Jazz Pharmaceuticals Presents New Data at Psych Congress 2024 Confirming Xywav® (calcium, magnesium, potassium, and sodium oxybates) Oral Solution Treatment Benefits in Narcolepsy and Idiopathic Hypersomnia

October 31, 2024

First presentation of top-line efficacy and safety results from the Phase 4 DUET (Develop hypersomnia Understanding by Evaluating low-sodium oxybate Treatment) trial of adults with narcolepsy or idiopathic hypersomnia

For U.S. media and investors only

DUBLIN, Oct. 31, 2024 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced that eight abstracts presenting data from across its sleep portfolio were featured at the 37th annual Psych Congress, held in Boston from October 29 through November 2, 2024. The data includes the top-line results of the Phase 4 DUET (Develop hypersomnia Understanding by Evaluating low-sodium oxybate Treatment) trial, evaluating the effectiveness of low-sodium oxybate on key sleep outcomes in adults with narcolepsy or idiopathic hypersomnia (IH). Notably, these DUET data are the first to show prospective improvements on excessive daytime sleepiness (EDS), as well as key polysomnography (PSG) outcomes of sleep disruption, among adults with narcolepsy treated with Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution. Further, new DUET data evaluating nighttime *Xywav* treatment in adults with IH demonstrate clinical improvements on daytime symptoms, including sleep inertia measured by the Patient Global Impression of Change (PGIc).

The DUET trial is a Phase 4, prospective, single-arm, open-label study to assess the effect of *Xywav* treatment on EDS, polysomnography parameters, and functional outcomes in adults with narcolepsy or IH. Observed adverse events were consistent with the known safety profile of *Xywav*, with the most common including nausea, dizziness and headache.

"The new DUET data presented today demonstrate the impact of low-sodium *Xywav* treatment on key narcolepsy and idiopathic hypersomnia symptoms," said Logan Schneider, MD, adjunct clinical associate professor of sleep medicine, Stanford Sleep Center and Consultant Neurologist, Stanford/VA Alzheimer's Center. "These data build on our confidence that appropriate treatment can meaningfully impact the outcomes that matter to patients and their functioning."

Presentation highlights include:

- **Xywav DUET Narcolepsy Top-line Results (P166):** Novel analysis of primary and key secondary outcomes in participants with narcolepsy show improvements in daytime and nighttime symptoms with *Xywav* treatment compared to baseline across daytime sleepiness and PSG-based measures of sleep disruption, including sleep stage shifts from deeper to lighter stages of sleep, time spent in deep sleep, and number of awakenings. Specifically, the statistically significant change (least square mean, standard error) from baseline on the Epworth Sleepiness Scale (ESS) was −7.7 (0.9), P<0.0001, while changes for total shifts from deeper to lighter stages of sleep, N3 sleep (deep sleep) duration in minutes, and number of awakenings were −13.1 (3.0), P<0.0001; 45.0 (8.8), P<0.0001; and −3.2 (0.9), P=0.0015, respectively (N=34 each).
- **Xywav DUET IH Top-line Results (P165):** First presentation of primary and key secondary outcomes in participants with IH show *Xywav* treatment resulted in improvements in EDS, measured by ESS and Idiopathic Hypersomnia Severity Scale (IHSS). Additionally, improvements were observed across PGIc measures of overall symptoms, with new data on sleep inertia measured within the PGIc. Statistically significant changes (least square mean, standard error) in ESS (N=40) and IHSS (N=36) from baseline to end of treatment were −8.4 (0.7), P<0.0001 and −15.5 (1.5), P<0.0001, respectively. Most participants reported improvement (very much, much, minimally) on the PGIc overall (94.6%; N=37) and PGIc sleep inertia inventory (81.1%; N=37).

