Pharmacy Policy Bulletin

Title: Sodium oxybate (Xyrem®)/calcium, magnesium, potassium and sodium oxybates (Xywav™)

Policy #: Rx.01.124

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

Intent:

The intent of this policy is to communicate the medical necessity criteria for **sodium oxybate (Xyrem®) and calcium, magnesium, potassium and sodium oxybates (Xywav™)** as provided under the member's prescription drug benefit.

Description:

Narcolepsy results from the loss of the neuropeptides, orexin-A and orexin-B (also known as hypocretin-1 and hypocretin-2), which have excitatory effects on the ox1 and ox2 receptors on postsynaptic neurons. Narcolepsy is a clinical syndrome of daytime sleepiness with cataplexy, hypnagogic hallucinations, and sleep paralysis. It is the second most common cause of disabling daytime sleepiness after obstructive sleep apnea. Typical age of onset of narcolepsy is teens to twenties. Patients with type 1 narcolepsy (narcolepsy with cataplexy) typically present with moderate to severe daytime sleepiness, transient facial weakness or falls triggered by joking or laughter (partial or complete cataplexy), or the inability to move for one or two minutes immediately after awakening or just before falling asleep. Patients with type 2 narcolepsy do not have cataplexy.

Sodium oxybate, a CNS depressant, is the sodium salt of gamma hydroxybutyrate, a metabolite of GABA. It is hypothesized that the therapeutic effects of Xyrem® on cataplexy and excessive daytime sleepiness are mediated through GABA-B actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons. The exact mechanism of sodium oxybate in narcolepsy is unknown.

Xywav™ is a CNS depressant. The exact mechanism of action in the treatment of narcolepsy is unknown. Xywav™ is a mixture of calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate (gamma-hydroxybutyrate). Gamma-hydroxybutyrate (GHB) is an endogenous compound and metabolite of the neurotransmitter GABA. It is hypothesized that the therapeutic effects of Xywav™ on cataplexy and excessive daytime sleepiness are mediated through GABA-B actions during sleep at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons. The active moiety of oxybate salts is the same as that of sodium oxybate (Xyrem®), and dosing is the same; the only difference is that oxybate salts (Xywav™) have 90 percent less sodium.

Sodium oxybate (Xyrem®) is indicated for the treatment of cataplexy in narcolepsy and excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

Calcium, magnesium, potassium and sodium oxybates (Xywav™) is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy and idiopathic hypersomnia (IH) in adults.

Policy:

Cataplexy with narcolepsy (Type 1)

INITIAL CRITERIA Sodium oxybate (Xyrem®) or calcium, magnesium, potassium and sodium oxybates (Xywav™) is approved when there is documentation of ALL of the following:

1. Diagnosis of Cataplexy with narcolepsy (Type 1); and
2. Diagnosis was confirmed by ONE of the following tests:
    a. Polysomnography (PSG); or
    b. Multiple sleep latency test (MSLT); and
3. Recommended by a neurologist or sleep specialist; and
4. No concurrent use of sedative hypnotics and alcohol

Initial authorization duration: 12 months

REAUTHORIZATION CRITERIA Sodium oxybate (Xyrem®) or calcium, magnesium, potassium and sodium oxybates (Xywav™) is re-approved when there is documentation of ALL of the following:

1. Documentation to support the efficacy associated with the current regimen (including but not limited to reduction in the frequency of cataplexy attacks or an improvement in the Epworth sleepiness scale); and
2. There is no claim history of a sedative hypnotic agents within one year of the request; and
3. Yearly evaluation by a neurologist or sleep specialist

Reauthorization duration: 12 months

Excessive daytime sleepiness in narcolepsy (Type 2)

INITIAL CRITERIA Sodium oxybate (Xyrem®) or calcium, magnesium, potassium and sodium oxybates (Xywav™) is approved when there is documentation of ALL of the following:

1. Diagnosis of Excessive daytime sleepiness in narcolepsy (Type 2); and
2. Diagnosis was confirmed by ONE of the following tests:
    a. Polysomnography (PSG); or
    b. Multiple sleep latency test (MSLT); and
3. Inadequate response or inability to tolerate ALL of the following:
    a. Modafinil or armodafinil; and
    b. One CNS stimulant; and
    c. Sunosi®
4. Recommended by a neurologist or sleep specialist; and
5. No concurrent use of sedative hypnotics and alcohol

