Description:

XYREM® (sodium oxybate, GHB) oral solution (brand and generic)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

Description:

Xyrem (sodium oxybate) is a central nervous system depressant indicated for the treatment of cataplexy in narcolepsy and for the treatment of excessive daytime sleepiness (EDS) in narcolepsy.

The American Academy of Sleep Medicine has subdivided narcolepsy into two types: narcolepsy type 1 and narcolepsy type 2. In both EDS is an essential feature, with cataplexy a core feature in narcolepsy type 1. Both types require laboratory tests to confirm the diagnosis. Laboratory testing includes sleep laboratory testing with overnight polysomnography (PSG) followed by a multiple sleep latency test (MSLT), and may also include cerebrospinal fluid (CSF) assessment of hypocretin-1 levels.

PSG testing, together with an MSLT, is indicated for assessing the potential for the presence of narcolepsy. PSG testing also helps identify whether other sleep pathologies, such as obstructive sleep apnea, are present. It can identify the nighttime occurrence of sleep onset rapid eye movement periods (SOREMP). A SOREMP on a nocturnal PSG is a highly specific marker for narcolepsy in the absence of another sleep disorder, but it has low sensitivity. The MSLT is indicated as part of the evaluation of patients with the potential for narcolepsy to confirm
XYREM® (sodium oxybate, GHB) oral solution (brand and generic) (cont.)

the diagnosis, and is performed immediately following overnight polysomnography. The MSLT assesses the ability or tendency to fall asleep (as indicated by mean sleep latency, or time to sleep onset) during normal waking hours and the presence of SOREMP.

A normal sleep cycle is 100-110 minutes long and starts with non-rapid eye movement (NREM) sleep before transitioning to rapid eye movement (REM) sleep after 80-100 minutes. People with Narcolepsy quickly enter REM sleep within a few minutes of falling asleep.

Narcolepsy is a chronic neurologic disorder of the central nervous system characterized by the brain's inability to control sleep-wake cycles, resulting in EDS and intermittent bouts of REM sleep during wakefulness. At various times throughout the day, individuals with narcolepsy experience irresistible and sudden bouts of sleep, which can last from a few seconds to several minutes. In addition to EDS, other major symptoms of narcolepsy include cataplexy (a sudden loss of voluntary muscle tone), hypnagogic hallucinations (vivid dream-like images or hallucinations during sleep onset or upon waking), and sleep paralysis (brief episodes of total paralysis, also during sleep onset or upon waking). Most individuals experience poor sleep quality that can involve frequent awakenings during nighttime sleep, and other sleep disorders. Sleep may be disrupted by insomnia, vivid dreaming, sleep talking, acting out while dreaming, and periodic leg movements.

Cataplexy occurs in approximately 70% of individuals with narcolepsy. It is believed to be due to loss of the hypothalamic neuropeptide orexin/hypocretin, as demonstrated by low to undetectable levels of hypocretin in the cerebral spinal fluid. Oxrexins/hypocretins are wake active and increase the firing rate of neurons in areas of the brain responsible for arousal and wakefulness. Loss of orexin neurons can result in hyper-somnolence and loss of muscle tone. The reason for such cell loss remains unknown but appears to be autoimmune in nature.

Xyrem® (sodium oxybate, GHB) is a central nervous system depressant that reduces EDS and cataplexy in patients with narcolepsy. The precise mechanism by which sodium oxybate produces an effect on cataplexy is unknown. Xyrem® has a high salt content. A 3 gram dose contains 550 mg of sodium.

Xyrem®, when used in the treatment of Narcolepsy, is classified as a Schedule III controlled substance by Federal law. The active ingredient, sodium oxybate or gamma-hydroxybutyrate (GHB), is listed in the most restrictive schedule of the Controlled Substances Act (Schedule I). Use of sodium oxybate (Xyrem® or GHB) for other conditions is classified under Schedule I.