"These DUET data are the first to show *Xywav's* impact on polysomnography measures of nighttime awakenings, sleep stage shifts, and deep sleep for people living with narcolepsy, as well as improvements among adults with IH in key outcomes important for daily life," said Kelvin Tan, MBBCh, MRCPCH, chief medical affairs officer of Jazz Pharmaceuticals. "Jazz is committed to our leadership in sleep, as exemplified by our presentations at Psych Congress of the DUET trial data, which studied the effectiveness of low-sodium *Xywav* on symptoms of narcolepsy and IH by demonstrating improvements in measures which are key for patients to wake up more refreshed with improved wakefulness during the day."

The Psych Congress 2024 presentations are available on-demand through the conference mobile application. Abstracts and posters will also be published on HMP Global's Psychiatry & Behavioral Health Learning Network 30-60 days after the event ends.

A full list of Jazz presentations follows below:

Presentation Title	Presenting Author	Poster Number
Effectiveness and Safety of Low-Sodium Oxybate in Participants With Narcolepsy: Top-line Results From the Phase 4 DUET Study	L. Schneider	P166

Effectiveness and Safety of Low-Sodium Oxybate in Participants With Idiopathic Hypersomnia: Top-line Results From the Phase 4 DUET Study	D. Nichols	P165
Efficacy and Safety of Low-Sodium Oxybate in Participants With Idiopathic Hypersomnia With or Without Psychiatric Comorbidities	S. Bronson	P83
A Conceptual Disease Model of the Symptoms and Impacts of Idiopathic Hypersomnia From the Patient Perspective	M. Whalen	P46
Understanding Sleep Inertia: A Qualitative Study of the Patient Experience With Idiopathic Hypersomnia	M. Whalen	P47
Qualitative Comparison of the Patient Experience of Excessive Daytime Sleepiness in Idiopathic Hypersomnia, Obstructive Sleep Apnea, and Major Depressive Disorder	A. Cutler	P117
The Clinical and Humanistic Burden of Idiopathic Hypersomnia in the United States: Analysis of the National Health and Wellness Survey	J. Sacks	P35
Design Elements for a Switch Study From High- to Low-Sodium Oxybate Evaluating Blood Pressure in Narcolepsy (XYLO)	J. Alexander	P82

About Narcolepsy

Narcolepsy is a chronic, debilitating neurologic sleep disorder characterized by 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), or EDS, and an inability to regulate sleep-wake cycles normally.[1] Patients with EDS due to narcolepsy experience sleep attacks and, despite fighting the urge to sleep, may unintentionally fall asleep for short periods.[2,3] These sleep attacks may happen at inappropriate or potentially dangerous times such as during driving, cycling, eating, or mid-conversation.[4]

There is no cure for narcolepsy, therefore this EDS is lifelong and has a substantial negative impact on a person's ability to function psychologically, socially and professionally.[5] Patients with narcolepsy are at increased risk for hypertension, cardiometabolic morbidity, stroke, myocardial infarction, heart failure, cardiac arrest, and death.[6,7,8,9] As narcolepsy is a chronic condition that requires lifelong, nightly treatment, early access to an effective, low-sodium treatment can transform lives and reduce the impact of narcolepsy on a person's physical and mental health.[5]

About Idiopathic Hypersomnia

Idiopathic hypersomnia is an often debilitating, neurologic sleep disorder that goes beyond chronic excessive daytime sleepiness.[10,11,12,13] Idiopathic hypersomnia is a 24-hour sleep disorder, and symptoms may include a prolonged but non-restorative 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 (prolonged difficulty waking, with frequent reentries into sleep, confusion, and irritability).[10,11,12,13,14] Although there are overlapping clinical features with narcolepsy, idiopathic hypersomnia is a condition with its own specific diagnostic criteria.[13,15]

Idiopathic hypersomnia is an often debilitating illness that can significantly affect social, educational, and occupational functioning.[16,17] In the U.S., approximately 37,000 adult patients have been diagnosed with idiopathic hypersomnia and are actively seeking healthcare.[18] This low number of people may be due to the many difficulties in identifying and diagnosing idiopathic hypersomnia, as well as distinguishing it from other similar sleep disorders. It is estimated that far fewer patients are currently receiving pharmacological treatment for their idiopathic hypersomnia.[18,19,20,21]

About Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution

Xywav is the only low-sodium oxybate approved by the U.S. Food and Drug Administration (FDA) for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. The FDA recognized seven years of Orphan Drug Exclusivity for *Xywav* for the treatment of cataplexy or EDS 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 EDS in patients 7 years of age and older with narcolepsy by means of greater cardiovascular safety compared to Xyrem® (sodium oxybate) oral solution. The decision of the OOPD is based on the FDA findings that *Xywav* provides a greatly reduced chronic sodium burden compared to *Xyrem*. *Xywav* has 131 mg of sodium at the maximum recommended nightly dose whereas other high sodium oxybates have 1640 mg at the equivalent dose. *Xywav* is comprised of a unique composition of cations resulting in 92% less sodium, or a reduction of approximately 1,000 to 1,500 mg/night at the recommended dose range of 6 g to 9 g/night. *Xywav* is the only oxybate therapy that does not carry a warning in the label related to use in patients sensitive to high sodium intake.

Xywav is also the first and only U.S. FDA-approved treatment option for idiopathic hypersomnia in adults. The FDA recognized seven years of Orphan Drug Exclusivity for *Xywav* for the treatment of idiopathic hypersomnia in adults. *Xywav* is the only FDA-approved treatment studied across the multiple symptoms of idiopathic hypersomnia, such as EDS, sleep inertia (severe grogginess or confusion when waking up), long sleep duration and cognitive impairment. *Xywav* can be administered as a twice- or once-nightly regimen for the treatment of idiopathic hypersomnia in adults.

The exact mechanism of action of *Xywav* in the treatment of adults with idiopathic hypersomnia and of cataplexy and EDS in narcolepsy is unknown. It is hypothesized that the therapeutic effects of *Xywav* are mediated through $GABA_B$ actions during sleep at noradrenergic and dopaminergic neurons, as well as 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.[1,2] Because of the risks of central nervous system (CNS) depression and abuse and misuse, *Xywav* is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XYWAV and XYREM REMS.

Important Safety Information for Xywav

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

- **Central Nervous System Depression**
  XYWAV is a CNS depressant. Clinically significant respiratory depression and obtundation may occur in patients treated with

XYWAV at recommended doses. Many patients who received XYWAV during clinical trials in narcolepsy and idiopathic hypersomnia were receiving CNS stimulants.

- **Abuse and Misuse**
  The active moiety of XYWAV is oxybate or gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death.

Because of the risks of CNS depression and abuse and misuse, XYWAV is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XYWAV and XYREM REMS.

Contraindications
XYWAV is contraindicated

- in combination with sedative hypnotics or alcohol and
- in patients with succinic semialdehyde dehydrogenase deficiency.

Warnings and Precautions
Central Nervous System Depression

The concurrent use of XYWAV with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with XYWAV is required, dose reduction or discontinuation of one or more CNS depressants (including XYWAV) should be considered. In addition, if short-term use of an opioid (eg, post- or perioperative) is required, interruption of treatment with XYWAV should be considered.

After first initiating treatment and until certain that XYWAV does not affect them adversely (eg, impair judgment, thinking, or motor skills), caution patients against hazardous activities requiring complete mental alertness or motor coordination such as operating hazardous machinery, including automobiles or airplanes. Also caution patients against these hazardous activities for at least 6 hours after taking XYWAV. Patients should be queried about CNS depression-related events upon initiation of XYWAV therapy and periodically thereafter.

Abuse and Misuse
XYWAV is a Schedule III controlled substance. The active moiety of XYWAV is oxybate, also known as gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with the amnestic features of GHB particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (eg, assault victim). Physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

XYWAV and XYREM REMS
Because of the risks of central nervous system depression and abuse and misuse, XYWAV is available only through a restricted distribution program called the XYWAV and XYREM REMS.

Notable requirements of the XYWAV and XYREM REMS include the following:

- Healthcare Providers who prescribe XYWAV are specially certified
- XYWAV will be dispensed only by the central pharmacy that is specially certified
- XYWAV will be dispensed and shipped only to patients who are enrolled in the XYWAV and XYREM REMS with documentation of safe use

Further information is available at www.XYWAVXYREMREMS.com or 1-866-997-3688.