Initial authorization duration: 12 months

REAUTHORIZATION CRITERIA Sodium oxybate (Xyrem®) or calcium, magnesium, potassium and sodium oxybates (Xywav™) is re-approved when there is documentation of ALL of the following:

1. Documentation to support the efficacy associated with the current regimen (including but not limited to reduction in the frequency of cataplexy attacks or an improvement in the Epworth sleepiness scale); and
2. There is no claim history of a sedative hypnotic agents within one year of the request; and
3. Yearly evaluation by a neurologist or sleep specialist

Reauthorization duration: 12 months

Idiopathic Hypersomnia (IH)

INITIAL CRITERIA Calcium, magnesium, potassium and sodium oxybates (Xywav™) is approved when there is documentation of ALL of the following:

1. Diagnosis of idiopathic hypersomnia; and
2. Diagnosis was confirmed by ONE of the following tests:
    a. Polysomnography (PSG); or
    b. Multiple sleep latency test (MSLT); and
3. Symptoms of excessive daytime sleepiness (e.g., nap duration of longer than 60 minutes) are present; and
4. Recommended by a neurologist or sleep specialist; and
5. No concurrent use of sedative hypnotics and alcohol

Initial authorization duration: 12 months

REAUTHORIZATION CRITERIA Calcium, magnesium, potassium and sodium oxybates (Xywav™) is re-approved when there is documentation of ALL of the following:

1. Documentation demonstrating a reduction in symptoms of excessive daytime sleepiness associated with therapy; and
2. There is no claim history of a sedative hypnotic agents within one year of the request; and
3. Yearly evaluation by a neurologist or sleep specialist

Reauthorization duration: 12 months

Black Box Warning as shown in the drug Prescribing Information:

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and ABUSE AND MISUSE.

Central Nervous System Depression

Xyrem®/Xywav™ is a CNS depressant. In clinical trials at recommended doses, obtundation and clinically significant respiratory depression occurred in adult patients treated with Xyrem®/Xywav™. Many patients who received Xyrem®/Xywav™ during clinical trials in narcolepsy were receiving central nervous system stimulants.

Abuse and Misuse

Xyrem®/Xywav™ is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death.

Because of the risks of CNS depression and abuse and misuse, Xyrem®/Xywav™ is available only through a restricted program called the Xyrem®/Xywav™ REMS Program

Guidelines:

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

References:

Scammel TE. Treatment of narcolepsy in adults. UpToDate. December 2020. Available at: https://www.uptodate.com/contents/treatment-of-narcolepsy-in-adults?source=search_result&search=modafinil%20narcolepsy&selectedTitle=1~143#H1. Accessed January 13, 2022.

Xyrem® (sodium oxybate) [package insert]. Palo Alto, CA. Jazz Pharmaceuticals. February 2021. Available at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=926eb076-a4a8-45e4-91ef-411f0aa4f3ca&type=display. Accessed January 13, 2022.

Xywav™ (calcium, magnesium, potassium, and sodium oxybates) [prescribing information]. Palo Alto, CA. Jazz Pharmaceuticals. February 2021. Available from: https://pp.jazzpharma.com/pi/xywav.en.USPI.pdf. Accessed January 13, 2022.

Scammell TE. Clinical features and diagnosis of narcolepsy in adults. UpToDate website. Last updated August 2020. Available at http://www.uptodate.com/. Accessed January 13, 2022.

Applicable Drugs:

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Drug name	Generic name
Xyrem®	sodium oxybate
Xywav™	calcium, magnesium, potassium and sodium oxybates

Cross References:

Off-label use Rx.01.33

Quantity Level Limits Covered for Pharmaceuticals Covered Under the Prescription Drug Benefit Rx.01.76

Policy Version Number:	12.00
P&T Approval Date:	December 09, 2021
Policy Effective Date:	April 01, 2022
Next Required Review Date:	December 09, 2022