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PHARMACY POLICY – 5.01.599

Pharmacologic Treatment of Sleep Disorders

Effective Date:	Sept. 1, 2024	RELATED MEDICAL POLICIES:
Last Revised:	Aug. 13, 2024	10.01.524 Sleep Disorder Management: Services Reviewed by Carelon Medical Benefits Management
Replaces:	N/A	

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Introduction

Excessive daytime sleepiness is a common complaint among those with sleep-related problems. Excessive daytime sleepiness itself is not a disorder. However, it can be a symptom caused by other medical problems. These are conditions like narcolepsy, obstructive sleep apnea, and Parkinson disease. People with daytime sleepiness describe feeling drowsy or sluggish most of the time. These symptoms can interfere with work or school. They also can increase the risk of accidents on the road or at work. The first step in treating daytime sleepiness is evaluating its underlying cause. In some cases, medication may be an appropriate treatment. This policy describes when medications may be medically necessary for specific types of sleep disorders and excessive daytime sleepiness.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity

Brand sodium oxybate, Xyrem (sodium oxybate)	**Brand sodium oxybate and Xyrem (sodium oxybate) may be considered medically necessary for the following labeled indications:**
	• Treatment of cataplexy in narcolepsy individuals aged 7 years and older and when cataplexy is documented by:
	  ○ Brief episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking
	  OR
	  ○ In children or in individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers
	OR
	• Treatment of excessive daytime sleepiness (recurrent periods within the same day of an irrepressible need to sleep, lapsing into sleep, or napping, that have been occurring at least 3 times per week over at least the previous 3 months) in narcolepsy individuals, when ALL of the following conditions are met:
	  ○ Diagnosis of narcolepsy* has been documented by a sleep study
	  AND
	  ○ Prior therapy with a stimulant medication (e.g., methylphenidate) was ineffective, not tolerated or contraindicated
	  AND
	  ○ Prior therapy with modafinil (Provigil) or armodafinil (Nuvigil) was ineffective, not tolerated, or contraindicated
	AND
	• Dose prescribed is ≤ 9 grams per day
	AND
	• Brand sodium oxybate and Xyrem (sodium oxybate) is not used in combination with Lumryz (sodium oxybate), Sunosi (solriamfetol), Wakix (pitolisant), or Xywav (calcium magnesium, potassium, and sodium oxybates)

Drug	Medical Necessity
	***Diagnosis of narcolepsy is defined as recurrent periods of excessive daytime sleepiness (recurrent periods within the same day of an irrepressible need to sleep, lapsing into sleep, or napping, that have been occurring at least 3 times per week over at least the previous 3 months), and at least one of the following:** • Episodes of cataplexy **OR** • Nocturnal sleep polysomnography (PSG) showing rapid eye movement (REM) sleep latency ≤ 15 minutes **OR** • Multiple sleep latency (MSLT) showing a mean sleep latency ≤ 8 minutes and 2 or more sleep onset REM periods **Medical records showing diagnosis suggestive of narcolepsy is not considered diagnostic of narcolepsy. For individuals unable to discontinue REM suppressing medications who do not meet the MSLT criteria, the diagnosis of narcolepsy will be determined on a case-by-case basis.** **Note:** Requirement trial with a stimulant and modafinil/armodafinil may be waived if medical records show symptoms consistent with cataplexy.
Lumryz (sodium oxybate)	**Lumryz (sodium oxybate) may be considered medically necessary for the following labeled indications:** • Treatment of cataplexy in narcolepsy individuals aged 18 years and older and when cataplexy is documented by: ○ Brief episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking **OR** • Treatment of excessive daytime sleepiness (recurrent periods within the same day of an irrepressible need to sleep, lapsing into sleep, or napping, that have been occurring at least 3 times per week over at least the previous 3 months) in narcolepsy individuals, when ALL of the following conditions are met:

Drug	Medical Necessity
	○ Diagnosis of narcolepsy* has been documented by a sleep study **AND** ○ Prior therapy with a stimulant medication (e.g., methylphenidate) was ineffective, not tolerated or contraindicated **AND** ○ Prior therapy with modafinil (Provigil) or armodafinil (Nuvigil) was ineffective, not tolerated, or contraindicated **AND** • Prior therapy with brand sodium oxybate or Xyrem (sodium oxybate) was ineffective, not tolerated, or contraindicated **AND** • Dose prescribed is ≤ 9 grams per day **AND** • Lumryz (sodium oxybate) is not used in combination with Sunosi (solriamfetol), Wakix (pitolisant), brand sodium oxybate, Xyrem (sodium oxybate), or Xywav (calcium magnesium, potassium, and sodium oxybates) ***Diagnosis of narcolepsy is defined as recurrent periods of excessive daytime sleepiness (recurrent periods within the same day of an irrepressible need to sleep, lapsing into sleep, or napping, that have been occurring at least 3 times per week over at least the previous 3 months), and at least one of the following:** • Episodes of cataplexy **OR** • Nocturnal sleep polysomnography (PSG) showing rapid eye movement (REM) sleep latency ≤ 15 minutes **OR** • Multiple sleep latency (MSLT) showing a mean sleep latency ≤ 8 minutes and 2 or more sleep onset REM periods **Medical records showing diagnosis suggestive of narcolepsy is not considered diagnostic of narcolepsy. For individuals unable to discontinue REM suppressing medications who do not meet**

Drug	Medical Necessity
	the MSLT criteria, the diagnosis of narcolepsy will be determined on a case-by-case basis. **Note:** Requirement trial with a stimulant and modafinil/armodafinil may be waived if medical records show symptoms consistent with cataplexy.

