09-J1000-06

Original Effective Date: 06/15/09

Reviewed: 04/10/24

Revised: 05/15/24

Subject: Oxybate Oral Solutions (Sodium Oxybate, Xyrem®, and Xywav®) and Suspension (Lumryz®)

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DESCRIPTION:

Sodium oxybate is the sodium salt of gamma hydroxybutyric acid (GHB), a naturally occurring central nervous system transmitter with sedative and anesthetic properties. Sodium oxybate oral solution (Xyrem) was first approved by the FDA in July 2002 for the treatment of cataplexy attacks in patients with narcolepsy. In November 2005 the indication was expanded to include the treatment of excessive daytime sleepiness in patients with narcolepsy. In October 2018, the FDA approved an expanded use of sodium oxybate oral solution for the treatment of cataplexy or excessive daytime sleepiness to pediatric patients 7 years of age and older with narcolepsy. In July 2020, a lower-sodium alternative [Xywav; calcium, magnesium, potassium, and sodium oxybates (a.k.a., mixed oxybate salts) oral solution] was approved by the FDA for the same indications as sodium oxybate oral solution. Sodium oxybate oral solution contains 1,640 mg of sodium in the maximum nightly dose of 9 grams, while the mixed oxybate salts oral solution contains 131 mg of sodium per 9 grams (92% less). In August 2021, Xywav was approved for a new indication for the treatment of idiopathic hypersomnia (IH) in adults. Xywav is the first FDA-approved treatment for IH; however, various stimulants (e.g., modafinil) have been used historically with success for the treatment of the excessive daytime sleepiness associated with IH. In January 2023, the first authorized generic of Xyrem, Sodium Oxybate Oral Solution, distributed by Hikma Pharmaceuticals entered the US marketplace. In July 2023, a second authorized generic of Xyrem, Sodium Oxybate Oral Solution, distributed by Amneal Pharmaceuticals, was launched. Like other authorized generics, Sodium Oxybate Oral Solution is the exact same drug product as brand Xyrem but with a different name on the drug label. Besides the drug name, the indications and the rest of the clinical labeling are identical. In June 2023, an extended-released sodium oxybate oral suspension (Lumryz) was approved by the FDA for the treatment of cataplexy or excessive daytime sleepiness (EDS)

in adults with narcolepsy. The advantage of the extended-released oral suspension is that it only requires a single dose prior to bedtime, while the oral solutions require a second dose to be taken 2.5 to 4 hours after the first dose. Of note, Lumryz is not FDA-approved for the treatment of pediatric patients 7 years of age and older with narcolepsy nor for the treatment of IH.

Oxybate products differ from modafinil and other stimulant treatments for narcolepsy in that they significantly decrease cataplexy episodes in addition to excessive daytime sleepiness (EDS); the drug is frequently prescribed along with stimulant therapies for narcolepsy. A mean decrease in the total number of weekly cataplexy episodes of nearly 70% has been reported in clinical trials. Cataplexy is a debilitating symptom characterized by loss of muscle control in response to strong emotions such as laughter, anger, or surprise and if severe can cause a person to collapse during waking hours.

Jazz Pharmaceuticals markets both sodium oxybate oral solution under the trade name Xyrem and calcium, magnesium, potassium, and sodium oxybates oral solution under the trade name Xywav. Amneal Pharmaceuticals and Hikma Pharmaceuticals are distributors of Xyrem authorized generics, and Avadel CNS Pharmaceuticals is the distributor of Lumryz. The drugs are only available from certified specialty pharmacies to approved practitioners as part of either the Xywav and Xyrem REMS Program or the Lumryz REMS Program. New prescribers of Lumryz, Sodium Oxybate Oral Solution, Xyrem or Xywav, and patients, must register as part of the REMS program.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of Sodium Oxybate oral solution (authorized generics of Xyrem), sodium oxybate oral solution (Xyrem), sodium oxybate extended-release oral suspension (Lumryz), or calcium, magnesium, potassium, and sodium oxybate oral solution (Xywav) **meets the definition of medical necessity** when **ALL** of the following criteria are met (“1” to “8”):

