

Drug and Biologic Coverage Policy



Effective Date 3/15/2021

Next Review Date... 3/1/2022

Coverage Policy Number IP0103

Oxybate

Table of Contents

Overview	1
Coverage Policy.....	1
Reauthorization Criteria	2
Authorization Duration	2
Conditions Not Covered.....	3
Background.....	3
References	4

Related Coverage Resources

[Modafinil / Armodafinil](#)
[Obstructive Sleep Apnea Diagnosis and Treatment Services](#)
[Sleep Testing Services](#)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for **Xyrem®** (sodium oxybate) and **Xywav™** (calcium, magnesium, potassium, and sodium oxybates).

Coverage Policy

Sodium Oxybate (Xyrem) and calcium, magnesium, potassium, and sodium oxybates (Xywav) are considered medically necessary when ONE of the following are met:

I. Cataplexy associated with Narcolepsy and ALL of the following criteria:

- Individual is 7 years of age or older
- The individual has daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months
- Cataplexy
- Mean Sleep Latency Test (MSLT) performed according to standard techniques, showing a mean sleep latency of ≤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.

Note: A SOREMP (within 15 minutes of sleep onset) on a nocturnal PSG may replace one of the SOREMPs on the MSLT

- 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
- No concurrent use with other sedative hypnotic drugs or alcohol
- Prescribed by or in consultation with a neurologist, pulmonologist or sleep specialist
- Documentation of inadequate efficacy OR contraindication according to FDA label, OR significant intolerance, OR is not a candidate due to being subject to a warning per the prescribing information (labeling), having a disease characteristic, individual clinical factor[s], or other attributes/conditions or is unable to administer and requires this dosage formulation of **ONE** of the following:
 - a tricyclic antidepressant (TCA) [for example, amitriptyline, desipramine, imipramine]
 - a selective serotonin reuptake inhibitor (SSRI) [for example, fluoxetine, sertraline, paroxetine]
 - venlafaxine

II. Excessive Daytime Sleepiness associated with Narcolepsy and ALL of the following criteria:

- Individual is 7 years of age or older
- The individual has daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months
- Mean Sleep Latency Test (MSLT) performed according to standard techniques, showing a mean sleep latency of ≤ 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

Note: A SOREMP (within 15 minutes of sleep onset) on a nocturnal PSG may replace one of the SOREMPs on the MSLT
- 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
- No concurrent use with other sedative hypnotic drugs or alcohol
- Prescribed by or in consultation with a neurologist, pulmonologist or sleep specialist
- Documentation of inadequate efficacy OR contraindication according to FDA label, OR significant intolerance, OR is not a candidate due to being subject to a warning per the prescribing information (labeling), having a disease characteristic, individual clinical factor[s], or other attributes/conditions or is unable to administer and requires this dosage formulation of **ONE** of the following:
 - modafinil* or armodafinil*
 - amphetamine, dextroamphetamine or methylphenidate

*May require prior authorization

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.

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

Documentation: When documentation is required, the prescriber must provide written documentation supporting the trials of these other agents. Documentation may include, but is not limited to, chart notes, prescription claims records, and/or prescription receipts

Reauthorization Criteria

Xyrem (sodium oxybate) and Xywav (calcium, magnesium, potassium, and sodium oxybates) are considered medically necessary for continued use when initial criteria are met AND documentation of beneficial response.

Authorization Duration

Initial approval and reauthorization duration is 12 months.

Conditions Not Covered

Xyrem (sodium oxybate) and Xywav (calcium, magnesium, potassium, and sodium oxybates) are considered experimental, investigational or unproven for ANY other use including the following (this list may not be all inclusive):

1. **Fibromyalgia.** The effectiveness of Xyrem in fibromyalgia has been evaluated in clinical trials of varying size.⁸⁻¹³ However, due to safety concerns, Xyrem is not recommended for approval for fibromyalgia at this time. Duloxetine, Lyrica® (pregabalin capsules and oral solution), and Savella® (milnacipran tablets) are indicated for the treatment of fibromyalgia.¹⁴⁻¹⁶ Other recommended treatments include TCAs (i.e., amitriptyline), cyclobenzaprine, gabapentin, and SSRIs (i.e., fluoxetine, sertraline, paroxetine).¹⁷

Background

Overview

Xyrem and Xywav, central nervous system (CNS) depressants, are indicated for the following uses:^{1,2}

- Cataplexy treatment in patients with narcolepsy, in patients ≥ 7 years of age.
- Excessive daytime sleepiness in narcolepsy, in patients ≥ 7 years of age.

Xyrem and Xywav have the same oxybate concentration; Xywav includes a mix of calcium, magnesium, potassium and sodium cations, while Xyrem includes only sodium cations.^{1,2} Dosing and administration of Xyrem and Xywav are the same.

Xyrem labeling includes a Warning with regard to patients sensitive to high sodium intake which states that Xyrem has a high salt content.¹ In patients 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 Xyrem. According to the manufacturer, Xywav has 92% less sodium (approximately 1,000mg to 1,500mg less per night) than Xyrem.²

Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy.³ 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 a MSLT in the evaluation of suspected narcolepsy; and in certain atypical or unusual parasomnias.⁴ The MSLT is indicated as part of the evaluation of patients with suspected narcolepsy to confirm the diagnosis. 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, and thus it is important to rule out or treat other sleep disorders before evaluating SOREMPs in the diagnosis of narcolepsy. For this reason, polysomnography and a MSLT performed on the day after the polysomnographic evaluation are routinely indicated in the evaluation of suspected narcolepsy.

