BlueCross BlueShield of Kansas
An Independent Licensee of the Blue Cross and Blue Shield Association.

Sodium Oxybate Prior Authorization with Quantity Limit Program Summary

FDA APPROVED INDICATION AND DOSAGE[1,7]

Agent	Indications	Dose
Xyrem® (sodium oxybate) Oral solution	Treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy	**Adults:** Initially 4.5 g given orally per night in two equal divided doses. Titrate dose to effect in increments of 1.5 g per night in weekly intervals to the effective dosage range of 6 g to 9 g per night. Max dose of 9 g per night. **Pediatrics:** administered twice nightly. Initial dose, titration regimen, and max dose are based patient weight.
Xywav™ (calcium, magnesium, potassium, and sodium oxybate) Oral solution	Treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy	**Adults:** Initially 4.5 g given orally per night in two equal divided doses. Titrate dose to effect in increments of 1.5 g per night in weekly intervals to the effective dosage range of 6 g to 9 g per night. Max dose of 9 g per night. **Pediatrics:** administered twice nightly. Initial dose, titration regimen, and max dose are based patient weight.

CLINICAL RATIONALE

Narcolepsy

Narcolepsy is a chronic neurological disorder caused by the inability to regulate sleep-wake cycles. At various times throughout the day, patients with narcolepsy experience irresistible bouts of sleep and could fall asleep. If left undiagnosed or untreated, narcolepsy can interfere with psychological, social, and cognitive function and development and can inhibit academic, work, and social activities.[2] Symptoms may include excessive daytime sleepiness, cataplexy, sleep paralysis, and hallucinations. All patients diagnosed with narcolepsy will have excessive daytime sleepiness. However, sleepiness in narcolepsy is more like a "sleep attack", where an overwhelming sense of sleepiness comes on quickly.[2] There is limited evidence to advise on treatment of special populations such as children, pregnant women, and breastfeeding mothers.[6]

The American Family Physician recommends referral to a sleep clinic if narcolepsy is suspected.[3] The American Academy of Sleep Medicine indicates treatment goals should be to alleviate daytime sleepiness and produce the fullest possible return of normal function for patients at work, school, home, and socially. Guidelines also indicate modafinil is an effective treatment for EDS associated with narcolepsy.[5]

Excessive Daytime Sleepiness (EDS)
Excessive daytime sleepiness (EDS) is characterized by persistent sleepiness regardless of how much sleep an individual gets at night. In between sleep attacks, individuals have normal levels of alertness, particularly if doing activities that keep their attention. The most common causes of EDS include narcolepsy, obstructive sleep apnea, shift work disorder, sleep deprivation, medication effects, and other medical and psychiatric conditions.[6]

Pharmacological agents that may be used for treatment of EDS include modafinil, sodium oxybate, amphetamine, methamphetamine, methylphenidate, and dextroamphetamine.[5]

Cataplexy
Narcolepsy with cataplexy involves the sudden loss of voluntary muscle tone while awake. It is often triggered by sudden, strong emotions such as laughter, fear, anger, stress, or excitement. The symptoms of cataplexy may appear weeks or even years after the onset of EDS.[2] Antidepressants, such as tricyclic antidepressants (TCAs), selective serotonin reupdate inhibitors (SSRIs), and venlafaxine, may be effective to treat cataplexy.[5]

Efficacy
Xyrem[1]
The effectiveness of sodium oxybate in the treatment of EDS in narcolepsy was established in two 8-week, randomized, double-blind, placebo-controlled trials in patients with narcolepsy. Patients were randomized to one of four groups: placebo, sodium oxybate 4.5 grams per night, sodium oxybate 6 grams per night, or sodium oxybate 9 grams per night. The primary efficacy was extent of sleepiness in everyday situations (determined using Epworth Sleepiness Scale) and change in symptoms of EDS (evaluated using Clinical Global Impression of Change tool). Sodium oxybate was associated with statistically significant differences for both primary outcomes when compared to placebo.

The effectiveness of sodium oxybate in the treatment of cataplexy was established in two 4-week, randomized, double-blind, placebo-controlled trials in patients with narcolepsy. Patients were randomized to receive placebo or sodium oxybate dosed at 3 grams to 9 grams nightly. The primary efficacy endpoint for both trials was frequency of cataplexy attacks. Both trials found that dose of 6 grams to 9 grams resulted in statistically significant reduction in frequency of cataplexy attacks. The trials also found that discontinuation of sodium oxybate in patient who had been treated with it long term resulted in a significant increase in cataplexy attacks.[1]

Xywav[7]
Efficacy of Xywav for the treatment of cataplexy and excessive daytime sleepiness in adult patients with narcolepsy was established in a double-blind, placebo-controlled, randomized-withdrawal study (Study 1; NCT03030599). This study had two parts, consisting of the main study, followed by an optional 24-week open-label extension (OLE). The main study consisted of a 12-week open-label optimized treatment and titration period (OL OTTP), followed by a 2-week stable-dose period (SDP), and finally a 2-week double-blind randomized-withdrawal period (DB RWP).