1. The member meets the following age requirement based on the condition being treated:
    a. Idiopathic hypersomnia - 18 years of age or older
    b. Type 1 or Type 2 narcolepsy - 7 years of age or older
2. The dosage does not exceed the following based on the member’s medication, condition, age, and weight:
    a. Idiopathic hypersomnia
        i. Once nightly dosing of oral solution – 6 grams/day (i.e., 12 mL/day or 360 mL per 30 days)

ii. Twice nightly dosing of oral solution, or once nightly dosing of extended-release oral suspension - 9 grams/day [i.e., 18 mL/day (540 mL per 30 days) for the oral solution, or one 9-gram packet/day (30 packets per 30 days) for the extended-release oral suspension]

b. Type 1 or Type 2 narcolepsy

i. Adult member (18 years of age or greater) - 9 grams/day [i.e., 18 mL/day (or 540 mL per 30 days) for the oral solution, or one 9-gram packet/day (30 packets per 30 days) for the extended-release oral suspension]

ii. Pediatric members (7 to 17 years of age)

- Less than 30 kg - 6 grams/day [i.e., 12 mL/day (or 360 mL per 30 days) for the oral solution, or one 6-gram packet/day (30 packets per 30 days) for the extended-release oral suspension]
- 30 kg to less than 45 kg - 7.5 grams/day [i.e., 15 mL/day (or 450 mL per 30 days) for the oral solution, or one 7.5-gram packet/day (30 packets per 30 days) for the extended-release oral suspension]
- 45 kg or greater - 9 grams/day [i.e., 18 mL/day (or 540 mL per 30 days) for the oral solution, or one 9-gram packet/day (30 packets per 30 days) for the extended-release oral suspension]

3. Treatment is prescribed by a neurologist, psychiatrist, pulmonologist, or sleep medicine specialist
4. Member is **NOT** being treated with any sedative hypnotic agents (e.g., benzodiazepines, barbiturates, zolpidem) as evidenced by paid claims history within the past 90 days, **OR** the provider attests that all hypnotic agents will be discontinued before initiating treatment with sodium oxybate or calcium, magnesium, potassium, and sodium oxybate
5. The requested agent will **NOT** be started in combination with pitolisant (Wakix)
6. The member will **NOT** be using the requested agent in combination with another oxybate agent
7. Member does not and will not consume any alcohol concomitantly with sodium oxybate or calcium, magnesium, potassium, and sodium oxybate
8. For brand Xyrem and Sodium Oxybate oral solution by Amneal Pharmaceuticals (the second approved authorized generic of Xyrem) **ONLY** - the member has tried and had intolerable adverse effect(s) or hypersensitivity to Sodium Oxybate oral solution by Hikma Pharmaceuticals (the first approved authorized generic of Xyrem) that is not expected to occur with brand Xyrem or Sodium Oxybate oral solution by Amneal Pharmaceuticals, **AND ALL** of the following are submitted ("a", "b", and "c"):

a. The specific intolerance(s) or hypersensitivity to Sodium Oxybate oral solution by Hikma Pharmaceuticals, and rationale for using either brand Xyrem or Sodium Oxybate oral solution by Amneal Pharmaceuticals

b. Completed MedWatch reporting form (FDA Form 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda

a. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf

9. Member has a diagnosis of **ONE** of the following central disorders of hypersomnolence ("a", "b", or "c"), and **ALL** condition-specific criteria are met:

a. Idiopathic hypersomnia

   i. Member has experienced daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months

   ii. Cataplexy is absent

   iii. Member's diagnosis has been confirmed by appropriately conducted overnight polysomnography (PSG) followed by multiple sleep latency test (MSLT) the next day - *documentation and results of both tests must be submitted and show both of the following*:

   - Fewer than two sleep onset REM periods (SOREMPs) on the MSLT, **OR** no SOREMPs if the REM latency of the preceding PSG was less than or equal to 15 minutes
   - **EITHER** of the following:
     - Mean sleep latency of less than or equal to 8 minutes on the MSLT
     - Total 24-hour sleep time is ≥660 minutes (11 hours) as measured by either 24-hour PSG monitoring (performed after correction of chronic sleep deprivation) OR wrist actigraphy in association with a sleep log (averaged over at least 7 days with unrestricted sleep) - *documentation and results of either test must be submitted*

   iv. Insufficient sleep syndrome has been ruled out as determined by lack of improvement of sleepiness after an adequate trial of increased nocturnal time in bed (preferably confirmed by at least a week of wrist actigraphy)

   v. The hypersomnolence and/or MSLT findings are not explained more clearly by another sleep disorder, other medical or psychiatric disorder, or use of drugs or medications

   vi. Member has had an inadequate therapeutic response with a trial of at least 8 weeks, had persistent intolerable adverse effects, or has a contraindication to treatment of at least **ONE** medication from **BOTH** of the following groups (the specific adverse effect and/or contraindication must be specified for each drug):

