Jazz Pharmaceuticals Announces FDA Approval of Xyrem® (sodium oxybate) for the Treatment of Cataplexy or Excessive Daytime Sleepiness in Pediatric Narcolepsy Patients

October 29, 2018

This approval of Xyrem by the FDA marks the first medicine approved to treat cataplexy or excessive daytime sleepiness in children and adolescents with narcolepsy ages seven and older

Efficacy and safety of Xyrem for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients with narcolepsy were established in a Phase 2/3 pivotal study

DUBLIN, Oct. 29, 2018 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced that the U.S. Food and Drug Administration (FDA) approved its supplemental new drug application (sNDA) on October 26, 2018, to revise labeling for Xyrem® (sodium oxybate) oral solution, CIII, to include an indication to treat cataplexy or excessive daytime sleepiness (EDS) in patients with narcolepsy ages seven and older.

"Narcolepsy is often misunderstood, misrepresented, misdiagnosed and underdiagnosed, especially in children," said Claire Crisp, executive director of Wake Up Narcolepsy and mother of a child with narcolepsy. "This approval of *Xyrem* in pediatric patients is a significant step forward for the narcolepsy community as we work to elevate awareness of the condition in children and ensure patients, both pediatric and adult, have meaningful treatment options available."

"*Xyrem* is the only FDA-approved treatment available for excessive daytime sleepiness and cataplexy in narcolepsy for adult patients," said Jed Black, M.D., senior vice president, Sleep and CNS Medicine at Jazz Pharmaceuticals and adjunct professor, Stanford Center for Sleep Sciences and Medicine. "In a pivotal study we demonstrated both safety and efficacy of *Xyrem* in pediatric patients with narcolepsy. We are pleased to lead the sleep community in advancing the science and identifying meaningful treatment options for children and adolescents."

The efficacy of *Xyrem* for the treatment of cataplexy or EDS in pediatric patients with narcolepsy was established in the multisite Phase 2/3 EXPRESS study, which enrolled patients seven to 17 years of age with narcolepsy with cataplexy.

Participants eligible for the study could either have been taking *Xyrem* or be *Xyrem*-naïve at study entry. *Xyrem*-naïve participants underwent open-label titration to reach a tolerable and effective dose. Following a stable dose period, all participants underwent a two week, double-blind, randomized-withdrawal period and were randomly assigned to either remain on *Xyrem* at their stable dose, or to receive placebo. The primary efficacy endpoint was the change in weekly number of cataplexy attacks, from the stable-dose period (baseline) to the end of the double-blind period. The change in EDS, as assessed by the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD), from baseline to the end of the double-blind period was a key secondary outcome measure. Following the randomized-withdrawal period, participants entered an open-label safety period for up to an additional 47 weeks, for a total study duration of up to one year.

Participants who were randomized to placebo (withdrawn from *Xyrem* (32 [51%] of 63 patients)) had increased weekly cataplexy attacks (median increase of 12·7 attacks per week [Q1, Q3=3·4, 19·8]) when compared with those who continued treatment with *Xyrem* (median increase of 0·3 attacks per week [Q1, Q3 = –1·0, 2·5]; p<0·0001).

The safety profile of *Xyrem* in children and adolescents in this study was similar to that reported in adults, and no new safety concerns were identified following the use of *Xyrem* for up to one year. The open-label portion of the study is still ongoing. As of February 2017 (the time of the data cut), the most common Treatment-Emergent Adverse Events (TEAEs) (>5%) were enuresis, nausea, vomiting, headache, decreased weight, decreased appetite, nasopharyngitis and dizziness. Two serious TEAEs occurred (acute psychosis which was severe and suicidal ideation which was moderate in severity).

For the data cut, safety assessments included measures of anxiety (Multidimensional Anxiety Scale for Children 10-item [MASC-10]), depressive symptoms (Children's Depression Inventory 2nd Edition Self-Report Short Version [CDI 2:SR(S)]) and suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS]), in addition to TEAEs. T-scores on the MASC-10 were within the average range throughout the study in participants who were *Xyrem*-naïve and on-*Xyrem* at study entry. T-scores on the CDI 2:SR(S) were within the average range throughout the study in participants who were *Xyrem*-naïve and on-*Xyrem* at study entry; a slight downward trend was observed in mean CDI 2:SR(S) T-scores over time.