Xywav (calcium magnesium, potassium, and sodium oxybates)	**Xywav (calcium magnesium, potassium, and sodium oxybates) may be considered medically necessary for the following labeled indications:**
	• Treatment of cataplexy in narcolepsy individuals aged 7 years and older and when cataplexy is documented by:
	  ○ Brief episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking
	  OR
	  ○ In children or in individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers
	OR
	• Treatment of excessive daytime sleepiness (recurrent periods within the same day of an irrepressible need to sleep, lapsing into sleep, or napping, that have been occurring at least 3 times per week over at least the previous 3 months) in narcolepsy individuals, when ALL of the following conditions are met:
	  ○ Diagnosis of narcolepsy* has been documented by a sleep study
	  AND
	  ○ Prior therapy with a stimulant medication (e.g., methylphenidate) was ineffective, not tolerated or contraindicated
	  AND
	  ○ Prior therapy with modafinil (Provigil) or armodafinil (Nuvigil) was ineffective, not tolerated, or contraindicated
	AND
	• Prior therapy with brand sodium oxybate or Xyrem (sodium oxybate) was ineffective, not tolerated, or contraindicated

Drug	Medical Necessity
	○ **Exception:** this may be granted if the individual has a concomitant diagnosis of heart failure, hypertension, or renal impairment **AND** • Dose prescribed is ≤ 9 grams per day **AND** • Xywav (calcium magnesium, potassium, and sodium oxybates) is not used in combination with Lumryz (sodium oxybate), Sunosi (solriamfetol), Wakix (pitolisant), brand sodium oxybate, or Xyrem (sodium oxybate) ***Diagnosis of narcolepsy is defined as recurrent periods of excessive daytime sleepiness (recurrent periods within the same day of an irrepressible need to sleep, lapsing into sleep, or napping, that have been occurring at least 3 times per week over at least the previous 3 months), and at least one of the following:** • Episodes of cataplexy **OR** • Nocturnal sleep polysomnography (PSG) showing rapid eye movement (REM) sleep latency ≤ 15 minutes **OR** • Multiple sleep latency (MSLT) showing a mean sleep latency ≤ 8 minutes and 2 or more sleep onset REM periods **Medical records showing diagnosis suggestive of narcolepsy is not considered diagnostic of narcolepsy. For individuals unable to discontinue REM suppressing medications who do not meet the MSLT criteria, the diagnosis of narcolepsy will be determined on a case-by-case basis.** **Note:** Requirement trial with a stimulant and modafinil/armodafinil may be waived if medical records show symptoms consistent with cataplexy. **Xywav (calcium magnesium, potassium, and sodium oxybates) may be considered medically necessary for the treatment of idiopathic hypersomnia when the following criteria are met:**

Drug	Medical Necessity

	• Individual is 18 years of age or older
	AND
	• Diagnosed with idiopathic hypersomnia** (requires documented sleep study)
	AND
	• Prior therapy with a stimulant medication (e.g., methylphenidate) was ineffective, not tolerated or contraindicated
	AND
	• Prior therapy with modafinil (Provigil) or armodafinil (Nuvigil) was ineffective, not tolerated, or contraindicated
	AND
	• Dose prescribed is ≤ 9 grams per day
	AND
	• Xywav (calcium magnesium, potassium, and sodium oxybates) is not used in combination with Lumryz (sodium oxybate), Sunosi (solriamfetol), Wakix (pitolisant), brand sodium oxybate, or Xyrem (sodium oxybate)
	
	****Diagnosis of idiopathic hypersomnia is defined as:**
	• Daily periods of irrepressible need to sleep or daytime lapses into sleep for at least three months
	AND
	• Absence of cataplexy
	AND
	• No other identifiable cause for hypersomnia such as another sleep disorder, medical or psychiatric disorder, or use of drugs
	AND
	• Multiple sleep latency (MSLT) showing:
	  ○ A mean sleep latency ≤ 8 minutes; **AND**
	  ○ Fewer than 2 sleep onset rapid eye movement (REM) periods across all 5 naps
	OR
	• Total 24-hour sleep time is ≥ 660 minutes on 24-hour polysomnography (PSG)