   - Group 1: modafinil (Provigil) or armodafinil (Nuvigil)
   - Group 2: an amphetamine-based stimulant or a methylphenidate-based stimulant

b. Type 1 narcolepsy (narcolepsy **with** cataplexy)

   i. Member has experienced daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months

   ii. Member has clear historic evidence of cataplexy

   iii. Member's diagnosis has been confirmed by appropriately conducted overnight PSG followed by MSLT the next day* - *documentation and results of both tests must be submitted and show both the following*:

   - Two or more SOREMPs on the MSLT. A SOREMP, within 15 minutes of sleep onset, on the preceding overnight PSG may replace one of the SOREMPs on the MSLT.
   - Mean sleep latency of less than or equal to 8 minutes

   **PSG with MSLT is not required if the member has laboratory confirmed hypocretin-1 deficiency defined as a cerebrospinal fluid (CSF) hypocretin-1 level less than or equal to 110*

pg/mL or less than one-third of the mean values obtain in normal subjects with the same standardized assay – laboratory documentation must be submitted

c. Type 2 narcolepsy (narcolepsy **without** cataplexy)

i. Member has experienced daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months

ii. Cataplexy is absent

iii. Member's diagnosis has been confirmed by appropriately conducted overnight PSG followed by MSLT the next day - *documentation and results of both tests must be submitted and show both of the following*:

- Two or more SOREMPs on the MSLT. A SOREMP, within 15 minutes of sleep onset, on the preceding overnight PSG may replace one of the SOREMPs on the MSLT.
- Mean sleep latency of less than or equal to 8 minutes

iv. The hypersomnolence and/or MSLT findings are not explained more clearly by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal

v. Member has had an inadequate therapeutic response with a trial of at least 8 weeks, had persistent intolerable adverse effects, or has a contraindication to treatment of at least **ONE** medication from **BOTH** of the following groups (the specific adverse effect and/or contraindication must be specified for each drug):

- Group 1: modafinil (Provigil) or armodafinil (Nuvigil)
- Group 2: an amphetamine-based stimulant or a methylphenidate-based stimulant

Duration of approval: 3 months

Continuation of Sodium Oxybate oral solution (authorized generics of Xyrem), sodium oxybate oral solution (Xyrem), sodium oxybate extended-release oral suspension (Lumryz), or calcium, magnesium, potassium, and sodium oxybate oral solution (Xywav) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "9"):

1. An authorization or reauthorization for **EITHER** sodium oxybate oral solution; sodium oxybate extended-release oral suspension; or calcium, magnesium, potassium, and sodium oxybate oral solution has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of idiopathic hypersomnia or Type 1 or 2 narcolepsy (if another health plan, documentation of a health plan-paid claim for either sodium oxybate oral solution; sodium oxybate extended-release oral suspension; or calcium, magnesium, potassium, and sodium oxybate oral solution during the 90 days immediately before the request must be submitted), **OR** the member previously met **ALL** indication-specific initiation criteria
2. Treatment is prescribed by a neurologist, psychiatrist, pulmonologist, or sleep medicine specialist
3. Member is not being treated with any sedative hypnotic agents (e.g., benzodiazepines, barbiturates, zolpidem) as evidenced by paid claims history within the past 90 days
4. The requested agent will **NOT** be used in combination with pitolisant (Wakix), **UNLESS** the member has Type 1 narcolepsy with a suboptimal response to either sodium oxybate **OR** calcium,

magnesium, potassium, and sodium oxybate monotherapy – details of the member's treatment history and justification for using combination therapy must be submitted

