RXADVANCE
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NEW DRUG APPROVAL

Brand Name	Xywav™
Generic Name	calcium, magnesium, potassium, and sodium oxybates
Drug Manufacturer	Jazz Pharmaceuticals, Inc.

New Drug Approval

FDA Approval Date: July 21, 2020
Review Designation: Priority; Orphan
Type of Review: Type N/A; New Drug Application (NDA) 212960
Dispensing Restrictions: Open Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Cataplexy is a sudden and uncontrollable muscle weakness or paralysis that comes on during the day and is often triggered by a strong emotion, such as excitement or laughter. Without much warning, the person loses muscle tone and can have a slack jaw, broken speech, buckled knees or total weakness in their face, arms, legs, and trunk. A person experiencing total cataplexy stays awake and is aware of what is happening, but cannot move. These episodes last up to a minute or two, and some people may fall asleep afterwards. The frequency of cataplexy episodes varies widely among people with narcolepsy. Some individuals avoid emotions that may bring on cataplexy.

The loss of muscle tone in cataplexy occurs because of the inability to regulate sleep and awake states — meaning that elements of each can overlap. During normal rapid eye movement (REM) sleep, there is a natural loss of muscle tone. In the case of cataplexy, that characteristic of REM sleep occurs suddenly during the day, causing weakness or full paralysis, even as the person remains awake during the episode.

Narcolepsy type 1 (narcolepsy with cataplexy) is estimated to have a prevalence of 25 to 50 per 100,000 people and an incidence of 0.74 per 100,000 person-years. It is equally common in men and women. Narcolepsy typically begins in the teens and early twenties, but occasionally occurs as early as five years of age or after 40 years of age. The prevalence of narcolepsy type 2 (narcolepsy without cataplexy) is uncertain because it is not as well studied and harder to diagnose; however, it has been estimated to be 20 to 34 per 100,000 people.

Efficacy

Cataplexy and Excessive Daytime Sleepiness (EDS) in Adult Narcolepsy

Efficacy of Xywav™ for the treatment of cataplexy and excessive daytime sleepiness in adult patients with narcolepsy was established in a double-blind, placebo-controlled, randomized-withdrawal study (Study 1; NCT03030599). This study had two parts, consisting of the main study, followed by an optional 24-week open-label extension (OLE). The main study consisted of a 12-week open-label optimized treatment and titration period (OL OTTP), followed by a 2-week stable-dose period (SDP), and finally a 2-week double-blind randomized-withdrawal period (DB RWP).

Study 1 enrolled 201 patients with narcolepsy with cataplexy, 18 to 70 years of age, with a baseline history of at least 14 cataplexy attacks in a typical 2-week period prior to any treatment for narcolepsy symptoms. Of the 201 patients, 134 were randomized 1:1 to continue treatment with Xywav™ or to placebo in the 2-week DB RWP. In the safety population, overall, the median age was 36.0 years (range: 18 to 70). The majority of subjects were female (61%), and most were white (88%) and not Hispanic or Latino (84%).

Patients entering the study were taking a stable dosage of 1) Xyrem™ only, 2) Xyrem™ + another anticataplectic, 3) a non-Xyrem™ anticataplectic, or 4) were cataplexy-treatment naïve. Patients taking Xyrem™ at study entry were switched (at a gram for gram dose) from Xyrem™ to Xywav™ for a minimum of 2 weeks and titrated, if needed, to a stable, tolerable, and effective dosage over 8 weeks. Most patients who switched from Xyrem™ to Xywav™ (41/59; 69%) had no change in dosage from study entry to the stable dose period; 27% (16/59) had an increase in dosage, and 3% (2/59) had a decrease in dosage. Among patients whose dosage was changed, most changes were within one titration step (≤1.5 g). Patients not taking Xyrem™ at study entry were initiated at 4.5 g/night of Xywav™ and titrated at a rate of 1 or 1.5 g/night/week to a tolerable dose of Xywav™. Patients taking an anticataplectic other than Xyrem™ were tapered off the non-Xyrem™ anticataplectic over 2 to 8 weeks. All patients continued to receive Xywav™ only, for the treatment of cataplexy during the last 2 weeks of the OL OTTP.

CNS stimulants were allowed at entry, and 39% (78/201) of patients continued taking a stable dose of stimulant throughout the SDP and DB RWP.

The total nightly dose of Xywav™ was administered in two equally divided doses in 90% (62/69) of patients. Unequal doses were administered in 10% (7/69) of patients treated with Xywav™.

The primary efficacy endpoint was the change in frequency of cataplexy attacks from the 2 weeks of the SDP to the 2 weeks of the DB RWP. The key secondary endpoint was the change in the Epworth Sleepiness Scale (ESS) score, as a measure of reduction in EDS from the end of the SDP to the end of the DB RWP.

Patients taking stable doses of Xywav™ who discontinued Xywav™ treatment and were randomized to placebo during the DB RWP experienced a significant worsening in the average weekly number of cataplexy attacks and in ESS score, compared with patients randomized to continue treatment with Xywav™.

