PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 11/16/2017
LAST REVIEW DATE: 11/18/2021
LAST CRITERIA REVISION DATE: 11/18/2021
ARCHIVE DATE:

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

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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. A confirmed diagnosis of **ONE** of the following:
    a. Cataplexy in Narcolepsy in an individual 7 years of age or older to use Xyrem or Xywav
    b. Idiopathic Hypersomnia in an individual 18 years of age or older to use Xywav only

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

4. Diagnosis is confirmed by the following:
    a. For Narcolepsy:
        i. Individual has daily periods of irrepressible (uncontrollable) need to sleep or daytime lapses into sleep occurring for at least three months
        ii. Individual has an Epworth Sleep Scale (ESS) score of 10 or more
        iii. **ONE** or **BOTH** of the following:
            1. Clear history of 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.
            2. CS hypocretin-1 concentration, is low measured by immunoreactivity is either ≤ 110 pg/mL or < 1/3 of mean values obtained in normal subjects with the same standardized assay
    b. For Idiopathic Hypersomnia:
        i. Individual has daily periods of irrepressible (uncontrollable) need to sleep or daytime lapses into sleep occurring for at least three months
        ii. Individual has an Epworth Sleep Scale (ESS) score of 11 or more
        iii. Mean sleep latency of ≤ 8 minutes and ***less than two*** sleep onset REM sleep periods (SOREMPs) on a multiple sleep latency test (MSLT) performed using standard techniques or no SOREMPs if the REM sleep latency on the preceding polysomnogram was less than or equal to 15 minutes
        iv. Total 24-hour sleep time is greater than or equal to 660 minutes (typically 12-14 hours) on a 24-hour polysomnography or by wrist actigraphy in association with a sleep log
        v. There is ***no*** history of cataplexy
        vi. If measured, CS hypocretin-1 concentration ***is not*** low or deficient

5. Individual has documented failure, contraindication per FDA label or intolerance to:
    a. For cataplexy in narcolepsy a three-month trial of:
        i. **Two** drugs for narcolepsy:

1. Methylphenidate or amphetamine
2. Modafinil

ii. **Two** drugs from REM sleep-suppressing drugs for cataplexy like:

1. Strattera (atomoxetine)
2. Clomipramine
3. Prozac (fluoxetine)
4. Vivactil (protriptyline)
5. Effexor XR (venlafaxine)

b. For idiopathic hypersomnia a three-month trial of each of the following:

i. Methylphenidate or amphetamine
ii. Modafinil

6. There are **NO** FDA-label contraindications, such as:
   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

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 does **NOT** use alcohol

9. Individual is **not** using in combination with armodafinil (generic or brand Nuvigil), Sunosi (solriamfetol), Wakix (pitolisant) or other oxybate product

10. Individual has been evaluated and must not have an active addiction to illicit substances or prescription drugs or a history of risky, harmful, non-medical or inappropriate use of these and other substances that might be unhealthy, hazardous or a problem (i.e.; multiple providers, multiple pharmacy or multiple controlled substances)

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

12. 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)

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

14. There are no significant interacting drugs

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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. Narcolepsy with cataplexy 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. Improvement in Epworth Sleepiness Scale of at least 3 points
    b. Idiopathic hypersomnia response is defined by improvement in **TWO** of the following:
        i. Improvement in Epworth Sleepiness Scale of at least 3 points
        ii. Decrease in morning sleep inertia
        iii. Decrease in naps or decrease in total duration of sleep in 24 hours

3. Individual has been adherent with the medication

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

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

7. Individual does **NOT** use alcohol

8. Individual is **not** using in combination with armodafinil (generic or brand Nuvigil), Sunosi (solriamfetol), Wakix (pitolisant) or other oxybate product

9. Individual has been evaluated and must not have an active addiction to illicit substances or prescription drugs or a history of risky, harmful, non-medical or inappropriate use of these and other substances that

might be unhealthy, hazardous or a problem (i.e.; multiple providers, multiple pharmacy or multiple controlled substances)

10. 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)

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

12. Individual has not developed any contraindications or other significant 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

13. There are no significant interacting drugs

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

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of a Non-cancer Medications**

2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

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. Xywav (calcium, magnesium, potassium, sodium oxybates) is also indicated for the treatment of idiopathic hypersomnia in an individual 18 years of age or older.