5. The member will **NOT** be using the requested agent in combination with another oxybate agent
6. Member is **NOT** consuming any alcohol concomitantly with sodium oxybate or calcium, magnesium, potassium, and sodium oxybate
7. For brand Xyrem and Sodium Oxybate oral solution by Amneal Pharmaceuticals (the second approved authorized generic of Xyrem) **ONLY** - the member has tried and had intolerable adverse effect(s) or hypersensitivity to Sodium Oxybate oral solution by Hikma Pharmaceuticals (the first approved authorized generic of Xyrem) that is not expected to occur with brand Xyrem or Sodium Oxybate oral solution by Amneal Pharmaceuticals, **AND ALL** of the following are submitted ("a", "b", and "c"):
    a. The specific intolerance(s) or hypersensitivity to Sodium Oxybate oral solution by Hikma Pharmaceuticals, and rationale for using brand Xyrem or Sodium Oxybate oral solution by Amneal Pharmaceuticals,
    b. Completed MedWatch reporting form (FDA Form 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda
    c. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf
8. The dosage does not exceed the following based on member's medication, condition, age and weight:
    a. Idiopathic hypersomnia
        i. Once nightly dosing of oral solution – 6 grams/day (i.e., 12 mL/day or 360 mL per 30 days)
        ii. Twice nightly dosing of oral solution, or once nightly dosing of extended-release oral suspension - 9 grams/day [i.e., 18 mL/day (540 mL per 30 days) for the oral solution, or one 9-gram packet/day (30 packets per 30 days) for the extended-release oral suspension]
    b. Type 1 or Type 2 narcolepsy
        i. Adult member (18 years of age or greater) - 9 grams/day [i.e., 18 mL/day (or 540 mL per 30 days) for the oral solution, or one 9-gram packet/day (30 packets per 30 days) for the extended-release oral suspension]
        ii. Pediatric members (less than 18 years of age)
            - Less than 30 kg - 6 grams/day [i.e., 12 mL/day (or 360 mL per 30 days) for the oral solution, or one 6-gram packet/day (30 packets per 30 days) for the extended-release oral suspension]
            - 30 kg to less than 45 kg - 7.5 grams/day [i.e., 15 mL/day (or 450 mL per 30 days) for the oral solution, or one 7.5-gram packet/day (30 packets per 30 days) for the extended-release oral suspension]
            - 45 kg or greater - 9 grams/day [i.e., 18 mL/day (or 540 mL per 30 days) for the oral solution, or one 9-gram packet/day (30 packets per 30 days) for the extended-release oral suspension]

9. The member has a beneficial response to therapy as indicated by either of the following (corresponding to the condition being treated):
    a. Idiopathic hypersomnia – member has had a reduction in symptoms of excessive daytime sleepiness as compared to before treatment with sodium oxybate or calcium, magnesium, potassium, and sodium oxybate – medical record documentation must be provided
    b. Type 1 narcolepsy (narcolepsy with cataplexy) - member has had a reduction in frequency of cataplexy attacks or symptoms of excessive daytime sleepiness as compared to before treatment with sodium oxybate or calcium, magnesium, potassium, and sodium oxybate – medical record documentation must be provided
    c. Type 2 narcolepsy (narcolepsy **without** cataplexy) - member has had a reduction in symptoms of excessive daytime sleepiness as compared to before treatment with sodium oxybate or calcium, magnesium, potassium, and sodium oxybate – medical record documentation must be provided

Duration of approval: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

Sodium Oxybate oral solution, Xyrem, and Xyvaw

Sodium Oxybate Oral Solution, sodium oxybate (Xyrem), and calcium, magnesium, potassium, and sodium oxybate (Xywav) are indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. Xywav is also indicated for the treatment of idiopathic hypersomnia (IH) in adults. For the treatment of narcolepsy in adults, the recommended starting dosage is 4.5 g per night administered orally, divided into two doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later. Increase the dosage by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dosage range of 6 g to 9 g per night orally. Doses higher than 9 g per night have not been studied and should not ordinarily be administered. For pediatric patients, the recommend dosage is based on weight. Refer to the package labeling for the specific dosage recommendations. For the treatment of IH in adults, the Xywav dosage can be administered as a twice nightly or once nightly regimen. Refer to the package labeling for the specific dosage recommendations and titrations. The maximum dosage is 9 g for the twice nightly regimen and 6 g for the once nightly regimen.

Take the first dose of Sodium Oxybate Oral Solution, Xyrem or Xywav at least 2 hours after eating. Prepare both doses prior to bedtime. Prior to ingestion, each dose should be diluted with approximately ¼ cup (approximately 60 mL) of water in the empty pharmacy containers provided. Patients should take both doses while in bed and lie down immediately after dosing as Sodium Oxybate Oral Solution, Xyrem or Xywav may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking, and will usually fall asleep within 15 minutes, though the time it takes

any individual patient to fall asleep may vary from night to night. Patients should remain in bed following ingestion of the first and second doses and should not take the second dose until 2.5 to 4 hours after the first dose. Patients may need to set an alarm to awaken for the second dose. Rarely, patients may take up to 2 hours to fall asleep. If the second dose is missed, that dose should be skipped and Sodium Oxybate Oral Solution, Xyrem or Xywav should not be taken again until the next night. Both doses should never be taken at one time.

For patients transitioning from Xyrem or Sodium Oxybate Oral Solution to Xywav, on the first night of dosing with Xywav, initiate treatment at the same dose (gram for gram) and regimen as Xyrem or Sodium Oxybate Oral Solution. Titrate as needed based on efficacy and tolerability.

