Jazz Pharmaceuticals Announces U.S. FDA Approval of Xywav™ (calcium, magnesium, potassium, and sodium oxybates) Oral Solution for Cataplexy or Excessive Daytime Sleepiness Associated with Narcolepsy

July 22, 2020

Xywav is the first FDA approved new treatment option indicated for both cataplexy and excessive daytime sleepiness in people living with narcolepsy in more than 15 years

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

Narcolepsy is a chronic sleep disorder and is associated with an increased prevalence of certain comorbid conditions, including hypertension and cardiovascular disease

DUBLIN, July 22, 2020 /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 on July 21, 2020 for the treatment of cataplexy or excessive daytime sleepiness (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 – than sodium oxybate at the recommended dosage range of 6 to 9 grams.[1]

The company plans to launch *Xywav* by the end of the 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.

The FDA approval of *Xywav* is based on a global Phase 3 double-blind, placebo-controlled, randomized-withdrawal, multicenter study that demonstrated the efficacy and safety of *Xywav* in the treatment of cataplexy and EDS in patients with narcolepsy. In the study, which enrolled 201 patients, *Xywav* demonstrated highly statistically significant differences ($p<0.0001$) in weekly number of cataplexy attacks and Epworth Sleepiness Scale scores compared to placebo.[3]

Multiple *Xywav* dosing options are available for adult and pediatric patients. Prescribers can titrate *Xywav* into unequal doses taken over the course of the night. When patients start *Xywav* after sodium oxybate, *Xywav* treatment is initiated at the same dose and regimen as sodium oxybate (gram for gram) and titrated as needed based on efficacy and tolerability.[1]

"Based on the efficacy demonstrated in the clinical program, the approval of *Xywav* is important for people living with cataplexy or EDS associated with narcolepsy.[1] *Xywav* makes it possible for patients to have a lower-sodium oxybate treatment option. This may help patients taking sodium oxybate better align with daily sodium intake recommendations including those by the American Heart Association,[4]" said Richard K. Bogan, MD, FCCP, FAASM, associate clinical professor at the University of South Carolina School of Medicine, a medical officer at SleepMed in Columbia, SC and lead investigator of the Phase 3 study. "The average American consumes too much sodium.[5] Excess sodium intake has been linked with increases in blood pressure, hypertension, stroke, and other cardiovascular disease.[6,7,8,9]"

Sodium oxybate carries warnings about its high sodium content,[10] and was previously the only product approved to treat both cataplexy and EDS in patients with narcolepsy 7 years of age and older[11] and designated as a standard of care for the treatment of cataplexy and EDS by the American Academy of Sleep Medicine.[12] With the goal of establishing a new standard of care, *Xywav* was developed to provide people with narcolepsy an oxybate therapy with lower sodium, and does not carry warnings about sodium content.

Xywav has a Boxed Warning as a central nervous system 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 under a REMS called the *Xywav* and *Xyrem* REMS Program. Most common adverse reactions in adults (≥5%) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety and vomiting.[1]

"We have been working for nearly a decade to develop *Xywav*, a unique oxybate product with a significant reduction in sodium. We are proud to advance the science behind our sleep research program in order to continue making a difference for people living with narcolepsy," said Bruce Cozadd, chairman and CEO of Jazz Pharmaceuticals. "Jazz is committed to addressing unmet needs in sleep medicine, which includes our innovative and long-standing oxybate program."

Narcolepsy is a chronic neurologic condition with no cure and the illness burden can have a far-reaching impact on a patient's health over time.[13,14,15,16] As an established leader in sleep medicine, Jazz is commited to raising awareness about narcolepsy and helping patients find strategies to manage this sleep disorder.

"Many people with narcolepsy can go years before being properly diagnosed and this can have a significant impact to their everyday life," said Julie Flygare, president and CEO of Project Sleep. "Narcolepsy is a life-long condition so it is important to have new options to help treat EDS and cataplexy."

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.[17]

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 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 also being studied 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, 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.[1]

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 Narcolepsy
Narcolepsy is a chronic, debilitating neurological disorder characterized by EDS and the inability to regulate sleep-wake cycles normally.[2,15,18] It affects an estimated one in 2,000 people in the United States, with symptoms typically appearing in childhood or adolescence.[19,20,21] Studies have shown it may take 10 years or more for people with narcolepsy to receive a diagnosis.[22,23] There are five main symptoms of narcolepsy, including EDS, cataplexy, disrupted nighttime sleep, sleep-related hallucinations, and sleep paralysis.[24] While all people with narcolepsy experience EDS, not all individuals with narcolepsy experience all five symptoms.[15,23] EDS is the primary symptom of narcolepsy and is present in all people with the disorder.[21,25] EDS is characterized by the inability to stay awake and alert during the day resulting in drowsiness and unplanned lapses into sleep.[19,21,22] Narcolepsy is associated with an increased prevalence of cardiometabolic comorbidities, including obesity, hypertension, diabetes and hypercholesterolemia.[13,14,26,27]

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.[19,21] Although many emotions can potentially trigger cataplexy, those associated with mirth are usually the most potent.[21] Cataplexy occurs in about 70 percent of people with narcolepsy.[29] 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.[19,21] Complete collapse is less common.[19,21] 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).[19,21,28,29]

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 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' belief in the potential of *Xywav* to make a difference for people living with narcolepsy; expectations regarding the timing of commercial launch of *Xywav* and other statements that are not historical facts. These forward-looking statements are based on the company's 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, effectively launching and commercializing new products; obtaining and maintaining adequate coverage and reimbursement for the company's products; the scale, duration and evolving effects of the COVID-19 pandemic and resulting global economic, financial and healthcare system disruptions that could have an effect on the successful commercialization of new products; 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 the company's Annual Report on Form 10-Q for the year ended March 31, 2020 and future filings and reports. Other risks and uncertainties of which the company is not currently aware also may affect the company's forward-looking statements and may cause actual results and the timing of events to differ materially from those anticipated.

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