Original Effective Date: 10/01/2013
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Policy Number: C3925-A

Xyrem (sodium oxybate), Xywav (calcium, magnesium, potassium, and sodium oxybates)

PRODUCTS AFFECTED

Xyrem (sodium oxybate), sodium oxybate, Xywav (calcium, magnesium, potassium, and sodium oxybates)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This 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 Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Excessive daytime sleepiness (EDS) or cataplexy with narcolepsy, Idiopathic hypersomnia

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. EXCESSIVE DAYTIME SLEEEPINESS (EDS) IN NARCOLEPSY:
   1. Documented diagnosis of narcolepsy confirmed by overnight polysomnography (PSG) followed by multiple sleep latency test (MSLT) [DOCUMENTATION REQUIRED]

AND

2. Prescriber attests that member is not taking other narcolepsy therapies with the same mechanism of action
   AND
3. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal (e.g., symptoms of excessive daytime sleepiness, OR Epworth Sleepiness Scale (ESS), Clinical Global Impression of Change or Maintenance of Wakefulness Test (MWT))
   AND
4. Documented treatment failure, serious side effects or FDA labeled contraindication to BOTH of the following for at least 90 days: (i) ONE formulary central nervous system (CNS) stimulant (e.g., methylphenidate, dexmethylphenidate, dextroamphetamine); AND (ii) ONE wakefulness promoting agent (i.e., modafinil, armodafinil)
   AND
5. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Xyrem and Xywav include: use in combination with sedative hypnotics or alcohol, and succinic semialdehyde dehydrogenase deficiency]

B. CATAPLEXY WITH NARCOLEPSY:
   1. Documented diagnosis of narcolepsy confirmed by polysomnography and multiple sleep latency test (MSLT) [DOCUMENTATION REQUIRED]
      AND
   2. Documentation member experiences episodes of cataplexy
      AND
   3. Prescriber attests that member is not taking other narcolepsy therapies with the same mechanism of action
      AND
   4. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal (e.g., frequency or severity of cataplexy events/attacks, symptoms of excessive daytime sleepiness, OR Epworth Sleepiness Scale (ESS), Clinical Global Impression of Change or Maintenance of Wakefulness Test (MWT))
      AND
   5. Documented treatment failure, serious side effects, or FDA labeled contraindication to ONE of the following: a tricyclic antidepressant (TCA) [e.g., amitriptyline, desipramine, imipramine], a selective serotonin reuptake inhibitor (SSRI) [e.g., fluoxetine, sertraline, paroxetine], or venlafaxine
      AND
   6. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Xyrem and Xywav include: use in combination with sedative hypnotics or alcohol, and succinic semialdehyde dehydrogenase deficiency]

C. IDIOPATHIC HYPERSOMNIA (IH) - XYWAV ONLY
   1. Documented diagnosis of idiopathic hypersomnia confirmed by polysomnography and multiple sleep latency test (MSLT) [DOCUMENTATION REQUIRED]
      AND
   2. Documentation prescriber has ruled out all other causes of excessive daytime sleepiness (EDS) (i.e., chronically insufficient sleep, medication side effects, narcolepsy type 1 or type 2, sleep-related breathing disorders, and psychiatric disorders)
      AND
   3. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be

used to evaluate efficacy of therapy at renewal (e.g., symptoms of idiopathic hypersomnia, OR Epworth Sleepiness Scale (ESS), Clinical Global Impression of Change or Idiopathic Hypersomnia Severity Scale (IHSS))
AND

4. Documentation of a trial (minimum of 4 weeks) and failure of modafinil or armodafinil
AND
5. Prescriber attests that member is not taking other narcolepsy therapies with the same mechanism of action
AND
6. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Xywav include: use in combination with sedative hypnotics or alcohol, and succinic semialdehyde dehydrogenase deficiency]

CONTINUATION OF THERAPY:

A. ALL INDICATIONS:
1. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)
AND
2. Prescriber attests that member is not taking CNS depressants concomitantly (e.g., ethanol, sedative hypnotics, anxiolytics, barbiturates, benzodiazepines OR consuming any alcohol concomitantly with Xyrem (sodium oxybate) or Xywav (calcium, magnesium, potassium, and sodium oxybates)
AND
3. Documentation of positive response to therapy as noted by prescriber's assessment (e.g., decrease or reduction in the frequency or severity of cataplexy events/attacks, decrease or reduction in symptoms of excessive daytime sleepiness or idiopathic hypersomnia, OR Improvement in the Epworth Sleepiness Scale (ESS), Clinical Global Impression of Change or Maintenance of Wakefulness Test (MWT), or Idiopathic Hypersomnia Severity Scale (IHSS))
AND
4. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
AND
5. Prescribed dose is within FDA labeled limit

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified Sleep Medicine Specialist, neurologist, or psychiatrist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

Narcolepsy: 7 years of age and older
Idiopathic Hypersomnia: 18 years of age and older

QUANTITY:

Narcolepsy: 9 grams per day; 18 mL per day OR 540 mL per 30 days
Idiopathic Hypersomnia: ONCE nightly dosing: 6 grams per day; 12 mL/day OR 360 mL per 30 days
Twice nightly dosing: 9 grams per day; 18 mL per day OR 540 mL per 30 days

MAX FDA LIMIT: 9 grams per day The efficacy and safety at doses higher than 9 grams per night have not been established and doses greater than 9 grams per night generally should not be administered.

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Anti-Cataplectic Agents, Anti-Cataplectic Combinations

FDA-APPROVED USES:
Xyrem (sodium oxybate): 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, and sodium oxybates): 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

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Xyrem (sodium oxybate) is a central nervous system depressant that reduces excessive daytime sleepiness (EDS) and cataplexy in patients with narcolepsy. Sodium oxybate is intended for oral administration. Sodium oxybate is GHB, a known drug of abuse. Abuse has been associated with some important central nervous system (CNS) adverse events (including death). Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Xyrem is subject to the Xyrem REMS program.

Xywav and Xyrem REMS
Xyrem or Xywav is available only through a restricted distribution program called the XYWAV and XYREM REMS because of the risks of central nervous system depression and abuse and misuse. Notable requirements of the XYWAV and XYREM REMS include the following:
• Healthcare Providers who prescribe Xyrem or Xywav are specially certified
• Xyrem or Xywav will be dispensed only by the central pharmacy that is specially certified
• Xyrem or Xywav will be dispensed and shipped only to patients who are enrolled in the XYWAV and XYREM REMS with documentation of safe use
Further information is available at www.XYWAVXYREMREMS.com or 1-866-997-3688.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Xyrem (sodium oxybate) and Xywav (calcium, magnesium, potassium, and sodium oxybates) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy.
Contraindications to Xyrem (sodium oxybate) and Xywav (calcium, magnesium, potassium, and sodium

oxybates) include: use in combination with sedative hypnotics or alcohol, and succinic semialdehyde dehydrogenase deficiency.

OTHER SPECIAL CONSIDERATIONS:
Xyrem and Xywav have a black box warning for central nervous system (CNS) depression and abuse and misuse.

Xyrem and Xywav are Schedule III drugs under the Controlled Substances Act

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Xyrem SOLN 500MG/ML (180mL bottle), Xywav SOLN 500MG/ML (180mL bottle), Sodium Oxybate SOLN 500MG/ML (180mL bottle)

REFERENCES

1. Xyrem oral solution (prescribing information). Indianapolis, IN: Jazz Pharmaceuticals; October 2022.
2. Xywav (calcium, magnesium, potassium, and sodium oxybate) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals Inc; October 2022
3. Morgenthaler TI, Kapur VK,.Brown TM, et al. Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin: An American Academy of Sleep Medicine Report. Available at: http://www.aasmnet.org/Resources/PracticeParameters/PP_Narcolepsy.pdf.Accessed on 13 August 2018
4. Wise MS, Arand DL, Auger R, et al. Treatment of narcolepsy and other hypersomnias of central origin: An American Academy of Sleep Medicine Review. Available at: http://www.aasmnet.org/Resources/PracticeParameters/Review_Narcolepsy.pdf. Accessed on13 August 2018.
5. Food and Drug Administration (FDA) drug safety communication: warning against the use of Xyrem (sodium oxybate) with alcohol or drugs causing respiratory depression. Page last updated:1/19/2016. Available at:http://www.fda.gov/Drugs/DrugSafety/ucm332029.htm..
6. Spaeth, Michael, et al. “Long-Term Tolerability and Maintenance of Therapeutic Response to Sodium Oxybate in an Open-Label Extension Study in Patients with Fibromyalgia.” Arthritis Research & Therapy, vol. 15, no. 6, 2013, doi:10.1186/ar4375.
7. Mayer, G., Benes, H., Young, P., Bitterlich, M., & Rodenbeck, A. (2015). Modafinil in the treatment of idiopathic hypersomnia without long sleep time--a randomized, double-blind, placebo-controlled study. Journal of sleep research, 24(1), 74–81. https://doi.org/10.1111/jsr.12201

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy Duration of Approval Prescriber Requirements Quantity Drug Class Background Conclusions/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms References	Q2 2023
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy Age Restrictions FDA-Approved Uses References	Q3 2022
REVISION- Notable revisions: Prescriber Requirements References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file