Dosage Adjustments

- Renal Impairment - no pharmacokinetic studies in patients with renal impairment have been conducted, and specific guidelines for dosage adjustments in renal impairment are not available. It appears that no dosage adjustments are needed.
- 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
- Drug Interactions - pharmacokinetic and pharmacodynamic interactions have been observed when Sodium Oxybate Oral Solution, Xyrem or Xywav is co-administered with divalproex sodium. For patients already stabilized on Sodium Oxybate Oral Solution, Xyrem or Xywav, it is recommended that addition of divalproex sodium should be accompanied by an initial reduction in the nightly dose of Sodium Oxybate Oral Solution, Xyrem or Xywav by at least 20%. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting Sodium Oxybate Oral Solution, Xyrem or Xywav dose when introducing Sodium Oxybate Oral Solution, Xyrem or Xywav. Prescribers should monitor patient response and adjust dose accordingly.

Lumryz

Lumryz is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy. The recommended starting dosage is 4.5 grams once per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the recommended dosage range of 6 g to 9 g once per night orally. The dosage may be gradually titrated based on efficacy and tolerability. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

Lumryz is taken orally as a single dose at bedtime. Prepare the dose prior to bedtime. Prior to ingestion, the dose should be suspended in approximately 1/3 cup (approximately 80 mL) of water in the mixing cup provided. Do not use hot water. After mixing, consume within 30 minutes. Take at least 2 hours after eating. Patients should take while in bed and lie down immediately after dosing as Lumryz may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night. Patients should remain in bed following ingestion.

Patients who are currently being treated with immediate-release sodium oxybate may be switched to Lumryz at the nearest equivalent dosage in grams per night (e.g., 7.5 g sodium oxybate divided into two 3.75 g doses per night to 7.5 g Lumryz once per night).

Dosage Adjustments

- Renal Impairment - no pharmacokinetic studies in patients with renal impairment have been conducted, and specific guidelines for dosage adjustments in renal impairment are not available. It appears that no dosage adjustments are needed.
- Hepatic Impairment - Because of an increase in exposure to Lumryz, Lumryz should not be initiated in patients with hepatic impairment because appropriate dosage adjustments for initiation cannot be made with the available dosage strengths. Patients with hepatic impairment who have been titrated to a maintenance dosage of another oxybate product can be switched to Lumryz if the appropriate dosage strength is available.
- Drug Interactions - A drug interaction study in healthy adults (age 18 to 55 years) was conducted with Lumryz and divalproex sodium. Co-administration of a single dose of Lumryz (6 g) with divalproex sodium ER at steady state resulted in an approximate 18% increase in AUC (90% CI ratio range of 112% to 123%), which is not expected to be clinically meaningful, while Cmax was comparable. A single dose of Lumryz (6 g) did not appear to affect the pharmacokinetics of divalproex sodium. However, a pharmacodynamic interaction between LUMRYZ and divalproex sodium, a sedative antiepileptic drug, cannot be ruled out.

Drug Availability

- Lumryz - Each carton contains either 7 or 30 packets of Lumryz, a mixing cup, Prescribing Information and Medication Guide, and Instructions for Use. Dose packets contain a single dose of Lumryz provided in 4.5 g, 6 g, 7.5 g, or 9 g doses. Lumryz should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Suspensions should be consumed within 30 minutes. Lumryz comes in a child-resistant package. Keep Lumryz out of the reach of children and pets.
- Sodium Oxybate Oral Solution (authorized generics by Amneal and Hikma Pharmaceuticals) - Each prescription includes a carton containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle-adaptor, an oral measuring device (plastic syringe), and a Medication Guide. The bottle contains 180 mL of sodium oxybate oral solution at a concentration of 0.5 g per mL (90 g per bottle). Each bottle of sodium oxybate is provided with a child-resistant cap. The pharmacy provides 2 dosing cups with child-resistant caps with each sodium oxybate shipment. Care should be taken to prevent access to this medication by children and pets.
- Xyrem - Each prescription includes a carton containing one bottle of Xyrem, a press-in-bottle-adaptor, an oral measuring device (plastic syringe), and a Medication Guide. The bottle contains 180 mL of Xyrem oral solution at a concentration of 0.5 g per mL (90 g per bottle). Each bottle of sodium oxybate is provided with a child-resistant cap. The pharmacy provides 2 dosing cups with child-resistant caps with each sodium oxybate shipment. Care should be taken to prevent access to this medication by children and pets.
- Xywav - Each prescription includes a carton containing one bottle of Xywav, a press-in-bottle-adaptor, an oral measuring device (plastic syringe), and a Medication Guide. The bottle contains 180 mL of Xywav oral solution at a concentration of 0.5 g per mL (90 g per bottle). Each bottle of calcium, magnesium, potassium, and sodium oxybate is provided with a child-resistant cap. The pharmacy provides 2 dosing cups with child-resistant caps with each calcium, magnesium, potassium, and sodium oxybate shipment. Care should be taken to prevent access to this medication by children and pets.

