

## Xywav (calcium, magnesium, potassium, and sodium oxybates)

### Disclaimer

*Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.*

*Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.*

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### Summary

Narcolepsy is a chronic neurological disorder characterized by excessive daytime sleepiness (EDS) and abnormal rapid eye movement (REM) sleep manifestations, including cataplexy, sleep paralysis, and hypnagogic hallucinations. It affects approximately 1 in 2,000 people in the United States and is caused by the loss of hypothalamic neurons that produce hypocretin (orexin), a neuropeptide that regulates

wakefulness and REM sleep. Idiopathic hypersomnia (IH) is a neurological sleep disorder characterized by excessive daytime sleepiness despite adequate or prolonged nighttime sleep.

The goal of narcolepsy management is to improve the sleep-wake cycle by reducing EDS, improving wakefulness, and maximizing sleep during the nighttime. Treatment options for narcolepsy include central nervous system stimulants (e.g., modafinil, armodafinil, methylphenidate, amphetamines), Z-drugs (e.g., zolpidem, zopiclone), sodium oxybate, Wakix (pitolisant), or Sunosi (solriamfetol) to improve EDS and/or cataplexy. Behavioral modifications, such as scheduled naps and sleep hygiene, are also important components of management.

For idiopathic hypersomnia, similar wake-promoting medications are used as first-line treatments.

Xywav (calcium, magnesium, potassium, and sodium oxybates) is a central nervous system depressant approved by the FDA for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy, and for the treatment of idiopathic hypersomnia in adults. It offers a lower-sodium alternative to Xyrem (sodium oxybate) and is typically considered after other treatments have failed or are contraindicated. It is classified as a central nervous system depressant and is believed to act through GABA-B receptors, although its exact mechanism of action in narcolepsy is not fully understood. Xywav (calcium, magnesium, potassium, and sodium oxybates) is typically administered in two equally divided doses: the first dose at bedtime and the second dose 2.5 to 4 hours later. For idiopathic hypersomnia, Xywav (calcium, magnesium, potassium, and sodium oxybates) is typically dosed once or twice nightly and titrated to effect.

Sodium oxybate products have a boxed warning for the risk of central nervous system depression and abuse and misuse. Because sodium oxybate is a sodium salt of GBH, it can have similar serious and life-threatening adverse reactions including: seizures, respiratory depression, decreased consciousness, coma and death. Because of this, sodium oxybate products are only available through a restricted program - for Xywav (calcium, magnesium, potassium, and sodium oxybates) this is called the XYWAV REMS.

## Definitions

"Cataplexy" refers to a sudden, transient episode of muscle weakness accompanied by full conscious awareness, typically triggered by emotions such as laughing, crying, or terror.

"Documentation" refers to written information, including but not limited to:

- Up-to-date chart notes, relevant test results, and/or relevant imaging reports to support diagnoses; or
- Prescription claims records, and/or prescription receipts to support prior trials of formulary alternatives.

"Excessive daytime sleepiness (EDS)" is the inability to stay awake and alert during the day, resulting in unintended lapses into drowsiness or sleep.

"Hypnagogic hallucinations" are vivid, often frightening, dreamlike experiences that occur while falling asleep.

"Hypocretin-1" is a natural chemical in the brain that helps regulate wakefulness.

"Idiopathic hypersomnia (IH)" is a neurological disorder characterized by excessive daytime sleepiness that is not caused by disturbed sleep at night, other medical conditions, or medications.

"Multiple Sleep Latency Test (MSLT)" is a sleep study that measures how quickly a person falls asleep during the day and whether they enter rapid eye movement (REM) sleep.

"Narcolepsy" is a chronic neurological disorder that affects the brain's ability to control sleep-wake cycles.

"No evidence of" indicates that the reviewer has not identified any records of the specified item or condition within the submitted materials or claims history. In the absence of such evidence, the member is considered eligible. If any evidence of the item or condition is present upon review of the request, the member does not qualify.

"Polysomnography (PSG)" is a sleep study used to diagnose sleep disorders by measuring certain components such as brain activity, oxygen levels, heart rate, breathing, eye movements, and leg movements.

"[s]" indicates state mandates may apply.

"Sleep latency" is the amount of time it takes to fall asleep.

"Sleep-onset REM periods (SOREMPs)" are periods of rapid eye movement sleep that occur within 15 minutes of falling asleep, which are characteristic of narcolepsy.

## Medical Necessity Criteria for Initial Clinical Review

### Initial Indication-Specific Criteria

#### Narcolepsy and Idiopathic Hypersomnia

The Plan considers Xywav (calcium, magnesium, potassium, and sodium oxybates) medically necessary when ALL of the following criteria are met:

