Clinical Policy: Sodium Oxybate (Xyrem) and Calcium, Magnesium, Potassium, and Sodium Oxybate (Xywav)

Reference Number: ERX.NPA.23
Effective Date: 06.01.15
Last Review Date: 11.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Sodium oxybate (Xyrem®) and calcium, magnesium, potassium, and sodium oxybate (Xywav™) are central nervous system (CNS) depressants.

FDA Approved Indication(s)

Xyrem and Xywav are indicated for the treatment of patients 7 years of age and older with:

- Cataplexy in narcolepsy
- Excessive daytime sleepiness (EDS) in narcolepsy

Xywav is also indicated for the treatment of idiopathic hypersomnia (IH) in adults.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Xyrem and Xywav are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Narcolepsy with Cataplexy (must meet all)**:**

1. Diagnosis of narcolepsy with cataplexy;
2. Prescribed by or in consultation with a neurologist or sleep medicine specialist;
3. Age ≥ 7 years;
4. Documentation of one of the following (a or b):
   a. EDS associated with narcolepsy as confirmed by documented multiple sleep latency test (MSLT) and one of the following (i or ii):
      i. Mean sleep latency ≤ 8 minutes with evidence of two or more sleep-onset rapid eye movement periods (SOREMPs);
      ii. At least one SOREMP on MSLT and a SOREMP (less than 15 minutes) on the preceding overnight polysomnography (PSG);
   b. Lumbar puncture shows cerebrospinal fluid (CSF) hypocretin-1 level ≤ 110 pg/mL;
5. Failure of 2 of the following antidepressants, each used for ≥ 1 month, unless clinically significant adverse effects are experienced or all are contraindicated: venlafaxine, fluoxetine, atomoxetine, clomipramine*, protriptyline*;
   **If member's age is ≥ 65 years, tricyclic antidepressants are not required for trial.*
6. Dose does not exceed 9 grams (18 mL) per day.

Approval duration: 12 months

B. Narcolepsy with Excessive Daytime Sleepiness (must meet all)**:**

1. Diagnosis of narcolepsy with EDS;
2. Prescribed by or in consultation with a neurologist or sleep medicine specialist;
3. Age ≥ 7 years;

4. Documentation of both of the following (a and b):
   a. EDS associated with narcolepsy as confirmed by documented MSLT and one of the following (i or ii):
      i. Mean sleep latency ≤ 8 minutes with evidence of two or more SOREMPs;
      ii. At least one SOREMP on MSLT and a SOREMP (less than 15 minutes) on the preceding overnight PSG;
   b. Member has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months;

   Failure of a 1-month trial of one of the following generic central nervous system stimulant-containing agent at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced: amphetamine, dextroamphetamine, methylphenidate;
   **Prior authorization may be required for CNS stimulants*
5. If member is ≥ 17 years of age, failure of a 1-month trial of armodafinil or modafinil at up to maximally indicated doses, unless clinically significant adverse effects are experienced or both are contraindicated;
   **Prior authorization may be required for armodafinil and modafinil*
6. Failure of a 1-month trial of Sunosi™ at up to maximally indicated doses, unless contraindicated or clinically significant side effects are experienced;
   **Prior authorization may be required for Sunosi*
7. If request is for concomitant therapy with other antinarcoleptic agents (e.g., Wakix®, Sunosi) for members ≥ 18 years of age, failure of combination therapy with modafinil or armodafinil and Sunosi, unless contraindicated or clinically significant adverse effects are experienced;
8. Dose does not exceed 9 grams (18 mL) per day.

Approval duration: 12 months

C. Idiopathic Hypersomnia (must meet all):

1. Diagnosis of IH;
2. Request is for Xywav;
3. Prescribed by or in consultation with a neurologist or sleep medicine specialist;
4. Age ≥ 18 years;
5. Exclusion of all of the following (a, b, and c):
   a. Narcolepsy of cataplexy;
   b. Narcolepsy of EDS;
   c. Insufficient sleep syndrome;
6. Documentation of all of the following (a, b, and c):
   a. MSLT documents either (i or ii):
      i. Fewer than two SOREMPs;
      ii. No SOREMPs if the REM sleep latency on the preceding PSG was ≤ 15 minutes;
   b. Presence of at least one of the following (i or ii):
      i. MSLT shows a mean sleep latency of ≤ 8 minutes;
      ii. Total 24-hour sleep time is ≥ 660 minutes on 24-hour PSG or by wrist actigraphy in association with a sleep log;
   c. Minimal scoring on at least one of the following (i or ii):
      i. Score ≥ 10 on Epworth Sleepiness Scale (ESS);
      ii. Score ≥ 22 on Idiopathic Hypersomnia Severity Scale (IHSS);
7. Failure of a 1-month trial of armodafinil or modafinil at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for armodafinil and modafinil*
8. Failure of a 1-month trial of one of the following generic central nervous system stimulant-containing agent at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced: amphetamine, dextroamphetamine, methylphenidate;
   **Prior authorization may be required for CNS stimulants*
9. Dose does not exceed 6 grams (12 mL) per day for once nightly dosing and 9 grams (18 mL) per day for twice nightly dosing.

