

























**Table 5: Adverse Reactions Occurring in  $\geq 2\%$  of Patients Treated with XYWAV in the Open-Label Titration and Stable Dose Periods in Study 2**

| Adverse Reaction | Open-Label Titration Period + Stable Dose Period<br>(up to 16 weeks)<br>(N=154)<br>% |
|------------------|--------------------------------------------------------------------------------------|
|------------------|--------------------------------------------------------------------------------------|

\*includes anxiety, nervousness, and panic attack

†includes middle insomnia, initial insomnia, insomnia, and terminal insomnia

‡ includes hyperhidrosis and night sweats

§ includes fatigue and asthenia

¶includes somnolence and sedation

# includes confusional arousal, sleep paralysis, nightmare, sleep talking, somnambulism, and hypnopompic hallucination

•includes balance disorder and ataxia

### Additional Adverse Reactions

Adverse reactions observed in clinical studies with Xyrem ( $\geq 2\%$ ), but not observed in Study 1 or Study 2 at a frequency of higher than 2%, and which may be relevant for XYWAV:

Pain, pain in extremity, cataplexy, disturbance in attention, sleep paralysis, and disorientation.

## **6.2 Postmarketing Experience**

The following adverse reactions have been identified during postapproval use of sodium oxybate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Arthralgia, fall\*, fluid retention, hangover, hypersensitivity, hypertension, memory impairment, nocturia, and vision blurred.

\*The sudden onset of sleep in patients taking sodium oxybate, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization.

## **7 DRUG INTERACTIONS**

### **7.1 Alcohol, Sedative Hypnotics, and CNS Depressants**

XYWAV is contraindicated for use in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of XYWAV [see *Warnings and Precautions (5.1)*].

### **7.2 Divalproex Sodium**

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 [see *Clinical Pharmacology (12.3)*]. 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 [see *Dosage and Administration (2.7)*]. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of XYWAV and divalproex sodium is warranted.







one patient reported visual and auditory hallucinations following abrupt discontinuation of XYWAV.

### Tolerance

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). 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. Clinical studies of sodium oxybate in the treatment of alcohol withdrawal suggest a potential cross-tolerance with alcohol. The safety and effectiveness of XYWAV in the treatment of alcohol withdrawal have not been established.

## **10 OVERDOSAGE**

### **10.1 Human Experience**

Information regarding overdose with XYWAV is derived largely from reports in the medical literature that describe symptoms and signs in individuals who have ingested GHB illicitly. In these circumstances the co-ingestion of other drugs and alcohol was common, and may have influenced the presentation and severity of clinical manifestations of overdose.

In adult clinical trials with Xyrem (same active moiety as XYWAV), two cases of overdose were reported. In the first case, an estimated dose of 150 g, more than 15 times the maximum recommended dose, caused a patient to be unresponsive with brief periods of apnea and to be incontinent of urine and feces. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of Xyrem and numerous other drugs. No cases of overdose (greater than 9 g) with XYWAV were reported in the XYWAV clinical trials.

### **10.2 Signs and Symptoms**

Information about signs and symptoms associated with overdosage with XYWAV derives from reports of illicit use of GHB. Patient presentation following overdose is influenced by the dose ingested, the time since ingestion, the co-ingestion of other drugs and alcohol, and the fed or fasted state. Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even when obtunded), diaphoresis, headache, and impaired psychomotor skills have been observed. No typical pupillary changes have been described to assist in diagnosis; pupillary reactivity to light is maintained. Blurred vision has been reported. An increasing depth of coma and acidosis have been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported. Respiration may be unaffected or compromised in rate and depth. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact.

### **10.3 Recommended Treatment of Overdose**

General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with GHB overdose has been responsive to atropine intravenous administration. No reversal of the central depressant





















not take a subsequent nightly dose until at least 2.5 to 4 hours after the previous dose [*see Dosage and Administration (2.4)*].

#### Administration Instructions

Inform patients to administer XYWAV at least 2 hours after eating. Inform patients and/or caregivers of patients taking XYWAV twice nightly, that the total nightly dosage of XYWAV is divided into two doses [*see Dosage and Administration (2.4)*].

Inform patients if their nightly dose requires multiple draws. Instruct patients on how to perform the draws from the bottle.

#### Respiratory Depression and Sleep-Disordered Breathing

Inform patients that XYWAV may impair respiratory drive, especially in patients with compromised respiratory function, and may cause apnea [*see Warnings and Precautions (5.4)*].

#### Depression and Suicidality

Instruct patients and/or caregivers to contact a healthcare provider immediately if the patient develops depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or suicidal ideation [*see Warnings and Precautions (5.5)*].