Drug	Medical Necessity
Sunosi (solriamfetol)	**Sunosi (solriamfetol) may be considered medically necessary for the following labeled indications:** • Treatment of excessive daytime sleepiness (recurrent periods within the same day of an irrepressible need to sleep, lapsing into sleep, or napping, that have been occurring at least 3 times per week over at least the previous 3 months) in adult individuals with narcolepsy or obstructive sleep apnea, when ALL of the following conditions are met: ○ Diagnosis of narcolepsy* or obstructive sleep apnea** has been documented by a sleep study **AND** ○ Prior therapy with a stimulant medication (e.g., methylphenidate) was ineffective, not tolerated or contraindicated **AND** ○ Prior therapy with modafinil (Provigil) or armodafinil (Nuvigil) was ineffective, not tolerated or contraindicated **AND** ○ Dose prescribed is ≤ 150 mg once daily **AND** ○ Sunosi (solriamfetol) is not used in combination with Lumryz (sodium oxybate), Wakix (pitolisant), brand sodium oxybate, Xyrem (sodium oxybate), or Xywav (calcium magnesium, potassium, and sodium oxybates) ***Diagnosis of narcolepsy is defined as recurrent periods of excessive daytime sleepiness (recurrent periods within the same day of an irrepressible need to sleep, lapsing into sleep, or napping, that have been occurring at least 3 times per week over at least the previous 3 months), and at least one of the following:** • Episodes of cataplexy **OR** • Nocturnal sleep polysomnography (PSG) showing rapid eye movement (REM) sleep latency ≤ 15 minutes **OR**

Drug	Medical Necessity

	• Multiple sleep latency (MSLT) showing a mean sleep latency ≤ 8 minutes and 2 or more sleep onset REM periods
	
	****Diagnosis of obstructive sleep apnea in adults is defined as:**
	• The apneic/hypopneic index (AHI) is ≥ 15 events per hour, including a minimum of 30 events documented per sleep study
	OR
	• The AHI is ≥ 5 events per hour and < 15 events per hour, including a minimum of 10 events documented per sleep study, **AND** documentation of:
	  ○ History of stroke; **OR**
	  ○ Hypertension (systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg); **OR**
	  ○ Ischemic heart disease; **OR**
	  ○ Symptoms of impaired cognition, mood disorders, or insomnia; **OR**
	  ○ Excessive daytime sleepiness (documented by either Epworth Sleepiness Scale > 10 or MSLT < 6); **OR**
	  ○ Greater than 20 episodes of desaturation (i.e., oxygen saturation of less than 85%) during a full night sleep study, or any 1 episode of oxygen desaturation (i.e., oxygen saturation of less than 70%); **OR**
	  ○ Obesity (BMI > 35)
	
	Medical records showing diagnosis suggestive of narcolepsy or obstructive sleep apnea are not considered diagnostic. For individuals unable to discontinue REM suppressing medications who do not meet the MSLT criteria, the diagnosis of narcolepsy will be determined on a case-by-case basis.

Wakix (pitolisant)	**Wakix (pitolisant) may be considered medically necessary for the following labeled indications:** • Treatment of cataplexy in adult individuals with narcolepsy when cataplexy is documented by: ○ Brief episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking **OR**

Drug	Medical Necessity
	○ In individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers **OR** • Treatment of excessive daytime sleepiness (recurrent periods within the same day of an irrepressible need to sleep, lapsing into sleep, or napping, that have been occurring at least 3 times per week over at least the previous 3 months) in individuals aged 6 years and older with narcolepsy when ALL of the following conditions are met: ○ Diagnosis of narcolepsy* has been documented by a sleep study **AND** ○ Prior therapy with modafinil (Provigil) or armodafinil (Nuvigil) was ineffective, not tolerated or contraindicated **AND** • Individual does not have severe hepatic impairment (**Child-Pugh C**) as documented by laboratory tests **AND** • Dose prescribed is ≤ 35.6 mg once daily **AND** • Wakix (pitolisant) is not used in combination with Lumryz (sodium oxybate), Sunosi (solriamfetol), brand sodium oxybate, Xyrem (sodium oxybate), or Xywav (calcium magnesium, potassium, and sodium oxybates) ***Diagnosis of narcolepsy is defined as recurrent periods of excessive daytime sleepiness (recurrent periods within the same day of an irrepressible need to sleep, lapsing into sleep, or napping, that have been occurring at least 3 times per week over at least the previous 3 months), and at least one of the following:** • Episodes of cataplexy **OR** • Nocturnal sleep polysomnography (PSG) showing rapid eye movement (REM) sleep latency ≤ 15 minutes

Drug	Medical Necessity
	OR • Multiple sleep latency (MSLT) showing a mean sleep latency ≤ 8 minutes and 2 or more sleep onset REM periods **Medical records showing diagnosis suggestive of narcolepsy are not considered diagnostic. For individuals unable to discontinue REM suppressing medications who do not meet the MSLT criteria, the diagnosis of narcolepsy will be determined on a case-by-case basis.**

Drug	Investigational
Brand sodium oxybate, Xyrem (sodium oxybate), Lumryz (sodium oxybate), Xywav (calcium magnesium, potassium, and sodium oxybates), Sunosi (solriamfetol), Wakix (pitolisant)	**All other uses of brand sodium oxybate, Xyrem (sodium oxybate), Lumryz (sodium oxybate), Xywav (calcium magnesium, potassium, and sodium oxybates), Sunosi (solriamfetol), or Wakix (pitolisant) for conditions not outlined in this policy are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Brand sodium oxybate, Xyrem (sodium oxybate), Lumryz (sodium oxybate), Xywav (calcium magnesium, potassium, and sodium oxybates), Sunosi (solriamfetol), or Wakix (pitolisant) may be approved up to 1 year.**
Re-authorization criteria	**Future re-authorization of brand sodium oxybate, Xyrem (sodium oxybate), Lumryz (sodium oxybate), or Xywav (calcium magnesium, potassium, and sodium oxybates) may be approved up to 1 year in duration when documentation provided at the time of re-authorization show:** • Diagnosis of narcolepsy has been documented by a sleep study performed prior to starting brand sodium oxybate, Xyrem Lumryz, or Xywav or diagnosis of idiopathic hypersomnia has