Approval duration: 12 months

D. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by, but not limited to, improvement in any of the following parameters: reduction in frequency of cataplexy attacks, reported daytime improvements in wakefulness;
3. If request is for a dose increase, new dose does not exceed 9 grams (18 mL) per day.

Approval duration: 12 months

B. Other diagnoses/ indications (must meet 1 or 2):
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CNS: central nervous system
EDS: excessive daytime sleepiness
ESS: Epworth Sleepiness Scale
FDA: Food and Drug Administration
IHSS: Idiopathic Hypersomnia Severity ScaleIR: immediate-release
MSLT: multiple sleep latency test
PSG: polysomnography
SOREMP: sleep-onset rapid eye movement period

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Cataplexy		
venlafaxine (Effexor®)†	75–150 mg PO BID, or 75–150 mg (extended release) PO QAM	375 mg/day* (IR tablets); 225* mg/day (extended release)
fluoxetine (Prozac®)†	20 to 80 mg PO QAM	80 mg/day
clomipramine (Anafranil®)†	10 to 150 mg PO as a single dose every morning or in divided doses	250 mg/day*
protriptyline (Vivactil®)†	5 to 60 mg PO as a single dose every morning or in divided doses	60 mg/day
atomoxetine (Strattera®)†	40–60 mg PO QD	100 mg/day*
Excessive daytime sleepiness		
amphetamine (Evekeo®)	5 to 60 mg/day PO in divided doses	60 mg/day
amphetamine/ dextroamphetamine (Adderall®)		

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
dextroamphetamine ER (Dexedrine® Spansule®)		
dextroamphetamine IR (Zenzedi®, Procentra®)		
methylphenidate (Ritalin® LA or SR, Concerta®, Metadate® CD or ER, Methylin® ER, Daytrana®)	Dosing varies; 10-60 mg PO divided 2 to 3 times daily 30-45 min before meals	60 mg/day
armodafinil (Nuvigil®)	150 mg to 250 mg PO once a day	250 mg/day
modafinil (Provigil®)	200 mg PO QD as a single dose in the morning	400 mg/day
Idiopathic hypersomnia		
modafinil (Provigil®)†	200 mg PO Q AM	400 mg/day
armodafinil (Nuvigil®)†	150 mg to 250 mg PO once a day	250 mg/day
methylphenidate (Ritalin® LA or SR, Concerta®, Metadate® CD or ER, Methylin® ER, Daytrana®)†	Dosing varies; 10-60 mg PO divided 2 to 3 times daily 30-45 min before meals	60 mg/day
amphetamine (Evekeo®)†	5 to 60 mg/day PO in divided doses	60 mg/day
amphetamine/ dextroamphetamine (Adderall®)†		
dextroamphetamine ER (Dexedrine® Spansule®)†		
dextroamphetamine IR (Zenzedi®, Procentra®)†		

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
†Off-label indication
**Non-indication specific (maximum dose for the drug)*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - In combination with sedative hypnotics or alcohol
  - Succinic semialdehyde dehydrogenase deficiency
- Boxed warning(s):
  - Central nervous system depression: In clinical trials at recommended doses, obtundation and clinically significant respiratory depression occurred in adult patients treated with Xyrem or Xywav.
  - Abuse and misuse: Xyrem and Xywav are a 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.

Appendix D: General Information

- PSG:
  - In IH, PSG may show a short sleep latency, increased total sleep time, increased sleep spindles, and variable changes in sleep efficiency and sleep stage distribution
  - Used in diagnostic criteria of IH
    - If no SOREMPs are present on MSLT, REM sleep latency on preceding PSG can be $\leq$ 15 minutes for diagnosis
    - Presence of total 24-hour sleep time $\geq$ 660 minutes on 24-hour PSG or by wrist actigraphy in association with a sleep log

- MSLT:
  - This test is a series of five daytime nap opportunies that allow objective characterization of the patient's level of daytime sleepiness, physiological sleep tendency, as reflected by the mean sleep latency
  - In IH, mean sleep latency is shortened and less than 8 minutes and number of SOREMPs is less than two
- IHSS:
  - Ranges from 0 to 50 and made up of 2 components: 5 questions about night and inertia, 9 questions about day and performances
  - Cutoff value of 22 out of 50 can discriminate patients with IH from patients without EDS
  - A cutoff value of 29 out of 50 can discriminate patients with IH from patients with narcolepsy type 1
- ESS:
  - Score is based on scale of 0 to 24
    - 0-5 Lower normal daytime sleepiness
    - 6-10 Higher normal daytime sleepiness
    - 11-12 Mild excessive daytime sleepiness
    - 13-15 Moderate excessive daytime sleepiness
    - 16-24 Severe excessive daytime sleepiness

