Xywav [package insert] 2021).

Idiopathic hypersomnia Xywav was approved by the FDA for IH based on a phase 3 study of adult patients, which was similar in design to the narcolepsy study. Patients with IH were treated with Xywav for a 10- to 14-week titration and optimization period, followed by a 2-week stable-dose period. In a 2-week double-blind randomized withdrawal period, 115 patients were randomized to continue treatment or switch to placebo. During the open-label titration period, improvements in EDS as measured by the Epworth Sleepiness Scale, and in IH symptom severity as measured by the Idiopathic Hypersomnia Severity Scale, were observed. These observed changes in the Epworth Sleepiness Scale and Idiopathic Hypersomnia Severity Scale scores remained stable during the

double-blind randomized withdrawal period in patients who were randomized to continue taking Xywav (Dauvilliers 2021; Xywav [package insert] 2021). Patients randomized to discontinue Xywav and switch to placebo in the double-blind randomized withdrawal period showed a significant worsening of these scores, compared with patients randomized to continue taking Xywav. They also rated their IH symptoms significantly worse on the Patient Global Impression of Change scale. The most common adverse reactions (≥10% incidence) were nausea, headache, dizziness, and anxiety (Xywav [package insert] 2021).

REMS Xywav is a schedule III controlled substance and has a black box warning associated with central nervous system 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.

Summary In summary, Xywav is an approved agent for the treatment of cataplexy or EDS in patients 7 years of age or older diagnosed with narcolepsy and for the treatment of IH in adults. It has 92% less sodium than sodium oxybate and does not have the sodium warning associated with sodium oxybate. The results from phase 3 clinical trials demonstrated the efficacy of Xywav for the treatment of cataplexy and EDS in adult patients with narcolepsy, and for the treatment of IH in adult patients. Adverse events are consistent with those of sodium oxybate (Bogan 2021). Xywav allows patients with narcolepsy to benefit from oxybate therapy while providing a clinically relevant reduction in daily sodium intake compared with sodium oxybate, and it is the first FDA-approved treatment option for patients with IH.