Length of Approval	
Approval	**Criteria**
	been documented by a sleep study performed prior to starting Xywav. **Note:** This requirement only applies to individuals started on brand sodium oxybate, Xyrem, Lumryz, or Xywav with a prior insurer **AND** • Documentation of continued clinical response **AND** • Dose prescribed is ≤ 9 grams per day **Future re-authorization of Sunosi (solriamfetol) may be approved up to 1 year in duration when documentation provided at the time of re-authorization show:** • Diagnosis of narcolepsy or obstructive sleep apnea has been documented by a sleep study performed prior to starting Sunosi **Note:** This requirement only applies to individuals started on Sunosi with a prior insurer **AND** • Documentation of continued clinical response **AND** • Dose prescribed is ≤ 150 mg once daily **Future re-authorization of Wakix (pitolisant) may be approved up to 1 year in duration when documentation provided at the time of re-authorization show:** • Diagnosis of narcolepsy has been documented by a sleep study performed prior to starting Wakix **Note:** This requirement only applies to individuals started on Wakix with a prior insurer **AND** • Documentation of continued clinical response **AND**

Length of Approval	
Approval	**Criteria**
	• Dose prescribed is ≤ 35.6 mg once daily

Drug	Dosage and Quantity Limit
Brand sodium oxybate, Xyrem (sodium oxybate), Xywav (calcium magnesium, potassium, and sodium oxybates)	• Brand sodium oxybate, Xyrem, and Xywav 0.5 g per mL, quantity limit of 270 grams (540 mL; 3 bottles) per 30 days • Doses greater than 9 grams per day are not supported by clinical evidence and therefore are considered not medically necessary.
Lumryz (sodium oxybate)	• Lumryz (sodium oxybate) 4.5 g per packet, 6 g per packet, 7.5 g per packet, 9 g per packet, quantity limit of 30 packets per 30 days • Doses greater than 9 grams per day are not supported by clinical evidence and therefore are considered not medically necessary.
Sunosi (solriamfetol)	• Sunosi 75 mg tablet, quantity limit of 60 tablets per 30 days • Sunosi 150 mg tablet, quantity limit of 30 tablets per 30 days • Doses greater than 150 mg once daily are not supported by clinical evidence and therefore are considered not medically necessary.
Wakix (pitolisant)	• Wakix 17.8 mg tablet, quantity limit of 60 tablets per 30 days • Doses greater than 35.6 mg once daily are not supported by clinical evidence and therefore are considered not medically necessary.

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the relevant history, diagnosis, and medication history **AND** • Documented sleep study results when required

Child-Pugh Score

Child Pugh Score is a scoring system used to measure the severity of chronic liver disease (including cirrhosis). The purpose of this scoring system is to allow clinicians to objectively describe liver function.

The score is composed of the following components:

- Total bilirubin (mg/dL):
  - <34: 1 point
  - 34 to 50: 2 points
  - >50: 3 points
- Serum albumin (g/L):
  - >35: 1 point
  - 28 to 35: 2 points
  - <28: 3 points
- INR:
  - <1.7: 1 point
  - 1.7 to 2.3; 2 points
  - >2.3: 3 points
- Presence/absence of ascites:
  - None: 1 point
  - Mild: 2 points
  - Moderate to severe: 3 points
- Presence/absence of hepatic encephalopathy:
  - None: 1 point
  - Grades I to II (or suppressed with medication): 2 points
  - Grades III to IV (or refractory): 3 points
- Then the point scores are added together and classified as follows:
  - Class A: 5 to 6 points (well-compensated disease)
  - Class B: 7 to 9 points (significant functional compromise)
  - Class C: 10 to 15 points (decompensated disease)
- If individual has primary biliary cirrhosis or sclerosing cholangitis, then bilirubin is classified differently:
  - <68: 1 point
  - 68 to 170: 2 points
  - >170: 3 points

Coding

N/A

Related Information

Consideration of Age

The ages noted in the policy statement for brand sodium oxybate, Xyrem (sodium oxybate), Lumryz (sodium oxybate), Xywav (calcium magnesium, potassium, and sodium oxybates), Sunosi (solriamfetol), and Wakix (pitolisant) are based on FDA approval.

Benefit Application

This policy is managed through the pharmacy benefit.

Evidence Review

Background

Excessive daytime sleepiness (EDS) is defined as the inability to stay awake and alert during usual waking hours that occurs almost daily and persists for at least three months. Among obstructive sleep apnea (OSA) individuals, men are twice as likely as women to suffer from EDS. Approximately 7.5 million Americans suffer from EDS due to OSA or narcolepsy. EDS puts individuals at increased risk of impaired cognitive functioning and accidental injuries, as well as decreased work productivity and quality of life. Tiredness, fatigue, and lack of energy are common complaints. The potential causes of EDS are numerous and fall under several general classifications: central disorders (e.g., narcolepsy), breathing disorders (e.g., OSA), circadian rhythm issues (e.g., jet lag), movement disorders (e.g., restless leg syndrome), psychiatric disorders, substance abuse, and various diseases (e.g., Parkinson).

