Sodium Oxybate

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Related Coverage Resources

Modafinil / Armodafinil
Obstructive Sleep Apnea Diagnosis and Treatment Services
Sleep Testing Services

INSTRUCTIONS FOR USE

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

Coverage Policy

Xyrem (sodium oxybate) is considered medically necessary when ALL of the following criteria are met:

- Individual is 7 years of age or older
- No concurrent use with other sedative hypnotic drugs or alcohol
- Prescribed by or in consultation with a neurologist, pulmonologist or sleep specialist
- Treatment of ONE of the following:
  - Narcolepsy Type 1 (with cataplexy) and ALL of the following:
    - The individual has daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months.
    - Cataplexy
  - ONE of the following:
    - A mean sleep latency of ≤8 minutes and two or more sleep-onset rapid eye movement periods (SOREMPs) on a multiple sleep latency test (MSLT) performed according to standard techniques with a preceding nocturnal PSG to rule out other causes of excessive daytime sleepiness. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram (PSG) may replace one of the SOREMPs on the MSLT.
    - CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg/mL or <1/3 of mean values obtained in normal subjects with the same standardized assay.
Narcolepsy Type 2 (absence of cataplexy) and ALL of the following:

- The individual has daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months.
- A mean sleep latency of ≤8 minutes and two or more sleep-onset rapid eye movement periods (SOREMPs) are found on a multiple sleep latency test (MSLT) performed according to standard techniques with a preceding nocturnal polysomnogram (PSG) to rule out other causes of excessive daytime sleepiness. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT.
- Either CSF hypocretin concentration has not been measured or CSF hypocretin concentration measured by immunoreactivity is either >110 pg/mL or >1/3 of mean values obtained in normal subjects with the same standardized assay.
- The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.

Coverage for Xyrem (sodium oxybate) varies across plans. Refer to the customer's benefit plan document for coverage details.

Where coverage requires the use of preferred products, the following criteria apply.

<table>
<thead>
<tr>
<th>For Employer Group and Individual and Family Plans:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• For the treatment of Narcolepsy Type 1 (with cataplexy):</td>
</tr>
<tr>
<td>o Documented failure/ inadequate response, contraindication per FDA label, intolerance, or not a candidate for ONE of the following: a tricyclic antidepressant (TCA) [for example, amitriptyline, desipramine, imipramine], a selective serotonin reuptake inhibitor (SSRI) [for example, fluoxetine, sertraline, paroxetine], or venlafaxine</td>
</tr>
<tr>
<td>• For the treatment of Narcolepsy Type 2 (absence of cataplexy), BOTH of the following:</td>
</tr>
<tr>
<td>o Documented failure/ inadequate response, contraindication per FDA label, intolerance, or not a candidate for modafinil* OR armodafinil*</td>
</tr>
<tr>
<td>o Documented failure/ inadequate response, contraindication per FDA label, intolerance, or not a candidate for ONE of the following: amphetamine, dextroamphetamine or methylphenidate</td>
</tr>
<tr>
<td>*May require prior authorization</td>
</tr>
</tbody>
</table>

Initial authorization is up to 12 months.

Xyrem (sodium oxybate) is considered medically necessary for continued use when initial criteria are met and ONE of the following is met:

- For Type 1: Documented reduction in cataplexy episodes or reduction in daily sleep attacks
- For Type 2: Documented reduction in excessive daytime sleepiness or reduction in daily sleep attacks

Reauthorization for up to 12 months.

