Xywav™ (calcium, magnesium, potassium, and sodium oxybates) – New orphan drug approval

- On July 22, 2020, Jazz Pharmaceuticals announced the FDA approval of Xwav (calcium, magnesium, potassium, and sodium oxybates), for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

- Narcolepsy is a chronic, debilitating neurological disorder characterized by EDS and the inability to regulate sleep-wake cycles normally. It affects an estimated one in 2,000 people in the U.S. Cataplexy, the most specific symptom of narcolepsy, is the sudden, generally brief loss of muscle tone with retained consciousness. Cataplexy occurs in about 70% of people with narcolepsy.

- Xywav is an oxybate product with a unique composition of cations resulting in 92% less sodium than Jazz Pharmaceuticals' Xyrem® (sodium oxybate). Xyrem shares the same indication as Xywav.

- The efficacy of Xywav for the treatment of cataplexy and EDS in 201 adult patients with narcolepsy was established in a double-blind, placebo-controlled, randomized-withdrawal study. The main study consisted of a 12-week open-label optimized treatment and titration period, followed by a 2-week stable-dose period (SDP), and finally a 2-week double-blind randomized-withdrawal period (DB RWP). The primary 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.

    - The mean change from baseline (2 weeks of the SDP) to the 2 weeks of the DB RWP in the number of weekly cataplexy attacks was 11.5 and 0.1 for placebo and Xywav, respectively ($p < 0.0001$).
    - The mean change from end of SDP to end of DB RWP in the ESS score was 3.0 and 0.0 for placebo and Xywav, respectively ($p < 0.0001$).

- The effectiveness of Xywav in pediatric patients is based upon a clinical study in patients treated with Xyrem and additional pharmacokinetic information.

- Xywav carries a boxed warning for central nervous system (CNS) depression and abuse and misuse.

    - 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.

- Xywav is contraindicated for use in:

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

- Additional warnings and precautions for Xywav include respiratory depression and sleep-disordered breathing; depression and suicidality; other behavioral or psychiatric adverse reactions; and parasomnias.

Continued . . .

- The most common adverse reactions in adults (≥ 5%) with Xywav use were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting.

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

- The recommended starting dosage in adults for Xywav is 4.5 grams per night administered orally, divided into two doses: 2.25 grams at bedtime and 2.25 grams taken 2.5 to 4 hours later. The dosage can be increased by up to 1.5 grams per night per week (eg, 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later), to the recommended dosage range of 6 grams to 9 grams per night. Doses higher than 9 grams per night have not been studied and ordinarily should not be administered.

- For pediatric patients 7 years of age and older, Xywav is administered orally twice per night. The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight, as specified in the table below. Doses higher than 9 grams per night have not been studied and ordinarily should not be administered.

Patient weight (kg)	Initial dosage		Max weekly dosage increase		Max 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*	There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.					
20 to < 45	≤1 g	≤1 g	0.5 g	0.5 g	3 g	3 g
30 to < 45	≤ 1.5 g	≤ 1.5 g	0.5 g	0.5 g	3.75 g	3.75 g
≥ 45	≤ 2.25 g	≤ 2.25 g	0.75 g	0.75 g	4.5 g	4.5 g

*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.

- Refer to the Xywav drug label for complete dosing and administration recommendations.

- Jazz Pharmaceuticals plans to launch Xywav by the end of 2020. Xywav will be available as an oral solution at a total salt concentration of 0.5 grams/mL; each mL contains 0.5 grams of total salts present as 0.234 g calcium oxybate, 0.096 g magnesium oxybate, 0.13 g potassium oxybate, and 0.04 g sodium oxybate (equivalent to 0.413 g total oxybate).