This program applies to FlexRx Open, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard prior authorization program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

Program specific denial language for prerequisite step therapy component does not apply. Instead, supplemental program denial language will apply.

**FDA APPROVED INDICATION AND DOSAGE**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indications</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xyrem® (sodium oxybate)</td>
<td>Cataplexy in patients 7 years and older with narcolepsy</td>
<td>Adults: 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. Pediatrics: Weight based dosing, titrate dose to effect</td>
</tr>
<tr>
<td></td>
<td>Excessive daytime sleepiness (EDS) in patients 7 years and older with narcolepsy</td>
<td></td>
</tr>
</tbody>
</table>

**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. There is limited evidence to advise on treatment of special populations such as children, pregnant women, and breastfeeding mothers.

The American Family Physician recommends referral to a sleep clinic if narcolepsy is suspected. 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.

**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, and dextroamphetamine.²,⁴,⁵ Modafinil is considered the 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 Epworth 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 reuptake 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.¹ 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

**Safety¹**

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**


Sodium Oxybate Prior Authorization with Quantity Limit

OBJECTIVE
The intent of the Sodium Oxybate 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 the target agent when prescribed for indications according to product labeling. Patients with excessive daytime sleepiness (EDS) in narcolepsy and cataplexy in narcolepsy must be 7 years or over. The PA criteria considers the target agent to be a second-line agent for treatment of narcolepsy with cataplexy and narcolepsy with excessive daytime sleepiness. Target agents will not be covered for patients with any FDA labeled contraindication. The program will approve the target agent 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)

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xyrem (sodium oxybate)</td>
<td>62450060202020</td>
<td>M, N, O, or Y</td>
<td>9 gm/night (540mL/30 days)</td>
</tr>
</tbody>
</table>

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation

**Target Agent** will be approved when ALL of the following are met:

1. The patient is 7 years of age or greater
   **AND**
2. ONE of the following:
   A. The patient has a diagnosis of narcolepsy with cataplexy **AND** ONE of the following:
      i. The patient has tried and had an inadequate response to 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 is under 18 years of age **OR**
         b. ONE of the following:
            1. The patient’s medication history indicates the use of modafinil or armodafinil **OR**
            2. 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 ALL standard stimulant agents

OR
C. The patient has another FDA approved indication for the requested agent and route of administration

AND
3. The prescriber is a specialist in the area of the patient’s diagnosis (e.g. sleep specialist, neurologist, psychiatrist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis

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 is NOT greater than the program quantity limit
   OR
   B. ALL of the following:
      i. The requested quantity is greater than the program quantity limit
      AND
      ii. The requested quantity does not exceed the maximum FDA labeled dose for the requested indication
      AND
      iii. The requested quantity cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 12 months
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT

OBJECTIVE
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL
The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
   AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

OR

2. The patient’s medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
   OR
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria