Wakefulness Agents

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO319

Description

Solriamfetol (Sunosi) is a dopamine and norepinephrine reuptake inhibitor (DNRI).
Pitolisant (Wakix) is a histamine-3 receptor antagonist/reverse agonist.
Sodium oxybate (Xyrem, Lumryz) 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: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
solriamfetol (Sunosi)	75 mg tablets	Excessive sleepiness associated with either OSA or narcolepsy in adults	60 tablets/30 days
	150 mg tablets		30 tablets/30 days
pitolisant (Wakix)	4.45 mg tablets	Excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy	60 tablets/30 days
	17.8 mg tablets	Excessive daytime sleepiness (EDS) in pediatric patients 6 years of age and older with narcolepsy	60 tablets/30 days
generic sodium oxybate	500 mg/mL solution	Narcolepsy with cataplexy or excessive daytime sleepiness in patients greater than 7 years of age Idiopathic hypersomnia in adults	540 mL/30 days
sodium oxybate (Xyrem)			
calcium, magnesium, potassium, sodium oxybates (Xywav)			
sodium oxybate oral powder for suspension (Lumryz)	4.5 g packet	Narcolepsy with cataplexy or excessive daytime sleepiness in patients 7 years of age and older Idiopathic hypersomnia in adults	135 grams/30 days
	6 g packet		180 grams/ 30 days
	7.5 g packet		225 grams/ 30 days
	9 g packet		270 grams/ 30 days
sodium oxybate oral powder for suspension (Lumryz Starter Pack)	Starter Pack		28 packets/28 days

Initial Evaluation

I. **Solriamfetol (Sunosi), pitolisant (Wakix), generic sodium oxybate, sodium oxybate (Xyrem), sodium oxybate ER (Lumryz), or calcium, magnesium, potassium, sodium oxybate (Xywav)** may be considered medically necessary when the following criteria below are met:

A. Medication is prescribed by, or in consultation with, a sleep specialist, psychiatrist, or neurologist; **AND**

B. If request is for generic sodium oxybate, sodium oxybate (Xyrem), sodium oxybate ER (Lumryz), or calcium, magnesium, potassium, sodium oxybate (Xywav):

1. Medication will not be used in combination with sedative hypnotic agents (e.g. benzodiazepines, barbiturates, zolpidem tartrate); **AND**
2. Provider attestation the member does not have a succinic semialdehyde dehydrogenase deficiency; **AND**
3. Provider attestation the member does not have a history of substance abuse; **AND**
4. The request is for brand Xyrem; **AND**
    i. Documentation of intolerance or contraindication to generic sodium oxybate; **AND**

C. A diagnosis of one of the following:

1. **Type 1 Narcolepsy (narcolepsy <u>with cataplexy</u>); AND**
    i. Confirmation of cataplexy defined as episodes of sudden loss of muscle tone; **AND**
    ii. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving); **AND**
    iii. The request is for pitolisant (Wakix); **AND**
        a. Member is six years of age or older**; OR**
    iv. The request is for generic sodium oxybate, sodium oxybate (Xyrem), sodium oxybate ER (Lumryz), or calcium, magnesium, potassium, sodium oxybate (Xywav); **AND**
        a. Member is seven years of age or older; **AND**
        b. Documentation that treatment with pitolisant (Wakix) has been ineffective, contraindicated or not tolerated; **OR**
2. **Type 2 Narcolepsy (narcolepsy <u>without cataplexy</u>)**; **AND**
    i. Confirmation of diagnosis with a sleep study (including polysomnography and multiple sleep latency test); **AND**
    ii. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving); **AND**
    iii. Treatment with the following has been ineffective, contraindicated, or not tolerated:

a. A stimulant (e.g., methylphenidate, amphetamine salts, or dextroamphetamine, etc.); **AND**
b. Modafinil (Provigil) or armodafinil (Nuvigil); **AND**

iv. The request is for solriamfetol (Sunosi); **AND**
a. Member is 18 years of age and older; **OR**

v. The request is for pitolisant (Wakix); **AND**
a. Member is six years of age or older; **AND**
b. Treatment with solriamfetol (Sunosi) has been ineffective, contraindicated, or not tolerated for those 18 years of age and older; **OR**

vi. The request is for generic sodium oxybate, sodium oxybate (Xyrem), sodium oxybate ER (Lumryz), or calcium, magnesium, potassium, sodium oxybate (Xywav); **AND**
a. Member is seven years of age or older; **AND**
b. Treatment with solriamfetol (Sunosi) has been ineffective, contraindicated, or not tolerated for those 18 years of age and older; **AND**
c. Treatment with pitolisant (Wakix) has been ineffective, contraindicated, or not tolerated; **OR**

3. **Excessive Daytime Sleepiness associated with Obstructive Sleep Apnea (OSA); AND**
i. The request is for solriamfetol (Sunosi); **AND**
ii. Member is 18 years of age and older; **AND**
iii. The member has current or prior use of a primary OSA therapy (e.g., CPAP, mandibular advancement device or surgical intervention); **AND**
iv. Treatment with modafinil (Provigil) or armodafinil (Nuvigil) has been ineffective, contraindicated, or not tolerated; **OR**

4. **Idiopathic hypersomnia**; **AND**
i. Member is 18 years of age or older; **AND**
ii. The request is for generic sodium oxybate, sodium oxybate (Xyrem), sodium oxybate ER (Lumryz), or calcium, magnesium, potassium, sodium oxybate (Xywav); **AND**
iii. Provider attestation that hypersomnia is not better explained by medical or neurological disorder, mental disorder, medication use, or substance use disorder; **AND**
iv. Provider attestation that diagnosis has been confirmed via the following:
a. Polysomnography; **AND**
b. Multiple sleep latency test; **AND**

v. Treatment with ALL of the following has been ineffective, contraindicated, or not tolerated:
   a. Modafinil (Provigil) or armodafinil (Nuvigil); **AND**
   b. A stimulant (e.g., methylphenidate, amphetamine salts, or dextroamphetamine, etc.)

II. Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav), solriamfetol (Sunosi), and pitolisant (Wakix) are considered investigational when used for all other conditions, including but not limited to:
   1. Excessive sleepiness associated with Parkinson's Disease or glioblastoma
   2. Shift work sleep disorder (SWSD)
   3. Attention-deficit/hyperactivity disorder (ADHD)
   4. Fatigue not related to narcolepsy or OSA
   5. Fibromyalgia
   6. Insomnia

   A. Solriamfetol (Sunosi)
      1. Major depressive disorder
      2. Steinert myotonic dystrophy syndrome
      3. Type 1 narcolepsy (narcolepsy with cataplexy)

   B. Pitolisant (Wakix)
      1. Excessive daytime sleepiness associated with obstructive sleep apnea
      2. Idiopathic hypersomnia
      3. Refractory restless legs syndrome
      4. Autism spectrum disorders
      5. Prader-Willi Syndrome

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. 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. If request is for generic sodium oxybate, sodium oxybate (Xyrem), sodium oxybate ER (Lumryz), or calcium, magnesium, potassium, sodium oxybate (Xywav) medication will not be used in

combination with sedative hypnotic agents (e.g., benzodiazepines, barbiturates, zolpidem tartrate, etc.)

Supporting Evidence

I. Narcolepsy is a chronic neurological disorder that affects the brain's ability to control sleep-wake cycles. Narcolepsy can greatly affect daily activities. All individuals with narcolepsy have excessive daytime sleepiness (EDS), and it is often the most obvious symptom. Excessive daytime sleepiness is characterized by persistent sleepiness, regardless of how much sleep an individual gets at night. Similarly, many patients with obstructive sleep apnea (OSA) and idiopathic hypersomnia (IH) experience excessive daytime sleepiness, which can negatively affect daily functioning, cognition, mood, and other aspects of well-being. Given the complexities of diagnosis and treatment of these conditions, supervision of treatment by a sleep specialist, psychiatrist, or neurologist is required.

II. Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav) are a part of REMS programs which only allow certified prescribers and pharmacies to dispense these medications. 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, Lumryz) 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, Lumryz) 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). Both agents are oral solutions taken twice nightly. Sodium oxybate (Lumryz) is an extended-release oral powder for suspension that is taken once nightly and contains the same active ingredient as sodium oxybate (Xyrem). Although falls while receiving oxybate treatment have been reported in clinical trials and post-marketing reports, no basis exists to attribute an increased risk of falls to a second nightly dose. Furthermore, each product's drug information label discourages getting out of bed after any oxybate dosing due to sedation. Pitolisant (Wakix) is FDA-approved for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients and adults with narcolepsy.

Solriamfetol (Sunosi) is FDA-approved for the treatment of excessive daytime sleepiness associated with OSA and narcolepsy in adults.

V. There are no direct head-to-head studies comparing pitolisant (Wakix), solriamfetol (Sunosi), sodium oxybate (Xyrem, Lumryz), 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.

Type 1 Narcolepsy (narcolepsy with cataplexy) and Type 2 Narcolepsy (narcolepsy without cataplexy)

VI. All individuals with narcolepsy have EDS, and it is often the most obvious symptom of the disease. While all individuals with narcolepsy will have EDS, cataplexic attacks may or not be characteristic of the patient's disease. Cataplexy is defined as the sudden loss of muscle tone while a person is awake leads to weakness and a loss of voluntary muscle control. It is often triggered by sudden, strong emotions such as laughter, fear, anger, stress, or excitement. The symptoms of cataplexy may appear weeks or even years after the onset of EDS. Some people may only have one or two attacks in a lifetime, while others may experience many attacks a day. Attacks may be mild and involve only a momentary sense of minor weakness in a limited number of muscles, such as a slight drooping of the eyelids. The most severe attacks result in a total body collapse during which individuals are unable to move, speak, or keep their eyes open. But even during the most severe episodes, people remain fully conscious, a characteristic that distinguishes cataplexy from fainting or seizure disorders. The loss of muscle tone during cataplexy resembles paralysis of muscle activity that naturally occurs during REM sleep. Episodes last a few minutes at most and resolve almost instantly on their own. The presence or absence of cataplexy helps distinguish between type 1 and type 2 narcolepsy. Type 1 narcolepsy (previously known as narcolepsy with cataplexy) is diagnosed based on the individual either having low levels hypocretin or reporting cataplexy and having excessive daytime sleepiness via polysomnography or multiple sleep latency test. Type 2 narcolepsy (previously known as narcolepsy without cataplexy) includes patients with EDS that usually do not have muscle weakness triggered by emotions. They frequently have less severe symptoms and have normal levels of the brain hormone hypocretin. Type 2 narcolepsy is also diagnosed with polysomnography or multiple sleep latency test per ICSD-3-TR diagnostic criteria.

VII. The American Academy of Sleep Medicine clinical practice guideline (2021) establishes clinical practice recommendations for treatment of central disorders of hypersomnolence. In adults with narcolepsy, there are strong recommendations for modafinil, pitolisant (Wakix), sodium oxybate, and solriamfetol (Sunosi) for the treatment of narcolepsy in adults. There are conditional recommendations for armodafinil, dextroamphetamine, and methylphenidate for the treatment of narcolepsy in adults. However, only pitolisant (Wakix), sodium oxybate, and dextroamphetamine have shown clinically significant improvements in cataplexy. For pediatric patients with narcolepsy, the guidelines place conditional recommendations for modafinil and sodium oxybate. Similar to adult populations, only pitolisant (Wakix) have critical outcomes showing clinically significant improvements in the treatment of cataplexy in children. Guidelines have not been updated since the FDA approved pitolisant (Wakix) for the treatment of

treatment of excessive daytime sleepiness (EDS) in pediatric patients 6 years of age and older with narcolepsy.

