# Jazz Pharmaceuticals Announces U.S. FDA Approval of Xywav® (calcium, magnesium, potassium, and sodium oxybates) Oral Solution for Idiopathic Hypersomnia in Adults

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**Xywav is the first and only FDA-approved treatment for idiopathic hypersomnia**
**Individualized Xywav dosing regimens for idiopathic hypersomnia include twice- and once-nightly options**

DUBLIN, Aug. 12, 2021 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced that the U.S. Food and Drug Administration (FDA) approved Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution for the treatment of idiopathic hypersomnia in adults.[1] The company plans to make *Xywav* available to patients with idiopathic hypersomnia later this year following Risk Evaluation and Mitigation Strategies (REMS) implementation.

"We are excited that with today's approval *Xywav* will become the first and only medicine indicated to treat idiopathic hypersomnia, a unique medical condition that can have significant effects on the lives of those diagnosed with the condition," said Bruce Cozadd, chairman and chief executive officer of Jazz Pharmaceuticals. "*Xywav* is a meaningful treatment for patients as demonstrated by the statistically significant results from the Phase 3 clinical trial. We are proud to build on our leadership in sleep medicine and, with this approval, are expanding beyond our *Xywav* narcolepsy indications to bring this treatment to adults living with idiopathic hypersomnia who currently have no FDA-approved options available. This milestone exemplifies our patient-focused R&D strategy and internal development capabilities, and underscores oxybate as a key growth opportunity for Jazz. With this launch we will have achieved our goal of five product launches in two years."

Idiopathic hypersomnia is a 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). In addition to excessive daytime sleepiness, symptoms may include severe sleep inertia or sleep drunkenness (prolonged difficulty waking with frequent reentries into sleep, confusion and irritability), a core symptom of idiopathic hypersomnia, as well as prolonged, non-restorative nighttime sleep, cognitive impairment, and long and unrefreshing naps.[2,3,4,5] An estimated 37,000 people in the U.S. have been diagnosed with IH and are actively seeking healthcare.[6]

"The clinical program for *Xywav* has demonstrated that this lower-sodium oxybate is an effective therapy for the treatment of idiopathic hypersomnia," said Yves Dauvilliers, M.D., director of the Sleep Disorders Centre at the Gui de Chauliac Hospital in Montpellier, France, and lead investigator of the Phase 3 study. "Having an FDA-approved treatment option that manages symptoms associated with idiopathic hypersomnia, including excessive daytime sleepiness and severe sleep inertia, is a significant step forward for patients. *Xywav* fulfills an unmet need for those diagnosed with this sleep disorder, offering them management of their debilitating symptoms."

"Idiopathic hypersomnia can have a significant impact on the social, educational and occupational functioning of people living with the condition. Today's FDA approval is a major milestone for the entire idiopathic hypersomnia community as *Xywav* becomes the first medicine approved to manage this chronic sleep disorder," said Diane Powell, board chair and chief executive officer of the Hypersomnia Foundation. "Our mission and values have consistently centered around supporting patients and scientific discovery and this announcement truly provides a sense of hope for those living with idiopathic hypersomnia."

*Xywav* received Fast Track designation by the FDA in September 2020 for the treatment of idiopathic hypersomnia and was granted Priority Review designation as part of the supplemental New Drug Application (sNDA) acceptance in April 2021. This milestone marks the second FDA approval for *Xywav* since it was first approved in July 2020 for the treatment of cataplexy or excessive daytime sleepiness in patients seven years of age and older with narcolepsy.

This FDA approval is based on the global Phase 3 double-blind, multicenter, placebo-controlled, randomized withdrawal study that demonstrated the efficacy and safety of *Xywav* for the treatment of idiopathic hypersomnia in adults. In the study, *Xywav* demonstrated statistically significant and clinically meaningful differences compared to placebo in change in the primary endpoint of Epworth Sleepiness Scale score (p-value <0.0001) and secondary endpoints of Patient Global Impression of Change (p-value <0.0001) and the Idiopathic Hypersomnia Severity Scale (p-value <0.0001).[7]

The most common adverse reactions in adults (≥5%) were nausea, headache, dizziness, anxiety, insomnia, decreased appetite, hyperhidrosis, vomiting, diarrhea, dry mouth, parasomnia, somnolence, fatigue and tremor. Please see below for additional safety information.

