Jazz Pharmaceuticals Announces SLEEP Publication of Phase 3 Xywav™ (calcium, magnesium, potassium, and sodium oxybates) Oral Solution Study in Cataplexy or Excessive Daytime Sleepiness in Patients with Narcolepsy

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Xywav demonstrated highly statistically significant differences in median change in weekly number of cataplexy attacks and Epworth Sleepiness Scale scores compared to placebo

Xywav contains 92 percent less sodium per nightly dose than sodium oxybate, a current standard of care in this patient population as designated by the American Academy of Sleep Medicine Guidelines

DUBLIN, Oct. 20, 2020 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced the publication of the global Phase 3 double-blind, placebo-controlled, randomized-withdrawal, multicenter study of Xywav™ (calcium, magnesium, potassium and sodium oxybates) oral solution, for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy. The results were published in *SLEEP*, the peer-reviewed, international journal of the Sleep Research Society.

In the trial, *Xywav* achieved the primary and key secondary endpoints demonstrating highly statistically significant differences ($p<0.0001$) in median change in weekly number of cataplexy attacks and Epworth Sleepiness Scale (ESS) scores compared to placebo. Results of the study were previously presented in an oral presentation at World Sleep 2019.[1]

"This publication reinforces the option *Xywav* provides for those living with cataplexy or EDS associated with narcolepsy," said Robert Iannone, M.D., M.S.C.E., executive vice president, research and development of Jazz Pharmaceuticals. "*Xywav* was approved in July by the FDA as a new treatment option indicated for both cataplexy and EDS in people living with narcolepsy and I am proud to be part of the organization that developed this groundbreaking therapy for people living with this debilitating neurological disorder."

This Phase 3 study served as the basis of the U.S. Food and Drug Administration approval of *Xywav* for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy.[1,2] *Xywav* is an oxybate product with a unique composition of cations resulting in 92 percent less sodium – or approximately 1,000 to 1,500 mg/night less – than sodium oxybate at the recommended dosage range of 6 to 9 grams.[2] Meaningfully lowering the level of sodium ingested by patients taking oxybate therapy may help patients align with American Heart Association recommended levels of daily sodium intake.[3]

The study enrolled 201 participants and randomized 134 participants, which included those previously treated with sodium oxybate and naïve to sodium oxybate, with or without other anticataplectic treatments. During the two week double-blind randomized withdrawal period, there was a significant increase in median weekly number of cataplexy attacks in participants randomized to take placebo compared with participants randomized to continue *Xywav* treatment (median [Q1, Q3]: 2.35 [0.00, 11.61] vs 0.00 [−0.49, 1.75], respectively; treatment difference, $P<0.0001$).[1]

At the end of the double-blind randomized-withdrawal period, there was a significant increase in median ESS scores in participants randomized to take placebo compared with participants randomized to continue *Xywav* (median [Q1, Q3]: 2.0 [0.0, 5.0] vs 0.0 [−1.0, 1.0], respectively; treatment difference, $P<0.0001$).[1] The most common adverse reactions reported by participants (≥5%) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety and vomiting.[2]

The company plans to launch *Xywav* in the fourth quarter of this year, following Risk Evaluation and Mitigation Strategy (REMS) implementation. Jazz is committed to ensuring access to our medicines and will work to secure the broadest access possible for appropriate patients.

About Xywav ™(calcium, magnesium, potassium, and sodium oxybates) oral solution
Xywav (JZP-258) oral solution, 0.5 g/mL total salts (equivalent to 0.413 g/mL of oxybate), is approved by the FDA for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy. It is also being studied and developed for the treatment of idiopathic hypersomnia in adult patients. *Xywav* is comprised of a unique composition of cations resulting in 92 percent less sodium, or approximately 1,000 to 1,500 mg/night less, than sodium oxybate at the recommended dosage range of 6 to 9 grams. *Xywav* has the same oxybate concentration as sodium oxybate and includes a mix of calcium, magnesium, potassium and sodium cations. 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.[2]

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.

Please find full prescribing information here: https://pp.jazzpharma.com/pi/xywav.en.USPI.pdf

About Narcolepsy

Narcolepsy is a chronic, debilitating neurological disorder characterized by EDS and the inability to regulate sleep-wake cycles normally.[4,5,6] It affects an estimated one in 2,000 people in the United States, with symptoms typically appearing in childhood or adolescence.[7,8,9] Studies have shown it may take 10 years or more for people with narcolepsy to receive a diagnosis.[10,11] There are five main symptoms of narcolepsy, including EDS, cataplexy, disrupted nighttime sleep, sleep-related hallucinations, and sleep paralysis.[12] While all people with narcolepsy experience EDS, not all individuals with narcolepsy experience all five symptoms.[5,11] EDS is the primary symptom of narcolepsy and is present in all people with the disorder.[9,13] EDS is characterized by the inability to stay awake and alert during the day resulting in drowsiness and unplanned lapses into sleep.[7,9,10] Narcolepsy is associated with an increased prevalence of cardiometabolic comorbidities, including obesity, hypertension, diabetes and hypercholesterolemia.[14,15,16,17]

About Cataplexy

Cataplexy, the most specific symptom of narcolepsy, is the sudden, generally brief (<2 minutes) loss of muscle tone with retained consciousness. It is usually triggered by strong emotions, such as laughter, surprise, or anger.[7,9] Although many emotions can potentially trigger cataplexy, those associated with mirth are usually the most potent.[9] Cataplexy occurs in about 70 percent of people with narcolepsy.[18] Presentation differs widely among people with narcolepsy, ranging from sporadic partial attacks triggered by laughter to frequent complete collapse brought about by a variety of emotions.[7,9] Complete collapse is less common.[7,9] More commonly, episodes of cataplexy involve only certain muscle groups, such as arms and legs (e.g., knees buckling), the head and neck (e.g., head dropping), or the face and jaw (e.g., sagging, slurred speech, eyelid drooping).[7,9,18,19]

About Jazz Pharmaceuticals

Jazz Pharmaceuticals plc (Nasdaq: JAZZ) is a global biopharmaceutical company dedicated to developing and commercializing life-changing medicines that transform the lives of patients 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 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 Jazz Pharmaceuticals' plans to launch Xywav following REMS implementation and the timing; statements related to ensuring access to medicines and securing the broadest access possible for appropriate patients; 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 effectively launching and commercializing Xywav and other risks and uncertainties affecting the company, 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, 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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