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Cataplexy in narcolepsy EDS in narcolepsy	Adults: The recommended starting dose is 4.5 grams (g) per night administered PO in two equal, divided doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later. Increase the dose by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dose range of 6 g to 9 g per night PO Pediatrics: Dosing is weight-based as follows: *20 to < 30 kg*: ≤ 1 g at bedtime and ≤ 1 g taken 2.5 to 4 hours later. Increase the dose by 1 g per night at weekly intervals (additional 0.5 g at bedtime and 0.5 g taken 2.5 to 4 hours later) to a maximum dose of 6 g per night PO *30 to < 45 kg*: ≤ 1.5 g at bedtime and ≤ 1.5 g taken 2.5 to 4 hours later. Increase the dose by 1 g per night at weekly intervals (additional 0.5 g at bedtime and 0.5 g taken 2.5 to 4 hours later) to a maximum dose of 7.5 g per night PO ≥ *45 kg*: ≤ 2.25 g at bedtime and ≤ 2.25 g taken 2.5 to 4 hours later. Increase the dose by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to a maximum dose of 9 g per night PO	9 g/night
IH	Adults: Administered twice or once nightly regimen in adults. For twice nightly, initiate dose at 4.5 g or less per night PO, divided into two doses. Titrate to effect in increments of up to 1.5 g per night per week, up to 9 g total nightly dose. For once nightly, initiate dosage at 3 g or less per nightly PO, as one dose. Titrate to effect in increments of up to 1.5 g per night per week, up to 6 g total nightly dose.	9 g/night

VI. Product Availability

Drug Name	Availability
Xyrem (sodium oxybate)	Oral solution: 0.5 g per mL in 180 mL bottle
Xywav (calcium, magnesium, potassium, and sodium oxybate)	Oral solution: 0.5 g per mL in 180 mL bottle

VII. References

1. Xyrem Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; August 2021. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021196s036,212690s001s006lbl.pdf. Accessed September 3, 2021.
2. Xywav Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; July 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212690s000lbl.pdf. Accessed September 3, 2021.
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12. Dauvilliers Y, Evangelista E, Barateau L, Lopez R, Chenini S, Delbos C, Beziat S, Jaussent I. Measurement of symptoms in idiopathic hypersomnia: The Idiopathic Hypersomnia Severity Scale. Neurology. 2019 Apr 9;92(15):e1754-e1762. doi: 10.1212/WNL.0000000000007264. Epub 2019 Mar 13. PMID: 30867266.
13. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991 Dec;14(6):540-5. doi: 10.1093/sleep/14.6.540. PMID: 1798888.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template. Added age restriction; added safety requirement related to contraindications not addressed by REMS program. Cataplexy: modified to require trial/failure of 2 agents instead of 1; On re-auth, added that member is responding positively to therapy; Updated references.	06.17	08.17
2Q 2018 annual review: Modified age requirement from ≥ 16 years to ≥ 18 years as safety and efficacy in pediatric patients have not been established per PI. Removed safety requirement related to contraindications per safety guidance. References reviewed and updated.	01.23.18	05.18
Updated policy to reflect new pediatric indication expansion for patients aged 7 years and older for both cataplexy and EDS of narcolepsy; for Continued Therapy, added specific examples of a positive response to Xyrem therapy; references reviewed and updated.	12.04.18	
2Q 2019 annual review: no significant changes; references reviewed and updated.	02.26.19	05.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2020 annual review: no significant changes; expanded initial approval durations from 6 months to 12 months; allowed members 65 years old or older to bypass redirections to any TCA throughout the policy; references reviewed and updated.	03.27.20	05.20
RT4: added new salt formulation Xywav to policy; updated policy to only require T/F armodafinil/modafinil if member is ≥ 17 years given lack of evidence supporting armodafinil/modafinil use in pediatric populations; references reviewed and updated.	08.18.20	11.20
2Q 2021 annual review: added diagnostic criteria for narcolepsy with cataplexy and narcolepsy associated with excessive daytime sleepiness; added prescriber requirements for neurologist or sleep medicine specialist for all indications; for narcolepsy with excessive daytime sleepiness: added trial of Sunosi, and added requirement for combination use of preferred agents if request is for concomitant use; references reviewed and updated.	04.13.21	05.21
RT4: criteria added for new FDA indication of IH for Xywav; revised bypassing of redirections for age 65 years and older to apply only to TCAs for narcolepsy with cataplexy.	09.03.21	11.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.