PRECAUTIONS:

Boxed Warnings

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION AND ABUSE AND MISUSE

Central Nervous System Depression

- Lumryz\Sodium Oxybate\Xyrem\Xywav is a CNS depressant. Clinically significant respiratory depression and obtundation may occur in patients treated with Lumryz\Sodium Oxybate\Xyrem\Xywav at recommended doses. Many patients who received Lumryz\Sodium Oxybate\Xyrem\Xywav during clinical trials in narcolepsy (and idiopathic hypersomnia for Xywav) were receiving central nervous system stimulants.

Abuse and Misuse

- The active moiety of Lumryz\Sodium Oxybate\Xyrem\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, Lumryz\Sodium Oxybate\Xyrem\Xywav is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the LUMRYZ REMS or XYWAV and XYREM REMS.

Contraindications:

- Combination with sedative hypnotics
- Combination with alcohol
- Members with succinic semialdehyde dehydrogenase deficiency

Warnings/Precautions

- **Central Nervous System Depression**

Sodium oxybate and calcium, magnesium, potassium, and sodium oxybate are central nervous system (CNS) depressants. Alcohol and sedative hypnotics are contraindicated in members who are using sodium oxybate or calcium, magnesium, potassium, and sodium oxybate. The concurrent use of sodium oxybate or calcium, magnesium, potassium, and sodium oxybate with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, 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 sodium oxybate or calcium, magnesium, potassium, and sodium oxybate is required, dose reduction or discontinuation of one or more CNS depressants (including sodium oxybate or calcium, magnesium, potassium, and sodium oxybate) should be considered. In addition, if short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with sodium oxybate or calcium, magnesium, potassium, and sodium oxybate should be considered.

Healthcare providers should caution members about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that sodium oxybate or calcium, magnesium, potassium, and sodium oxybate does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Members should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking the second nightly dose of sodium oxybate or calcium, magnesium, potassium, and sodium oxybate. Members should be queried about CNS depression-related events upon initiation of sodium oxybate or calcium, magnesium, potassium, and sodium oxybate therapy and periodically thereafter.

- **Abuse and Misuse**

Sodium oxybate and calcium, magnesium, potassium, and sodium oxybate are Schedule III controlled substances. The active ingredient of sodium oxybate and calcium, magnesium, potassium, and sodium oxybate, or gamma-hydroxybutyrate (GHB), is 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 sodium oxybate or calcium, magnesium, potassium, and sodium oxybate, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim). Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate members for a history of drug abuse and follow such members closely, observing them for signs of misuse or abuse of GHB (e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy).

- **Xywav and Xyrem REMS Program**

Lumryz, Sodium Oxybate, Xyrem and Xywav are available only through a restricted distribution program called the LUMRYZ REMS and XYWAV and XYREM REMS because of the risks of central nervous system depression and abuse and misuse. Notable requirements of the LUMRYZ REMS and XYWAV and XYREM REMS include the following:

- Healthcare Providers who prescribe Lumryz, Sodium Oxybate, Xyrem or Xywav are specially certified
- Lumryz, Sodium Oxybate, Xyrem or Xywav will be dispensed only by the central pharmacy that is specially certified
- Lumryz, Sodium Oxybate, Xyrem or 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.LUMRYZREMS.com or 1-877-453-029, or at www.XYWAVXYREMREMS.com or 1-866-997-3688.

- **Respiratory Depression and Sleep-Disordered Breathing**

Sodium oxybate and calcium, magnesium, potassium, and sodium oxybate may impair respiratory drive, especially in members with compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported.

Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese members and in postmenopausal women not on hormone replacement therapy as well as among members with narcolepsy.

- **Depression and Suicidality**

In an adult clinical trial in patients with narcolepsy administered Lumryz, there were no suicide attempts, but one patient developed suicidal ideation at the 9 g dose In clinical trials in members with narcolepsy (n=781) administered immediate-release sodium oxybate, there were two suicides and two attempted suicides in sodium oxybate-treated members, including three members with a previous history of depressive psychiatric disorder. Of the two suicides, one member used immediate-release sodium oxybate in conjunction with other drugs. Immediate-release sodium oxybate was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 immediate-release sodium oxybate-treated members, with four members (< 1%) discontinuing because of depression. In most cases, no change in sodium oxybate treatment was required.