Respiratory Depression and Sleep-Disordered Breathing
XYWAV may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses of oxybate and with illicit use of GHB, life-threatening respiratory depression has been reported. Increased apnea and reduced oxygenation may occur with XYWAV administration in adult and pediatric patients. A significant increase in the number of central apneas and clinically significant oxygen desaturation may occur in patients with obstructive sleep apnea treated with XYWAV. Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not on hormone replacement therapy, and among patients with narcolepsy.

Depression and Suicidality
In Study 1, the randomized-withdrawal clinical trial in adult patients with narcolepsy (n=201), depression and depressed mood were reported in 3% and 4%, respectively, of patients treated with XYWAV. Two patients (1%) discontinued XYWAV because of depression. In most cases, no change in XYWAV treatment was required.

In Study 2, the randomized-withdrawal clinical trial in adult patients with idiopathic hypersomnia (n=154), depression and depressed mood were reported in 1% and 3%, respectively, of patients treated with XYWAV. All patients continued XYWAV treatment.

Two suicides and two attempted suicides occurred in adult clinical trials with oxybate (same active moiety as XYWAV). One patient experienced suicidal ideation and two patients reported depression in a pediatric clinical trial with oxybate. These events occurred in patients with and without previous histories of depressive disorders. The emergence of depression in patients treated with XYWAV requires careful and immediate evaluation. Monitor patients for the emergence of increased depressive symptoms and/or suicidality while taking XYWAV.

Other Behavioral or Psychiatric Adverse Reactions
In Study 1, confusion and anxiety occurred in 1% and 5% of patients with narcolepsy treated with XYWAV, respectively. One patient experienced visual hallucinations and confusion after ingesting approximately 9 grams of XYWAV.

In Study 2, confusion and anxiety occurred in 3% and 16% of patients with idiopathic hypersomnia, respectively. One patient experienced visual hallucinations, which led to discontinuation of XYWAV.

Other neuropsychiatric reactions reported with oxybate (same active moiety as XYWAV) in adult or pediatric clinical trials and in the postmarketing setting include hallucinations, paranoia, psychosis, aggression, agitation, confusion and anxiety. The emergence or increase in the occurrence of behavioral or psychiatric events in patients taking XYWAV should be carefully monitored.

Parasomnias
Parasomnias can occur in patients taking XYWAV.

In Study 1 and Study 2, parasomnias, including sleepwalking, were reported in 6% and 5% of adult patients treated with XYWAV, respectively.

In a clinical trial of XYREM (same active moiety as XYWAV) in adult patients with narcolepsy, five instances of sleepwalking with potential injury or significant injury were reported. Parasomnias, including sleepwalking, have been reported in a pediatric clinical trial with sodium oxybate (same active moiety as XYWAV) and in postmarketing experience with sodium oxybate.

Episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

Most Common Adverse Reactions
The most common adverse reactions (occurring in ≥5% of XYWAV-treated patients in adult clinical trials in either narcolepsy or IH) were nausea, headache, dizziness, anxiety, insomnia, decreased appetite, hyperhidrosis, vomiting, diarrhea, dry mouth, parasomnia, somnolence, fatigue, and tremor.

In the pediatric clinical trial with XYREM (same active moiety as XYWAV) that included pediatric patients 7 to 17 years of age with narcolepsy, the most common adverse reactions (≥5%) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%), and sleepwalking (6%). The overall adverse reaction profile of XYREM in the pediatric clinical trial was similar to that seen in the adult clinical trial program. The safety profile in pediatric patients with XYWAV is expected to be similar to that of adult patients treated with XYWAV and to that of pediatric patients treated with XYREM.

Additional Adverse Reactions
Adverse reactions that occurred in 2-<5% of adult patients treated with XYWAV in the Open Label Titration and Stable Dose Periods of the randomized-withdrawal study in adult patients with narcolepsy with cataplexy (Study 1) were fatigue, dry mouth, depressed mood, enuresis, irritability, paresthesia, depression, tremor, somnolence, and muscle spasms. Adverse reactions occurring in 2-<5% of patients treated with XYWAV in the IH study include balance disorder, muscle spasms, fall, paresthesia, snoring, weight decreased, bruxism, confusional state, depressed mood, feeling drunk, and irritability.