Xyrem® is available only through a restricted distribution program called the Xyrem Risk Evaluation and Mitigation Strategies (REMS) program using a centralized pharmacy that is specially certified and requires the provider and patient be enrolled into the program. Only providers and centralized pharmacies enrolled into the REMS may prescribe and dispense the drug, respectively, to individuals who are also in the program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks.

The REMS Program provides educational materials to the prescriber and the patient explaining the risks and proper use of sodium oxybate, and the required prescription form. Once it is documented that the patient has read and/or understood the materials, the drug will be shipped to the patient. The Xyrem REMS Program also ensures patient follow-up every 3 months. Physicians are expected to report all serious adverse events to the manufacturer.
XYREM® (sodium oxybate, GHB) oral solution (brand and generic) (cont.)

Definitions:

Xyrem® REMS items
- Enrollment and agreement information
- Treatment initiation information
- Treatment maintenance information
- Pharmacy requirements and responsibilities
- Counseling on serious risks and safe use

SOREMP
REM sleep that occurs within 15 minutes of sleep onset

Polysomnography (PSG)
An objective measure of nighttime physiology; it is a test that records sleep architecture (the amount of NREM and REM sleep, number of arousals) and a variety of body functions during sleep, including breathing patterns, heart rhythms and limb movements

Interpreting PSG testing results:
- Normal sleep:
  - Sleep stages cycle in periods alternating throughout the night in intervals of approximately 90-110 min
  - SOREMP usually absent
  - 4-5 cycles of REM and NREM sleep during a night
- Sleep suggestive of Narcolepsy:
  - Amount of Stage 1 sleep increased
  - One or more SOREMP present
  - Disruption of normal sleep pattern with frequent awakenings

Multiple Sleep Latency Test (MSLT)
An objective measurement of daytime physiology that assess the ability or tendency to fall asleep (as indicated by mean sleep latency, or time to sleep onset) during normal waking hours

Interpreting MSLT testing results:
- Normal sleep:
  - Mean sleep latency of > 10 min
  - SOREMP usually absent
- Narcolepsy:
  - Mean sleep latency of 8 min or less
  - Two or more SOREMP present (A SOREMP on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT)

Hypocretin-1 Concentration
An objective measurement of hypocretin-1 concentration, measured by immunoreactivity, in the cerebrospinal fluid (CSF). This requires a lumbar puncture (spinal tap) procedure.

Interpreting value results:
- Normal:
  - 110 pg/mL OR > 1/3 of mean values obtained in normal subjects with the same standardized assay
- Narcolepsy Type 1 (with cataplexy):
  - ≤ 110 pg/mL OR < 1/3 of mean values obtained in normal subjects with the same standardized assay
- Narcolepsy Type 2 (without cataplexy):
XYREM® (sodium oxybate, GHB) oral solution (brand and generic) (cont.)

> 110 pg/mL OR > 1/3 of mean values obtained in normal subjects with the same standardized assay

Drug related events:

Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual’s outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals’ body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

Intolerance – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

Non-adherence
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record
XYREM® (sodium oxybate, GHB) oral solution (brand and generic) (cont.)

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Xyrem® (sodium oxybate, GHB) oral solution (brand and generic) requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacist@azblue.com. Incomplete forms will be returned.

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Xyrem (brand and generic) is considered medically necessary when ALL of the following criteria are met:
  1. Individual is 18 years of age or older
  2. Request is from a Neurologist or Pulmonologist board certified as a sleep medicine specialist
  3. Individual has medical record documentation of a confirmed diagnosis of ONE of the following:
     - Cataplexy in Narcolepsy
     - Excessive daytime sleepiness (EDS) in Narcolepsy (without Cataplexy) who have failed OR are intolerant to OR have a contraindication to BOTH of the following:
       - Modafinil or Armodafinil
       - Methylphenidate or Amphetamine derivative
  4. Diagnosis is confirmed by ALL of the following:
     - Daily periods of irrepresible need to sleep or daytime lapses into sleep occurring for at least three months
     - One or both of the following:
       - A polysomnography test followed by a multiple sleep latency test that shows a mean sleep latency of 8 minutes or less and at least 2 sleep onset rapid eye movement periods (SOREMP) on a multiple sleep latency test (MSLT). A SOREMP on the nocturnal polysomnography test may replace one of the SOREMPs on the MSLT.
XYREM® (sodium oxybate, GHB) oral solution (brand and generic) (cont.)

