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Oxybate

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Overview

This policy supports medical necessity review for the following oxybate products:

- **Lumryz**™ (sodium oxybate) extended-release oral suspension
- **Xyrem**® (sodium oxybate) oral solution
- **Xywav**™ (calcium, magnesium, potassium, and sodium oxybates) oral solution

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Oxybate products (Lumryz, Xyrem, Xywav) are considered medically necessary when the following are met:

I. **Lumryz (sodium oxybate).** Individual meets **ONE** of the following:

1. **Narcolepsy Type 1 (Narcolepsy with Cataplexy).** Individual meets **ALL** of the following criteria:
    A. 18 years of age or older
    B. Daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months
    C. Cataplexy
    D. **ONE** of the following:
        i. Mean Sleep Latency Test (MSLT) performed according to standard techniques, showing a mean sleep latency of less than or equal to 8 minutes and two or more sleep-onset rapid eye movement periods (SOREMPs) following a nocturnal polysomnogram (PSG) that rules out other causes of excessive daytime sleepiness.
        ii. A SOREMP (within 15 minutes of sleep onset) on a nocturnal PSG
    E. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal
    F. No concurrent use with other sedative hypnotic drugs or alcohol
    G. Documentation of failure, contraindication or intolerance to **ONE** of the following:
        i. Treatment of Cataplexy and **ONE** of the following:
            1. dextroamphetamine
            2. a tricyclic antidepressant (TCA) [for example, amitriptyline, desipramine, imipramine]
            3. a selective serotonin reuptake inhibitor (SSRI) [for example, fluoxetine, sertraline, paroxetine]
            4. venlafaxine
        ii. Treatment of Excessive Daytime Sleepiness and **ONE** of the following:
            1. modafinil OR armodafinil
            2. dextroamphetamine, dexmethylphenidate OR methylphenidate
    H. Medication is being prescribed by, or in consultation with, a neurologist, pulmonologist or sleep specialist
    I. Preferred product criteria is met for the products listed in the below table(s)

2. **Narcolepsy Type 2 (Narcolepsy without Cataplexy).** Individual meets **ALL** of the following criteria:
    A. 18 years of age or older
    B. Daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months
    C. Mean Sleep Latency Test (MSLT) performed according to standard techniques, showing a mean sleep latency of less than or equal to 8 minutes and two or more sleep-onset rapid eye movement periods (SOREMPs) following a nocturnal polysomnogram (PSG) that rules out other causes of excessive daytime sleepiness
    A SOREMP (within 15 minutes of sleep onset) on a nocturnal PSG may replace one of the SOREMPs on the MSLT
    D. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal
    E. No concurrent use with other sedative hypnotic drugs or alcohol
    F. Documentation of failure, contraindication or intolerance to **ONE** of the following:
        i. modafinil OR armodafinil
        ii. dextroamphetamine, dexmethylphenidate OR methylphenidate
    G. Medication is being prescribed by, or in consultation with, a neurologist, pulmonologist or sleep specialist
    H. Preferred product criteria is met for the products listed in the below table(s)

Individual and Family Plans:

Product	Criteria
Lumryz (sodium oxybate)	There is documentation of failure, contraindication, or intolerance to Wakix (pitolisant) [may require prior authorization]

Product	Criteria
extended-release oral suspension	

II. **Sodium oxybate (Xyrem and sodium oxybate).** Individual meets **ONE** of the following:

1. **Narcolepsy Type 1 (Narcolepsy with Cataplexy).** Individual meets **ALL** of the following criteria:
   A. 7 years of age or older
   B. Daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months
   C. Cataplexy
   D. **ONE** of the following:
      i. Mean Sleep Latency Test (MSLT) performed according to standard techniques, showing a mean sleep latency of less than or equal to 8 minutes and two or more sleep-onset rapid eye movement periods (SOREMPs) following a nocturnal polysomnogram (PSG) that rules out other causes of excessive daytime sleepiness
      ii. A SOREMP (within 15 minutes of sleep onset) on a nocturnal PSG
   E. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal
   F. No concurrent use with other sedative hypnotic drugs or alcohol
   G. Documentation of failure, contraindication or intolerance to **ONE** of the following:
      i. Treatment of Cataplexy and **ONE** of the following:
         1. dextroamphetamine
         2. a tricyclic antidepressant (TCA) [for example, amitriptyline, desipramine, imipramine]
         3. a selective serotonin reuptake inhibitor (SSRI) [for example, fluoxetine, sertraline, paroxetine]
         4. venlafaxine
      ii. Treatment of Excessive Daytime Sleepiness and **ONE** of the following:
         1. modafinil OR armodafinil
         2. dextroamphetamine, dexmethylphenidate OR methylphenidate
   H. Medication is being prescribed by, or in consultation with, a neurologist, pulmonologist or sleep specialist
   I. Preferred product criteria is met for the products listed in the below table(s)