Results from the Phase 2/3 EXPRESS study were published in *The Lancet Child & Adolescent Health* in July 2018, and topline data was presented at APSS in June 2017 and 2018.

The Micromedex DRUGDEX® monograph for *Xyrem* contains a Class IIA recommendation (recommended, in most cases) for use to treat cataplexy in narcolepsy in the pediatric patient population. The Micromedex DRUGDEX® is one of several statutorily named compendia in the United States Medicaid and Medicare programs for use in the determination of prescription and non-prescription drugs.

About Xyrem

Xyrem oral solution, CIII, is the only product approved by the U.S. Food and Drug Administration (FDA) for both cataplexy and excessive daytime sleepiness in narcolepsy in adult and pediatric patients ages 7 and older. *Xyrem* may only be dispensed to patients enrolled in the *Xyrem* REMS Program. *Xyrem* was first approved in the U.S. in 2002, based on clinical trial data in adults.

IMPORTANT SAFETY INFORMATION

WARNING: Taking XYREM with other 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), dizziness (syncope), and death.

XYREM 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.

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

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

Keep XYREM in a safe place to prevent abuse and misuse. Selling or giving away XYREM 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 XYREM 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 XYREM. Those activities should not be done until you know how XYREM affects you or your child.

XYREM 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 XYREM.
- **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, or thoughts of killing yourself or trying to kill yourself. Tell your doctor if you or your child have or had depression or have tried to harm yourself. **Call your doctor right away if you have or your child has symptoms of mental health problems.**
- **Sleepwalking**. Sleepwalking can cause injuries. Call your doctor if you or your child starts sleepwalking. Your doctor should check you or your child.

Tell your doctor if you are or your child is on a salt-restricted diet or if you have or your child has high blood pressure, heart failure, or kidney problems. XYREM contains a lot of sodium (salt) and may not be right for you or your child.

The most common side effects of XYREM include nausea, sleepiness, dizziness, vomiting, bedwetting, and tremor (in adults). In pediatric patients, headache, decreased appetite, and weight decrease were also common. Your side effects may increase when you take higher doses of XYREM. XYREM 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 XYREM.

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: http://pp.jazzpharma.com/pi/xyrem.en.USPI.pdf

About Narcolepsy
Narcolepsy is a chronic neurologic condition (involving nerve cells and chemicals in the brain) in which the brain is not able to control sleep-wake cycles normally.[1] Patients with narcolepsy have excessive daytime sleepiness (EDS), which is an irresistible urge to sleep during the day.[2] Cataplexy is a major symptom of narcolepsy in which the muscles weaken when a person feels strong emotions like embarrassment, laughter, surprise or anger.[2-5] Cataplexy can cause the head to drop, the face to droop, the jaw to weaken or the knees to give way.[2-5] Narcolepsy affects an estimated one in 2,000 people in the United States, and often the symptoms begin during adolescence.[2-4] It is estimated that 50 percent or more patients with narcolepsy have not been diagnosed.[3] It may take 10 years or more from the time of symptom onset for people with narcolepsy to receive a diagnosis.[6]

About Jazz Pharmaceuticals plc
Jazz Pharmaceuticals plc (Nasdaq: JAZZ) is an international biopharmaceutical company focused on improving patients' lives by identifying, developing and commercializing meaningful products that address unmet medical needs. The company has a diverse portfolio of products and product candidates with a focus in the areas of sleep and hematology/oncology. In these areas, Jazz Pharmaceuticals markets Xyrem®(sodium oxybate) oral solution, Erwinaze® (asparaginase Erwinia chrysanthemi), Defitelio®(defibrotide sodium) and Vyxeos® (daunorubicin and cytarabine) liposome for injection in the U.S. and markets Erwinase®, Defitelio® (defibrotide) and Vyxeos®44 mg/100 mg powder for concentrate for solution for infusion in countries outside the U.S. For country-specific product information, please visit http://www.jazzpharmaceuticals.com/products. For more information, please visit http://www.jazzpharmaceuticals.com/ and follow us on Twitter at @JazzPharma.

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Media Contact: Jacqueline Kirby, Vice President, Corporate Affairs & Government Relations, Ireland +353 1 697 2141, U.S. +1 215 867 4910; Investor Contact: Kathee Littrell, Vice President, Investor Relations, Ireland +353 1 634 7887, U.S. +1 650 496 2717