In a controlled trial in adults with narcolepsy administered Lumryz where patients were titrated from 4.5 g to 9 g per night, the incidences of depression were 0% at 4.5 g, 1% at 6 g, 1.1% at 7.5 g, and 1.3% at 9 g. In a controlled trial, with members randomized to fixed doses of 3 g, 6 g, or 9 g per night immediate-release sodium oxybate or placebo, there was a single event of depression at the 3 g per night dose. In another controlled trial, with members titrated from an initial 4.5 g per night starting dose, the incidences of depression were 1 (1.7%), 1 (1.5%), 2 (3.2%), and 2 (3.6%) for the placebo, 4.5 g, 6 g, and 9 g per night doses, respectively.

The emergence of depression in members treated with sodium oxybate requires careful and immediate evaluation. Members with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking sodium oxybate.

- **Other Behavioral or Psychiatric Adverse Reactions**

During clinical trials in narcolepsy, 3% of 781 members treated with immediate-release sodium oxybate experienced confusion, with incidence generally increasing with dose. The rate was 2% of 107 patient for Lumryz.

Less than 1% of members discontinued the immediate-release sodium oxybate because of confusion. No patients treated with Lumryz discontinued treatment because of confusion. Confusion was reported at all recommended doses of immediate-release sodium oxybate from 6 g to 9 g per night. In a controlled trial where members were randomized to fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose-response relationship for confusion was demonstrated, with 17% of members at 9 g per night experiencing confusion. In all cases in that controlled trial, the confusion resolved soon after termination of treatment. In one trial where immediate-release sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in one member at the 9 g per night dose. In the majority of cases in all clinical trials in narcolepsy, confusion resolved either soon after termination of

dosing or with continued treatment. However, members treated with sodium oxybate who become confused should be evaluated fully, and appropriate intervention considered on an individual basis.

Anxiety occurred in 7.5% of 107 patients treated with Lumryz in the adult trial in patients with narcolepsy. Anxiety occurred in 5.8% of the 874 members receiving immediate-release sodium oxybate in clinical trials in another population. The emergence of or increase in anxiety in members taking sodium oxybate should be carefully monitored.

Other neuropsychiatric reactions reported in sodium oxybate clinical trials included hallucinations, paranoia, psychosis, and agitation. The emergence of thought disorders and/or behavior abnormalities requires careful and immediate evaluation.

- **Parasomnias**

Sleepwalking, defined as confused behavior occurring at night and at times associated with wandering, was reported in 6% of 781 members with narcolepsy treated with immediate-release sodium oxybate in controlled and long-term open-label studies, with < 1% of members discontinuing due to sleepwalking. The rate was 3% of 107 patient for Lumryz. Rates of sleepwalking were similar for members taking placebo and members taking immediate-release sodium oxybate in controlled trials It is unclear if some or all of the reported sleepwalking episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Five instances of significant injury or potential injury were associated with sleepwalking during a clinical trial of immediate-release sodium oxybate in members with narcolepsy.

Parasomnias including sleepwalking have been reported in post-marketing experience with immediate-release sodium oxybate. Therefore, episodes of sleepwalking should be fully evaluated, and appropriate interventions considered.

- **Use in Members Sensitive to High Sodium Intake (Lumryz, Xyrem and Sodium Oxybate Oral Solution ONLY)**

Sodium oxybate has a high salt content. In members sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment) consider the amount of daily sodium intake in each dose of sodium oxybate. The table below provides the approximate sodium content per sodium oxybate dose.

Approximate Sodium Content per Total Nightly Dose of Sodium oxybate (g = grams)

Sodium oxybate Dose	Sodium Content/Total Nightly Exposure
3 g per night	550 mg
4.5 g per night	820 mg
6 g per night	1,100 mg
7.5 g per night	1,400 mg
9 g per night	1,640 mg

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, not otherwise specified

ICD-10 Diagnosis Codes That Support Medical Necessity

G47.11	Idiopathic hypersomnia with long sleep time
G47.12	Idiopathic hypersomnia without long sleep time
G47.411	Narcolepsy, with cataplexy
G47.419	Narcolepsy, without cataplexy

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

Cataplexy: a condition, often associated with narcolepsy; marked by abrupt attacks of muscular weakness and hypotonia triggered by an emotional stimulus, such as mirth, anger, or fear.

