U.S. FDA Grants Orphan Drug Exclusivity (ODE) for Xywav® (calcium, magnesium, potassium, and sodium oxybates) Oral Solution for Idiopathic Hypersomnia in Adults

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ODE for IH for adults follows June 2021 grant of ODE for treatment of cataplexy or excessive daytime sleepiness in patients 7 years and older with narcolepsy

DUBLIN, Jan. 3, 2022 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced that the U.S. Food and Drug Administration (FDA) has granted Orphan Drug Exclusivity (ODE) for Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, for the treatment of idiopathic hypersomnia in adults, making it the second ODE for the medication following the exclusivity granted in the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

As Jazz was the first sponsor to obtain FDA approval for idiopathic hypersomnia, *Xywav* will have seven-year market exclusivity for this indication from its FDA approval on August 12, 2021. The FDA's Orphan Drug Designation program is designed to advance the development of drugs that treat a condition affecting 200,000 or fewer U.S. patients annually.

"Prior to the approval of *Xywav* no treatments were approved for people living with this debilitating and unique sleep disorder, so we are very proud of how we advanced the medicine from concept to commercial availability and are encouraged that FDA has recognized *Xywav's* impact by granting ODE for the treatment of idiopathic hypersomnia," said Robert Iannone, M.D., M.S.C.E., executive vice president, research and development and chief medical officer of Jazz Pharmaceuticals. "We believe FDA's decision also recognizes the importance of Jazz's commitment to developing differentiated new medicines where others have not to benefit people with limited treatment options."

Xywav for idiopathic hypersomnia was approved with multiple dosing options, offering healthcare providers the opportunity to individualize based on the patient need. The majority of clinical trial participants found optimal doses on a twice a night regimen. Idiopathic hypersomnia is characterized by chronic excessive daytime sleepiness, which is the inability to stay awake and alert during the day resulting in the irrepressible need to sleep or unplanned lapses into sleep or drowsiness. Core symptoms may include confusion, irritability and severe sleep inertia or sleep drunkenness (prolonged difficulty in waking up with frequent reentries into sleep).[1,2,3,4]

In June 2021, FDA recognized seven years of ODE for *Xywav* for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy. FDA also published its summary of clinical superiority findings for *Xywav* for the treatment of cataplexy or EDS associated with narcolepsy, stating that "the active moiety, oxybate, was previously approved as Xyrem® (sodium oxybate) for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy." According to FDA, "*Xywav* (calcium, magnesium, potassium, and sodium oxybates) is clinically superior to *Xyrem* by means of greater safety because *Xywav* provides a greatly reduced chronic sodium burden compared to *Xyrem."* The FDA's summary also stated that "the differences in the sodium content of the two products at the recommended doses will be clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated."

Please see the full Prescribing Information, including Boxed Warning, and Medication Guide, is available here. <http://pp.jazzpharma.com/pi/xywav.en.USPI.pdf>

About Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution
Xywav, also known as JZP258, is a lower-sodium oxybate approved by the U.S. Food and Drug Administration (FDA) for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy and for the treatment of idiopathic hypersomnia in adults. FDA recognized seven years of Orphan Drug Exclusivity for *Xywav* in June 2021 for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy, and in December 2021 for the treatment of idiopathic hypersomnia in adults. The Office of Orphan Product Development (OOPD) at FDA also published its summary of clinical superiority findings for *Xywav* for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy by means of greater safety compared to Xyrem® (sodium oxybate). The decision of the OOPD is based on FDA findings that *Xywav* provides a greatly reduced chronic sodium burden compared to *Xyrem*. There are no head-to-head data for *Xywav* and *Xyrem*. *Xywav* is comprised of a unique composition of cations resulting in 92% less sodium, or a reduction of approximately 1,000 to 1,500 mg/night, than sodium oxybate at the recommended adult dosage range of 6 to 9 grams. While the exact mechanism of action of *Xywav* is unknown, 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.[5] The U.S. Drug Enforcement Agency (DEA) has designated *Xywav* as a Schedule III medicine. The DEA defines Schedule III drugs, substances, or chemicals as drugs with a moderate to low potential for physical and psychological dependence.[5,6]

Important Safety Information

WARNING: Taking XYWAV with other central nervous system (CNS) depressants such as medicines used to make you or your child fall asleep, including opioid analgesics, benzodiazepines, sedating antidepressants, antipsychotics, sedating anti-epileptic medicines, general anesthetics, muscle relaxants, alcohol, or street drugs, may cause serious medical problems, including trouble breathing (respiratory depression), low blood pressure (hypotension), changes in alertness (drowsiness), fainting (syncope), and death.