#### Other Behavioral or Psychiatric Adverse Reactions

Inform patients and/or caregivers that XYWAV can cause behavioral or psychiatric adverse reactions, including confusion, anxiety, and psychosis. Instruct them to notify their healthcare provider if any of these types of symptoms occur [*see Warnings and Precautions (5.6)*].

#### Sleepwalking

Instruct patients and/or caregivers that XYWAV has been associated with sleepwalking and other behaviors during sleep, and to contact their healthcare provider if this occurs [*see Warnings and Precautions (5.7)*].

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Protected by U.S. Patent Nos. 8,591,922; 8,731,963; 8,772,306; 8,901,173; 9,050,302; 9,132,107; 9,486,426; 9,555,017; 10,195,168; 10,213,400; 10,675,258; 10,864,181; and 11,253,494.

**MEDICATION GUIDE**  
**XYWAV® (ZYE wave)**  
**(calcium, magnesium, potassium, and sodium oxybates)**  
**oral solution, CIII**

Read this Medication Guide carefully before you start or your child starts taking XYWAV, and each time you get or your child gets a refill. There may be new information. This information does not take the place of talking to your doctor about your or your child's medical condition or treatment.

**What is the most important information I should know about XYWAV?**

- XYWAV is a central nervous system (CNS) depressant. Taking XYWAV 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)
  - fainting (syncope)
  - death

Ask your doctor if you are not sure if you are, or your child is, taking a medicine listed above.

- XYWAV is a federal controlled substance (CIII). The active ingredient of XYWAV is a form of gamma-hydroxybutyrate (GHB) that is also a federal controlled substance (CI). Abuse of illegal GHB, either alone or with other CNS depressants, may cause serious medical problems, including:
  - seizure
  - trouble breathing (respiratory depression)
  - changes in alertness (drowsiness)
  - coma
  - death

Call your doctor right away if you have or your child has any of these serious side effects.

- 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.
- 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.
- Because of the risk of CNS depression, abuse, and misuse, XYWAV is available only by prescription, and filled through the central pharmacy in the XYWAV and XYREM REMS. You or your child must be enrolled in the XYWAV and XYREM REMS to receive XYWAV. For information on how to receive XYWAV, visit [www.XYWAVXYREMREMS.com](http://www.XYWAVXYREMREMS.com). Before you receive or your child receives XYWAV, your doctor or pharmacist will make sure that you understand how to take XYWAV safely and effectively. If you have any questions about XYWAV, ask your doctor or call the XYWAV and XYREM REMS at 1-866-997-3688.

**What is XYWAV?**

XYWAV is a prescription medicine used to treat:

- the following symptoms in people 7 years of age or older with narcolepsy:
  - sudden onset of weak or paralyzed muscles (cataplexy), or
  - excessive daytime sleepiness (EDS)
- idiopathic hypersomnia (IH) in adults

It is not known if XYWAV is safe and effective in children less than 7 years of age with narcolepsy.

It is not known if XYWAV is safe and effective in children with IH.

**Do not take XYWAV if you or your child:**

- takes other sleep medicines or sedatives (medicines that cause sleepiness)
- drinks alcohol
- has a rare problem called succinic semialdehyde dehydrogenase deficiency

**Before taking XYWAV, tell your doctor about all medical conditions, including if you or your child:**

- have a history of drug abuse.
- have short periods of not breathing while sleeping (sleep apnea).
- has trouble breathing or has lung problems. You or your child may have a higher chance of having serious breathing problems when taking XYWAV.
- have or had depression or has tried to harm yourself or themselves. You or your child should be watched carefully for new symptoms of depression.
- has or had behavior or other psychiatric problems such as:

|                                      |                                                               |
|--------------------------------------|---------------------------------------------------------------|
| ○ anxiety                            | ○ seeing or hearing things that are not real (hallucinations) |
| ○ feeling more suspicious (paranoia) | ○ being out of touch with reality (psychosis)                 |
| ○ acting aggressive                  | ○ agitation                                                   |

- have liver problems.
- are pregnant or plan to become pregnant. It is not known if XYWAV can harm your unborn baby.
- are breastfeeding or plan to breastfeed. XYWAV passes into breast milk. You and your doctor should decide if you or your child will take XYWAV or breastfeed.

**Tell your doctor about all the medicines you take or your child takes**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially, tell your doctor if you take or your child takes other medicines to help you or your child sleep (sedatives). Know the medicines you take or your child takes. Keep a list of them to show your doctor and pharmacist when you get or your child gets a new medicine.