2. **Narcolepsy Type 2 (Narcolepsy without Cataplexy).** Individual meets **ALL** of the following criteria:
   A. 7 years of age or older
   B. Daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months
   C. Mean Sleep Latency Test (MSLT) performed according to standard techniques, showing a mean sleep latency of less than or equal to 8 minutes and two or more sleep-onset rapid eye movement periods (SOREMPs) following a nocturnal polysomnogram (PSG) that rules out other causes of excessive daytime sleepiness
      A SOREMP (within 15 minutes of sleep onset) on a nocturnal PSG may replace one of the SOREMPs on the MSLT
   D. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal
   E. No concurrent use with other sedative hypnotic drugs or alcohol
   F. Documentation of failure, contraindication or intolerance to **ONE** of the following:
      i. modafinil OR armodafinil
      ii. dextroamphetamine, dexmethylphenidate OR methylphenidate

G. Medication is being prescribed by, or in consultation with, a neurologist, pulmonologist or sleep specialist
H. Preferred product criteria is met for the products listed in the below table(s)

Employer Plans:

Product	Criteria
Xyrem (sodium oxybate) oral solution	**EFFECTIVE 7/1/2024** Documented inability to obtain sodium oxybate oral solution (by Hikma) due to market availability
Sodium Oxybate oral solution (by Amneal)	**EFFECTIVE 7/1/2024** Documented inability to obtain sodium oxybate oral solution (by Hikma) due to market availability

Individual and Family Plans:

Product	Criteria
Xyrem (sodium oxybate) oral solution	There is documentation of **ONE** of the following: 1. Less than 18 years of age 2. Failure, contraindication, or intolerance to Wakix (pitolisant) [may require prior authorization]

III. **Xywav (calcium, magnesium, potassium, and sodium oxybates).** Individual meets **ONE** of the following:

1. **Narcolepsy Type 1 (Narcolepsy with Cataplexy).** Individual meets **ALL** of the following criteria:
   A. 7 years of age or older
   B. Daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months
   C. Cataplexy
   D. **ONE** of the following:
      i. Mean Sleep Latency Test (MSLT) performed according to standard techniques, showing a mean sleep latency of less than or equal to 8 minutes and two or more sleep-onset rapid eye movement periods (SOREMPs) following a nocturnal polysomnogram (PSG) that rules out other causes of excessive daytime sleepiness
      ii. A SOREMP (within 15 minutes of sleep onset) on a nocturnal PSG
   E. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal
   F. No concurrent use with other sedative hypnotic drugs or alcohol
   G. Documentation of failure, contraindication or intolerance to **ONE** of the following:
      i. Treatment of Cataplexy and **ONE** of the following:
         1. dextroamphetamine
         2. a tricyclic antidepressant (TCA) [for example, amitriptyline, desipramine, imipramine]
         3. a selective serotonin reuptake inhibitor (SSRI) [for example, fluoxetine, sertraline, paroxetine]
         4. venlafaxine
      ii. Treatment of Excessive Daytime Sleepiness and **ONE** of the following:
         1. modafinil OR armodafinil
         2. dextroamphetamine, dexmethylphenidate OR methylphenidate

H. Medication is being prescribed by, or in consultation with, a neurologist, pulmonologist or sleep specialist
I. Non-Covered Product Criteria is met, refer to below table(s)

2. **Narcolepsy Type 2 (Narcolepsy without Cataplexy).** Individual meets **ALL** of the following criteria:
   A. 7 years of age or older
   B. Daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months
   C. Mean Sleep Latency Test (MSLT) performed according to standard techniques, showing a mean sleep latency of less than or equal to 8 minutes and two or more sleep-onset rapid eye movement periods (SOREMPs) following a nocturnal polysomnogram (PSG) that rules out other causes of excessive daytime sleepiness
      A SOREMP (within 15 minutes of sleep onset) on a nocturnal PSG may replace one of the SOREMPs on the MSLT
   D. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal
   E. No concurrent use with other sedative hypnotic drugs or alcohol
   F. Documentation of failure, contraindication or intolerance to **ONE** of the following:
      i. modafinil OR armodafinil
      ii. dextroamphetamine, dexmethylphenidate OR methylphenidate
   G. Medication is being prescribed by, or in consultation with, a neurologist, pulmonologist or sleep specialist
   H. Non-Covered Product Criteria is met, refer to below table(s)

