Jazz Pharmaceuticals Completes Submission of Supplemental New Drug Application for Xywav™ (calcium, magnesium, potassium, and sodium oxybates) Oral Solution for Idiopathic Hypersomnia

February 16, 2021

DUBLIN, Feb. 16, 2021 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced the completion of the rolling submission for the supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) seeking marketing approval for Xywav™ (calcium, magnesium, potassium, and sodium oxybates) oral solution for the treatment of adult patients with idiopathic hypersomnia. If approved, *Xywav* will be the first and only approved treatment in the U.S. for adults with idiopathic hypersomnia.

Xywav received Fast Track designation by the FDA in September 2020 for the treatment of idiopathic hypersomnia. Jazz was granted rolling submission by FDA for this sNDA in December 2020, permitting the submission of portions of the proposed application as they were completed.

"This sNDA submission brings us one step closer to making this important treatment option available to patients living with idiopathic hypersomnia. As a long-standing leader in sleep medicine, Jazz continues to invest in developing innovative treatments for patients with significant unmet needs. Jazz has spent over a decade researching the lower-sodium oxybate product, *Xywav*, in both narcolepsy and idiopathic hypersomnia," said Robert Iannone, M.D., M.S.C.E., executive vice president, research and development & chief medical officer of Jazz Pharmaceuticals. "Our purpose is to innovate to transform the lives of patients and we are committed to collaborating with regulators, sleep experts and patients to deepen our understanding of sleep disorders, and the science around sleep medicine."

Jazz is planning to bring this treatment option to patients in the fourth quarter of this year, subject to FDA approval.

Idiopathic hypersomnia is a debilitating illness characterized by chronic and disabling excessive daytime sleepiness that can significantly affect social, school and occupational functioning.[1,2,3,4] Symptoms may also include prolonged, non-restorative nighttime sleep, long and unrefreshing naps and prolonged difficulty waking (sleep inertia), with frequent reentries into sleep, confusion, and irritability. Insurance claims data in the U.S. suggest that the diagnosed prevalence of idiopathic hypersomnia is more than 37,000 adult patients; however, many more are likely living with undiagnosed idiopathic hypersomnia.

"People with idiopathic hypersomnia often live without an accurate diagnosis for a long time — and some are never diagnosed at all. Meanwhile, they struggle to keep up with school, work and relationships," said Diane Powell, Board Chair and CEO, Hypersomnia Foundation. "We are encouraged by Jazz's progress and the possibilities for people living with idiopathic hypersomnia."

About the Phase 3 Study in Idiopathic Hypersomnia
The submission is based on a Phase 3 multi-national, double-blind, multicenter, placebo-controlled, randomized withdrawal study evaluating the efficacy and safety of *Xywav* for the investigational treatment of idiopathic hypersomnia in adult patients. The primary endpoint was the change in the Epworth Sleepiness Scale (ESS) score in the *Xywav* group compared to the placebo group over the randomized-withdrawal period. The key secondary endpoints were Patient Global Impression of Change (PGI-c) and change in Idiopathic Hypersomnia Severity Scale (IHSS) score. The IHSS is a recently developed, validated scale, and is a self-report measure of the severity, frequency, and consequences of the key symptoms of idiopathic hypersomnia.

The study design included a titration and optimization period of up to 14 weeks, a *Xywav* stable-dose period of two weeks, followed by a 1:1 randomization to either *Xywav* or placebo for 2 weeks. After the completion of the double-blind, placebo-controlled treatment period, patients entered a 24-week open-label safety extension period. More information about the study design is available at www.clinicaltrials.gov (identifier: NCT03533114).

The results of this study have been accepted for presentation at an upcoming medical meeting.

About Idiopathic Hypersomnia
Idiopathic hypersomnia is a sleep disorder characterized by chronic and disabling excessive daytime sleepiness (the inability to stay awake and alert during the day resulting in drowsiness and unplanned lapses into sleep) that is not caused by other medical, behavioral or psychiatric conditions known to induce excessive sleepiness.[1,2,3,4] Symptoms may also include prolonged nighttime sleep (with sleep duration in excess of 11 hours per night), long and unrefreshing naps and sleep inertia (prolonged difficulty waking, with frequent reentries into sleep, confusion, and irritability).[1,2,3,4] Although there are overlapping clinical features with narcolepsy, idiopathic hypersomnia is a distinct, identifiable condition with specific diagnostic criteria.[1] Idiopathic hypersomnia is a debilitating illness that can significantly affect social, school and occupational functioning.[4,5] Insurance claims data suggest diagnosed prevalence of idiopathic hypersomnia is approximately 37,000 patients; however, given known mis- and expected under-diagnoses of idiopathic hypersomnia, in addition to lack of FDA-approved therapies, the unmet need may be significantly greater.

More information about Xywav, including Full Prescribing Information 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 JZP-258, 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. It is an investigational product being evaluated for the treatment of idiopathic hypersomnia in adult patients. 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.[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 Program 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 you or your child starts sleepwalking. Your doctor should check you or your child.

The most common side effects of XYWAV in adults include headache, nausea, dizziness, decreased appetite, 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), diarrhea, excessive sweating (hyperhidrosis), anxiety and vomiting.

The most common side effects of XYWAV in children include bedwetting, nausea, headache, vomiting, weight decrease, decreased appetite, and dizziness.

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 Jazz Pharmaceuticals plc

Jazz Pharmaceuticals plc (Nasdaq: JAZZ) is a global biopharmaceutical company dedicated to developing life-changing medicines for people with serious diseases — often with limited or no options. We have a diverse portfolio of marketed medicines and novel product candidates, from early- to late-stage development, in key therapeutic areas. Our focus is in neuroscience, including sleep medicine and movement disorders, and in oncology, including hematologic malignancies and solid tumors. We actively explore new options for patients including novel compounds, small molecule advancements, biologics and innovative delivery technologies. Jazz is headquartered in Dublin, Ireland and has employees around the globe, serving patients in more than 90 countries. For more information, please visit www.jazzpharmaceuticals.com and follow @JazzPharma on Twitter.

"Safe Harbor" Statement under the Private Securities Litigation Reform Act of 1995

This press release contains forward-looking statements, including, but not limited to, statements related to the planned sNDA submission to FDA of *Xywav* for idiopathic hypersomnia and the potential timing of the availability of *Xywav* for people with idiopathic hypersomnia; 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 obtain approval by the FDA of its planned sNDA for *Xywav* in a timely manner or at all; effectively commercializing *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 September 30, 2020 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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