BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

**PHARMACY COVERAGE GUIDELINES**
**SECTION: DRUGS**

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| **ORIGINAL EFFECTIVE DATE:** | **11/16/2017** |
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# XYREM® (sodium oxybate, GHB) oral solution
# XYWAV™ (calcium, magnesium, potassium, sodium oxybates) oral solution

**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.**



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.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **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)

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864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

**Criteria**:

- **Criteria for initial therapy:** Xyrem (sodium oxybate) or Xywav (calcium, magnesium, potassium, sodium oxybates) is considered ***medically necessary*** when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist or Pulmonologist board certified as a sleep medicine specialist

2. Individual is 7 years of age or older

3. Individual has medical record documentation of a confirmed diagnosis of Cataplexy in Narcolepsy

4. Diagnosis is confirmed by **ALL** of the following:
    a. Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months

    b. **ONE** or **BOTH** of the following:
        i. Cataplexy and a mean sleep latency of ≤ 8 minutes and two or more sleep onset REM sleep periods (SOREMPs) on a multiple sleep latency test (MSLT) performed using standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.

        ii. CSF hypocretin-1 concentration, is low measured by immunoreactivity
            1. For Narcolepsy Type1: ≤ 110 pg/mL or < 1/3 of mean values obtained in normal subjects with the same standardized assay

5. Individual does **NOT** have another medical condition known to cause or contribute to sleepiness

6. Individual does **NOT** use alcohol

7. Individual is **NOT** receiving other drugs known to cause or contribute to sleepiness (benzodiazepines such as clonazepam, lorazepam, diazepam etc., sedating antidepressants or antipsychotics, sedating antiepileptic agents, general anesthetics, muscle relaxants, barbiturates, opioids, and others) **OR there is a** coordinated care treatment plan to taper their use

8. Individual is not using in combination with Sunosi (solriamfetol) or Wakix (pitolisant) or other sodium oxybate product

9. Individual must **NOT** be actively using **illicit substances** and must **NOT** have a drug seeking behavior

10. There must be coordination of care performed between different prescribers for **ALL** controlled substances

11. There is documentation for a **random urine or blood tests** twice a year that is negative for drugs of abuse and alcohol (most recent report must be submitted with request)

12. There is documentation of **PDMP (Prescription Drug Monitoring Program) reviewed** by the prescriber every time a prescription for controlled substance is provided

13. Individual has a failure, contraindication or intolerance to:
    a. Modafinil for Narcolepsy **AND**
    b. 2 drugs from REM sleep-suppressing drugs for cataplexy like:
        i. Effexor XR (venlafaxine)
        ii. Strattera (atomoxetine)
        iii. Prozac (fluoxetine)
        iv. Vivactil (protriptyline)
        v. Clomipramine

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

**Initial approval duration**:
Xyrem: 6-9 gms (18mL)/night x 30 days (up to 540mL) monthly for 6 months
Xywav: 6-9 gms (18mL)/night x 30 days (up to 540mL) monthly for 6 months

- **Criteria for continuation of coverage (renewal request):** Xyrem (sodium oxybate) or Xywav (calcium, magnesium, potassium, sodium oxybates) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist or Pulmonologist board certified as a sleep medicine specialist

2. Individual's condition responded while on therapy
    a. Response is defined by improvement **TWO** of the following:
        i. Achieved and maintains at least a 25% reduction in the frequency of cataplexy attacks over baseline
        ii. Achieved and maintains at least a 25% reduction in the severity of cataplexy attacks over baseline

iii. Overnight polysomnography (PSG)
iv. Multiple sleep latency test (MSLT)
v. Or other measure of improvement as measured by other tests such as:
    1. Epworth sleepiness scale
    2. Stanford sleepiness scale
    3. Osler test

3. Individual does **NOT** have another medical condition known to cause or contribute to sleepiness

4. Individual does **NOT** use alcohol

5. Individual is **NOT** receiving other drugs known to cause or contribute to sleepiness (benzodiazepines such as clonazepam, lorazepam, diazepam etc., sedating antidepressants or antipsychotics, sedating antiepileptic agents, general anesthetics, muscle relaxants, barbiturates, opioids, and others) **OR there is a** coordinated care treatment plan to taper their use

