Jazz Pharmaceuticals to Showcase Research Demonstrating Treatment Benefits of Xywav® (calcium, magnesium, potassium, and sodium oxybates) Oral Solution and Epidiolex® (cannabidiol) at American Academy of Neurology Annual Meeting

March 19, 2025

Updated top-line results demonstrate improved outcomes in adults with narcolepsy or idiopathic hypersomnia treated with Xywav as observed in the Phase 4 DUET (Developing Understanding of Hypersomnia by Evaluating Low-Sodium Oxybate Treatment) study

Novel analysis of real-world Epidiolex treatment patterns underscore importance of dose optimization for improved patient persistence

For U.S. media and investors only

DUBLIN, March 19, 2025 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced that seven abstracts from across its neuroscience portfolio will be featured at the 77th Annual American Academy of Neurology Meeting (AAN) being held April 5-9, 2025, in San Diego.

Data presented at the meeting includes an updated presentation of top-line results of the open-label, single-arm, Phase 4 DUET (Develop hypersomnia Understanding by Evaluating low-sodium oxybate Treatment) trial, evaluating the effectiveness and safety of low-sodium oxybate, Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, on key sleep outcomes and daytime symptoms, including excessive daytime sleepiness (EDS), in adults with narcolepsy or idiopathic hypersomnia (IH). Notably, the results from DUET demonstrated statistically significant improvements from baseline to end of treatment in Epworth Sleepiness Scale (ESS) scores, reduced sleep stage shifts, increased deep sleep and reduced number of awakenings among adults with narcolepsy treated with *Xywav*. In adults with IH, *Xywav* treatment also showed improvements in ESS and Idiopathic Hypersomnia Severity Scale scores. Further, new patient-reported data from DUET demonstrated the association of *Xywav* treatment with improvements in daytime symptoms and functional impacts, including cognitive complaints, among adults with narcolepsy or IH. *Xywav* is indicated for the treatment of EDS or cataplexy in patients 7 years of age and older with narcolepsy and for adults with idiopathic hypersomnia.

"This year's presentations at the AAN Annual Meeting reinforce our ongoing commitment to addressing debilitating neurological disorders, with limited or no treatment options including narcolepsy, idiopathic hypersomnia and epilepsy," said Sarah Akerman, MD, head of neuroscience global medical and scientific affairs of Jazz Pharmaceuticals. "We continually strive to expand our understanding, research and capabilities in neuroscience through ongoing data generation for *Xywav* and *Epidiolex* to ensure patients' lived experiences and needs are reflected holistically. By listening to our patients, their care teams and leading industry experts, we aim to better address the unmet needs of those living with these difficult-to-treat conditions and ultimately help redefine possibilities for their lives."

Highlights at the 2025 AAN Annual Meeting include:

- Two presentations showcasing updated results from the open-label, single-arm, Phase 4 DUET trial of adults with narcolepsy or IH, which evaluated the effectiveness and safety of *Xywav* on key sleep outcomes, daytime symptoms, and functional impacts, including cognitive complaints, work productivity, and daily activities.
- Novel analysis of real-world Epidiolex® (cannabidiol) treatment patterns from U.S. specialty pharmacy data found the overall probability of persistence at one year was nearly 70% (69.9%) among new patients and underscores the importance of dose optimization. The analysis shows how healthcare providers optimize dosing over time, with half (52%) of patients taking dosages >15 mg/kg/day at 12 months and those taking an average of >20 mg/kg/day having the lowest likelihood of discontinuation. This real-world data demonstrates the importance of dose optimization for long-term persistence, which could lead to improved seizure control and tolerability.

The 2025 AAN Annual Meeting abstracts are available online at index.mirasmart.com/AAN2025.