Table 4: Mean and Median Number of Weekly Cataplexy Attacks and Epworth Sleepiness Scale (ESS)

	Average Weekly Number of Cataplexy Attacks		ESS SCORE	
	Placebo (N = 65)	XYWAV (N = 69)	Placebo (N = 65)	XYWAV (N = 69)
Baseline (2 Weeks of the Stable Dose Period)				
Mean (SD)	7.2 (14.4)	8.9 (16.8)	12.6 (5.5)	13.6 (5.3)
Median	1.0	1.1	13.0	14.0
Change from Baseline (2 Weeks of the Stable Dose Period) to the 2 Weeks of the DB RWP			**Change from End of Stable Dose Period to End of DB RWP**	
Mean (SD)	11.5 (24.8)	0.1 (5.8)	3.0 (4.7)	0.0 (2.9)
Median	2.4	0.0	2.0	0.0
p-value	<0.0001		< 0.0001	

DB RWP = Double-blind Randomized-withdrawal Period; SD = standard deviation

Cataplexy and Excessive Daytime Sleepiness in Pediatric Narcolepsy

The effectiveness of Xywav™ in pediatric patients is based upon a clinical study in patients treated with Xyrem™, as described below, and additional pharmacokinetic information.

The effectiveness of Xyrem™ in the treatment of cataplexy and excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy was established in a double-blind, placebo-controlled, randomized-withdrawal study (NCT02221869). The study was conducted in 106 pediatric patients (median age: 12 years; range: 7 to 17 years) with a baseline history of at least 14 cataplexy attacks in a typical 2-week period prior to any treatment for narcolepsy symptoms. Of the 106 patients, 2 did not receive study drug and 63 patients were randomized 1:1 either to continued treatment with Xyrem™ or to placebo. Randomization to placebo was stopped early as the efficacy criterion was met at the pre-planned interim analysis.

Patients entered the study either taking a stable dosage of Xyrem™ or were Xyrem™-naïve. CNS stimulants were allowed at entry, and approximately 50% of patients continued taking a stable dose of stimulant throughout the stable-dose and double-blind periods. Xyrem™-naïve patients were initiated and titrated based on body weight over a period of up to 10 weeks. The total nightly dose was administered in two divided doses, with the first dose given at nighttime and the second given 2.5 to 4 hours later. Once a stable dosage of Xyrem™ had been achieved, these patients entered the 2-week stable-dose period; patients on a stable dosage of Xyrem™ at study entry remained on this dosage for 3 weeks, prior to randomization. Efficacy was established at dosages ranging from 3 g to 9 g of Xyrem™ per night.

The primary efficacy measure was the change in frequency of cataplexy attacks. In addition, change in cataplexy severity was evaluated with the Clinical Global Impression of Change for cataplexy severity. The efficacy of Xyrem™ in the treatment of excessive daytime sleepiness in pediatric patients with narcolepsy was evaluated with the change in the Epworth Sleepiness Scale (Child and Adolescent) score. The Epworth Sleepiness Scale (Child and Adolescent) is a modified version of the scale used in adult clinical trials described above. The overall change in narcolepsy condition was assessed by the Clinical Global Impression of Change for narcolepsy overall. Efficacy was assessed during or at the end of the 2-week double-blind treatment period, relative to the last 2 weeks or end of the stable-dose period.

Pediatric patients taking stable dosages of Xyrem™ who discontinued Xyrem™ treatment and were randomized to placebo during the double-blind treatment period experienced a statistically significant increase in weekly cataplexy attacks compared with patients who were randomized to continue treatment with Xyrem™. Patients randomized to receive placebo during the double-blind treatment period experienced a statistically significant worsening of EDS compared with patients randomized to continue receiving Xyrem™ (see Table 5).

Table 5: Number of Weekly Cataplexy Attacks and Epworth Sleepiness Scale (Child and Adolescent) Score

Treatment Group	Baseline*,†	Double-blind Treatment Period‡,§	Median Change from Baseline	Comparison to Placebo (p-value¶)
Median Number of Cataplexy Attacks (attacks/week)				
Placebo (n=32)	4.7	21.3	12.7	-
Xyrem (n=31)	3.5	3.8	0.3	<0.0001
Median Epworth Sleepiness Scale (Child and Adolescent) Score				
Placebo (n=31**)	11	12	3	-
Xyrem (n=30**)	8	9	0	0.0004

* For weekly number of cataplexy attacks, baseline value is calculated from the last 14 days of the stable-dose period.
† For Epworth Sleepiness Scale score, baseline value is collected at the end of stable-dose period.
‡ Weekly number of cataplexy attacks is calculated from all days within the double-blind treatment period.
§ For Epworth Sleepiness Scale, value is collected at the end of the double-blind treatment period.
¶ P-value from rank-based analysis of covariance (ANCOVA) with treatment as a factor and rank baseline value as a covariate.
** One patient in each of the treatment groups did not have baseline ESS score available and were not included in this analysis.

Patients randomized to receive placebo during the double-blind treatment period experienced a statistically significant worsening of cataplexy severity and narcolepsy overall according to the clinician's assessment compared with patients randomized to continue receiving Xyrem™ (see Table 6).