- CSF hypocretin-1 concentration, measured by immunoreactivity, is either:
  - For Narcolepsy Type 1: ≤ 110 pg/mL or < 1/3 of mean values obtained in normal subjects with the same standardized assay
  - For Narcolepsy Type 2: > 110 pg/mL OR > 1/3 of mean values obtained in normal subjects with the same standardized assay OR has not been measured

5. Absence of ALL of the following contraindications:
   - Simultaneous use with alcohol
   - Simultaneous use with sedative-hypnotic medications (such as benzodiazepine sedative-hypnotics or non-benzodiazepine sedatives-hypnotics)
   - Individual with succinic semi-aldehyde dehydrogenase deficiency. A rare inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia

- **Continuation of coverage (renewal request):** Xyrem (brand and generic) is considered *medically necessary* with documentation of ALL of the following:
  1. The individual has benefited from therapy but remains at high risk
  2. The condition has not progressed or worsened while on therapy
  3. Individual has not developed any contraindications or other exclusions to its continued use

- Xyrem (brand and generic) for all other indications not previously listed is considered *experimental or investigational* based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to:
- Fibromyalgia
- Insomnia
- Alcohol dependence and withdrawal
- Opioid dependence and withdrawal
- Parkinsonism
- Myoclonus and essential tremor
- Obstructive sleep apnea
- Night eating syndrome
- Excessive sleepiness due to other causes not associated with Narcolepsy
- Cataplexy due to other causes not associated with Narcolepsy
XYREM® (sodium oxybate, GHB) oral solution (brand and generic) (cont.)

**Resources:**

Xyrem® package insert PI-8511 reviewed on 08-03-2012

Xyrem® package insert reference ID: 3231956 revised by manufacturer on 12/2012, reviewed on 12-04-2013


Xyrem® package insert revised by manufacturer on 01/2017, reviewed on 02-16-2017.


**FDA -approved indication and dosage:**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xyrem (sodium oxybate) oral solution is indicated for the treatment of cataplexy in narcolepsy and for the treatment of excessive daytime sleepiness (EDS) in narcolepsy.</td>
<td>The recommended starting dose is 4.5 grams (g) per night administered orally in two equal, divided doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (see Table 1). Increase the dose by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dose range of 6 g to 9 g per night orally. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.</td>
</tr>
<tr>
<td>Healthcare professionals who prescribe Xyrem must enroll in the Xyrem REMS Program and must comply with the requirements to ensure safe use of Xyrem.</td>
<td></td>
</tr>
<tr>
<td>Xyrem may only be dispensed to individuals enrolled in the Xyrem REMS Program.</td>
<td></td>
</tr>
<tr>
<td>Xyrem is available through the Xyrem REMS Program, using a centralized pharmacy 1-866-XYREM88® (1-866-997-3688).</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1:**

<table>
<thead>
<tr>
<th>If total nightly dose is:</th>
<th>Take at bedtime:</th>
<th>Take 2½ to 4 hours later:</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 g per night</td>
<td>2.25 g</td>
<td>2.25 g</td>
</tr>
<tr>
<td>6 g per night</td>
<td>3 g</td>
<td>3 g</td>
</tr>
<tr>
<td>7.5 g per night</td>
<td>3.75 g</td>
<td>3.75 g</td>
</tr>
<tr>
<td>9 g per night</td>
<td>4.5 g</td>
<td>4.5 g</td>
</tr>
</tbody>
</table>