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

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

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 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)

FDA Approved Indications 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 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
Contraindications
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

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

RATIONALE

Xyrem (sodium oxybate) is a central nervous system depressant. Although the mechanism of action of sodium oxybate is unknown, it is hypothesized that its therapeutic effects are through mediation of GABA actions in the central nervous system.[1,2] Safety and efficacy of sodium oxybate has not been established in patients under the age of 18 years.[1,5]

Safety
Sodium oxybate carries boxed warnings for respiratory depression, CNS adverse 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.[1,6] The REMS program restricts distribution to one pharmacy and requires ALL physicians and patients are registered with the program.[1]

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.[1]

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.[1]

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.[1] 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.

Cataplexy in narcolepsy was traditionally treated with tricyclic antidepressants (TCAs).[4] However, the use of TCAs in these patients has decreased owing to availability of sodium oxybate which has demonstrated good symptom control especially in patients with severe cataplexy.[4]

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.[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 with regard to both of the primary outcomes when compared to placebo.

Other agents that may be used for treatment of narcolepsy and cataplexy include stimulants (e.g., modafinil, amphetamine, methamphetamine, methylphenidate, dextroamphetamine). These agents have shown benefit for treatment of EDS however, they are typically ineffective for cataplexy. [3,6]

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" ▪ 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

REFERENCES

1. Xyrem (sodium oxybate) prescribing information. Jazz Pharmaceuticals.
2. Robinson D, Keating G. Sodium oxybate. A review of its use in the management of narcolepsy. *CNS Drugs*. 2007;21(4):337-354.
3. Billiard M. Narcolepsy: Current treatment options and future approaches. *Neuopsych Dis Treat*. 2008;4(3):557-566.
4. Thorpy M. Cataplexy associated with narcolepsy. *CNS Drugs*. 2006;20(1):43-50.
5. Xyrem REMs Program. Available at: https://www.xyrem.com/healthcare-professionals/xyrem-prescriber-tools . Accessed November 2016.