Summary of Evidence

Xyrem (sodium oxybate)

Xyrem (sodium oxybate) is a CNS depressant. The mechanism of action of Xyrem in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB), an endogenous compound and metabolite of the neurotransmitter GABA. Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma and death. It is hypothesized that the therapeutic effects of Xyrem on cataplexy and excessive daytime sleepiness are mediated through GABA-B actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons. Xyrem is a Schedule III controlled substance. Because of its abuse/diversion potential, it is only available from a single pharmacy through a limited distribution scheme, the Xyrem Success Program. Both prescribers and individuals must be registered in this program to obtain the drug. Serious side effects observed in individuals taking Xyrem include hallucinations, agitation, severe confusion, abnormal thinking, sleep disturbances and depression.

The efficacy of Xyrem in the treatment of cataplexy was evaluated in two 4-week randomized, double-blind, placebo-controlled, multicenter, parallel-group trials, n=136 and 55 respectively. The high percentages of concomitant stimulant use in these studies make it impossible to assess the efficacy and safety independent of stimulant use. Doses of 6-9 g per night resulted in statistically significant reductions in frequency of cataplexy attacks. The 3 g per night dose had little effect. Overall, the evidence supporting this indication is of low quality.

The efficacy of Xyrem in the treatment of excessive daytime sleepiness in individuals with narcolepsy was evaluated in an 8-week randomized, double-blind, placebo-controlled trial, n=228. Most of these individuals were also being treated with CNS stimulants. Statistically significant improvements in Epworth Sleepiness Scores (ESS) were seen with 6 and 9 g doses. A second multicenter randomized, double-blind, placebo-controlled, parallel-group trial evaluated 222 individuals on modafinil at baseline, who were randomized to placebo, Xyrem, modafinil, or Xyrem plus modafinil. Xyrem dose was 6g per night for 4 weeks, followed by 9g per night for 4 weeks. Modafinil was continued in the modafinil groups at the individual's prior dose. A statistically significant improvement in the Maintenance of Wakefulness Test (MWT) score from baseline at Week 8 was seen in the Xyrem and Xyrem plus modafinil groups compared to placebo. The trial was not designed to compare Xyrem with modafinil.

Studies have been conducted to demonstrate the efficacy of Xyrem in fibromyalgia individuals; however, all of these have been placebo-controlled. In 2010, FDA rejected an application for use in fibromyalgia. FDA panel members expressed serious concerns about the potential for abuse and diversion of sodium oxybate. This concern was felt to outweigh any benefits that might accrue and is supported by the lack of any head-to-head comparison with alternative treatments for fibromyalgia, none of which have the level of abuse potential seen with Xyrem.

Xywav (calcium magnesium, potassium, and sodium oxybates)

Xywav (calcium magnesium, potassium, and sodium oxybates) is a CNS depressant and similar to Xyrem but with a lower sodium content than Xyrem. Efficacy of Xywav for the treatment of cataplexy and excessive daytime sleepiness in adult individuals with narcolepsy was established in a double-blind, placebo-controlled, randomized-withdrawal study. This study had two parts, consisting of the main study, followed by an optional 24-week open-label extension (OLE). The main study consisted of a 12-week open-label optimized treatment and titration period (OL OTTP), followed by a 2-week stable-dose period (SDP), and finally a 2-week double-blind randomized-withdrawal period (DB RWP). Study 1 enrolled 201 individuals with narcolepsy with cataplexy, 18 to 70 years of age, with a baseline history of at least 14 cataplexy attacks in a typical 2-week period prior to any treatment for narcolepsy symptoms. Of the 201 individuals, 134 were randomized 1:1 to continue treatment with Xywav or to placebo in the 2-week DB RWP. The total nightly dose of Xywav was administered in two equally divided doses in 90% (62/69) of individuals. Unequal doses were administered in 10% (7/69) of individuals treated with Xywav. The primary efficacy endpoint was the change in frequency of cataplexy attacks from the 2 weeks of the SDP to the 2 weeks of the DB RWP. The key secondary endpoint was the change in the Epworth Sleepiness Scale (ESS) score, as a measure of reduction in EDS from the end of the SDP to the end of the DB RWP. Individuals taking stable doses of Xywav who discontinued Xywav treatment and were randomized to placebo during the DB RWP experienced a significant worsening in the average weekly number of cataplexy attacks and in ESS score, compared with individuals randomized to continue treatment with Xywav.

The efficacy of Xywav for the treatment of idiopathic hypersomnia (IH) in adult individuals as a once or twice nightly regimen was established in a double-blind, placebo-controlled, randomized-withdrawal, study (Study 2, NCT03533114). Study 2 consisted of a minimum of 10-week open-label treatment titration and optimization period (OL OTTP), (with up to 4 additional weeks) to allow for an optimally effective and tolerable dose and regimen followed by a 2-week stable dose period (SDP), a 2-week double-blind, randomized withdrawal period (DB RWP), and a 24-week open label safety extension period (OLE).