*Xywav* can be administered as a twice- or once-nightly regimen for the treatment of idiopathic hypersomnia in adults. To optimize response, a patient's healthcare provider may consider prescribing a twice-nightly regimen in equally or unequally divided doses at bedtime and 2.5 to 4 hours later and gradually titrate *Xywav* so that a patient may receive an individualized dose and regimen based on efficacy and tolerability.

*Xywav* has a Boxed Warning as a central nervous system (CNS) depressant, and for its potential for abuse and misuse. Because of the risks of CNS depression and abuse and misuse, *Xywav* is available only through a restricted program called the *Xywav* and *Xyrem* REMS.

Jazz is committed to the safe distribution and use of our medicines, including a well-controlled distribution system for its oxybate medicines. The *Xywav* and *Xyrem* REMS was developed with the FDA and designed to ensure that *Xywav* and *Xyrem* are provided to patients securely and that patients are educated on the appropriate use of the medicines, understand the risks and safe use conditions of these medicines, and agree to follow the requirements of the *Xywav* and *Xyrem* REMS. Both prescribers and patients must enroll in the program.

Improving care and patient support are priorities to Jazz. A Nurse Case Management program is available for people taking *Xyrem* and *Xywav* to help address questions about their treatment. With this program, dedicated Nurse Case Managers support patients from the very beginning of their treatment experience, and education is tailored to each person's needs.

Jazz is also committed to removing barriers to access for eligible, commercially or privately insured patients through JazzCares' Savings Program.

Additionally, the JazzCares Patient Assistance Program may be able to provide free product to those without insurance or insurance coverage who meet certain income and other eligibility criteria.

**Please see the full Prescribing Information, including Boxed Warning, and Medication Guide 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. In June 2021, the FDA recognized seven years of Orphan Drug Exclusivity for *Xywav* for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy. The Office of Orphan Product Development (OOPD) at the 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 percent 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.[1] 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.[1,8]

**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.** XYWAV can cause sleepwalking which 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.[2,3,4,5] 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 or sleep drunkenness (prolonged difficulty waking, with frequent reentries into sleep, confusion, and irritability). [2,3,4,5,9] Although there are overlapping clinical features with narcolepsy, idiopathic hypersomnia is a condition with its own specific diagnostic criteria.[2,5,10] Idiopathic hypersomnia is a debilitating illness that can significantly affect social, educational and occupational functioning.[11,12] In the U.S., approximately 37,000 adult patients have been diagnosed with IH and are actively seeking healthcare.[6] This low number of people may be due to the many difficulties in identifying and diagnosing IH, as well as distinguishing it from other similar sleep disorders. It is estimated that far fewer patients are currently receiving pharmacological treatment for their IH.[6,13,14,15]

**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.

**Caution Concerning Forward-Looking Statements**

This press release contains forward-looking statements, including, but not limited to, statements related to the potential timing of the availability of *Xywav* for people with idiopathic hypersomnia and the potential impact on that community and other statements that are not historical facts. These forward-looking statements are based on Jazz Pharmaceuticals' current plans, objectives, estimates, expectations and intentions and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, risks and uncertainties associated with: pharmaceutical product development; the regulatory approval process, including the risk that the company may be unable to effectively commercialize *Xywav*; and other risks and uncertainties affecting the company and its development programs, including those described from time to time under the caption "Risk Factors" and elsewhere in Jazz Pharmaceuticals plc's Securities and Exchange Commission filings and reports (Commission File No. 001-33500), including Jazz Pharmaceuticals' Quarterly Report on Form 10-Q for the quarter ended June 30, 2021 and future filings and reports by Jazz Pharmaceuticals. Other risks and uncertainties of which Jazz Pharmaceuticals is not currently aware may also affect Jazz Pharmaceuticals' forward-looking statements and may cause actual results and the timing of events to differ materially from those anticipated. The forward-looking statements herein are made only as of the date hereof or as of the dates indicated in the forward-looking statements, even if they are subsequently made available by Jazz Pharmaceuticals on its website or otherwise. Jazz Pharmaceuticals undertakes no obligation to update or supplement any forward-looking statements to reflect actual results, new information, future events, changes in its expectations or other circumstances that exist after the date as of which the forward-looking statements were made.

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