



## Xyrem® (sodium oxybate) Prior Authorization with Quantity Limit Criteria Program Summary

This prior authorization applies to Commercial, NetResults A series, NetResults F series and Health Insurance Marketplace formularies.

### OBJECTIVE

The intent of the Xyrem Prior Authorization (PA) Criteria is to appropriately select patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies and according to dosing recommended in product labeling. The PA criteria will approve Xyrem when prescribed according to product labeling. Patients with excessive daytime sleepiness (EDS) in narcolepsy and cataplexy in narcolepsy must be 18 years and older. The PA criteria will consider Xyrem to be a first-line agent for treatment of cataplexy and a second-line agent to a stimulant for patients with a diagnosis of narcolepsy with excessive daytime sleepiness. Xyrem will not be covered for patients with a listed contraindication: patient is using a sedative hypnotic agent concurrently or patient has succinic semialdehyde dehydrogenase deficiency. The program will approve Xyrem for doses within the set limit. Doses above the set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized.

### TARGET DRUGS

#### Xyrem® (sodium oxybate)

Brand (generic)	GPI	Multisource Code	Quantity per Day Limit
<b>Xyrem (sodium oxybate)</b>			
500 mg/mL oral solution (180 mL bottle)	62450060*****	M, N, O, or Y	9 gm/night (540mL/30 days)

### PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Xyrem will be approved when ALL of the following are met:

1. ONE of the following:
  - a. The patient has a diagnosis of narcolepsy with cataplexy **AND** the following:
    - i. The patient is 18 years of age or older
  - OR**
  - b. The patient has a diagnosis of narcolepsy with excessive daytime sleepiness **AND** ALL of the following:
    - i. ONE of the following:
      - a. The patient's medication history includes use of a standard stimulant agent
      - OR**
      - b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity, to a standard stimulant agent
    - AND**
    - ii. The patient is 18 years of age or older

**OR**

- c. The patient has a diagnosis of another FDA approved indication for the requested agent

**AND**

- 2. The patient does not have any FDA labeled contraindications to the requested agent

**AND**

- 3. ONE of the following

- a. The requested quantity (dose) is NOT greater than the program quantity limit

**OR**

- b. ALL of the following

- i. The requested quantity (dose) is greater than the program quantity limit

**AND**

- ii. The requested quantity (dose) is less than or equal to the FDA labeled dose

**AND**

- iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit

**Length of Approval:** 12 months

**FDA Labeled Contraindications**

<b>Contraindications</b>
Concomitant use with alcohol
Concomitant treatment with a sedative hypnotic (e.g. temazepam, triazolam, insomnia agents (e.g. eszopiclone, zaleplon, zolpidem))
Succinic semialdehyde dehydrogenase deficiency

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

**FDA Indication:** Sodium oxybate (Xyrem) is indicated for treatment of excessive daytime sleepiness (EDS) in narcolepsy and cataplexy in narcolepsy. Safety and effectiveness in patients under 18 years of age have not been established.<sup>1</sup>

**Dosing:** The recommended starting dose is 4.5 g/night divided into two equal doses of 2.25 g. First dose should be taken at bedtime (allow 2 hours after eating before dosing), while sitting up in bed, and the second should be taken again 2.5-4 hours later. The effective dose is 6 to 9 g/night and titration should be done in increments of 1.5 g/night (0.75 g/dose) with 1 week between dose increases. Doses greater than 9 g/night are not recommended. Dilute each dose with 2 oz. of water. Sodium oxybate is available as 500 mg/mL oral solution.<sup>1</sup>

Patients with hepatic impairment or those on valproate should have doses reduced as recommended in prescribing information.<sup>1</sup>

## **CLINICAL RATIONALE**

### **Efficacy**

Up to 85% of narcolepsy patients in clinical trials of sodium oxybate for treatment of cataplexy and excessive daytime sleepiness (EDS) were concomitantly taking central nervous system (CNS) stimulants (e.g., modafinil, methylphenidate, amphetamines, etc.). This makes it difficult to assess the efficacy and safety of sodium oxybate independent of stimulant use.<sup>1</sup>

### **Cataplexy**

The effectiveness of sodium oxybate in the treatment of cataplexy was established in two 4 week, randomized, double-blind, placebo-controlled trials in patients with narcolepsy.<sup>1</sup> Other agents such as antidepressants (e.g., tricyclics, selective serotonin reuptake inhibitors) have been used (off-label) for treatment of cataplexy for many years.<sup>5,8</sup>

### **Excessive Daytime Sleepiness (EDS)**

The effectiveness of sodium oxybate in the treatment of EDS in narcolepsy was established in two 8 week, randomized, double-blind, placebo-controlled trials in patients with narcolepsy.<sup>1</sup> Other agents such as stimulants (e.g., modafinil, amphetamine, methamphetamine, methylphenidate, dextroamphetamine) have primarily been used for EDS but are typically ineffective for cataplexy.<sup>5</sup>

The position of sodium oxybate in clinical practice has been difficult to determine. Although guidelines and some reviews suggest sodium oxybate is a first line treatment, there is controversy over use of this drug. There is a lack of comparative efficacy and safety data for sodium oxybate vs the other agents that have been used in treatment of narcolepsy and cataplexy.

