Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

Title: Xyrem® (sodium oxybate)

- **Prime Therapeutics will review Prior Authorization requests**

Prior Authorization Form:
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6104KS-XYRE.pdf

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

Professional	**Institutional**
Original Effective Date: June 1, 2015	Original Effective Date: June 1, 2015
Revision Date(s): June 1, 2015; January 1, 2016; June 1, 2016; May 15, 2017; May 1, 2018	Revision Date(s): June 1, 2015; January 1, 2016; June 1, 2016; May 15, 2017; May 1, 2018
Current Effective Date: May 1, 2018	Current Effective Date: May 1, 2018

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

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 of narcolepsy 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)

FDA Approved Indication and Dosage[1]

Agent	Indications	Dose
Xyrem® (sodium oxybate)	Cataplexy in narcolepsy Excessive daytime sleepiness (EDS) 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.

POLICY

Prior Authorization and Quantity Limits 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 contraindications 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

FDA Labeled Contraindications	
Agent	**Contraindications**
Xyrem (sodium oxybate)	▪ Succinic semialdehyde dehydrogenase deficiency ▪ In combination with sedative hypnotics*

*Examples of sedative hypnotics: benzodiazepines, butabarbital, eszopiclone, Rozerem (ramelteon), Silenor (doxepin), zaleplon, zolpidem

Program Quantity Limits	
Brand (generic)	**Quantity Limit**
Xyrem (sodium oxybate)	
500 mg/mL oral solution	9 gm/night (540mL/30 days)

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] Patient's 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 of the 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.

REVISIONS	
06-01-2015	Policy added to the bcbsks.com web site on 04-21-2015.
01-01-2016	Published 12-30-2015. Effective 01-01-2016.
	Description updated
	In Policy section: ▪ Removed “The prescriber has documented that the patient is enrolled in the Xyrem Success Program” ▪ In Program Quantity Limits corrected Quantity Per Day Limit by adding “9 gm/night (540mL/30 days)” and removing “500 mg/mL oral solution (180 mL bottle)”
	Rationale section updated
	References updated
06-01-2016	Published 05-11-2016. Effective 06-01-2016.
	In Policy section: ▪ In Item 2 removed "therapy" and added "the requested agent" to read "The patient does not have any FDA labeled contraindications to the requested agent"

REVISIONS	
	▪ Updated FDA Labeled Contraindications chart to give examples of sedative hypnotics "(e.g. benzodiazepines [e.g. triazolam, alprazolam], insomnia agents [e.g. eszopiclone, zaleplon, zolpidem])"
	References updated
05-15-2017	Description section updated
	In Policy section: ▪ Updated FDA Labeled Contraindications and Quantity Limits charts.
	Rationale section updated
	References updated
05-01-2018	In Description section updated
	In Policy section: ▪ In Item 2 A added "i. The patient's medication history includes use of a TCA (e.g. clomipramine, protriptyline), SSRIs (e.g., fluoxetine), or venlafaxine The patient is 18 years of age or older OR ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL prerequisite agents" ▪ In Item 2 B i a) removed "a standard stimulant agent" and added "modafinil or armodafinil" ▪ In Item 2 B i added "b) The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to both modafinil AND armodafinil" ▪ In Item 2 B added "ii. ONE of the following: a) The patient's medication history includes use of a standard stimulant agent" ▪ Added "3. The prescriber is a specialist (e.g. sleep specialist, neurologist, psychiatrist) or the prescriber has consulted with a specialist" ▪ Updated Contraindications chart
	Rationale section updated
	References updated

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).