6. Individual is not using in combination with Sunosi (solriamfetol) or Wakix (pitolisant) or other sodium oxybate product
7. Individual must **NOT** be actively using **illicit substances** and must **NOT** have a drug seeking behavior

8. There must be coordination of care performed between different prescribers for **ALL** controlled substances

9. There is documentation for a **random urine or blood tests** twice a year that is negative for drugs of abuse and alcohol (most recent report must be submitted with request)

10. There is documentation of **PDMP (Prescription Drug Monitoring Program) reviewed** by the prescriber every time a prescription for controlled substance is provided

11. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Seizure
        ii. Respiratory depression
        iii. Decreases in level of consciousness
        iv. Psychosis/hallucinations/paranoia
        v. Agitation
        vi. Depression/suicidality
        vii. Sleepwalking

12. There are no significant interacting drugs

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**Renewal duration**:
Xyrem: 6-9 gms (18mL)/night x 30 days (up to 540mL) monthly for 6 months
Xywav: 6-9 gms (18mL)/night x 30 days (up to 540mL) monthly for 6 months

**Description:**

Xyrem (sodium oxybate) and Xywav (calcium, magnesium, potassium, sodium oxybates) are central nervous system depressants indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with 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 type1. 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 a 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 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 often frightening tactile 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. Cataplexy is a sudden, brief loss of voluntary muscle tone triggered by fatigue or strong emotions such as laughter, excitement, or fear that occurs during waking hours. During a mild attack, there may be a barely visible weakness in a muscle, such as drooping of the eyelids. The duration of an attack is brief, generally lasting anywhere from a few seconds to a few minutes (usually less than 2 minutes) followed by a rapid return of normal muscle tone and function. More severe episodes may involve a total body collapse. During an episode of cataplexy, an individual is awake but temporarily paralyzed.

The condition is most commonly associated with narcolepsy and can occur after suddenly stopping antidepressant medication. It also occurs with other disorders such as Niemann-Pick type C disease, Prader-Willi syndrome, Wilson's disease, other medical conditions including stroke, multiple sclerosis, head injury and encephalitis.

Xyrem and Xywav are central nervous system depressants that reduce EDS and cataplexy in patients with narcolepsy. The precise mechanism by which they produce an effect on cataplexy is unknown. Xyrem has a high salt content. A 3 gram dose contains 550 mg of sodium.

Xyrem and Xywav, when used in the treatment of narcolepsy, are classified as a Schedule III controlled substances by Federal law. Sodium oxybate or gamma-hydroxybutyrate (GHB) is an endogenous compound and a metabolite of the neurotransmitter gamma-aminobutyric acid (GABA). GHB is listed in the most restrictive schedule of the Controlled Substances Act (Schedule I). Use of GHB for other conditions is classified under Schedule I.

Xyrem and Xywav are available only through a restricted distribution program called the Xyrem Risk Evaluation and Mitigation Strategies (REMS) and Xywav REMS program, respectively, 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 calcium, magnesium, potassium, sodium oxybates, 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 REMS Program also ensures patient follow-up every 3 months. Physicians are expected to report all serious adverse events to the manufacturer.

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**Definitions:**

**Xyrem and Xywav 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):
> 110 pg/mL OR > 1/3 of mean values obtained in normal subjects with the same standardized assay

**Resources:**

Xyrem (sodium oxybate) product information, revised by manufacturer Jazz Pharmaceuticals, Inc. 09-2020, at DailyMed http://dailymed.nlm.nih.gov accessed October 16, 2020.

Xywav (calcium, magnesium, potassium, sodium oxybates) product information, revised by manufacturer Jazz Pharmaceuticals, Inc. 07-2020, at DailyMed http://dailymed.nlm.nih.gov accessed October 16, 2020.

Scammell TE. Treatment of narcolepsy in adults. In: UpToDate, Benca R, Eichler AF (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on October 20, 2020.

Kotaqal S. Narcolepsy in children. In: UpToDate, Scammell TE, Chervin RD, Eichler AF (Edd), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on October 20, 2020.