Guidelines

Guidelines for the treatment of narcolepsy and for cataplexy due to narcolepsy are dated and do not include Xywav.^{5,6} The American Academy of Sleep Medicine (AASM) practice parameters for the treatment of narcolepsy and other hypersomnias of central origin (2007) list Xyrem as effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy (*Standard*) and modafinil as an effective treatment of daytime sleepiness due to narcolepsy (*Standard*). Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are considered effective for the treatment of daytime sleepiness due to narcolepsy (*Guideline*). Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and venlafaxine may be effective for the treatment of cataplexy (*Guideline*). Selegiline may be an effective treatment for

cataplexy and daytime sleepiness (*Option*). *Standard* recommendations are considered to be generally accepted patient-care strategies that reflect a high degree of clinical certainty based on Level I evidence or overwhelming Level II evidence. *Guideline* recommendations are considered to be patient-care strategies that reflect a moderate degree of clinical certainty based on Level II evidence or a consensus of Level III evidence. *Option* recommendations are considered to be patient-care strategies that reflect uncertain clinical use based on inconclusive or conflicting evidence or conflicting expert opinion. At the time this practice parameter was written, published studies involving Nuvigil® (armodafinil tablets) were limited.

The European League Against Rheumatism (EULAR) issued updated evidence-based recommendations for the management of fibromyalgia (2016) stating that initial management should involve patient education and focus on nonpharmacological therapies.⁷ In case of non-response, further therapies should be tailored to the specific needs of the individual and may involve psychological therapies (for mood disorders and unhelpful coping strategies), pharmacotherapy (for severe pain or sleep disturbance) and/or a multimodal rehabilitation program (for severe disability). EULAR notes that the European Medicines Agency and the FDA refused approval of Xyrem for fibromyalgia because of safety concerns. EULAR's position on Xyrem for fibromyalgia is strongly against with 94% agreement.

Safety

Xyrem is the sodium salt of gamma hydroxybutyrate (GHB) and Xywav is a mixed salt formulation of GHB.^{1,2} 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, Xyrem and Xywav are available only through a restricted distribution program called the Xyrem/Xywav Success Program, using a centralized pharmacy. Healthcare professionals who prescribe Xyrem 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.

References

1. Xyrem® oral solution (prescribing information). Palo Alto, CA: Jazz Pharmaceuticals, Inc.; October 2018.
2. Xywav™ oral solution (prescribing information). Palo Alto, CA: Jazz Pharmaceuticals, Inc.; July 2020.
3. National Institutes of Health. Narcolepsy Fact Sheet. National Institute of Neurological Disorders and Stroke. Date last modified: September 30, 2020. Available at: <https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Narcolepsy-Fact-Sheet>. Accessed on October 2, 2020.
4. Kushida CA, Littner MR, Morgenthaler T, et al. Practice Parameters for the Indications for Polysomnography and Related Procedures: An Update for 2005. *SLEEP*. 2005; 28(4):499-521.
5. Morgenthaler TI, Kapur VK, Brown TM, et al. Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin: An American Academy of Sleep Medicine Report. Available at: http://www.aasmnet.org/Resources/PracticeParameters/PP_Narcolepsy.pdf. Accessed on October 2, 2020.
6. Wise MS, Arand DL, Auger R, et al. Treatment of narcolepsy and other hypersomnias of central origin: An American Academy of Sleep Medicine Review. *Sleep*. 2007; 30(12):1712-27. Available at: http://www.aasmnet.org/Resources/PracticeParameters/Review_Narcolepsy.pdf. Accessed on October 2, 2020.
7. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis*. 2017; 76(2):318-328.
8. Spaeth M, Bennett RM, Benson BA, et al. Sodium oxybate therapy provides multidimensional improvement in fibromyalgia: results of an international phase 3 trial. *Ann Rheum Dis*. 2012; 71:935-942.
9. Russel IJ, et al. Sodium oxybate reduces pain, fatigue, and sleep disturbance and improves functionality in fibromyalgia: results from a 14-week, randomized, double-blind, placebo-controlled study. *Pain*. 2011; 152(5):1007-17.
10. Moldofsky H, Inhaber NH, Guinta DR, et al. Effects of sodium oxybate on sleep physiology and sleep/wake-related symptoms in patients with fibromyalgia syndrome: a double-blind, randomized, placebo-controlled study. *J Rheumatol*. 2010; 37(10):2156-2166.

11. Russel IJ, Perkins AT, Michalek JE, et al. Sodium oxybate relieves pain and improves function in fibromyalgia syndrome. A randomized, double-blind, placebo-controlled, multicenter clinical trial. *Arthritis Rheum.* 2009; 60(1):299-309.
12. Scharf MB, et al. The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia. *J Rheumatol.* 2003; 30(5):1070-1074.
13. Scharf MB, et al. Effect of gamma-hydroxybutyrate on pain, fatigue, and the alpha sleep anomaly in patients with fibromyalgia. Preliminary report. *J Rheumatol.* 1998; 25(10):1986-1990.
14. Lyrica® (prescribing information). New York, NY: Pfizer Inc.; May 2019.
15. Cymbalta® (prescribing information). Indianapolis, IN: Lilly USA, LLC; October 2019.
16. Savella® tablets (prescribing information). St. Louis, MO: Forest Pharmaceuticals, Inc.; November 2017.
17. Clauw DJ. Fibromyalgia: a clinical review. *JAMA.* 2014; 311(15):1547-1555.

"Cigna Companies" refers to operating subsidiaries of Cigna Corporation. All products and services are provided exclusively by or through such operating subsidiaries, including Cigna Health and Life Insurance Company, Connecticut General Life Insurance Company, Cigna Behavioral Health, Inc., Cigna Health Management, Inc., QualCare, Inc., and HMO or service company subsidiaries of Cigna Health Corporation. The Cigna name, logo, and other Cigna marks are owned by Cigna Intellectual Property, Inc. © 2021 Cigna.