Individual and Family Plans:

Product	Criteria
Xywav (calcium, magnesium, potassium, and sodium oxybates)	There is documentation of **ONE** of the following: 1. Less than 18 years of age 2. Failure, contraindication, or intolerance to Wakix (pitolisant) [may require prior authorization]

3. **Idiopathic Hypersomnia.** Individual meets **ALL** of the following criteria:
   A. 18 years of age or older
   B. Daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months
   C. A Multiple Sleep Latency Test (MSLT) performed according to standard techniques demonstrating an average sleep latency of less than or equal to 8 minutes with a total of less than 2 sleep onset rapid eye movement periods (SOREMPs)
   D. Absence of cataplexy
   E. The hypersomnolence and/or MSLT findings are not better explained by other sleep disorders (for example, insufficient sleep syndrome [if deemed necessary, by lack of improvement of sleepiness after an adequate trial of increased nocturnal time in bed], delayed sleep phase disorder, other medical or psychiatric disorders, the effect of medication or substances or their withdrawal)
   F. No concurrent use with other sedative hypnotic drugs or alcohol
   G. Documentation of failure, contraindication or intolerance to **ONE** of the following:
      i. armodafinil or modafinil
      ii. methylphenidate
   H. Medication is being prescribed by, or in consultation with, a neurologist, pulmonologist or sleep specialist

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of oxybate products is considered medically necessary for **ALL** covered diagnosis when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration is up to 12 months.
Reauthorization approval duration is up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Fibromyalgia.** The European League Against Rheumatism (EULAR) issued evidence-based recommendations for the management of fibromyalgia (2016) stating that initial management should involve patient education and focus on non-pharmacological therapies.[7] EULAR's position on sodium oxybate for fibromyalgia is strongly against with 94% agreement. Duloxetine, pregabalin capsules and oral solution, and Savella® (milnacipran tablets) are indicated for the treatment of fibromyalgia.[9-11] Other recommended treatments include tricyclic antidepressants (i.e., amitriptyline), cyclobenzaprine, gabapentin, and selective serotonin reuptake inhibitors (i.e., fluoxetine, sertraline, paroxetine).[12]

2. **Concomitant use of Lumryz, sodium oxybate oral solution, Xyrem and/or Xywav.** Lumryz, sodium oxybate oral solution, Xyrem and Xywav have the same active ingredient (oxybate, a CNS depressant) and have not been studied for use in combination or as alternating treatments.[1-3]

Background

OVERVIEW
Lumryz, sodium oxybate oral solution, and Xywav, central nervous system (CNS) depressants, are indicated for the following uses:[1-3]

- **Cataplexy treatment in patients with narcolepsy**. Sodium oxybate oral solution and Xywav are indicated in patients ≥ 7 years of age, and Lumryz is indicated in adults.
- **Excessive daytime sleepiness in narcolepsy**. Sodium oxybate oral solution and Xywav are indicated in patients ≥ 7 years of age, and Lumryz is indicated in adults.

Additionally, Xywav is indicated for the treatment of **idiopathic hypersomnia** in adults.[2]

Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy or idiopathic hypersomnia.[4] Polysomnography is an overnight recording of brain and muscle activity, breathing, and eye movements. The multiple sleep latency test (MSLT) assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter rapid eye movement (REM) sleep. Polysomnography is routinely indicated for the diagnosis of sleep-related breathing disorders; for continuous positive airway pressure titration in patients with sleep-related breathing disorders; with an MSLT in the evaluation of suspected narcolepsy; and in certain atypical or unusual parasomnias.[5] The MSLT is indicated as part of the evaluation of patients with suspected narcolepsy to confirm the diagnosis or patients who are thought to have idiopathic hypersomnia to exclude other causes of hypersomnia. Most patients with narcolepsy have objective evidence of hypersomnia as determined by a mean sleep latency < 5 minutes. In studies, the presence of two or more sleep-onset REM episodes (SOREMPs) was associated with a sensitivity of 0.78 and a specificity

of 0.93 for the diagnosis of narcolepsy. SOREMPs do not occur exclusively in patients with narcolepsy; thus, it is important to rule out or treat other sleep disorders before evaluating SOREMPs in the diagnosis of narcolepsy. Diagnostic criteria for patients with idiopathic hypersomnia include a mean sleep latency ≤ 8 minutes and MSLT results showing < 2 SOREMPs or no SOREMPs if the REM sleep latency preceding polysomnogram is ≤ 15 minutes; also, these patients do not have cataplexy. For these reasons, polysomnography and an MSLT performed on the day after the polysomnographic evaluation are routinely indicated in the evaluation of suspected narcolepsy or idiopathic hypersomnia.

