

## Xyrem<sup>®</sup> (sodium oxybate) Prior Authorization Criteria

Brand	Generic	Dosage Form
Xyrem <sup>®</sup>	sodium oxybate	oral solution

### PROGRAM OBJECTIVES

The intent of the Prior Authorization (PA) Criteria for Xyrem (sodium oxybate) is to appropriately select patients for treatment according to product labeling and/or clinical studies and/or guidelines. A patient who is 16 years of age or older may be considered for sodium oxybate therapy if the patient has narcolepsy and also has cataplexy or has excessive daytime sleepiness after trial and failure of at least one other stimulant used for narcolepsy. Patients receiving sodium oxybate must be documented to be enrolled in the Xyrem Success Program by their treating physician. Sodium oxybate will not be approved for patients who have succinic semialdehyde dehydrogenase deficiency; patients who are also receiving sedative hypnotic drugs; or patients with a history of drug abuse. A quantity limit of 540 ml/30 days will allow up to the maximum FDA-labeled dose of 9 gm/day.

### PROGRAM FUNCTIONALITY

#### Electronic Edits

The overall process for a prior authorization will not allow the targeted drug(s) to adjudicate through the claims system. When a patient requests sodium oxybate, the system will reject the claim with the message indicating that prior authorization is necessary. The Prior Authorization (PA) Criteria for Approval would then be applied to requests submitted by the patient's practitioner for evaluation.

**Table 1: Targeted Agents for Xyrem Prior Authorization**

Agent	GPI (multisource code)
<b>Xyrem (sodium oxybate)</b>	
500 mg/mL (180 mL bottle)	62450060202020 (M, N, O, or Y)

### Prior Authorization (PA) Criteria for Approval

No claims for sodium oxybate will be automatically paid at the point of sale. The PA Criteria for Approval provide the manual review process for all claims for targeted agents in this PA program.

## ***Xyrem (sodium oxybate)***

### **Initial and Renewal Evaluation**

1. Is the patient 16 years of age or older?  
If yes, continue to 2. If no, deny.
2. Does the patient have a diagnosis of narcolepsy with cataplexy?  
If yes, continue to 6. If no, continue to 3.
3. Does the patient have a diagnosis of narcolepsy with excessive daytime sleepiness?  
If yes, continue to 4. If no, deny.
4. Is the patient currently receiving or has the patient previously tried and failed therapy with a standard stimulant agent (modafinil, armodafinil, methylphenidate, dextroamphetamine, or amphetamine/dextroamphetamine)?  
If yes, continue to 6. If no, continue to 5.
5. Does the patient have an allergy, contraindication, or intolerance to standard stimulant treatment?  
If yes, continue to 6. If no, deny.
6. Has the prescriber documented that the patient is enrolled in the Xyrem Success Program?  
If yes, continue to 7. If no, deny.
7. Does the patient have succinic semialdehyde dehydrogenase deficiency?  
If yes, deny. If no, continue to 8.
8. Is the patient being treated with any sedative hypnotic agents?  
If yes, deny. If no, continue to 9.
9. Does the patient have a history of substance abuse?  
If yes, deny. If no, approve for 12 months, for a maximum quantity of 540 mL/30 days.

### **RATIONALE FOR PRIOR AUTHORIZATION**

The intent of the Prior Authorization (PA) Criteria for Xyrem (sodium oxybate) is to appropriately select patients for treatment according to product labeling and/or clinical studies and/or guidelines. Special consideration is given to black box warnings of CNS adverse events and abuse potential.

#### **Efficacy**

Limited data from two placebo-controlled trials of short duration indicate that sodium oxybate is effective for cataplexy associated with narcolepsy; it is the first drug with this indication. One study is published and includes findings from an extension period;<sup>2,4</sup> the other is available through the Food and Drug Administration's (FDA's) drug approval package.<sup>3</sup> A small study suggests patients on Xyrem for up to 44 months had increased cataplectic attacks when switched to placebo. Most patients in clinical trials evaluating sodium oxybate were also taking CNS stimulants (e.g., modafinil, methylphenidate, amphetamines, etc.) while taking sodium oxybate. [see also Chapter 9.6G: Anti-Cataplectic Agents]<sup>2</sup>

Approval for sodium oxybate in treatment of excessive daytime sleepiness (EDS) was based on two 8-week trials in patients with narcolepsy. The first study, in which most patients were also being treated with stimulants (e.g., modafinil), found that sodium oxybate significantly decreased scores on the Epworth Sleepiness Scale from 19 to 15 with 6 gm per night, and from 19 to 12 with 9 gm per night. The drug also produced a clinical response (Clinical Global Impression of Change in Day/Nighttime Symptoms) as rated by trial investigators in the following percent of patients: 6 g (52%), 9 g (64%) versus 22% on placebo.<sup>2,5</sup>