**How should I take or give XYWAV?**

- Read the **Instructions for Use** at the end of this Medication Guide for detailed instructions on how to take XYWAV.
- Take or give XYWAV exactly as your doctor tells you to take or give it. Your doctor may change the dose or dosing routine if needed.
- Wait at least 2 hours after eating before taking or giving XYWAV.
- XYWAV can cause physical dependence and craving for the medicine when it is not taken as directed.
- Never change the dose without talking to your doctor.
- XYWAV can cause sleep very quickly without feeling drowsy. Some people fall asleep within 5 minutes and most fall asleep within 15 minutes. The time it takes to fall asleep might be different from night to night.
- Falling asleep quickly, including while standing or while getting up from the bed, has led to falls with injuries that have required some people to be hospitalized.
- XYWAV can be taken 1 time or 2 times a night as prescribed by your doctor.
- **If you or your child have been prescribed XYWAV 2 times a night:** divide the total nightly dose into 2 doses to be taken at bedtime and 2½ to 4 hours later.
  - **Adults:** Take the first XYWAV dose at bedtime while you are in bed and lie down immediately. Take the second XYWAV dose 2½ to 4 hours after the first XYWAV dose. You may want to set an alarm clock to make sure you wake up to take the second XYWAV dose. You should remain in bed after taking the first and second doses of XYWAV.
  - **Children:** Give the first XYWAV dose at bedtime or after an initial period of sleep, while your child is in bed and have them lie down immediately. Give the second XYWAV dose 2½ to 4 hours after the first XYWAV dose. You may want to set an alarm clock to make sure you wake up to give the second XYWAV dose. Your child should remain in bed after taking the first and second doses of XYWAV.
  - If you miss or your child misses the second XYWAV dose, skip that dose and do not take or give XYWAV again until the next night. Never take or give 2 XYWAV doses at 1 time.
- **If you have been prescribed XYWAV 1 time a night:** Take your XYWAV dose at bedtime while you are in bed and lie down immediately. You should remain in bed after taking XYWAV.
- If you take or your child takes too much XYWAV, call your doctor or go to the nearest hospital emergency room right away.

**What are the possible side effects of XYWAV?**

**XYWAV can cause serious side effects, including:**

- See “**What is the most important information I should know about XYWAV?**”
- **breathing problems, including:**
  - slower breathing.
  - trouble breathing.
  - 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 take 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
  - difficulty concentrating

**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 start or your child starts sleepwalking. Your doctor should check you or your child.

**The most common side effects of XYWAV in adults with narcolepsy or IH include:**

- nausea
- headache
- dizziness
- anxiety
- insomnia
- decreased appetite
- excessive sweating (hyperhidrosis)
- vomiting
- diarrhea
- dry mouth
- 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, sleepwalking and other abnormal sleep-related events)
- somnolence
- fatigue
- tremor

**The most common side effects of XYREM (which also contains oxybate like XYWAV) in children include:**

- nausea
- bedwetting
- vomiting
- headache
- weight decrease
- decreased appetite
- dizziness
- sleepwalking

These are not all the possible side effects of XYWAV. **For more information, ask your doctor or pharmacist.**

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

**How should I store XYWAV?**

- Store XYWAV in the original bottle prior to mixing with water. After mixing with water, store XYWAV in the pharmacy containers with child-resistant caps provided by the pharmacy.
- Store XYWAV at room temperature between 68°F to 77°F (20°C to 25°C).
- XYWAV solution prepared after mixing with water should be taken within 24 hours.
- When you have finished using a XYWAV bottle:
  - empty any unused XYWAV down the sink drain.
  - cross out the label on the XYWAV bottle with a marker.
  - place the empty XYWAV bottle in the trash.

XYWAV comes in a child-resistant package.

**Keep XYWAV and all medicines out of the reach of children and pets.**

**General information about the safe and effective use of XYWAV.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XYWAV for a condition for which it was not prescribed. Do not give XYWAV to other people, even if they have the same symptoms. It may harm them.

You can ask your pharmacist or doctor for information about XYWAV that is written for health professionals.

**What are the ingredients in XYWAV?**

**Active ingredients:** calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate (gamma-hydroxybutyrate (GHB)).

**Inactive ingredients:** purified water and sucralose

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For more information, go to [www.XYWAVXYREMREMS.com](http://www.XYWAVXYREMREMS.com) or call the XYWAV and XYREM REMS at 1-866-997-3688.

This Medication Guide has been approved by the U.S. Food and Drug Administration

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