Guidelines
Pertinent medical guidelines related to oxybate products are summarized below; of note, Lumryz and Xywav are not addressed in any of the guidelines.

Narcolepsy and Cataplexy
The American Academy of Sleep Medicine (AASM) practice parameters for the treatment of central disorders of hypersomnolence were updated in 2021.[6,7]

- Modafinil, Wakix® (pitolisant tablets), sodium oxybate, and Sunosi® (solriamfetol tablets) are recommended as effective treatments for daytime sleepiness due to narcolepsy and reducing disease severity in adults (Strong Recommendation for each).
- Wakix and sodium oxybate have also demonstrated efficacy for the treatment of cataplexy in patients with narcolepsy (Strong Recommendation for each).
- Sodium oxybate and armodafinil have Conditional Recommendations for the treatment of narcolepsy, showing efficacy for daytime sleepiness due to narcolepsy and reducing disease severity.
- Dextroamphetamine has a Conditional Recommendation for the treatment of narcolepsy, showing efficacy for excessive daytime sleepiness and cataplexy.
- Methylphenidate has a Conditional Recommendation for the treatment of narcolepsy, showing efficacy in reducing disease severity.
- There was insufficient and inconclusive evidence to make recommendations for l-carnitine, scheduled naps, selegiline, triazolam, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs).
- Modafinil and sodium oxybate have Conditional Recommendations for the treatment of narcolepsy in pediatric patients.

Note: A Strong Recommendation should be followed by clinicians under most circumstances. A Conditional Recommendation requires that the clinician use clinical knowledge and experience and strongly consider the individual patient's values and preferences to determine the best course of action.

Idiopathic Hypersomnia
The AASM guideline includes recommendations for the treatment of idiopathic hypersomnia.[6,7]

- Only modafinil has a Strong recommendation for use.
- Clarithromycin, methylphenidate, Wakix, and sodium oxybate have Conditional recommendations for the treatment of idiopathic hypersomnia in adults.

Safety
Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB) and Xywav is a mixed salt formulation of GHB.[1-3] They are both Schedule III controlled substances. Abuse of GHB (a Schedule I controlled substance), 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, abuse, and misuse, sodium oxybate oral solution and Xywav are available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the Xyrem/Xywav Success Program, using a centralized pharmacy. Healthcare professionals who prescribe sodium oxybate oral solution or Xywav and patients must enroll in the Xyrem/Xywav Success Program and must comply with the requirements to ensure the drug's safe use. Similarly, Lumryz is only available through a restricted distribution program under a REMS called the Lumryz REMS. Healthcare providers who prescribe Lumryz must be specially certified; Lumryz will be dispensed only by pharmacies that are specially certified; and Lumryz will be dispensed and shipped only to patients who are enrolled in the Lumryz REMS with documentation of safe use conditions.

References

1. Xyrem® oral solution [prescribing information]. Palo Alto, CA: Jazz; March 2022.
2. Xywav® oral solution [prescribing information]. Palo Alto, CA: Jazz; March 2022.
3. Lumryz™ extended-release oral suspension [prescribing information]. Chesterfield, MO: Avadel; May 2023.
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5. Krahn LE, Arand DL, Avidan AY, et al. Recommended protocols for the multiple sleep latency test and maintenance of wakefulness test in adults: guidance from the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2021;17(12):2489-2498.
6. Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline. Available at: https://jcsm.aasm.org/doi/10.5664/jcsm.9328. Accessed on June 6, 2023.
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8. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis*. 2017;76(2):318-328.
9. Lyrica® capsules and oral solution [prescribing information]. New York, NY: Pfizer; April 2020.
10. Cymbalta® delayed-release capsules [prescribing information]. Indianapolis, IN: Lilly; July 2021.
11. Savella® tablets [prescribing information]. Madison, NJ: Allergan; December 2022.
12. Clauw DJ. Fibromyalgia: a clinical review. *JAMA*. 2014;311(15):1547-1555.
13. Sunosi® tablets [prescribing information]. New York, NY: Axsome; November 2022.
14. Wakix® tablets [prescribing information]. Plymouth Meeting, PA: Harmony Biosciences; December 2022.

Supplemental References

15. American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3rd ed, text revision, American Academy of Sleep Medicine, 2023.

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