VIII. A joint European guideline from the European Academy of Neurology (EAN), the European Sleep Research Society (ESRS) and the European Narcolepsy Network (EU-NN) (2021) establishes clinical practice recommendations for the management of narcolepsy in both adults and children. EAN/ESRS/EU-NN guidelines recommend therapies in a sequential manner dependent on primary symptomatology (EDS unique, EDS with cataplexy, and EDX with cataplexy and disturbed nocturnal sleep). Guidelines acknowledge that given a lack of head-to-head studies, comparisons of efficacy between different stimulants/wake-promoting drugs are difficult. The main pharmacotherapy recommendations can be summarized as follows:

- Excessive daytime sleepiness (EDS) in adults – modafinil, pitolisant (Wakix), sodium oxybate (SXB), solriamfetol (Sunosi) (all strong); methylphenidate, amphetamine derivatives (both weak)
- EDS with cataplexy in adults – SXB, venlafaxine, clomipramine (all strong) and pitolisant (Wakix) (weak)
- EDS in children– SXB (strong), modafinil, methylphenidate, pitolisant (Wakix), amphetamine derivatives (all weak)
- EDS with cataplexy in children – SXB (strong), antidepressants (weak).

IX. Pitolisant (Wakix) is FDA-approved for the treatment of excessive daytime sleepiness in patients six years of age or older with narcolepsy. Pitolisant (Wakix) was studied in adults in three randomized controlled trials, and one open-label, single-arm, long term safety & efficacy trial. HARMONY I and I bis included modafinil as an active comparator to pitolisant (Wakix). In pediatric patients six years of age or older with narcolepsy, pitolisant (Wakix) was studied in one multicenter, randomized, double-blinded, placebo-controlled study (Study 4).

- 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. The ESS score has been commonly used in standard practice and was originally validated through a study in 1991.
- 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 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.

- 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).
- Study 4 (n=110): The primary efficacy outcome was the change in Ullanlinna Narcolepsy Scale (UNS) total score though the FDA approved on the bases of change in in excessive daytime sleepiness as measured by the Pediatric Daytime Sleepiness Scale (PDSS). Pitolisant (Wakix) demonstrated statistically significantly greater improvement on the least square mean change from baseline to the end of treatment in final PDSS total score compared to placebo, of -3.41 points (95% CI: -5.52, -1.31).
- The use of pitolisant (Wakix) in the treatment of narcolepsy with cataplexy was established in HARMONY CTP with supporting evidence in HARMONY I. Primary outcomes of HARMONY CTP evaluated weekly rate of cataplexy (WRC) while HARMONY I, Daily Rate of Cataplexy (DRC) was evaluated as a secondary endpoint to support the use in cataplexy. Secondary outcomes of DRC in HARMONY I showed a significant improvement DRC.

X. Solriamfetol (Sunosi) is FDA-approved for the treatment of adult patients with excessive daytime sleepiness associated with narcolepsy. The efficacy and safety of solriamfetol (Sunosi) was established in a Phase 3, multi-center, double-blind, placebo-controlled, randomized trial which included patients with either type I or type II narcolepsy (n=239). Compared to the placebo group (n= 114), patients randomized to 150 mg solriamfetol (Sunosi) (n=116) showed statistically significant improvements on the MWT (treatment effect difference: 7.7 minutes) and on the ESS (treatment effect difference: 3.8 points). Change in the mean and median weekly number of cataplexy attacks was an exploratory endpoint among the subgroup of patients who reported the presence of cataplexy. These patients completed a cataplexy frequency diary to record the number of cataplexy attacks that they had each day, beginning after discontinuation of narcolepsy medication and through week 12. There was no clear effect of solriamfetol (Sunosi) on the number of cataplexy attacks per week among patients with cataplexy.