Study 2 enrolled 154 individuals with idiopathic hypersomnia, 19 to 75 years of age. Of the 154 individuals, 115 were evaluable for efficacy data and were randomized 1:1 to continue treatment with Xywav or to placebo in the 2-week DB RWP. In the safety population, overall, the median age was 39 years (range: 19 to 75). At baseline, 2% of individuals were taking Xyrem only, 4% of individuals were taking Xyrem and an additional stimulant or alerting agent, 54% of individuals were not currently taking Xyrem but were taking a stimulant or alerting agent, and 41% were treatment naïve. CNS stimulants were allowed at entry, and approximately 57% of individuals continued taking a stable dose of stimulant throughout the SDP and DB RWP.

The primary efficacy endpoint was the change in Epworth Sleepiness Scale (ESS) score, as a measure of reduction in EDS from the end of the SDP to the end of the DB RWP. The ESS is an 8-item self-reported questionnaire by which individuals rate their perceived likelihood of falling asleep during usual daily life activities. Each of the 8 items on the ESS is rated from 0 (would never doze) to 3 (high chance of dozing), with a maximum score of 24. Key secondary efficacy endpoints included individual global impression of change (PGIc) and the Idiopathic Hypersomnia Severity Scale (IHSS), both assessed as a change from the end of the SDP to the end of the DB RWP. The IHSS is a 14-item self-reported questionnaire assessing the severity of IH symptoms of excessive sleepiness, prolonged sleep duration, cognitive impairment, and sleep inertia. Total scores can range from 0-50, with higher scores indicating a greater severity or frequency of symptoms.

Individuals in Study 2 taking stable doses of Xywav who were withdrawn from Xywav treatment and randomized to placebo during DB RWP experienced significant worsening in ESS score compared with individuals randomized to continue treatment with Xywav ($p<0.0001$) across all dosing regimens. These two treatment groups had comparable median ESS scores (Placebo=17; Xywav=16) at entry into the OTTP.

Individual Global Impression of change (PGIc) ratings showed that individuals randomized to placebo experienced a worsening of symptoms of idiopathic hypersomnia overall compared with individuals randomized to Xywav. The percentage of individuals with worsening PGIc scores for IH overall (defined as scores of Minimally, Much Worse, or Very Much Worse) was greater for individuals receiving placebo (88.1%) compared with individuals receiving Xywav (21.4%) ($p<0.0001$).

At end of DB RWP, individuals randomized to placebo experienced a worsening in IHSS total score, compared to individuals randomized to Xywav ($p<0.0001$). These two treatment groups had comparable median IHSS scores (Placebo=33; Xywav=33) at entry into the OTTP.

Sunosi (solriamfetol)

The mechanism of action of Sunosi (solriamfetol) is unclear; however, it's efficacy could be mediated through its activity as a dopamine and norepinephrine reuptake inhibitor. The published pivotal trials evaluating the efficacy and safety of Sunosi in excessive daytime sleepiness (EDS) are referred to as the TONES trials (Treatment of OSA and Narcolepsy Excessive Sleepiness). TONES 2 is a fair quality, unpublished, randomized controlled trial (RCT) that enrolled 239 adults with narcolepsy and EDS. Maintenance of Wakefulness Test (MWT) was improved in all Sunosi groups compared to placebo, but these differences were statistically significant in only the 300mg and 150mg groups (12.3 and 9.8 vs. 2.1, $p<0.05$). It is uncertain if this 7.7 to 10.2 minute increase in sleep latency is clinically meaningful. Sunosi improved Epworth Sleepiness Score (ESS) compared to placebo, but only the 300mg group had both a statistically and clinically significant treatment effect (-6.4 vs. -1.6, $p<0,05$). There was a clear dose-response relationship seen in both MWT and ESS.

TONES 3&4 are two fair quality, published, RCTs that enrolled 648 adults with OSA and EDS. In TONES 3 all doses of Sunosi (37.5mg-300mg) improved ESS and MWT compared to placebo ($p<0.05$). MWT scores showed a dose-response, with treatment effect values ranging from 4.5 to 12.8 (low dose to high dose Sunosi). The placebo-adjusted change in ESS was clinically meaningful in only the 300mg and 150mg groups (-4.7 and -4.5, respectively). There was a dose-response between high and low dose groups, however, the benefit appeared to plateau at 150mg. In TONES 4 the end of treatment differences between Sunosi (pooled data of all doses) and placebo were statistically significant for MWT (12.1), ESS (-4.4), and Functional Outcomes of Sleep Questionnaire-10 (1.0). The magnitude of benefit in ESS was clinically meaningful, but the observed treatment effect on functional score (Functional Outcomes of Sleep Questionnaire-10) was not clinically meaningful.

Available safety data are limited to 8-12 weeks of observation in the pivotal trials described above. Serious adverse events (SAEs) were few and none were deemed related to treatment. Most adverse events were mild to moderate in nature and resolved without intervention. The most common AEs across trials were headache, nausea, decreased appetite, and anxiety. A human use liability (HAL) study in 43 adult recreational drug users showed Sunosi was similar in abuse potential to phenteramine, a stimulant assigned to Schedule IV, and greater than that of placebo. Of note, this study included doses of Sunosi that were up to four times greater than those studied in pivotal trials.