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

Xyrem (sodium oxybate) is considered experimental, investigational or unproven for ANY other use including the following:

- Chronic Fatigue Syndrome
- Essential Tremor
- Fibromyalgia
- Idiopathic Hypersomnia
- Parkinson's disease related excessive daytime somnolence (EDS)
- Post-traumatic Hypersomnia
- Use in an individual diagnosed with succinic semialdehyde dehydrogenase deficiency

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

### FDA Approved Indications

**FDA Approved Indication**

Xyrem is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

### Recommended Dosing

**FDA Recommended Dosing**

**Adult Dosing Information**

The recommended starting dosage is 4.5 grams (g) per night administered orally divided into two doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (see Table 1). Increase the dosage by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dosage range of 6 g to 9 g per night orally. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

<table>
<thead>
<tr>
<th>If A Patient’s Total Nightly Dose is:</th>
<th>Take at Bedtime:</th>
<th>Take 2.5 to 4 Hours Later:</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 grams per night</td>
<td>2.25 grams</td>
<td>2.25 grams</td>
</tr>
<tr>
<td>6 grams per night</td>
<td>3 grams</td>
<td>3 grams</td>
</tr>
<tr>
<td>7.5 grams per night</td>
<td>3.75 grams</td>
<td>3.75 grams</td>
</tr>
<tr>
<td>9 grams per night</td>
<td>4.5 grams</td>
<td>4.5 grams</td>
</tr>
</tbody>
</table>

**Pediatric Dosing Information**

Xyrem is administered orally twice nightly. The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight, as specified in Table 2. The dosage may be gradually titrated based on efficacy and tolerability.

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>Initial Dosage</th>
<th>Maximum Weekly Dosage Increase</th>
<th>Maximum Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Take at Bedtime:</td>
<td>Take 2.5 to 4 Hours Later:</td>
<td>Take at Bedtime:</td>
</tr>
<tr>
<td>&lt;20 kg**</td>
<td>There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 kg to &lt;30 kg</td>
<td>≤1 g</td>
<td>≤1 g</td>
<td>0.5 g</td>
</tr>
<tr>
<td>30 kg to &lt;45 kg</td>
<td>≤1.5 g</td>
<td>≤1.5 g</td>
<td>0.5 g</td>
</tr>
<tr>
<td>≥45 kg</td>
<td>≤2.25 g</td>
<td>≤2.25 g</td>
<td>0.75 g</td>
</tr>
</tbody>
</table>

* For patients who sleep more than 8 hours per night, the first dose of Xyrem may be given at bedtime or after an initial period of sleep.

**Note:** Unequal dosages may be required for some patients to achieve optimal treatment.

**Xyrem REMS Program**
Xyrem is available only through a restricted distribution program called the Xyrem REMS Program because of the risks of central nervous system depression and abuse and misuse.

Notable requirements of the Xyrem REMS Program include the following:
- Healthcare Providers who prescribe Xyrem are specially certified
- Xyrem will be dispensed only by the central pharmacy that is specially certified
- Xyrem will be dispensed and shipped only to patients who are enrolled in the XYREM REMS Program with documentation of safe use

Further information is available at www.XYREMREMS.com or 1-866-XYREM88® (1-866-997-3688).

In 2012, the Food and Drug Administration (FDA) issued a safety communication for Xyrem, reminding healthcare professionals and patients that the combined use of Xyrem with alcohol or CNS depressant drugs can markedly impair consciousness and may lead to severe respiratory depression. The use of Xyrem with other CNS depressant drugs (such as opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, general anesthetics, and muscle relaxants) should generally be avoided. (FDA, 2016)

### General Background

#### Disease Overview

Narcolepsy is a rare, chronic neurologic disorder that affects the brain’s ability to control sleep-wake cycles. There are two types of narcolepsy: Type 1 narcolepsy (previously termed narcolepsy with cataplexy) and Type 2 narcolepsy (previously termed narcolepsy without cataplexy). People with narcolepsy usually feel rested after waking, but then feel very sleepy throughout much of the day. The most typical symptoms are excessive daytime sleepiness, cataplexy, sleep paralysis, and hallucinations. Sleepiness in narcolepsy is described as a “sleep attack”, where an overwhelming sense of sleepiness comes on quickly. People may unwillingly fall asleep even if they are in the middle of an activity like driving, eating, or talking. Symptoms can partially improve over time, but they will never disappear completely. If left undiagnosed or untreated, narcolepsy can interfere with psychological, social, and cognitive function and development and can inhibit academic, work, and social activities. (NIH, 2019)

Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy. Polysomnogram (PSG) is an overnight recording of brain and muscle activity, breathing, and eye movements. The multiple sleep latency test (MSLT) assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter rapid eye movement (REM) sleep. On the day after PSG, the patient is asked to take five short naps separated by two hours over the course of a day. If an individual falls asleep in <8 minutes on average over the five naps, this indicates excessive daytime sleepiness. However, patients with narcolepsy also have an abnormally quick start to REM sleep. If REM sleep happens within 15 minutes at least two times out of the five naps and the sleep study the night before, this is likely an abnormality caused by narcolepsy. (NIH, 2019)

The American Academy of Sleep Medicine (AASM) provides diagnostic guidance for both Type 1 and Type 2 narcolepsy. For Type 1 narcolepsy, AASM recommends the individual has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months. As well as, the presence of one or both of the following: Cataplexy and a mean sleep latency of ≤8 minutes and two or more SOREMPs on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT and, or a CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg/mL or <1/3 of mean values obtained in normal subjects with the same standardized assay. (AASM, 2014)

For Type 2 narcolepsy, AASM recommends the individual has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months. A mean sleep latency of ≤8 minutes and two or more SOREMPs are found on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT. A lack of cataplexy. Either CSF hypocretin concentration has not been measured or CSF hypocretin concentration measured by immunoreactivity is either >110 pg/mL or >1/3 of mean values obtained in normal subjects with the
same standardized assay. And, the hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal. (AASM, 2014)

**Professional Societies/Organizations**

**American Academy of Sleep Medicine (AASM)** Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin list Xyrem as effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy (Standard) and modafinil as an effective for treatment of daytime sleepiness due to narcolepsy (Standard). Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are considered effective for the treatment of daytime sleepiness due to narcolepsy (Guideline). Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and venlafaxine may be effective for the treatment of cataplexy (Guideline). Selegiline may be an effective treatment for cataplexy and daytime sleepiness (Option). At the time this practice parameter was written, published studies involving Nuvigil® (armodafinil tablets) were limited. (Morgenthaler, 2007)

**AASM Levels of Recommendations**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>This is a generally accepted patient-care strategy that reflects a high degree of clinical certainty. The term standard generally implies the use of level 1 evidence, which directly addresses the clinical issue, or overwhelming level 2 evidence.</td>
</tr>
<tr>
<td>Guideline</td>
<td>This is a patient-care strategy that reflects a moderate degree of clinical certainty. The term guideline implies the use of level 2 evidence or a consensus of level 3 evidence.</td>
</tr>
<tr>
<td>Option</td>
<td>This is a patient-care strategy that reflects uncertain clinical use. The term option implies either inconclusive or conflicting evidence or conflicting expert opinion.</td>
</tr>
</tbody>
</table>

**The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative:**

No recommendations are available for narcolepsy.

**Other Covered Uses**

AHFS Drug Information 2020 Edition does not support any off-label uses of Xyrem (sodium oxybate).

**Compendium and Other Published Studies**

The effectiveness of Xyrem in fibromyalgia has been evaluated in clinical trials of varying size. However, due to safety concerns, Xyrem is not recommended for approval for fibromyalgia at this time. Duloxetine, Lyrica® (pregabalin capsules and oral solution), and Savella® (milnacipran tablets) are indicated for the treatment of fibromyalgia. Other recommended treatments include TCAs (i.e., amitriptyline), cyclobenzaprine, gabapentin, and SSRIs (i.e., fluoxetine, sertraline, paroxetine). (Fitzcharles, 2012)

There is no published data evaluating the safety and efficacy of sodium oxybate for the treatment of Chronic Fatigue Syndrome, Essential Tremor, Fibromyalgia, Idiopathic Hypersomnia, Parkinson’s disease related excessive daytime somnolence (EDS) or Post-traumatic Hypersomnia.

**Coding/Billing Information**

Note: Sodium Oxybate is typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.
References


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