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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.

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

Cataplexy:

Sudden loss of muscle tone triggered by strong emotions (fear, surprise, joking or laughing); this is transient (less than 2 minutes); symptoms may involve the entire body, or only the knees, neck, or face

Epworth Sleepiness Scale (ESS):

The ESS subjectively measures sleepiness as it occurs in ordinary life situations
Can be used to screen for excessive sleepiness or to follow a subjective response to an intervention

The ESS can be performed in the examination room or waiting room
It is relatively simple and generally takes only a few minutes to complete
It should be repeated at subsequent visits to assess for change
A questionnaire describes eight situations:
- Sitting and reading
- Watching television
- Sitting inactively in a public place
- Riding as a passenger in a car for one hour without a break
- Lying down to rest in the afternoon when circumstances permit
- Sitting and talking with someone
- Sitting quietly after lunch without alcohol
- Sitting in a car as the driver, while stopped for a few minutes in traffic

Each situation receives a score of 0-3, which relates to the likelihood that sleep will be induced:
- 0 = would never doze
- 1 = slight chance of dozing
- 2 = moderate chance of dozing
- 3 = high chance of dozing

The total ESS score ranges from 0-24, with higher scores correlating with increasing degrees of sleepiness
- A score > 10 is consistent with excessive sleepiness

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

MSLT is the tendency to fall asleep
It tests for excessive daytime sleepiness (EDS) by measuring how quickly one falls asleep in a quiet environment during the day
- EDS occurs when you are sleepy when you should be awake and alert

MSLT is the standard tool used to diagnose narcolepsy and idiopathic hypersomnia
MSLT is a full-day test that consists of five scheduled naps separated by two-hour breaks
During the MSLT
- Lying flat in bed for the MSLT
- Instructed to lie quietly, assume a comfortable position, keep eyes closed, and try to fall asleep
- The test will measure how long it takes for to fall asleep
- You will be awakened after sleeping 15 minutes
- If you do not fall asleep within 20 minutes, the nap trial ends

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)

Maintenance of Wakefulness Test (MWT):
MWT is the ability to stay awake
It objectively measures the ability of an individual to remain awake for a defined period of time
It is based on the premise that individuals with a greater degree of sleepiness are less likely to remain awake than individuals with less sleepiness
- MWT may be used to assess an individual's response to therapy

It is the direction of change, not the degree of change, that is meaningful
During the MWT:
- Sit in a recumbent position
- Instructed to sit still and try to remain awake for as long as possible
- Look directly ahead and do not look directly at the light
- Avoid extraordinary measures to stay awake (e.g., slapping the face, singing)
- A session is ended after unequivocal sleep, or after 40 minutes if sleep does not occur
- Sleep is considered unequivocal after three consecutive periods of stage 1 sleep or one period of any other stage of sleep
- For each session, the sleep latency is recorded
- It is documented as being 40 minutes if the patient does not fall asleep
- This is repeated every two hours, until the patient has completed four sessions

The primary measure from the MWT is the mean sleep latency
Healthy individuals who complete four 40-minute protocol sessions, the mean sleep latency is approximately 30 minutes, with > 97% of individuals having a mean sleep latency of ≥ 8 minutes
- A mean sleep latency of < 8 minutes is generally considered abnormal
- Staying awake for at least 40 minutes during all four sessions is strong objective evidence that an individual can stay awake
- A mean sleep latency between 8 and 40 minutes has uncertain significance

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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 Jazz Pharmaceuticals, Inc. 12-2020, at DailyMed http://dailymed.nlm.nih.gov. Accessed October 06, 2021.

Xywav (calcium, magnesium, potassium, sodium oxybates) product information, revised by Jazz Pharmaceuticals, Inc. 08-2021, at DailyMed http://dailymed.nlm.nih.gov. Accessed October 06, 2021.

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