Wakix (pitolisant)

Pitolisant is a histamine-3 (H3) receptor antagonist/inverse agonist and was studied in two pivotal trials. HARMONY I is a double-blind, randomized, parallel-group controlled trial conducted in 32 sleep disorder centers in 5 European countries. After at least 14 days of no psychostimulant, individuals were randomized (1:1:1) to receive either pitolisant, modafinil, or placebo. Treatment lasted 8 weeks: 3 weeks of tapering dosing according to response (10 mg, 20mg, or 40 mg a day of pitolisant; 100 mg, 200 mg, or 400 mg a day of modafinil) followed by 5 weeks of stable dosing. There were two primary endpoints being difference in change in Epworth sleepiness scale (ESS) score between pitolisant and placebo group after 8-week treatment period (superiority test) and difference in change in (ESS) score between pitolisant and modafinil after 8-week treatment period (non-inferiority test). The mean difference in ESS score of -3.0 (95% CI -5.6 to -0.4 p=0.024) showed pitolisant to be superior to placebo, but not non-inferior to modafinil with an ESS score mean difference of 0.12 (95% CI -2.5 to 2.7 p=0.250). The non-inferiority margin was 2 ESS points. Maintenance of wakefulness test (MWT) values improved in pitolisant groups compared to placebo's mean difference of 1.47 (1.01 to 2.14, p=0.044), but no statistically significant difference compared to modafinil with a mean difference of 0.77 (0.52 to 1.13, p=0.173). The total sustained attention to response task (SART) score showed no difference in changes from baseline between either pitolisant versus placebo or pitolisant versus modafinil. The proportion of individuals who had improved in excessive daytime sleepiness (EDS) assessed with the clinical global impression of change (CGI-C) by the end of treatment was largest in modafinil group (86%), then pitolisant group (73%), and smallest in placebo group (56%). There was also little difference in severity of cataplexy assessed with CGI-C. European quality of life questionnaire (EQ-5D) values were much the same in the 3 groups, whereas the individual's local impression on treatment improved only slightly more for pirolisant or modafinil than for placebo.

HARMONY CPT is a randomized, double-blind, placebo-controlled trial conducted in 9 countries (Bulgaria, Czech Republic, Hungary, Macedonia, Poland, Russia, Serbia, Turkey, and Ukraine). Similar to HARMONY I, after 14 days of washout period, individuals were randomized (1:1) to either receive pitolisant or placebo once per day. Treatment was 7 weeks: 3 weeks of tapering dosing based on efficacy and tolerance (5 mg, 10 mg, or 12 mg pitolisant), followed by 4 weeks of stable dosing (5 mg, 10 mg, 20 mg, or 40 mg). The primary endpoint was a change in average weekly cataplexy rate (WCR). Pitolisant reduced cataplexy by 75% (WCR = 0.25), which is more than placebo did (38%, WCR=0.62).

The efficacy of pitolisant for the treatment of cataplexy in adult individuals with narcolepsy was evaluated in two multicenter, randomized, double-blind, placebo-controlled studies (Study 3 and Study 1). Individuals ≥18 years of age who met the International Classification of Sleep

Disorders (ICSD-2) criteria for narcolepsy with cataplexy with at least 3 cataplexy attacks per week and an ESS score of ≥12 were eligible to enroll in Study 3; individuals meeting the ICSD-2 criteria for narcolepsy (with or without cataplexy) and an ESS score of ≥14 were eligible to enroll in Study 1.

Study 3 included a 7-week treatment period: a 3-week dose titration phase followed by a 4-week stable dose phase. 105 individuals were randomized to receive pitolisant or placebo. The dose of pitolisant was initiated at 4.45 mg once daily for the first week, increased to 8.9 mg for the second week, and could remain the same or be decreased or increased at the next two weekly intervals to a maximum of 35.6 mg, based on clinical response and tolerability. No dose adjustments were permitted during the 4-week stable dose phase. 65% of individuals reached a stable dose of 35.6 mg. Median age in the study was 37 years and 51% of the individuals were male.

Pitolisant demonstrated statistically significantly greater improvement on the primary endpoint, the change in geometric mean number of cataplexy attacks per week from baseline to the average of the 4-week stable dosing period for pitolisant compared to placebo.

In Study 1 the subset of individuals with a history of cataplexy (n=49), pitolisant demonstrated statistically significantly greater improvement on the secondary endpoint, the change from baseline in geometric mean daily rate of cataplexy at Week 8 for pitolisant compared to placebo.

The most common adverse reaction for pitolisant were headaches (35%), insomnia (10%), nausea (6%), and anxiety (5%). Pitolisant is contraindicated in individuals with severe hepatic impairment and should be administered with caution in individuals with moderate hepatic impairment or renal impairment. There is a risk of mild to moderate prolongation of QTc interval with supratherapeutic doses of pitolisant, therefore monitoring is required in individuals with cardiac disease, those taking other QT-prolonging medication, and medications known to increase pitolisant levels (CYP2D6 inhibitors).