XI. 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 9 g 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).

XII. 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 ($p<0.001$).

XIII. For the treatment of narcolepsy with cataplexy and excessive daytime sleepiness in pediatrics, 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 ($p=0.0004$).

XV. Sodium oxybate (Lumryz) is FDA-approved for treatment of narcolepsy with cataplexy and excessive daytime sleepiness in pediatric patients seven years of age and older as well as adults. Safety and efficacy in adult populations was evaluated in the REST-ON trial, a double-blind, randomized, placebo-controlled trial that evaluated once nightly administration of sodium oxybate (Lumryz) in 212 patients with narcolepsy, 16 years of age or older. Patients were randomized 1:1 to receive sodium oxybate (Lumryz) or placebo. The study consisted of 13-weeks of treatment of escalating doses (g/night) of sodium oxybate (Lumryz) at 4.5 g week one, 6 g weeks two-three, 7.5 g weeks four-eight, and 9 g weeks nine-thirteen. The three co-primary endpoints were the maintenance of wakefulness test (MWT), clinical global Impression-improvement (CGI-I), and mean change in weekly cataplexy attacks. A statistically significant improvement was seen on the MWT, CGI-I, and mean weekly cataplexy attacks, for the 6 g (Week 3), 7.5 g (Week 8), and 9 g (Week 13) dose of sodium oxybate (Lumryz) compared to the placebo group ($p<0.001$).

XVI. The effectiveness of sodium oxybate (Lumryz) for cataplexy and excessive daytime sleepiness (EDS) in pediatric narcolepsy is based upon a clinical study in patients treated with immediate-release sodium oxybate (Xyrem).

Excessive Daytime Sleepiness associated with Obstructive Sleep Apnea

XVI. Obstructive sleep apnea (OSA) is a sleep-related breathing disorder resulting from repetitive collapse of the upper airway, which causes intermittent episodic hypoxia and impaired ventilation during sleep. OSA is diagnosed based on the presence of positive polysomnography (PSG) or home sleep apnea test findings of predominantly obstructive respiratory events (e.g., apneas, hypopneas, or respiratory effort–related arousals).

XVII. Per AASM guidelines for the Evaluation, Management, and Long-Term Care of Obstructive Sleep Apnea in Adults state positive airway pressure (PAP) is the treatment of choice for mild, moderate, and sever OSA and should be offered as an option to all patients. Additionally,

custom made oral appliances (OA), such as mandibular repositioning appliances, may improve upper airway patency during sleep by enlarging the upper airway and/or by decreasing upper airway collapsibility. Although not as efficacious as CPAP, OAs are indicated for use in patients with mild to moderate OSA who prefer OAs to CPAP, or who do not respond to CPAP, are not appropriate candidates for CPAP, or who fail CPAP or behavioral measures such as weight loss or sleep position change.

XVIII. EDS can be a prominent symptom of OSA and occurs when sleepiness intrudes into activities of daily living. Although EDS can be reduced with primary OSA treatment, such as continuous positive airway pressure (CPAP) therapy, a substantial proportion of patients continue to experience EDS despite receiving optimized primary OSA therapy.

XIX. AASM guidelines recommend use of modafinil for the treatment of residual excessive daytime sleepiness in OSA patients who have sleepiness despite effective PAP treatment who are lacking any other identifiable cause for their sleepiness. Prior to use of modafinil other causes of residual sleepiness should be ruled out including suboptimal objective adherence with PAP, ill-fitting PAP masks, insufficient sleep, poor sleep hygiene, and other sleep disorders (e.g., narcolepsy, restless leg syndrome, depression, etc.).