Excessive Daytime Sleepiness: This refers to a condition where a person feels very drowsy during the day, even after getting adequate nighttime rest, and has a tendency to fall asleep or requires extra effort to avoid sleeping in inappropriate situations, such as at work or driving. This condition is also defined as a score greater than 10 on the Epworth Sleepiness Scale.

Epworth Sleepiness Scale: A short, self-administered questionnaire designed to measure sleep propensity in a simple, standardized way (only 8 questions on a total scale of 0 to 24)

Multiple Sleep Latency Test (MSLT): This is a test used in conjunction with polysomnography (PSG) to determine the presence and severity of sleepiness. During this test, the subject is given the opportunity to take naps at specified time intervals. The test consists of four or five nap opportunities at two-hour intervals. Each nap opportunity is 20 minutes in duration. Individuals with excessive daytime sleepiness may fall asleep almost immediately, while those without excessive sleepiness may not fall asleep at all. Severe sleepiness is usually associated with an MSLT mean sleep latency of less than 5 minutes. The presence of sleep onset rapid eye movement (REM) and the number of naps in which sleep REM occurs are also determined.

Narcolepsy: recurrent, uncontrollable, brief episodes of sleep often associated with hallucinations just beforehand or just afterward.

Parasomnias: a category of sleep disorders that involve abnormal and unnatural movements, behaviors, emotions, perceptions, and dreams that occur while falling asleep, sleeping, between sleep stages, or during arousal from sleep.

Type 1 Narcolepsy: narcolepsy with cataplexy in which patients have very low CSF hypocretin/orexin levels resulting from extensive loss of hypothalamic neurons

Type 2 Narcolepsy: narcolepsy without cataplexy in which patients have normal or mildly decrease CSF hypocretin/orexin levels

RELATED GUIDELINES:

Pitolisant (Wakix) Tablet, 09-J3000-52
Sleep Testing, 01-95828-01

OTHER:

None applicable.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/10/24.

GUIDELINE UPDATE INFORMATION:

06/15/09	New Medical Coverage Guideline.
04/15/10	Review and revision to guideline; consisting of updating precautions and references.
05/15/10	Revision to guideline; consisting of modifying coverage criteria.
04/15/11	Review and revision to guideline; consisting of updating references.
04/15/12	Review and revision to guideline; consisting of adding maximum dose to position statement and updating references.
03/15/13	Review and revision to guideline; consisting of updating description, position statement, precautions, definitions and references.
05/11/14	Revision: Program Exceptions section updated.
10/15/14	Review and revision to guideline; consisting of position statement.
05/15/15	Revision to guidelines; consisting of updating the position statement, addition of definitions, addition of coding information, and updating and addition of references.
10/15/15	Revision to guidelines; consisting of updating the position statement and references.
11/01/15	Revision: ICD-9 Codes deleted.
05/15/16	Review and revision to guideline consisting of updating the description section, position statement, definitions, related guidelines, and references.
05/15/17	Review and revision to guideline consisting of updating the description section, position statement, dosage/administration, precautions, and references.
05/15/18	Review and revision to guideline consisting of updating the position statement and references.
05/15/19	Review and revision to guideline consisting of updating the description section, position statement, dosage/administration, precautions, and references.
01/01/20	Revision to guideline consisting of updating the position statement.
05/15/20	Review and revision to guideline consisting of updating the related guidelines and references.

12/15/20	Revision to guideline consisting of updating the description section, position statement, dosage/administration, precautions, and references based on the addition of Xywav.
05/15/21	Review and revision to guideline consisting of updating the position statement, precautions, and references.
10/15/21	Revision to guideline consisting of updating the description section, position statement, dosage/administration, precautions, and references based on the addition of Xywav.
08/15/22	Review and revision to guideline consisting of updating the position statement and references.
03/15/23	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions and references due to the market entry of an authorized generic of Xyrem, Sodium Oxybate Oral Solution, distributed by Hikma Pharmaceuticals.
10/01/23	Review and revision to guideline consisting of updating the position statement to include sodium oxybate extended-release solution (Lumryz) and a step though Sodium Oxybate oral solution by Hikma Pharmaceuticals (an authorized generic) for brand Xyrem only. Updates to the description, dosage/administration, precautions, and billing/coding sections, and references.
05/15/24	Review and revision to guideline consisting of updating the description, position statement, and references. Added Sodium Oxybate oral solution by Amneal Pharmaceuticals, the second approved authorized generic of Xyrem, as a non-preferred and excluded product.