Ongoing and Unpublished Clinical Trials

An unpublished meta-analysis of six randomized control trials involving subjects with obstructive sleep apnea (OSA) and excessive daytime sleepiness (EDS) showed there was no clinically meaningful difference in Epworth Sleepiness Score (ESS) outcomes between Sunosi 150mg daily and modafinil 200mg or 400mg daily [-1.7 (95% CI -3.3, -0.01) and -1.7 (-3.3, -0.04), respectively]. The forty-minute Maintenance of Wakefulness Test (MWT) results were not shown for modafinil, so could not be compared to Sunosi trial results.

2020 Update

Reviewed prescribing information for all drugs in policy and the diagnostic criteria for narcolepsy and obstructive sleep apnea. Added criteria that Xyrem (sodium oxybate), Sunosi (solriamfetol), and Wakix (pitolisant) are not to be used as combination therapy with each other as efficacy and safety has not been evaluated. No additional changes were identified for policy.

2021 Update

Reviewed prescribing information for all drugs in policy. Added criteria to Xywav (calcium magnesium, potassium, and sodium oxybates) for the treatment of idiopathic hypersomnia (IH) in adults and added the diagnostic criteria for IH. No additional changes were identified for policy.

2022 Update

Reviewed prescribing information for all drugs and information from UpToDate on the treatment of narcolepsy in adults. No additional changes were identified for policy.

2023 Update

Reviewed prescribing information for all drugs in the policy. Added brand sodium oxybate to Xyrem (sodium oxybate) criteria. Added coverage criteria for Lumryz (sodium oxybate) to policy for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy. Lumryz is an extended-release formulation of sodium oxybate. Xyrem must be taken twice nightly, one dose at bedtime and then another between 2.5 and 4 hours later, whereas Lumryz is indicated to be taken once at bedtime.

2024 Update

Reviewed prescribing information for all drugs in the policy. Updated Wakix (pitolisant) coverage criteria age requirement from adults to 6 years or older for the treatment of excessive daytime sleepiness (EDS) with narcolepsy.

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2. Xywav (calcium magnesium, potassium, and sodium oxybates) prescribing information. Jazz Pharmaceuticals; Palo Alto, CA. Revised April 2023.
3. Lumryz (sodium oxybate) prescribing information. Avadel CNS Pharmaceuticals LLC, Inc.; Chesterfield, MO. Revised May 2023.
4. Sunosi (solriamfetol) prescribing information. Axsome Therapeutics, Inc.; New York, NY. Revised June 2023.
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History

Date	Comments
06/01/19	New policy, approved May 14, 2019. Xyrem (sodium oxybate) moved from policy 5.01.605. Criteria added for Sunosi (solriamfetol).
03/01/20	Interim Review, approved February 11, 2020. Updated Xyrem coverage criteria and added definition for cataplexy. Criteria added for Wakix (pitolisant).
04/01/20	Interim Review, approved March 3, 2020. Added under diagnosis of narcolepsy that for patients unable to discontinue REM suppressing medications who do not meet the MSLT criteria, the diagnosis of narcolepsy will be determined on a case-by-case basis.
05/01/20	Annual Review, approved April 23, 2020. Added criteria that Xyrem (sodium oxybate), Sunosi (solriamfetol), and Wakix (pitolisant) are not to be used as combination therapy with each other.
07/13/20	Correction made in policy section to read: Hypertension (systolic blood pressure > 140 mm Hg and (previously stated 140 mg Hg which was a typo). No other changes.
11/01/20	Interim Review, approved October 13, 2020. Added coverage criteria for Xywav (calcium magnesium, potassium, and sodium oxybates) for the treatment of cataplexy or EDS in patients with narcolepsy.
12/01/20	Interim Review, approved November 10, 2020. Added new indication to Wakix (pitolisant) for the treatment of cataplexy in adult patients with narcolepsy. For Xywav (calcium magnesium, potassium, and sodium oxybates) added a concomitant

Date	Comments
	diagnosis of heart failure, hypertension, or renal impairment as exception to requirement to use Xyrem (sodium oxybate) first.
10/01/21	Annual Review, approved September 14, 2021. Added new indication to Xywav (calcium magnesium, potassium, and sodium oxybates) for the treatment of adult patients with idiopathic hypersomnia.
01/01/23	Annual Review, approved December 23, 2022. No changes to policy statements. Added Related Policy 10.01.524 Sleep Disorder Management: Services Reviewed by AIM. Changed the wording from "patient" to "individual" throughout the policy for standardization.
11/01/23	Annual Review, approved October 10, 2023. Added brand sodium oxybate to Xyrem (sodium oxybate) criteria. Added coverage criteria for Lumryz (sodium oxybate) to policy for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy. Updated coverage criteria for Xyrem, Xywav, Sunosi, and Wakix regarding concurrent use with Lumryz. Updated Related Policy 10.01.524 – title changed from "Sleep Disorder Management: Services Reviewed by AIM" to "Sleep Disorder Management: Services Reviewed by Carelon Medical Benefits Management".
09/01/24	Annual Review, approved August 13, 2024. Updated Wakix (pitolisant) coverage criteria age requirement from adults to 6 years or older for the treatment of excessive daytime sleepiness (EDS) with narcolepsy.

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