PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Oxybate Products Prior Authorization Policy
- Xyrem® (sodium oxybate oral solution – Jazz Pharmaceuticals)
- Xywav™ (calcium, magnesium, potassium, and sodium oxybates oral solution – Jazz Pharmaceuticals)

REVIEW DATE: 09/29/2021

OVERVIEW

Xyrem and Xywav, central nervous system (CNS) depressants, are indicated for the following uses:[1,2]
- **Cataplexy treatment in patients with narcolepsy**, in patients ≥ 7 years of age.
- **Excessive daytime sleepiness in narcolepsy**, in patients ≥ 7 years of age.

Additionally, Xywav is indicated for the treatment of **idiopathic hypersomnia** in adults.[2]

Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy or idiopathic hypersomnia.[3] Polysomnography is an overnight recording of brain and muscle activity, breathing, and eye movements. The multiple sleep latency test (MSLT) assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter rapid eye movement (REM) sleep. Polysomnography is routinely indicated for the diagnosis of sleep-related breathing disorders; for continuous positive airway pressure titration in patients with sleep-related breathing disorders; with a MSLT in the evaluation of suspected narcolepsy; and in certain atypical or unusual parasomnias.[4] The MSLT is indicated as part of the evaluation of patients with suspected narcolepsy to confirm the diagnosis or patients who are thought to have idiopathic hypersomnia to exclude other causes of hypersomnia. Most patients with narcolepsy have objective evidence of hypersomnia as determined by a mean sleep latency < 5 minutes. In studies, the presence of two or more sleep-onset REM episodes (SOREMPs) was associated with a sensitivity of 0.78 and a specificity of 0.93 for the diagnosis of narcolepsy. SOREMPs do not occur exclusively in patients with narcolepsy, and thus it is important to rule out or treat other sleep disorders before evaluating SOREMPs in the diagnosis of narcolepsy. Diagnostic criteria for patients with idiopathic hypersomnia include a mean sleep latency ≤ 8 minutes and MSLT results showing < 2 SOREMPs or no SOREMPs if the REM sleep latency preceding polysomnogram is ≤ 15 minutes; also, these patients do not have cataplexy. For these reasons, polysomnography and a MSLT performed on the day after the polysomnographic evaluation are routinely indicated in the evaluation of suspected narcolepsy or idiopathic hypersomnia.

Guidelines

Guidelines for the treatment of central disorders of hypersomnolence do not include Xywav.[5,6] The American Academy of Sleep Medicine (AASM) practice parameters for the treatment of central disorders of hypersomnolence (2021) recommend modafinil, Wakix® (pitolisant tablets), Xyrem, and Sunosi™ (solriamfetol tablets) as effective treatments for daytime sleepiness due to narcolepsy and reducing disease severity in adults (Strong Recommendation for each). Wakix and Xyrem have also demonstrated efficacy for the treatment of cataplexy in patients with narcolepsy. Xyrem, dextroamphetamine, methylphenidate, and armodafinil each have Conditional Recommendations for the treatment of narcolepsy: Xyrem and armodafinil showing efficacy for daytime sleepiness due to narcolepsy and reducing disease severity, dextroamphetamine showing efficacy for excessive daytime sleepiness and cataplexy, and methylphenidate showing efficacy in reducing disease severity. There was insufficient and inconclusive evidence to make recommendations for l-carnitine, scheduled naps, selegiline, triazolam, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Modafinil and Xyrem have

Conditional Recommendations for the treatment of narcolepsy in pediatric patients. A Strong Recommendation should be followed by clinicians under most circumstances. A Conditional Recommendation requires that the clinician use clinical knowledge and experience and strongly consider the individual patient's values and preferences to determine the best course of action. The interventions in all the recommendation statements were compared with no treatment. AASM clarified that "insufficient evidence" does not mean that a particular intervention does not work, but that evidence is lacking to guide decision-making; additional research is required to determine the effectiveness of the intervention.

The AASM guideline includes recommendations for the treatment of idiopathic hypersomnia.[5,6] Only modafinil has a Strong recommendation for use. Clarithromycin, methylphenidate, Wakix, and Xyrem have Conditional recommendations for the treatment of idiopathic hypersomnia in adults.