Patients entering the study were taking a stable dosage of 1) Xyrem only, 2) Xyrem + another anticataplectic, 3) a non-Xyrem anticataplectic, or 4) were cataplexy-treatment naïve. The primary efficacy endpoint was the change in frequency of cataplexy attacks from the 2 weeks of the SDP to the 2 weeks of the DB RWP. The key secondary endpoint was the change in the

Epworth Sleepiness Scale (ESS) score, as a measure of reduction in EDS from the end of the SDP to the end of the DB RWP.

Patients taking stable doses of Xywav who discontinued Xywav treatment and were randomized to placebo during the DB RWP experienced a significant worsening in the average weekly number of cataplexy attacks and in ESS score, compared with patients randomized to continue treatment with Xywav.

The effectiveness of Xywav in pediatric patients is based upon a clinical study in patients treated with Xyrem.

Safety

Xyrem[1]

Xyrem carries the following contraindications:

- Use in combination with sedative hypnotics
- Use in combination with alcohol
- Use in patients with succinic semialdehyde dehydrogenase deficiency

Black box warnings include:

- Central Nervous System Depression. Sodium oxybate is a CNS depressant. Clinically significant respiratory depression occurred in adult patients treated with Xyrem at recommended doses
- Abuse and Misuse. Sodium oxybate 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

Xyrem is available only through a restricted program under a Risk Evaluation and Mitigation Strategy due to the risks of CNS depression, abuse, and misuse.

Xywav[7]

Xywav carries the following contraindications:

- Use in combination with sedative hypnotics
- Use in combination with alcohol
- Use in patients with succinic semialdehyde dehydrogenase deficiency

Black box warnings include:

- 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
- 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

Xywav is available only through a restricted program under a Risk Evaluation and Mitigation Strategy due to the risks of CNS depression, abuse, and misuse.

REFERENCES

1. Xyrem prescribing information. Jazz Pharmaceuticals, Inc. October 2018.
2. National Institute of Neurological Disorders and Stroke. Narcolepsy Fact Sheet. NIH Publication No. 17-1637. Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Narcolepsy-Fact-Sheet. Last updated August 2019. Accessed September 2019.
3. Ramar, Kannan MD and Olson, Eric MD. Management of Common Sleep Disorders. *Am Fam Physician*. 2013 Aug 15; 88(4): 231-238.

4. Morgenthaler, Thomas MD, et al. Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin. The American Academy of Sleep Medicine Report. SLEEP. 2007; Vol. 30 (12).
5. Krahn, Lois MD, et al. Quality Measures for the Care of Patients with Narcolepsy. *Journal of Clinical Sleep Medicine*. 2015; Vol. 11(3).
6. Pagel J. Excessive daytime sleepiness. *Am Fam Physician*. 2009;79(5): 391-395.
7. Xywav prescribing information. Jazz Pharmaceuticals, Inc. July 2020.

Sodium Oxybate Prior Authorization with Quantity Limit

TARGET AGENT
Xyrem® (sodium oxybate)
Xywav™ (calcium, magnesium, potassium, and sodium oxybate)

Brand (generic)	GPI	Multisource Code	Quantity Limit
Xyrem (sodium oxybate)			
500 mg/mL oral solution	62450060202020	M, N, O, or Y	9 gm/night (540mL/30 days)
Xywav (calcium, magnesium, potassium, and sodium oxybate)			
500 mg/mL oral solution	62459904202020	M, N, O, or Y	9 gm/night (540mL/30 days)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Evaluation
Target Agent will be approved when ALL of the following are met:

1. The patient is 7 years of age or over
   AND
2. ONE of the following:
   A. The patient has a diagnosis of narcolepsy with cataplexy **AND** ONE of the following:
      i. The patient has tried and had an inadequate response to a tricyclic antidepressant [TCA (e.g., amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, protriptyline)], selective serotonin reuptake inhibitor [SSRIs (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)], or venlafaxine
      OR
      ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL prerequisite agents

   OR

   B. The patient has a diagnosis of narcolepsy with excessive daytime sleepiness **AND** BOTH of the following:
      i. ONE of the following:
         a. The patient has tried and had an inadequate response to modafinil or armodafinil
         OR
         b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to BOTH modafinil AND armodafinil

      AND

      ii. ONE of the following:
         a. The patient has tried and had an inadequate response to a standard stimulant agent (i.e., amphetamine/dextroamphetamine, dextroamphetamine, methylphenidate)
         OR
         b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity, to ALL standard stimulant agents

   OR

C. The patient has another FDA approved indication for the requested agent

AND

3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., sleep specialist, neurologist, psychiatrist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

4. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

5. ONE of the following
   A. The requested quantity (dose) does NOT exceed the program quantity limit

   OR

   B. ALL of the following
      i. The requested quantity (dose) is greater than the program quantity limit

      AND

      ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication

      AND

      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 12 months

FDA Labeled Contraindications

Agent	Contraindications
Xyrem (sodium oxybate)	• Succinic semialdehyde dehydrogenase deficiency • In combination with sedative hypnotics or alcohol*
Xywav (calcium, magnesium, potassium, and sodium oxybate)	• Succinic semialdehyde dehydrogenase deficiency • In combination with sedative hypnotics or alcohol*

*Examples of sedative hypnotics: benzodiazepines, butabarbital, eszopiclone, Rozerem (ramelteon), Silenor (doxepin), zaleplon, zolpidem