The second study was conducted in 222 patients with narcolepsy who were taking 200 mg to 600 mg of modafinil for treatment of EDS. During a 2 week baseline phase, patients received unchanged modafinil doses (plus sodium oxybate placebo). Then patients were randomly assigned to 1 of 4 treatment groups: sodium oxybate placebo plus modafinil placebo, sodium oxybate plus modafinil placebo, modafinil plus

sodium oxybate placebo, or sodium oxybate plus modafinil. Sodium oxybate was given as 6 g nightly for 4 weeks, increasing to 9g nightly for the other 4 weeks. Following the switch from modafinil to placebo, the mean average daytime sleep latency on the Maintenance of Wakefulness Test decreased from 9.74 minutes at baseline to 6.87 minutes after 8 weeks ( $p < 0.001$ ). In the sodium oxybate group, there was no decrease in sleep latency; authors suggest this shows that sodium oxybate is as efficacious as the previously administered modafinil. The sodium oxybate/modafinil group showed an increase in daytime sleep latency from 10.43 minutes to 13.15 minutes ( $p < 0.001$ ), suggesting that the combination of drugs produces an additive effect.<sup>2</sup> The sodium oxybate group showed a decrease in median average Epworth Sleepiness Scale scores from 15 to 12; the sodium oxybate/modafinil group decreased from 15 to 11 (for both  $p < 0.001$ ). The Clinical Global Impression Change scale showed similar results. Xyrem product information states that this trial was not designed to compare the effects of sodium oxybate and modafinil because patients on modafinil were not titrated to a maximally effective dose. The combination group reported a greater number of adverse effects than the other groups.<sup>2,5</sup>

## Safety

Sodium oxybate is the official generic name for gamma hydroxybutyrate (GHB). GHB has been used as a drug of abuse, and has been implicated as a date-rape drug. GHB can induce profound CNS and respiratory depression when given alone, and especially if given with other CNS depressants.<sup>7</sup> Due to rapid onset of CNS depressant effects, drug should be administered only at bedtime, when the patient is in bed. After ingestion, patient must not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination for  $\geq 6$  hours.<sup>1,2,4</sup>

To guard against diversion/misuse, only a single pharmacy dispenses Xyrem, and there is a risk management protocol prescribers must adhere to, called the Xyrem Success Program. The Success Program provides educational materials to the prescriber and the patient explaining the risks and proper use of sodium oxybate, and the required prescription form. Once it is documented that the patient has read and/or understood the materials, the drug will be shipped to the patient. The Xyrem success Program also recommends patient follow-up every 3 months. Physicians are expected to report all serious adverse events to the manufacturer.<sup>1-3</sup>

However, not included in this program is a step by which the lone dispensing pharmacy confirms that the patient has cataplexy associated with narcolepsy. The lack of this step was a major concern of the FDA medical reviewer, as GHB has been used in multiple other disease states, for which there is scant or no data. Given the abuse potential, and the apparent narrow therapeutic window (respiratory depression a concern), off-label use where the risk/benefit ratio is undefined is a concern with GHB. Without the provision for verifying that the drug was being used only in those with cataplexy, the FDA medical reviewer recommended against approval; the drug was approved anyway. The FDA approved form of sodium oxybate is controlled under Schedule III; unapproved forms of GHB are subject to Schedule I penalties for illegal use.<sup>1-3</sup>

In clinical trials, the most commonly reported adverse events associated with use of sodium oxybate ( $\geq 5\%$  of patients; frequency greater than placebo), were dizziness, headache, nausea, pain, sleep disorder, confusion, infection, vomiting, and urinary incontinence. Several patients with pre-existing obstructive sleep apnea reported worsening of their apnea.<sup>1,2</sup> Sodium oxybate can induce profound CNS and respiratory depression when given alone, and especially if given with other CNS depressants. Some of the more concerning adverse effects are sleepwalking, incontinence, and respiratory depression. Approximately 80% of the subjects in clinical trials received concomitant stimulants, which may mitigate the CNS effects of sodium oxybate; whether those taking sodium oxybate without stimulants are more likely to have significant CNS depression is unknown. The therapeutic index of sodium oxybate is likely narrow. Current prescribing information lists a maximum nightly dose of 9 gm.<sup>1,2</sup>

## Guidelines, Reviews

A 2007 practice report from the American Academy of Sleep Medicine<sup>6</sup> lists modafinil as the standard for treatment of daytime sleepiness due to narcolepsy; amphetamine, methamphetamine, dextroamphetamine and methylphenidate are also listed as effective treatments for EDS due to narcolepsy. These guidelines stated that sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy, and is a standard treatment for cataplexy. The guideline also stated that sodium

oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis, but this is listed as an “option,” meaning that this represents a more uncertain clinical use, based on inconclusive or conflicting evidence or conflicting expert opinion.<sup>6</sup>

Guidelines from the European Federation of Neurological Societies (EFNS, 2006)<sup>7</sup> recommend the following:

