sodium oxybate (Xyrem®); calcium, magnesium, potassium, sodium oxybates (Xywav™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO186

Description

Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) are orally administered metabolites of the neurotransmitter GABA that act as central nervous system depressants with an unknown mechanism of action.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
sodium oxybate (Xyrem)	500 mg/mL	Narcolepsy with cataplexy Narcolepsy with excessive daytime sleepiness in patients greater than 7 years of age Idiopathic hypersomnia in adults	540 mL/30 days
calcium, magnesium, potassium, sodium oxybates (Xywav)		Narcolepsy with excessive daytime sleepiness in patients greater than 7 years of age Idiopathic hypersomnia in adults	

Initial Evaluation

I. **Sodium oxybate (Xyrem)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a sleep specialist, psychiatrist, or neurologist; **AND**
   B. Medication is not used in combination with sedative hypnotic agents (e.g. benzodiazepines, barbiturates, zolpidem tartrate); **AND**
   C. Confirmation the member does not have a succinic semialdehyde dehydrogenase deficiency; **AND**
   D. Provider attestation the member does not have a history of substance abuse; **AND**
   E. A diagnosis of one of the following:
      1. **Narcolepsy with cataplexy**; **AND**

i. Member is seven years of age or older; **AND**
ii. Confirmation of cataplexy defined as episodes of sudden loss of muscle tone; **AND**
iii. Symptoms have been present for at least three months; **AND**
iv. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving); **OR**

2. **Narcolepsy with excessive daytime sleepiness**; **AND**
   i. Member is seven years of age or older; **AND**
   ii. Confirmation of diagnosis with a sleep study (including polysomnography and multiple sleep latency test); **AND**
   iii. Symptoms have been present for at least three months; **AND**
   iv. For members that are 18 years of age or older, treatment with ALL of the following has been ineffective, contraindicated, or not tolerated:
      a. Modafinil (Provigil) or armodafinil (Nuvigil); **AND**
      b. Solriamfetol (Sunosi); **AND**
   v. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving); **OR**
3. **Idiopathic hypersomnia**; **AND**
   i. Member is 18 years of age or older; **AND**
   ii. Provider attestation that hypersomnia is not better explained by medical or neurological disorder, mental disorder, medication use, or substance use disorder; **AND**
   iii. Provider attestation that diagnosis has been confirmed via the following:
      a. Polysomnography; **AND**
      b. Multiple sleep latency test; **AND**
   iv. Treatment with ALL of the following has been ineffective, contraindicated, or not tolerated:
      a. Modafinil (Provigil) or armodafinil (Nuvigil); **AND**
      b. Methylphenidate, amphetamine salts, or dextroamphetamine

II. **Calcium, magnesium, potassium, sodium oxybates (Xywav)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(E) above have been met; **AND**
   B. The member has an FDA labeled contraindication or intolerance to Xyrem; **OR**
      1. Provider attestation member has tried and can not further reduce dietary salt intake via other means (i.e. salt restricted diet, others); **AND**
      2. The member is sensitive to sodium intake due to at least one of the following:
         i. Heart failure
         ii. Hypertension

iii. Impaired renal function; **AND**

C. For the settings of narcolepsy with cataplexy or narcolepsy with excessive daytime sleepiness:
   1. Treatment with pitolisant (Wakix) has been ineffective, contraindicated, or not tolerated

III. Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) are considered investigational when used for all other conditions, including but not limited to:
   A. Fibromyalgia
   B. Insomnia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in cataplexy attacks, improvement in ability to complete activities of daily living, improvement in ability to stay awake); **AND**
IV. Medication will not be used in combination with sedative hypnotic agents (e.g. benzodiazepines, barbiturates, zolpidem tartrate)

Supporting Evidence

I. The American Academy of Sleep Medicine does not make recommendations on preferring any agents over one another in the settings of narcolepsy or idiopathic hypersomnia. Guidance on the treatment of narcolepsy recommends modafinil and armodafinil as first-line treatment options, stimulants as second-line options due to their adverse event profile, and sodium oxybate (Xyrem) as a third-line option due to its adverse event profile and requirement for a REMS program. Similarly guidance on the treatment of idiopathic hypersomnia recommends modafinil and armodafinil as first-line treatment, stimulants as second-line, sodium oxybate (Xyrem) as third-line. Guidelines have not been updated to include calcium, magnesium, potassium, sodium oxybates (Xywav) at this time for either indication.
II. These agents are a part of a REMS program which only allows certified prescribers and pharmacies to dispense sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav). Prescribers must screen each patient for a history of alcohol or substance abuse, sleep-related breathing disorders, compromised respiratory function, depression or

suicidality, and concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents.

III. Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) are contraindicated in patients taking sedative hypnotic agents (e.g. benzodiazepines, barbiturates, zolpidem tartrate), and in patients with a succinic semialdehyde dehydrogenase deficiency. Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) have serious side effects such as, central nervous system depression, abuse and misuse, respiratory depression and sleep-disordered breathing, depression and suicidality, parasomnias, other psychiatric reactions (e.g. anxiety, hallucinations, psychosis), and elevates salt content (use with caution in patients that have heart failure, hypertension, or renal impairment).

IV. Outside of salt content, there is no clinical difference between sodium oxybate (Xyrem), and calcium, magnesium, potassium, sodium oxybates (Xywav). Weighing the safety, efficacy, cost, and clinical experience, sodium oxybate (Xyrem) is the plan's preferred product over calcium, magnesium, potassium, sodium oxybates (Xywav). Medical necessity of treating with Xywav over Xyrem is limited to members with comorbidities that place them at increased sensitivity to their daily sodium intake (e.g., heart failure, hypertension, impaired renal function). However, allowance of Xywav does not negate the need for the member to continue reduction of dietary salt intake and is not a means of a convenience option for those unwilling to reduce dietary salt intake.

Narcolepsy with cataplexy/excessive daytime sleepiness:

V. Patients included in clinical trials had a history of narcolepsy for three months or greater and had chronic narcolepsy that was ongoing.

VI. For the treatment of narcolepsy with cataplexy, sodium oxybate (Xyrem) was evaluated in two randomized, double-blind, placebo-controlled, multicenter, parallel-group trials with a total of 191 patients. Over 80% of patients in these trials were on stimulants as background therapy. The primary efficacy endpoint was the median change from baseline in cataplexy attacks. The baseline number of cataplexy attacks was 20 and 23 for the placebo group and Xyrem 9g group, respectively. Trial one had a reduction of 16 attacks per week in the 9g treatment group and 4 attacks per week in the placebo group ($p=0.0016$). Trial two was a randomized withdrawal trial, and the placebo group had 21 attacks within two weeks, while the sodium oxybate (Xyrem) group had zero attacks within two weeks ($p<0.001$).

VII. For the treatment of narcolepsy with excessive daytime sleepiness, sodium oxybate (Xyrem) was evaluated in two randomized, double-blind, placebo-controlled trials with a total of 450 patients. The primary efficacy endpoint for trial three was the change from baseline in the Epworth Sleepiness Scale (EPSS). Sodium oxybate (Xyrem) had a -2 and -5 median change from baseline at week 8 for the 6g and 9g treatment groups, and both groups had statistically greater reductions than the placebo group ($p<0.001$). The primary efficacy endpoint for trial four was the change from baseline in the Maintenance of Wakefulness Test (MWT). Sodium oxybate

(Xyrem) had a mean change from baseline of 0.6 compared to -2.7 for placebo at week 8 ($p<0.001$).

VIII. For the treatment of narcolepsy with cataplexy and excessive daytime sleepiness, sodium oxybate (Xyrem) was evaluated in one double-blind, placebo-controlled, randomized-withdrawal trial with 106 pediatric patients. Patients included in this study were seven to 16 years of age. The primary efficacy endpoints were the change in the frequency of cataplexy attacks and EPSS. The median change from baseline in the number of cataplexy attacks per week was 0.3 for sodium oxybate (Xyrem) compared to 12.7 for placebo ($p<0.0001$). The median change in the EPSS was zero for sodium oxybate (Xyrem) and three for placebo ($p=0.0004$).

IX. Solriamfetol (Sunosi) is FDA-approved for the treatment of excessive daytime sleepiness associated with OSA and narcolepsy in adults. The efficacy and safety of solriamfetol (Sunosi) was established in two Phase 3, multi-center, double-blind, placebo-controlled, randomized trials of fair quality that evaluated the use of solriamfetol (Sunosi) in patients with excessive daytime sleepiness associated with OSA (n=459) or either type I or type II narcolepsy (n=231). Solriamfetol (Sunosi) demonstrated a change in MWT of 7.7 minutes from baseline, and a change in EPSS of -3.8 from baseline, at week 12 ($p<0.0001$) for both endpoints against placebo.

X. The efficacy and safety of calcium, magnesium, potassium, sodium oxybates (Xywav) was established in a Phase 3, multi-center, double-blind, placebo-controlled, randomized trial that evaluated the use of calcium, magnesium, potassium, sodium oxybates (Xywav) in patients with narcolepsy with cataplexy. Patients were all transitioned to the use of calcium, magnesium, potassium, sodium oxybates (Xywav) and optimized regardless of prior anti-cataplectic therapy or being naïve to treatment (n=201). Once optimized, efficacy was confirmed in the double blind, randomized withdrawal period (DB RWP) of this trial. During the DB RWP, outcomes showed a statistically significant worsening of cataplexy symptoms in patients on placebo when compared to those in the calcium, magnesium, potassium, sodium oxybates (Xywav) arm. The safety profile in pediatric patients with Xywav is expected to be similar to that of adult patients treated with Xywav and to that of pediatric patients treated with Xyrem.