Adverse reactions that occurred in ≥2% of patients in clinical studies with oxybate (but not in Study 1) and which may be relevant for XYWAV, were pain, feeling drunk, pain in extremity, cataplexy, disturbance in attention, sleep paralysis, and disorientation.

Discontinuation: In Study 1, 9 of 201 patients (4%) reported adverse reactions that led to withdrawal from the study (anxiety, decreased appetite, depressed mood, depression, fatigue, headache, irritability, nausea, pain in extremity, parasomnia, somnolence, and vomiting). The most common adverse reaction leading to discontinuation was nausea (1.5%). In Study 2, 17 of 154 (11%) patients across all study periods (excluding placebo during the DB RWP) (up to 42 weeks) reported adverse reactions that led to withdrawal from the study (anxiety, nausea, insomnia, vomiting, fatigue, feeling abnormal, fall, decreased appetite, dizziness, paresthesia, tremor, parasomnia, confusional state, hallucination visual, and irritability). The most common adverse reaction leading to discontinuation was anxiety (3.2%). In Study 1 and Study 2, the majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.

In the pediatric clinical trial with XYREM (same active moiety as XYWAV), 7 of 104 patients reported adverse reactions that led to withdrawal from the study (hallucination, tactile; suicidal ideation; weight decreased; sleep apnea syndrome; affect lability; anger, anxiety, depression; and headache).

Drug Interactions
XYWAV is contraindicated in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of XYWAV.

Concomitant use of sodium oxybate with divalproex sodium results in an increase in systemic exposure to GHB, which was shown to cause a greater impairment on some tests of attention and working memory in a clinical study. A similar increase in exposure is expected with concomitant use of XYWAV and divalproex sodium; therefore, an initial dose reduction of XYWAV is recommended when used concomitantly with divalproex sodium. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of XYWAV and divalproex sodium is warranted.

Pregnancy and Lactation
There are no adequate data on the developmental risk associated with the use of XYWAV or sodium oxybate in pregnant women. XYWAV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. GHB is excreted in human milk after oral administration of sodium oxybate. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XYWAV and any potential adverse effects on the breastfed infant from XYWAV or from the underlying maternal condition.

Pediatric Use
The safety and effectiveness of XYWAV for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy have been established. XYWAV has not been studied in a pediatric clinical trial for narcolepsy or IH. Use of XYWAV in pediatric patients 7 years of age and older with narcolepsy is supported by evidence from an adequate and wellcontrolled study of sodium oxybate in pediatric patients 7 to 17 years of age, a study in adults showing a treatment effect of XYWAV similar to that observed with sodium oxybate, pharmacokinetic data of sodium oxybate from adult and pediatric patients, and pharmacokinetic data of XYWAV from healthy adult volunteers.

Safety and effectiveness of XYWAV in pediatric patients below the age of 7 years with narcolepsy have not been established.

Safety and effectiveness of XYWAV for the treatment of idiopathic hypersomnia in pediatric patients have not been established.

Geriatric Use
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment
The starting dose of XYWAV should be reduced in patients with liver impairment.

Dosage Modification in Patients with Hepatic Impairment: The recommended starting dosage in patients with hepatic impairment is one-half of the original dosage per night, administered orally, divided into two doses.

Dependence and Tolerance
There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the recommended dosage range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required.

In the clinical trial experience with XYREM in narcolepsy/cataplexy patients at recommended doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time. In the XYWAV clinical trial in adult narcolepsy/cataplexy patients at recommended doses, one patient reported insomnia following abrupt discontinuation of XYWAV. In the XYWAV clinical trial in adult idiopathic hypersomnia patients at recommended doses, six patients reported insomnia, two patients reported early insomnia, and one patient reported visual and auditory hallucinations following abrupt discontinuation of XYWAV.