A full list of Jazz Pharmaceuticals' presentations follows below:

Presentation Title	**Lead Author**	**Poster Number / Session Title / Date & Time (PT)**
Xywav Data		
Self-Reported Cognitive Complaints and Work Productivity in Participants With Narcolepsy After Low-Sodium Oxybate treatment: Results From the Phase 4 DUET Study	LD Schneider	Poster #: 002 Session: P8 Sleep 2 Session Date/Time: Tuesday, April 8, 8:00 AM – 9:00 AM
Effectiveness and Safety of Low-Sodium Oxybate in Participants With Narcolepsy: Top-line Results From the Phase 4 DUET Study	LD Schneider	Poster #: 008 Session: P10: General Neurology: New, Potential, and Innovative Treatments 2 Session Date/Time: Tuesday, April 8, 5:00 PM – 6:00 PM

Efficacy and Safety of Low-Sodium Oxybate in Narcolepsy Patients With/Without Psychiatric/Neurologic Comorbidities	C Chepke	Poster #: 004 Session: P12 General Neurology Posters 5 Session Date/Time: Wednesday, April 9, 11:45 AM – 12:45 PM
Epidiolex Data		
Dosing Patterns and Persistence on Cannabidiol (CBD) – Insights From US Specialty Pharmacy Data	G Pohl	Poster #: 005 Session: P12: Epilepsy/Clinical Neurophysiology (EEG): Retrospective Studies, Reviews, and Meta-analyses in Epilepsy Session Date/Time: Wednesday, April 9, 11:45 AM – 12:45 PM
Tuberous Sclerosis Complex (TSC)–Associated Neuropsychiatric Disorder (TAND) Outcomes Following Add-on Cannabidiol (CBD) Treatment: 3-Month Analysis of Open-Label Phase 3b/4 Trial EpiCom	A van Eeghen	Poster #: 005 Session: P8: Epilepsy/Clinical Neurophysiology (EEG): Anti-seizure Medications: Clinical Trials Session Date/Time: Tuesday, April 8, 8:00 AM – 9:00 AM
Caregiver-Reported Real-World Use of Cannabidiol (CBD) and Effects on Seizures and Caregiver Burden: Results From the CARE-EpiC Survey	S Thomas	Poster #: 003 Session: P1: Epilepsy/Clinical Neurophysiology (EEG): Special Populations: Women with Epilepsy, Caregivers, Adolescents, and Elderly Session Date/Time: Saturday, April 5, 11:45 AM – 12:45 PM
Nurse-Reported Outcomes of Cannabidiol (CBD) Treatment in the Long-Term Care (LTC) Setting: Results From the BECOME-LTC Survey	N Wrobel	Poster #: 016 Session: P2: Epilepsy/Clinical Neurophysiology (EEG): Clinical Outcomes in Epilepsy Session Date/Time: Sunday, April 6, 8:00 AM – 9:00 AM PT

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 Ill 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.

About Epidiolex®/Epidyolex® (cannabidiol)
Epidiolex/Epidyolex is a prescription, plant-derived cannabis-based medicine administered as an oral solution which contains highly purified cannabidiol (CBD). Cannabidiol, the active ingredient in *Epidiolex*, is a cannabinoid that naturally occurs in the *Cannabis sativa* L. plant. The precise mechanisms by which *Epidiolex* exerts its anticonvulsant effect in humans are unknown. *Epidiolex* was approved by the U.S. Food and Drug Administration (FDA) for use in the U.S., the European Commission (EC) for use in Europe, the Medicines and Healthcare products Regulatory Agency (MHRA) for use in Great Britain, the Therapeutic Goods Administration for use in Australia, Swissmedic for use in Switzerland, the Food & Nutrition Services of the Israel Ministry of Health for use in Israel, and the New Zealand Medicines and Medical Devices Safety Authority for use in New Zealand, is an oral solution which contains highly purified cannabidiol (CBD). In the U.S., *Epidiolex* is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS) or tuberous sclerosis complex (TSC) in patients one year of age and older. *Epidiolex* has received approval in the European Union under the tradename *Epidyolex* for adjunctive use in conjunction with clobazam to treat seizures associated with LGS and DS in patients two years and older, and for adjunctive use to treat seizures associated with TSC, in patients two years of age and older. *Epidiolex* has received Orphan Drug Designation (ODD) from the U.S. FDA for the treatment of seizures associated with LGS, DS, and TSC. Similarly, *Epidyolex* received ODD from the European Medicines Agency (EMA) for the same indications.