The European League Against Rheumatism (EULAR) issued updated evidence-based recommendations for the management of fibromyalgia (2016) stating that initial management should involve patient education and focus on nonpharmacological therapies.[7] In case of non-response, further therapies should be tailored to the specific needs of the individual and may involve psychological therapies (for mood disorders and unhelpful coping strategies), pharmacotherapy (for severe pain or sleep disturbance) and/or a multimodal rehabilitation program (for severe disability). EULAR notes that the European Medicines Agency and the FDA refused approval of Xyrem for fibromyalgia because of safety concerns. EULAR's position on Xyrem for fibromyalgia is strongly against with 94% agreement.

Safety

Xyrem is the sodium salt of gamma hydroxybutyrate (GHB) and Xywav is a mixed salt formulation of GHB.[1,2] They are both Schedule III controlled substances. Abuse of GHB (a Schedule I controlled substance), either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. Because of the risks of CNS depression, abuse, and misuse, Xyrem and Xywav are available only through a restricted distribution program called the Xyrem/Xywav Success Program, using a centralized pharmacy. Healthcare professionals who prescribe Xyrem or Xywav and patients must enroll in the Xyrem/Xywav Success Program and must comply with the requirements to ensure the drug's safe use.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xyrem and Xywav. Because Xyrem and Xywav have been associated with significant risks, including CNS and respiratory depression, and have the potential for abuse, misuse, and overdose, approval requires Xyrem and Xywav to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xyrem or Xywav is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Cataplexy Treatment in Patients with Narcolepsy.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 7 years of age; AND
   - **B)** Patient has tried one of dextroamphetamine or Wakix (pitolisant tablets); AND
   - **C)** Patient has been evaluated using polysomnography and a multiple sleep latency test; AND
   - **D)** Diagnosis of narcolepsy has been confirmed, according to the prescriber; AND
   - **E)** The medication has been prescribed by a sleep specialist physician or a neurologist.

2. **Excessive Daytime Sleepiness in Patients with Narcolepsy.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 7 years of age; AND
   - **B)** Patient has tried one of the following treatments: a central nervous system (CNS) stimulant, modafinil, or armodafinil; AND
     Note: Examples of CNS stimulants include methylphenidate, dexmethylphenidate, and dextroamphetamine.
   - **C)** Patient has been evaluated using polysomnography and a multiple sleep latency test; AND
   - **D)** Diagnosis of narcolepsy has been confirmed, according to the prescriber; AND
   - **E)** The medication has been prescribed by a sleep specialist physician or a neurologist.

3. **Idiopathic Hypersomnia.** Approve Xywav for 1 year if the patient meets the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has tried one of modafinil, armodafinil, or methylphenidate; AND
   - **C)** Patient has been evaluated using polysomnography and a multiple sleep latency test; AND
   - **D)** Results of the polysomnography and a multiple sleep latency test are congruent with a diagnosis of idiopathic hypersomnia, according to the prescriber; AND
   - **E)** The medication has been prescribed by a sleep specialist physician or a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xyrem or Xywav is not recommended in the following situations:

1. **Fibromyalgia.** The effectiveness of Xyrem in fibromyalgia has been evaluated in clinical trials of varying size.[8-13] However, due to safety concerns, Xyrem is not recommended for approval for fibromyalgia at this time. Duloxetine, pregabalin capsules and oral solution, and Savella® (milnacipran tablets) are indicated for the treatment of fibromyalgia.[14-16] Other recommended treatments include TCAs (i.e., amitriptyline), cyclobenzaprine, gabapentin, and SSRIs (i.e., fluoxetine, sertraline, paroxetine).[17]

2. **Concomitant use of Xyrem, Xywav, Wakix (pitolisant tablets), Sunosi (solriamfetol tablets), modafinil, and/or armodafinil.** Xyrem and Xywav have the same active ingredient (oxybate, a central nervous system depressant) and have not been studied for use in combination or as alternating treatments.[1,2] Armodafinil and modafinil, agents with wake-promoting actions that are similar to sympathomimetic agents (e.g., amphetamine and methylphenidate), are indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, obstructive

sleep apnea, and shift work sleep disorder.[18,19] Sunosi, a dopamine and norepinephrine reuptake inhibitor, is indicated to improve wakefulness in adults with excessive daytime sleepiness due to narcolepsy or obstructive sleep apnea.[20] Wakix, an antagonist/inverse agonist of the histamine-3 (H3) receptor, is indicated for excessive daytime sleepiness and cataplexy in adults with narcolepsy.[21]

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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