The active ingredient of XYWAV is a form of gamma hydroxybutyrate (GHB). Abuse or misuse of illegal GHB alone or with other drugs that cause changes in alertness (or consciousness) has caused serious side effects. These effects include seizures, trouble breathing (respiratory depression), changes in alertness (drowsiness), coma, and death. Call your doctor right away if you or your child has any of these serious side effects.

Because of these risks, you have to go through the XYWAV and XYREM REMS to have your or your child's prescription for XYWAV filled.

Do not take XYWAV if you take or your child takes other sleep medicines or sedatives (medicines that cause sleepiness), drinks alcohol, or has a rare problem called succinic semialdehyde dehydrogenase deficiency.

Keep XYWAV in a safe place to prevent abuse and misuse. Selling or giving away XYWAV may harm others and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.

Anyone who takes XYWAV should not do anything that requires them to be fully awake or is dangerous, including driving a car, using heavy machinery, or flying an airplane, for at least 6 hours after taking XYWAV. Those activities should not be done until you know how XYWAV affects you or your child.

XYWAV can cause serious side effects, including the following:

- **Breathing problems, including** slower breathing, trouble breathing, and/or short periods of not breathing while sleeping (sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they use XYWAV.
- **Mental health problems, including** confusion, seeing or hearing things that are not real (hallucinations), unusual or disturbing thoughts (abnormal thinking), feeling anxious or upset, depression, thoughts of killing yourself or trying to kill yourself, increased tiredness, feelings of guilt or worthlessness, or difficulty concentrating. Tell your doctor if you or your child have or had depression or have tried to harm yourself or themselves. **Call your doctor right away if you have or your child has symptoms of mental health problems or a change in weight or appetite.**
- **Sleepwalking**. Sleepwalking can cause injuries. Call your doctor if this occurs.

The most common side effects of XYWAV in adults include nausea, headache, dizziness, anxiety, insomnia, decreased appetite, excessive sweating (hyperhidrosis), vomiting, diarrhea, dry mouth, parasomnia (a sleep disorder that can include abnormal dreams, abnormal rapid eye movement (REM) sleep, sleep paralysis, sleep talking, sleep terror, sleep-related eating disorder, sleep walking, and other abnormal sleep-related events), somnolence, fatigue, and tremor.

The most common side effects of XYREM (which also contains oxybate like XYWAV) in children include nausea, bedwetting, vomiting, headache, weight decrease, decreased appetite, dizziness, and sleepwalking.

XYWAV can cause physical dependence and craving for the medicine when it is not taken as directed. These are not all the possible side effects of XYWAV.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

About Idiopathic Hypersomnia

Idiopathic hypersomnia is an often debilitating, neurologic sleep disorder characterized by chronic excessive daytime sleepiness (the inability to stay awake and alert during the day resulting in the irrepressible need to sleep or unplanned lapses into sleep or drowsiness) that is not caused by other medical, behavioral or psychiatric conditions.[1,2,3,4] Symptoms may also include a prolonged main (nighttime) sleep episode of more than 9 hours or a sleep duration of 11 hours or longer over a 24-hour period, cognitive impairment, long and unrefreshing naps, brain fog, or the inability to focus for long periods of time, and severe sleep inertia (prolonged difficulty waking, with frequent reentries into sleep, confusion, and irritability).[1,2,3,4,7] Although there are overlapping clinical features with narcolepsy, idiopathic hypersomnia is a condition with its own specific diagnostic criteria.[1,4,8] Idiopathic hypersomnia is a debilitating illness that can significantly affect social, educational and occupational functioning.[9,10] In the U.S., approximately 37,000 adult patients have been diagnosed with idiopathic hypersomnia and are actively seeking healthcare.[11] This low number of people may be due to the many difficulties in identifying and diagnosing idiopathic hypersomnia, as well as distinguishing it from other similar sleep disorders. It is estimated that far fewer patients are currently receiving pharmacological treatment for their idiopathic hypersomnia.[11,12,13,14]

About Jazz Pharmaceuticals plc

Jazz Pharmaceuticals plc (NASDAQ: JAZZ) is a global biopharmaceutical company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing life-changing medicines for people with serious diseases—often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines and novel product candidates, from early- to late-stage development, in neuroscience and oncology. Within these therapeutic areas, we are identifying new options for patients by actively exploring small molecules and biologics, and through innovative delivery technologies and cannabinoid science. Jazz is headquartered in Dublin, Ireland and has employees around the globe, serving patients in nearly 75 countries. For more information, please visit www.jazzpharmaceuticals.com and follow @JazzPharma on Twitter.

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