XI. Pitolisant (Wakix) is FDA-approved for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy. The efficacy of pitolisant (Wakix) was established in three randomized controlled trials (HARMONY I, I bis, and III), and one open-label, single-arm, long term safety & efficacy trial, in a total of 468 patients with excessive daytime sleepiness. The use of pitolisant (Wakix) in the treatment of narcolepsy with cataplexy was established in HARMONY CTP with supporting evidence in HARMONY I.

- In HARMONY I (n = 95): The primary efficacy outcome was the change in the Epworth Sleepiness Scale (ESS) score after eight weeks. Pitolisant (Wakix) 35.6 mg demonstrated a statistically greater reduction in the ESS score compared to placebo (change of -3.1 points [-5.73, -0.46]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score.

- HARMONY I bis (n = 165): The primary efficacy outcome was the change in the ESS score and compared pitolisant (Wakix) 17.4 mg vs. placebo. Pitolisant (Wakix) demonstrated statistically significant reduction in the ESS score compared to placebo (change of -2.12 points [-4.10, -0.14]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score.
- HARMONY III (n = 102): Efficacy was a secondary endpoint and was measured by the change in the ESS score from baseline to one year. The mean decrease in ESS scores was -4.6 ± 0.59 (-5.82, -3.44).
- HARMONY CTP (n = 106): The primary efficacy outcome was the change in the average number of cataplexy attacks per week as documented by patient diaries. The cataplexy ratio rate was 0.51 (0.44-0.60, p<0.0001) for pitolisant (Wakix) compared to placebo.

XII. There are no direct head-to-head studies comparing pitolisant (Wakix), solriamfetol (Sunosi), sodium oxybate (Xyrem), and calcium, magnesium, potassium, sodium oxybates (Xywav) to establish superior safety or efficacy of one product over the other. However, there are substantial cost differences between products despite not having any evidence of improved clinical efficacy or safety.

Idiopathic Hypersomnia:

XIII. While sodium oxybate (Xyrem) does not carry an FDA approved indication for use in idiopathic hypersomnia (IH), the active moiety is the same as calcium, magnesium, potassium, sodium oxybates (Xywav). The chemical entity found in both of these products is expected to produce similar efficacy and safety for the treatment of IH.

XIV. The safety profile of calcium, magnesium, potassium, sodium oxybates (Xywav) and sodium oxybate (Xyrem) in pediatric patients for the treatment of IH has not been established.

XV. Idiopathic hypersomnia (IH) is a sleep disorder that presents as chronic excessive daytime sleepiness (EDS) and difficulty waking up from nighttime sleep or daytime naps. Symptomatic patients are unable to maintain wakefulness and alertness during major waking episodes of the day, with sleep occurring unintentionally. Diagnosis of IH is made by objective sleep tests as well as ruling out other sleep disorders, medical or psychiatric disorders, or use of drugs that may be causing EDS. Hypersomnia associated with psychiatric disorders (i.e., atypical depression, bipolar depression, dysthymia, etc.) is a differential diagnosis and commonly overlaps with complaints of excessive daytime sleepiness and may be mistaken for idiopathic hypersomnia if not ruled out. In patients where hypersomnia may be better explained by other sleep disorders, psychiatric disorders, or use of certain medications, use of sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium (Xywav) is not considered medically necessary, as treatment of hypersomnia in this setting is guided by correcting the underlying cause.

XVI. IH is diagnosed through combined evaluation of nocturnal polysomnography and a multiple sleep latency test (MSLT). Polysomnography can exclude causes of excessive daytime sleepiness (i.e., subtle forms of obstructive sleep apnea) while shortened mean sleep latency and the

number of sleep-onset rapid eye movement sleep periods (SOREMPs) can distinguish between narcolepsy and IH.

XVII. Stimulants and alerting agents (i.e., modafinil, armodafinil, methylphenidate, amphetamine salts) for IH are recommended based on experience with these medications in the setting of excessive daytime sleepiness (EDS) associated with narcolepsy. FDA approval of stimulants and alerting agents in related sleep conditions such as narcolepsy, American Academy of Sleep Medicine clinical guideline recommendations, large body of safety data, and proven effects on EDS support the use of stimulants and alerting agents in IH. Additionally, the majority of clinical trial population for calcium, magnesium, potassium, sodium oxybates (Xywav) were on a stimulant/alerting agent at baseline. Given the known safety profile, extensive clinical use, and cost-effectiveness of these therapies, a trial of stimulants and alerting agents is required.