1. The medication is prescribed by or in consultation with a sleep medicine specialist, neurologist, psychiatrist, or pulmonologist with expertise in treating sleep disorders; **AND**
2. The member meets the age requirement for the intended use:
  - a. For treatment of cataplexy or excessive daytime sleepiness (EDS) in narcolepsy - the member is 7 years of age or older; **or**
  - b. For treatment of idiopathic hypersomnia (IH) - the member is 18 years of age or older; **AND**
3. The member has a diagnosis of narcolepsy or idiopathic hypersomnia that has been confirmed by sleep lab testing or documented clinical symptoms:
  - a. For narcolepsy - excessive daytime sleepiness (EDS) persisting for at least 3 months **AND** at least **ONE (1)** of the following:
    - i. Cataplexy episodes (for narcolepsy type 1); **or**
    - ii. Hypocretin-1 (orexin A) deficiency ( $\leq 110$  pg/mL or  $< 1/3$  (one-third) of mean values of healthy individuals tested using the same standardized assay); **or**
    - iii. Nocturnal sleep polysomnography showing rapid eye movement (REM) sleep latency  $\leq 15$  minutes (also known as sleep-onset REM periods [SOREMP]), OR a Multiple Sleep Latency Test (MSLT) showing a mean sleep latency  $\leq 8$  minutes and  $\geq 2$  sleep-onset REM periods (SOREMPs). A SOREMP within 15 minutes of sleep onset on the preceding nocturnal polysomnography may replace one of the SOREMPs on the MSLT; **or**
  - b. For idiopathic hypersomnia - excessive daytime sleepiness (EDS) persisting for at least 3 months **AND** **ONE (1)** of the following:
    - i. A Multiple Sleep Latency Test (MSLT) showing a mean sleep latency of  $\leq 8$  minutes and fewer than 2 sleep-onset REM periods (SOREMPs), or no SOREMPs if the REM latency on the preceding polysomnogram was  $\leq 15$  minutes; **or**
    - ii. A total 24-hour sleep time of greater than or equal to ( $\geq$ ) 660 minutes (typically 12-14 hours) as measured by either 24-hour polysomnography or by wrist actigraphy in association with a sleep log, averaged over at least seven (7) days with unrestricted sleep; **AND**
4. The member is unable to use, or has tried and failed prior treatments as follows<sup>[s]</sup>.
  - a. IF the member is 18 years of age and older with narcolepsy, the member is unable to use, or has tried and failed, **ALL** of the following<sup>[s]</sup>:
    - i. Sunosi (solriamfetol); **and**
    - ii. Lumryz (sodium oxybate); **and**

- iii. Wakix (pitolisant); *or*
- b. IF the member is 7 to 17 years of age with narcolepsy and excessive daytime sleepiness (EDS), the member is unable to use, or has tried and failed, ALL of the following<sup>[s]</sup>:
  - i. Wakix (pitolisant); *and*
  - ii. Lumryz (sodium oxybate); *or*
- c. IF the member is 7 to 17 years of age with narcolepsy and cataplexy, the member is unable to use, or has tried and failed, Lumryz (sodium oxybate)<sup>[s]</sup>; *or*
- d. IF the member is an adult with idiopathic hypersomnia, the member is unable to use, or has adequately tried and failed at least THREE (3) of the following<sup>[s]</sup>:
  - i. Amphetamine-dextroamphetamine; *and/or*
  - ii. Dextroamphetamine; *and/or*
  - iii. Methylphenidate; *and/or*
  - iv. Armodafinil; *and/or*
  - v. Modafinil; **AND**

5. The member meets ALL of the following:

- a. No evidence of succinic semialdehyde dehydrogenase (SSADH) deficiency; *or*
- b. No evidence of documentation indicating concomitant use with, or inability to abstain from, any of the following while taking Xywav:
  - i. Alcohol (e.g., beer, wine, whisky); *or*
  - ii. Sedative hypnotics (e.g., alprazolam, diazepam, lorazepam, zolpidem); *or*
  - iii. Xyrem (sodium oxybate), Lumryz (sodium oxybate), or other sodium oxybate products; **AND**

6. Xywav (calcium, magnesium, potassium and sodium oxybates) is being prescribed at a dose and frequency that is within FDA approved labeling OR is supported by compendia or evidence-based published dosing guidelines for the requested indication.

If the above prior authorization criteria are met, the requested product will be authorized for up to 12 months.<sup>[s]</sup>

#### *Continued Care*

#### **Medical Necessity Criteria for Subsequent Clinical Review**

##### **Subsequent Indication-Specific Criteria**

##### Narcolepsy and Idiopathic Hypersomnia

The Plan considers Xywav (calcium, magnesium, potassium, and sodium oxybates) medically necessary when ALL of the following criteria are met:

1. The member has experienced a positive clinical response to Xywav (calcium, magnesium, potassium and sodium oxybates) therapy as demonstrated by a reduction in symptoms of cataplexy, EDS, and/or IH; **AND**

2. The member continues to abstain from alcohol and sedative hypnotics; *AND*
3. Xywav (calcium, magnesium, potassium and sodium oxybates) will not be used in combination with Xyrem (sodium oxybate), Lumryz (sodium oxybate), or other sodium oxybate products; *AND*
4. Xywav (calcium, magnesium, potassium and sodium oxybates) continues to be prescribed at a dose and frequency that is within FDA approved labeling OR is supported by compendia or evidence-based published dosing guidelines for the requested indication.

If the above reauthorization criteria are met, the requested product will be authorized for up to 12-months.<sup>[s]</sup>

#### Experimental or Investigational / Not Medically Necessary<sup>[s]</sup>

Xywav (calcium, magnesium, potassium, and sodium oxybates) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- When used in combination with alcohol, sedative hypnotics, or other medications containing sodium oxybate, gamma-hydroxybutyrate (GHB), or GHB precursors.
- When used in members with succinic semialdehyde dehydrogenase deficiency, a rare inborn error of metabolism.
- For members under 7 years of age, safety and efficacy have not been established in this pediatric population.

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#### Clinical Guideline Revision / History Information

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