Important Safety Information & Indications

CONTRAINDICATION: HYPERSENSITIVITY

EPIDIOLEX (cannabidiol) oral solution is contraindicated in patients with a history of hypersensitivity to cannabidiol or any ingredients in the product.

WARNINGS & PRECAUTIONS

Hepatic Injury:
EPIDIOLEX can cause dose-related transaminase elevations. Concomitant use of valproate and elevated transaminase levels at baseline increase this risk. Obtain transaminase and bilirubin levels prior to starting treatment, at 1, 3, and 6 months after initiation of treatment, and periodically thereafter, or as clinically indicated. Resolution of transaminase elevations occurred with discontinuation of EPIDIOLEX, reduction of EPIDIOLEX and/or concomitant valproate, or without dose reduction. For patients with elevated transaminase levels, consider dose reduction or discontinuation of EPIDIOLEX or concomitant medications known to affect the liver (e.g., valproate or clobazam). Dose adjustment and slower dose titration is recommended in patients with moderate or severe hepatic impairment. Consider not initiating EPIDIOLEX in patients with evidence of significant liver injury. There have been postmarketing reports of cholestatic or mixed patterns of liver injury. Elevated ammonia levels were reported in some patients with transaminase elevations; most taking concomitant valproate, clobazam, or both. Consider discontinuation or dose adjustment of valproate or clobazam if ammonia is elevated.

Somnolence and Sedation:
EPIDIOLEX can cause somnolence and sedation that generally occurs early in treatment and may diminish over time; these effects occur more commonly in patients using clobazam and may be potentiated by other CNS depressants.

Suicidal Behavior and Ideation:
Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior. Inform patients, caregivers, and families of the risk and advise them to monitor and report any signs of depression, suicidal thoughts or behavior, or unusual changes in mood or behavior. If these symptoms occur, consider if they are related to the AED or the underlying illness.

Withdrawal of Antiepileptic Drugs:
As with most AEDs, EPIDIOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

ADVERSE REACTIONS:
The most common adverse reactions in patients receiving EPIDIOLEX (≥10% and greater than placebo) include transaminase elevations; somnolence; decreased appetite; diarrhea; pyrexia; vomiting; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder and poor-quality sleep; and infections. Hematologic abnormalities were also observed.

PREGNANCY:
EPIDIOLEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage women who are taking EPIDIOLEX during pregnancy to enroll in the EPIDIOLEX Pregnancy Surveillance Program and the North American Antiepileptic Drug (NAAED) Pregnancy Registry.

DRUG INTERACTIONS:

Strong inducers of CYP3A4 and CYP2C19 may affect EPIDIOLEX exposure. EPIDIOLEX may affect exposure to CYP2C19 substrates (e.g., clobazam, diazepam, stiripentol), orally administered P-gp substrates, or other substrates (see full Prescribing Information). Consider dose reduction of orally administered everolimus, with appropriate therapeutic drug monitoring, when everolimus is combined with EPIDIOLEX. A lower starting dose of everolimus is recommended when added to EPIDIOLEX therapy. Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations. Pneumonia was observed more frequently with concomitant use of EPIDIOLEX and clobazam. Dosage adjustment of EPIDIOLEX or other concomitant medications may be necessary.

INDICATIONS:
EPIDIOLEX (cannabidiol) oral solution is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 1 year of age and older.

Please read the EPIDIOLEX full Prescribing Information for additional important information here.

About Jazz Pharmaceuticals
Jazz Pharmaceuticals plc (Nasdaq: JAZZ) 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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1. Xywav (calcium, magnesium, potassium and sodium oxybates) oral solution. Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2021.
2. United States Drug Enforcement Agency. Drug Scheduling. https://www.dea.gov/drug-information/drug-scheduling. Accessed March 2025.

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