- First line pharmacological treatment of EDS should rely on modafinil. Second line pharmacological treatment is methylphenidate. Sodium oxybate is a potential agent for first line therapy in the treatment of excessive daytime sleepiness of narcolepsy. The guidelines note that this is an increasingly common practice in the U.S. and is based on grade A evidence. In severe cases the combination of modafinil and sodium oxybate appears to be beneficial.
- Based on class I evidence (level A rating) studies, first-line pharmacological treatment of cataplexy is sodium oxybate at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night. The dose may be increased to a maximum dosage of 9 g/night divided into two equal doses of 4.5 g/night, by increments of 1.5 g. Antidepressants are recommended as second line. TCAs, particularly clomipramine, are the most potent anticataplectic drugs. However, they have the drawback of anticholinergic adverse effects. SSRIs are slightly less active but have less adverse effects. Venlafaxine is widely used but lacks any published clinical evidence of efficacy.<sup>7</sup>

A 2006 systematic review on treatment of cataplexy<sup>8</sup> concluded:

- Pharmacologic treatment of narcolepsy has primarily consisted of treating excessive daytime sleepiness (EDS) and patient specific symptoms such as cataplexy. Stimulants (e.g., modafinil, amphetamine, methamphetamine, methylphenidate, and dextroamphetamine) are primarily used for EDS but are typically ineffective for cataplexy. Agents used for cataplexy have included Tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs). TCAs have been proven effective but are frequently associated with anticholinergic adverse effects; sudden withdrawal may result in rebound cataplexy attacks or status cataplecticus. SSRIs have the advantage of a reduced side effect profile but have been considered less effective for cataplexy compared with TCAs.
- Clinical trials have shown that sodium oxybate significantly decreases the number of weekly cataplexy attacks, improves daytime sleepiness, and decreases number of nighttime awakenings.
- Authors of this review concluded that sodium oxybate should be used after an unsuccessful trial of a TCA and/or an SSRI in treatment of cataplexy. Their rationale to support sodium oxybate as a second line agent is its potential for abuse, multiple dosing schedule, patient counseling issues, cost issues, and the closed pharmacy distribution system for physicians and patients. Also, the majority of patient in sodium oxybate studies continued to receive stimulant medications, making it difficult to determine efficacy of sodium oxybate without concurrent use of stimulants. Clinical trials comparing sodium oxybate with the TCAs or SSRIs have not been completed.<sup>8</sup>

Based on the above clinical information, the prior authorization (PA) criteria for sodium oxybate will consider it to be a first-line agent for cataplexy but an agent that is currently recommended after other stimulants for EDS of narcolepsy. Documentation of enrollment in the Xyrem Success Program will be required. The PA criteria will also consider concomitant use of sedative hypnotic agents, history of drug abuse, or diagnosis of succinic semialdehyde dehydrogenase deficiency as contraindications to the use of sodium oxybate.

## **FDA APPROVED INDICATIONS<sup>1</sup>**

*The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the section “Prior Authorization (PA) Criteria for Approval.”*

Xyrem (sodium oxybate) oral solution is indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. In Xyrem clinical trials, approximately 80% of patients maintained concomitant stimulant use.

## Black Box Warning<sup>1</sup>

**Warning: Central nervous system depressant with abuse potential.  
Should not be used with alcohol or other CNS depressants.**

Sodium oxybate is GHB, a known drug of abuse. Abuse has been associated with some important central nervous system (CNS) adverse events (including death). Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Reports of respiratory depression occurred in clinical trials. Almost all of the patients who received sodium oxybate during clinical trials were receiving CNS stimulants.

Important CNS adverse events associated with abuse of GHB include seizure, respiratory depression and profound decreases in level of consciousness, with instances of coma and death. For events that occurred outside of clinical trials, in people taking GHB for recreational purposes, the circumstances surrounding the events are often unclear (e.g., dose of GHB taken, the nature and amount of alcohol or any concomitant drugs).

Xyrem is available through the Xyrem Success Program, using a centralized pharmacy 1-866-XYREM88® (1-866-997-3688). The Success Program provides educational materials to the prescriber and the patient explaining the risks and proper use of sodium oxybate, and the required prescription form. Once it is documented that the patients has read and/or understood the materials, the drug will be shipped to the patient. The Xyrem success Program also recommends patient follow-up every 3 months. Physicians are expected to report all serious adverse events to the manufacturer.

## REFERENCES

1. Xyrem prescribing information. Jazz Pharmaceuticals, Inc. November 2005.
2. Prime Therapeutics Formulary Chapter 9.6G: Anti-Cataleptic Agents. December 2008.
3. United States Food and Drug Administration, Drug Approval Package, Xyrem (sodium oxybate) oral solution. [http://www.fda.gov/cder/foi/nda/2002/21-196\\_Xyrem.htm](http://www.fda.gov/cder/foi/nda/2002/21-196_Xyrem.htm). Accessed January 8, 2003.
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8. Lemon M, Strain J, Farver D. Sodium oxybate for cataplexy. *Ann Pharmacother*. 2006;40:433-440.

### Document History

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