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

This prior authorization applies to Commercial NetResults A series, SourceRx 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 for indications according to product labeling. Patients with excessive daytime sleepiness (EDS) in narcolepsy and cataplexy in narcolepsy must be 18 years and over. The PA criteria considers Xyrem to be a second-line agent for treatment ofnarcolepsy with cataplexy and narcolepsy with excessive daytime sleepiness. Xyrem will not be covered for patients with any FDA labeled contraindication. 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 AGENT

Xyrem® (sodium oxybate)

Brand (generic)	GPI	Multisource Code	Quantity Limit
Xyrem (sodium oxybate)			
500 mg/mL oral solution	62450060202020	M, N, O, or Y	9 gm/night (540mL/30 days)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Xyrem (sodium oxybate) will be approved when ALL of the following are met:

1. The patient is 18 years of age or over
   AND
2. ONE of the following:
   - A. The patient has a diagnosis of narcolepsy with cataplexy **AND** ONE of the following:
     - i. The patient's medication history includes use of a TCA (e.g. clomipramine, protriptyline), SSRIs (e.g., fluoxetine), or venlafaxine
       OR
     - ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL prerequisite agents

     OR
   - B. The patient has a diagnosis of narcolepsy with excessive daytime sleepiness **AND** BOTH of the following:
     - i. ONE of the following:
       - a. The patient's medication history includes use of modafinil or armodafinil
         OR

b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to both modafinil AND armodafinil

AND

ii. 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

OR

C. The patient has another FDA approved indication for the requested agent

AND

3. The prescriber is a specialist (e.g. sleep specialist, neurologist, psychiatrist) or the prescriber has consulted with a specialist

AND

4. The patient does NOT have any FDA labeled contraindication(s) to the requested agent

AND

5. 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

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

FDA APPROVED INDICATION AND DOSAGE[1]

Agent	Indications	Dose
Xyrem® (sodium oxybate)	Cataplexy in narcolepsy	Initiate dose at 4.5 grams (g) given orally per night in two equal divided doses. Titrate dose to effect in increments of 1.5 g per night in weekly intervals. Recommended dose range is 6 g to 9 g per night orally.
	Excessive daytime sleepiness (EDS) in narcolepsy	

CLINICAL RATIONALE

Narcolepsy is a chronic neurological disorder caused by the inability to regulate sleep-wake cycles. At various times throughout the day, patients with narcolepsy experience irresistible bouts of sleep and could fall asleep. If left undiagnosed or untreated, narcolepsy can interfere with psychological, social, and cognitive function and development and can inhibit academic, work, and social activities.[2] There is limited evidence to advise on treatment of special populations such as children, pregnant women, and breastfeeding mothers.[6]

The American Family Physician recommends referral to a sleep clinic if narcolepsy is suspected.[3] Treatment goal for narcolepsy is to obtain normal alertness during conventional waking hours or to maximize alertness at important times of the day (e.g. during work, school, or while driving). Non-pharmacological treatments include avoidance of medications that can cause drowsiness, such as benzodiazepines, opiates, antipsychotics, napping, and improved sleep hygiene.[4]

Excessive Daytime Sleepiness (EDS)

EDS is characterized by persistent sleepiness regardless of how much sleep an individual gets at night. However, sleepiness in narcolepsy is more like a "sleep attack", where an overwhelming sense of sleepiness comes on quickly. In between sleep attacks, individuals have normal levels of alertness, particularly if doing activities that keep their attention. All patients with narcolepsy have EDS, and it is often the most obvious symptom.[2]

Pharmacological agents that may be used for treatment of EDS include stimulants such as modafinil, amphetamine, methamphetamine, methylphenidate, dextroamphetamine. These agents have shown benefit for treatment of EDS however, they are typically ineffective for cataplexy.[2,4,5] Modafinil is considered first-line agent.[4]

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.[1] Patients were randomized to one of four groups: placebo, sodium oxybate 4.5 grams per night, sodium oxybate 6 grams per night, or sodium oxybate 9 grams per night. The primary efficacy was extent of sleepiness in everyday situations (determined using Epwirth Sleepiness Scale) and change in symptoms of EDS (evaluated using Clinical Global Impression of Change tool). Sodium oxybate was associated with statistically significant differences regarding both of the primary outcomes when compared to placebo. [1]

Narcolepsy with Cataplexy

Narcolepsy with cataplexy involves the sudden loss of voluntary muscle tone while awake. 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.[2]

Antidepressants, such as tricyclic antidepressants (TCAs) and selective serotonin reupdate inhibitors (SSRIs), could be used to treat cataplexy.[2-6] TCAs are effective for cataplexy, however, the side effects can be bothersome to patients.[5] REMS-sleep suppressing agents, such as venlafaxine, atomoxetine, and fluoxetine, may substantially reduce cataplexy with relatively few side effects. Extended-release venlafaxine has shown to be effective.[3,4,6]

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. Patients were randomized to receive placebo or sodium oxybate dosed at 3 grams to 9 grams nightly. The primary efficacy endpoint for both trials was frequency of cataplexy attacks. Both trials found that dose of 6 grams to 9 grams resulted in statistically significant reduction in frequency of cataplexy attacks. The trials also found that discontinuation of sodium oxybate in patient who had been treated with it long term resulted in a significant increase in cataplexy attacks.[1]

Safety[1]
Sodium oxybate carries boxed warnings for respiratory depression, CNS adverse reactions (e.g. seizure, decreased consciousness, coma and death), and risk for substance abuse. For these reasons, sodium oxybate is classified as a Schedule III controlled substance and is subject to Xyrem REMs program.

The most common adverse reactions associated with sodium oxybate include nausea, dizziness, vomiting, somnolence, enuresis, and tremor. Sodium oxybate is contraindicated in patients currently taking sedative hypnotic agents or alcohol and in patients with succinic semialdehyde dehydrogenase deficiency.

REFERENCES

1. Xyrem prescribing information. Jazz Pharmaceuticals, Inc. November 2017.
2. National Institute of Neurological Disorders and Stroke. Narcolepsy Fact Sheet. NIH Publication No. 17-1637. Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Narcolepsy-Fact-Sheet. Accessed October 25, 2017.
3. Ramar, Kannan MD and Olson, Eric MD. Management of Common Sleep Disorders. *Am Fam Physician*. 2013 Aug 15; 88(4): 231-238.
4. Scammell, Thomas E., et al. Treatment of Narcolepsy in Adults. UptoDate. Topic 7681. Version 24.0. Last Updated June 2017.
5. Morgenthaler, Thomas MD, et al. Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin. The American Academy of Sleep Medicine Report. SLEEP. 2007; Vol. 30 (12).
6. Krahn, Lois MD, et al. Quality Measures for the Care of Patients with Narcolepsy. *Journal of Clinical Sleep Medicine*. 2015; Vol. 11(3).