Tolerance to XYWAV has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended XYWAV dosage regimen.

Important Safety Information for Xyrem

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

- **Central Nervous System Depression**
  XYREM is a Central Nervous System (CNS) depressant. In clinical trials at recommended doses, obtundation and clinically significant respiratory depression occurred in adult patients treated with XYREM. Many patients who received XYREM during clinical trials in narcolepsy were receiving CNS stimulants.

- **Abuse and Misuse**
  XYREM is the sodium salt of gamma hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death.

Because of the risks of CNS depression and abuse and misuse, XYREM is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XYWAV and XYREM REMS.

Contraindications
XYREM is contraindicated for use in combination with sedative hypnotics or alcohol and in patients with succinic semialdehyde dehydrogenase deficiency.

Warnings and Precautions
CNS Depression: Use caution when considering the concurrent use of Xyrem with other CNS depressants. If concurrent use is required, consider dose reduction or discontinuation of one or more CNS depressants (including XYREM). Consider interrupting XYREM treatment if short-term opioid use is required. After first initiating treatment and until certain that XYREM does not affect them adversely, caution patients against hazardous activities requiring complete mental alertness or motor coordination such as operating hazardous machinery, including automobiles or airplanes. Also caution patients against these hazardous activities for at least 6 hours after taking XYREM. Patients should be queried about CNS depression-related events upon initiation of XYREM therapy and periodically thereafter.

- Abuse and Misuse: XYREM is a Schedule III controlled substance. The rapid onset of sedation, coupled with the amnestic features of XYREM, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (eg, assault victim).
- Respiratory Depression and Sleep-Disordered Breathing: XYREM may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported. Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with XYREM administration in adult and pediatric patients. Sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not on hormone replacement therapy and among patients with narcolepsy.
- Depression and Suicidality: In adult clinical trials in patients with narcolepsy (n=781), depression was reported by 7% of XYREM-treated patients, with four patients (<1%) discontinuing because of depression. In the pediatric clinical trial in patients with narcolepsy (n=104), one patient experienced suicidal ideation and two patients reported depression while taking XYREM. Monitor patients for emergent or increased depression and/or suicidality, which require

careful and immediate evaluation.

- Other Behavioral or Psychiatric Adverse Reactions: Monitor patients for impaired motor/cognitive function or the emergence of or increase in anxiety and/or confusion. The emergence or increase in the occurrence of behavioral or psychiatric events in adult and pediatric patients taking XYREM should be carefully monitored.
- Parasomnias: Episodes of sleepwalking should be fully evaluated and appropriate interventions considered. Five instances of significant injury or potential injury were associated with sleepwalking during a clinical trial of XYREM in adult patients with narcolepsy. Parasomnias, including sleepwalking, also have been reported in the pediatric clinical trial and in postmarketing experience with XYREM.
- Patients Sensitive to High Sodium Intake: XYREM has a high salt content. In patients sensitive to salt intake (eg, those with heart failure, hypertension, or renal impairment), consider the amount of daily sodium intake in each dose of XYREM.

Most Common Adverse Reactions

In three controlled adult clinical trials in patients with narcolepsy, the most common adverse reactions (incidence ≥5% and twice the rate of placebo) in XYREM-treated patients were nausea, dizziness, vomiting, somnolence, enuresis, and tremor. In the pediatric clinical trial in patients 7 years of age and older with narcolepsy, the most common adverse reactions (≥5%) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%) and sleepwalking (6%).

About Jazz Pharmaceuticals

Jazz Pharmaceuticals plc is a global biopharma company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing potentially life-changing medicines for people with serious diseases — often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines, including leading therapies for sleep disorders and epilepsy, and a growing portfolio of cancer treatments. Our patient-focused and science-driven approach powers pioneering research and development advancements across our robust pipeline of innovative therapeutics in oncology and neuroscience. Jazz is headquartered in Dublin, Ireland with research and development laboratories, manufacturing facilities and employees in multiple countries committed to serving patients worldwide. Please visit www.jazzpharmaceuticals.com for more information.

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