XVIII. The efficacy and safety of calcium, magnesium, potassium, sodium oxybates (Xywav) was established in a Phase 3, interventional, double-blind, placebo-controlled, randomized withdrawal trial that evaluated the use of calcium, magnesium, potassium, sodium oxybates (Xywav) in adult patients with IH. Participants were a median age of 39 years, 71% female, 81% white and non-Hispanic or Latino. At baseline 2% of patients were taking Xyrem only, 4% were taking Xyrem in addition to another stimulant/alerting agent, 54% were taking a stimulant/alerting agent, and 41% were naïve to therapy. CNS stimulants were allowed to continue throughout the SDP and DB RWP – this occurred in 57% of patients. Baseline Epworth Sleepiness Scale ESS scores were 16 in calcium, magnesium, potassium, sodium oxybates (Xywav) and 17 in the placebo groups. Efficacy was confirmed in the double blind, randomized, 2-week withdrawal period (DB RWP). Primary outcome showed a statistically significant worsening of median ESS in patients on placebo (Δ 5 to 14 points) when compared to those in the calcium, magnesium, potassium, sodium oxybates (Xywav) arm (Δ 6.5 to 7 points) ($p<0.0001$).

XIX. No new safety signals were seen in calcium, magnesium, potassium, sodium oxybates (Xywav) for its evaluation for use in IH. The most commonly reported adverse events were nausea (21%), headache (16%), anxiety (12%), dizziness (12%), insomnia (9%), hyperhidrosis (8%), decreased appetite (8%), vomiting (7%), and dry mouth (6%). Across all study periods (excluding placebo-controlled patients during DB RWP) 17 (11%) reported adverse effects that led to withdrawal from the study (e.g., anxiety, nausea, insomnia, fatigue, feeling abnormal, fall, decreased appetite, dizziness, parathesis, tremor, parasomnia, confused state, hallucination (visual), and irritability). TEAEs leading to discontinuation that were reported by >1 participant included anxiety (n=4), insomnia (n=3), nausea (n=3), and confusion (n=2).

XX. The calcium, magnesium, potassium, sodium oxybates (Xywav) study population included patients previously treated with stimulant/alerting therapy and allowed patients to continue these agents throughout the study. There is evidence to support concominant use of stimulants and alerting agents (i.e., methylphenidate, solriamfetol, modafinil, etc.) with calcium, magnesium, potassium, sodium oxybates (Xywav) or sodium oxybate (Xyrem).

Investigational or Not Medically Necessary Uses

I. Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Fibromyalgia
   B. Insomnia

References

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2. SUNOSI [Prescribing Information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. October 2019.
3. Scammell TE. Treatment of narcolepsy in adults. UpToDate Inc. https://www.uptodate.com. (Accessed on April 27, 2020.)
4. Scammell TE. Clinical features and diagnosis of narcolepsy in adults. UpToDate Inc. https://www.uptodate.com. Accessed on April 27, 2020.
5. Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007;30(12):1705-11.
6. XyremREMS. Xyrem REMS Program. https://www.xyremrems.com/. Accessed April 27, 2020.
7. Chervin RD. Idiopathic hypersomnia. UpToDate Inc. https://www.uptodate.com. Accessed on September 24, 2021.
8. Freedman N. Quantifying sleepiness. UpToDate Inc. https://www.uptodate.com. Accessed on September 24, 2021.
9. Xywav [Prescribing Information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. October 2021.
10. Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021;17(9):1881–1893.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria for new indication for idiopathic hypersomnia (IH). Removal of idiopathic hypersomnia from Investigational or Not Medically Necessary Uses section. Added IH criteria to both Xyrem and Xywav sections for policy. Updates to supporting evidence.	12/2021
Updated route of approval of Xywav to require trial of Wakix; updated language around trial of Xyrem prior to Xywav to require member has a FDA labeled contraindication or intolerance to Xyrem OR member is sensitive to sodium intake and provider attests dietary salt intake cannot be reduced further. Updates to supporting evidence.	04/2021
Removed need to trial and fail stimulates prior to use with Xyrem for Narcolepsy with excessive daytime sleepiness	01/2021
Update to add new to market Xywav with requirement to trial and fail or demonstrate contraindication or intolerance to Xyrem. Updated clinical trial background on Xywav.	10/2020
Transitioned from criteria to policy. Included information on: • Requirement to be prescribed by or in consultation with a sleep specialist, psychiatrist, or neurologist	05/2020

• Confirmation of diagnosis for narcolepsy • Requirement for chronic narcolepsy defined as three-month history • Requirement that member has functional impairment for activities of daily living • Updated requirements for trial and failure to one stimulant, and modafinil or armodafinil, and Sunosi	
Policy created	02/2012