An American Academy of Sleep Medicine Review (AASM, 2007) found that the majority of studies meeting inclusion criteria were supported by the pharmaceutical industry and pertained to modafinil and sodium oxybate. Authors suggest that these findings reflect the shift toward investigation and reporting of newer agents, mostly supported by the pharmaceutical industry.<sup>7,11</sup>

- Narcolepsy: Although the supporting evidence from randomized controlled trials is less than for the newer agents, the traditional stimulants (e.g., amphetamine, dextroamphetamine, methylphenidate) are considered mainstays of treatment for sleepiness associated with narcolepsy. Clinical practice patterns also suggest that modafinil is currently viewed as the initial drug of choice for treatment of sleepiness associated with narcolepsy. However, there are no data available to indicate what

proportion of patients treated initially with modafinil requires transition to a traditional stimulant, to sodium oxybate, or to combination therapy. AASM Practice Parameters (2007) state that several large randomized, placebo-controlled studies indicate that modafinil and sodium oxybate are effective for treatment of hypersomnia associated with narcolepsy. Traditional stimulants are available in generic form, are less expensive, and have a long history of use in clinical practice, but have limited high-level evidence from published studies. There is a need for randomized trials that compare the newer agents to the traditional stimulants to establish relative efficacy and safety of these agents to guide the clinician in choosing between them for individual patients.<sup>7,11</sup>

- Cataplexy: The AASM reported that antidepressants (e.g. tricyclics, SSRIs) may be effective treatment for cataplexy based on limited clinical trials. They suggest that the paucity of formal clinical trials involving treatment of cataplexy may reflect the widespread "off-label" clinical use of antidepressants for treating cataplexy. The literature regarding antidepressant treatment of cataplexy consists primarily of case reports and small open-label studies. In contrast, several large randomized, placebo-controlled studies demonstrate that sodium oxybate is effective for treatment of cataplexy. There were no studies comparing antidepressants and sodium oxybate for treatment of cataplexy.<sup>7,11</sup>

The European Federation of Neurological Societies Guidelines (EFNS, 2011) states "in cases when the most disturbing symptom is excessive daytime sleepiness, modafinil should be prescribed based on its efficacy, limited adverse effects, and easiness of manipulation. Modafinil can be taken in variable doses from 100 to 400 mg/day, given in one dose in the morning or two doses, one in the morning and one early in the afternoon. However, it is possible to tailor the schedule and dose of administration according to the individual needs of the patient." On the other hand, sodium oxybate is a potential first line therapy in the treatment of excessive daytime somnolence coexistent with cataplexy and poor sleep associated with narcolepsy. EFNS suggests most patients will start to feel better within the first few days, but the optimal response at any given dose may take as long as 8-12 weeks. The drug should not be used in association with other sedatives, respiratory depressants, and muscle relaxants, vigilance should be held for the possible development of sleep disordered breathing, and depressed patients should not be treated with the drug.<sup>4</sup>

The Canadian Expert Drug Advisory Committee (CEDAC) provides formulary listing recommendations to publicly funded drug plans. CEDAC recommended in 2009 that sodium oxybate not be listed for cataplexy/narcolepsy. Based on uncertainty regarding clinical effectiveness, the Committee felt that the cost effectiveness of sodium oxybate had not been demonstrated.<sup>9</sup>

The Scottish Medicines Consortium informs drug and therapeutic committees of Scotland to aid in determining medicines for use and formulary inclusion.<sup>3,10</sup>

- In March 2006, the Consortium did not recommend sodium oxybate for use within the National Health System of Scotland in treatment of cataplexy due to narcolepsy for the following reasons. In the pivotal studies, most patients continued to take a stimulant to control the symptoms of EDS; therefore stimulants may be required concomitantly in clinical practice. The drug can cause respiratory depression; sleep apnea is estimated to occur in up to 50% of patients with narcolepsy. Unclear whether the night time dosing regimen may be a problem in patients with this condition.
- In August 2007, after a resubmission of sodium oxybate for the same indications, the consortium again would not recommend the drug for use within the NHS Scotland, stating the drug costs vs. benefits were not sufficient to gain acceptance.

A European review (2008) suggests that for cataplexy, newer antidepressants tend to replace TCAs and SSRIs, despite a lack of randomized controlled trials of these compounds. The review states that due to its efficacy in treatment of narcolepsy, sodium oxybate is considered an alternative to conventional treatment; however, its position versus modafinil and newer antidepressants is not yet clear.<sup>6</sup>

### **Safety**

There are disadvantages associated with the use of sodium oxybate, including its safety concerns and potential for abuse. As the sodium salt of gamma hydroxybutyrate (GHB), it has been used illegally as a date-rape drug.<sup>2</sup> Sodium oxybate is a schedule III substance which holds a boxed warning indicating a risk of neuropsychiatric events, respiratory depression, potential for misuse and abuse, and discourages use with alcohol or other central nervous system depressants.

Sodium oxybate is contraindicated in patients currently taking sedative hypnotic agents and in patients with succinic semialdehyde dehydrogenase deficiency. It is also contraindication with the use of alcohol.<sup>12</sup> The Xyrem REMS Program restricts distribution to one pharmacy and requires ALL physicians and patients to register.<sup>1</sup>

### **REFERENCES**

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