Table 6: Clinical Global Impression of Change (CGIc) for Cataplexy Severity and Narcolepsy Overall

	CGIc Cataplexy Severity*		CGIc Narcolepsy Overall*	
Worsened, %†	Placebo (n=32)	Xyrem (n=29)‡	Placebo (n=32)	Xyrem (n=29)‡
Much worse or very much worse	66%	17%	59%	10%
p-value§	0.0001		<0.0001	

* Responses indicate change of severity or symptoms relative to receiving Xyrem treatment at baseline.
† Percentages based on total number of observed values.

‡ Two patients randomized to Xyrem did not have the CGIc assessments completed and were excluded from the analysis.
§ P-value from Pearson's chi-square test.

Safety

ADVERSE EVENTS

Most common adverse reactions in adults (≥5%) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting.

In a pediatric study with sodium oxybate (same active moiety as Xywav™), the most common adverse reactions (≥5%) were enuresis, nausea, headache, vomiting, weight decreased, decreased appetite, and dizziness.

WARNINGS & PRECAUTIONS

- CNS depression: Use caution when considering the concurrent use of Xywav™ with other CNS depressants.
- Caution patients against hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that Xywav™ does not affect them adversely.
- Depression and suicidality: Monitor patients for emergent or increased depression and suicidality.
- Confusion/Anxiety: Monitor for impaired motor/cognitive function.
- Parasomnias: Evaluate episodes of sleepwalking.

CONTRAINDICATIONS

It is contraindicated for use in:

- Combination with sedative hypnotics.
- Combination with alcohol.
- Patients with succinic semialdehyde dehydrogenase deficiency.

Clinical Pharmacology

MECHANISMS OF ACTION

It is a CNS depressant. The exact mechanism of action of Xywav™ in the treatment of narcolepsy is unknown. Xywav™ is a mixture of calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate (gamma-hydroxybutyrate). Gamma-hydroxybutyrate (GHB) is an endogenous compound and metabolite of the neurotransmitter GABA. It is hypothesized that the therapeutic effects of Xywav™ on cataplexy and excessive daytime sleepiness are mediated through $GABA_B$ actions during sleep at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.

Dose & Administration

ADULTS

Initial: 4.5 g per night orally, divided into 2 doses. Titrate to effect in increments of up to 1.5 g per night per week.
Maintenance: 6 g to 9 g per night orally.

Total Nightly Dose	Take at Bedtime	Take 2.5 to 4 Hours Later
4.5 g per night	2.25 g	2.25 g
6 g per night	3 g	3 g
7.5 g per night	3.75 g	3.75 g
9 g per night	4.5 g	4.5 g
• Some patients may achieve better responses with unequal doses at bedtime and 2.5 to 4 hours later.		

Important Administration Information:

- Prepare both doses prior to bedtime; dilute each dose with approximately ¼ cup of water in pharmacy-provided containers.
- Take the first nightly dose of Xywav™ at least 2 hours after eating.
- Take each dose while in bed and lie down after dosing.

For Patients Transitioning from Xyrem™ to Xywav™: Initiate at the same dose and regimen as Xyrem™ (gram for gram). Titrate as needed based on efficacy and tolerability.

PEDIATRICS

Age ≥ 7 years: The recommended starting dosage, titration regimen, and maximum total nightly dosage are based on body weight, as specified in Table 2. Administered orally twice per night. The dosage may be gradually titrated based on efficacy and tolerability. Doses higher than 9 g per night have not been studied and ordinarily should not be administered.

Table 2: Recommended Initial XYWAV Dosage for Patients 7 Years of Age and Older*

Patient Weight	Initial Dosage		Maximum Weekly Dosage Increase		Maximum Recommended Dosage	
	Take at Bedtime:	Take 2.5 to 4 Hours Later:	Take at Bedtime:	Take 2.5 to 4 Hours Later:	Take at Bedtime:	Take 2.5 to 4 Hours Later:
<20 kg**	There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.					
20 kg to <30 kg	≤1 g	≤1 g	0.5 g	0.5 g	3 g	3 g
30 kg to <45 kg	≤1.5 g	≤1.5 g	0.5 g	0.5 g	3.75 g	3.75 g
≥45 kg	≤2.25 g	≤2.25 g	0.75 g	0.75 g	4.5 g	4.5 g

* For patients who sleep more than 8 hours per night, the first nightly dose of XYWAV may be given at bedtime or after an initial period of sleep.

**If XYWAV is used in patients 7 years of age and older who weigh less than 20 kg, a lower starting dosage, lower maximum weekly dosage increases, and lower total maximum nightly dosage should be considered.

Note: Some patients may achieve better responses with unequal nightly doses at bedtime and 2.5 to 4 hours later.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No pharmacokinetic study in patients with renal impairment has been conducted, however, not renally eliminated.

HEPATIC IMPAIRMENT

Reduce dose by 50%.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Oral solution: 0.5 g/mL total salts (equivalent to 0.413 g/mL of oxybate).