XX. The efficacy and safety of solriamfetol (Sunosi) for the treatment of adults (18 and older) with EDS and OSA was demonstrated in a 12-week, multi-center, randomized, double-blind, placebo-controlled trial of 476 patients. In clinical trials, patients with OSA were required to be stable for greater than one month on primary OSA therapy (e.g. CPAP, mandibular advancement device, or surgical intervention) prior to use of solriamfetol (Sunosi). Participants were randomized to receive solriamfetol (Sunosi) 37.5 mg, 75 mg, 150 mg, or 300 mg (two times the maximum recommended daily dose). Compared to the placebo group, patients randomized to 37.5 mg, 75 mg, and 150 mg solriamfetol (Sunosi) showed statistically significant improvements on the MWT (treatment effect difference: 4.5 minutes, 8.9 minutes, and 10.7 minutes respectively) and ESS (treatment effect difference: 1.9 points, 1.7 points, and 4.5 points respectively) at Week 12.

Idiopathic Hypersomnia

XXI. While sodium oxybate (Xyrem, Lumryz) 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.

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

XXIII. 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.

XXIV. 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.

XXV. 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.

XXVI. 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) ($p<0.0001$).

XXVII. 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) ($p<0.0001$).

Investigational or Not Medically Necessary Uses

I. Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav), solriamfetol (Sunosi), and pitolisant (Wakix) currently have insufficient evidence supporting efficacy or safety in the following conditions:
   A. Shift work sleep disorder (SWSD)
   B. Attention-deficit/hyperactivity disorder (ADHD)
   C. Fatigue not related to narcolepsy or OSA
   D. Excessive sleepiness associated with Parkinson's Disease
   E. Fibromyalgia
   F. Insomnia

II. Solriamfetol (Sunosi) is currently being studied in multiple clinical trials; however, evidence is currently limited to proof-of-concept. There is insufficient safety and efficacy information to support use in the following conditions:
   A. Major depressive disorder
   B. Steinert myotonic dystrophy syndrome

III. Pitolisant (Wakix) is currently being studied in multiple clinical trials; however, evidence is currently limited to proof-of-concept. There is insufficient safety and efficacy information to support use in the following conditions:
   A. Excessive daytime sleepiness associated with obstructive sleep apnea
   B. Idiopathic hypersomnia
   C. Refractory restless legs syndrome
   D. Autism spectrum disorders
   E. Prader-Willi Syndrome

Appendix

I. Treatment Table

	Type 1 Narcolepsy (narcolepsy with cataplexy)	Type 2 Narcolepsy (narcolepsy without cataplexy)	EDS w/ OSA	IH
Generic sodium oxybate	X	X*		X†
Xyrem IR oral soln	X	X*		X†
Lumryz ER oral susp	X*	X*		X†
Xywav	X*	X*		X
Wakix	X¥	X¥		
Sunosi		X	X	

* Adult + Pediatric indication (patients ≥7yo)
¥ Adult + Pediatric indication (patients ≥6yo)
† Used off label per policy

II. Dose conversion for patients switching from twice nightly oxybate to once nightly sodium oxybate (Lumryz)
   a. Switching from immediate-release sodium oxybate solution, patients may be switched to sodium oxybate extended-release at the nearest equivalent dosage in grams per

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Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updates to combine Xyrem, Lumryz, Xywav, Wakix, and Sunosi into one Wakefulness Agents policy. Update to include age expansion of pitolisant (Wakix) for pediatrics 6 years and older and sodium oxybate ER (Lumryz) for pediatric patients 7 years and older. Update supporting evidence to include disease state background and terminology of type 1 or type 2 narcolepsy. Updated to allow initial authorization of 12 months.	04/2025
Removed criteria "Use will not be in combination with sodium oxybate (Xyrem) or calcium, magnesium, potassium, sodium oxybates (Xywav)"	12/2021
Updated policy to include new indication for Wakix use in patients with narcolepsy with cataplexy.	**12/2020**
Updated policy to require trial and failure of solriamfetol (Sunosi) prior to approval of pitolisant (Wakix) for narcolepsy.	**06/2020**
Addition of pitolisant (Wakix) information for coverage including: experimental/investigational, coverage for narcolepsy, quantity limits, and evidence base.	09/2019
New policy for solriamfetol (Sunosi).	08/2019