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

Reference Number: PA.CP.PMN.42
Effective Date: 01/2020
Last Review Date: 11/2024

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

FDA approved indication
Lumryz, Xyrem/generic 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 (including office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of PA Health & Wellness ® that Xyrem/generic Xyrem, Xywav and Lumryz are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Prescribed for the treatment of cataplexy in narcolepsy;
2. Prescribed by or in consultation with a neurologist or sleep medicine specialist;
3. Age ≥ 7 years;
4. For Lumryz requests, one of the following (a or b):
   a. Member weighs ≥ 45 kg;
   b. Member weighs < 45 kg, and dose has been titrated to ≥ 4.5 grams per day with an alternative sodium oxybate product;
5. Documentation of one of the following (a or b):
   a. Excessive daytime sleepiness associated with narcolepsy as confirmed by documented multiple sleep latency test 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;

6. Failure of 2 of the following agents, each trialed for ≥ 1 month, unless member's age is ≥ 65, clinically significant adverse effects are experienced, or all are contraindicated: venlafaxine, fluoxetine, atomoxetine, clomipramine*, or protriptyline*;
   **If member's age is ≥ 65, tricyclic antidepressants are not required for trial.*
7. For brand Xyrem requests, member must use generic Xyrem, unless contraindicated or clinically significant side effects are experienced;
8. Documentation of results of a recent urine drug screen (UDS) (including testing for licit and illicit drugs with the potential for abuse, including specific testing for oxycodone, fentanyl, and tramadol) that is consistent with prescribed controlled substances;
9. Does not have active or untreated substance abuse or addiction or a history of diversion;
10. Documentation the prescriber or the prescriber's delegate conducted a search of the Pennsylvania Prescription Drug Monitoring Program (PDMP) for the beneficiary's controlled substance prescription history;
11. If request is for Xywav or Lumryz requests: failure of sodium oxybate (Xyrem) at up to maximally indicated doses, unless contraindicated or clinically significant side effects are experienced;
12. Dose does not exceed 9 grams per day.

Approval duration: 12 months

B. Narcolepsy with Excessive Daytime Sleepiness (EDS) (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. For Lumryz requests, one of the following (a or b):
   a. Member weighs ≥ 45 kg;
   b. Member weighs < 45 kg, and dose has been titrated to ≥ 4.5 grams per day with an alternative sodium oxybate product;
5. Documentation of both of the following (a and b):
   a. Excessive daytime sleepiness associated with narcolepsy as confirmed by documented multiple sleep latency test 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. Member has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months;
6. 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 clinically significant adverse effects are experienced or all are contraindicated: amphetamine, dextroamphetamine, or methylphenidate;
   **Prior authorization may be required for CNS stimulants*

7. If member is ≥ 17 years of age, 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 or both are contraindicated;
   **Prior authorization may be required for armodafinil and modafinil*
8. If member is ≥ 18 years of age, 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*
9. For brand Xyrem requests: member must use generic Xyrem, unless contraindicated or clinically significant side effects are experienced;
10. For Xywav and Lumryz requests: If member has failed Sunosi (if ≥ 18 years of age), then failure of sodium oxybate (Xyrem) at up to maximally indicated doses, unless contraindicated or clinically significant side effects are experienced;
11. 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 clinically significant adverse effects are experienced or all are contraindicated;
12. Documentation of results of a recent urine drug screen (UDS) (including testing for licit and illicit drugs with the potential for abuse, including specific testing for oxycodone, fentanyl, and tramadol) that is consistent with prescribed controlled substances;
13. Does not have active or untreated substance abuse or addiction or a history of diversion;
14. Documentation the prescriber or the prescriber's delegate conducted a search of the Pennsylvania Prescription Drug Monitoring Program (PDMP) for the beneficiary's controlled substance prescription history;
15. Dose does not exceed 9 grams per day.

Approval duration: 6 months

C. Idiopathic Hypersomnia (must meet all)**:**

1. Diagnosis of Idiopathic Hypersomnia;
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 clinically significant adverse effects are experienced or both are contraindicated;
   **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 clinically significant adverse effects are experienced or all are contraindicated: amphetamine, dextroamphetamine, methylphenidate;
   **Prior authorization may be required for CNS stimulants*
9. Documentation of results of a recent urine drug screen (UDS) (including testing for licit and illicit drugs with the potential for abuse, including specific testing for oxycodone, fentanyl, and tramadol) that is consistent with prescribed controlled substances;
10. Does not have active or untreated substance abuse or addiction or a history of diversion;
11. Documentation the prescriber or the prescriber's delegate conducted a search of the Pennsylvania Prescription Drug Monitoring Program (PDMP) for the beneficiary's controlled substance prescription history;
12. 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: 6 months

D. Other diagnoses/indications

1. Refer to PA.CP.PMN.53 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 PA Health & Wellness benefit or member has previously met initial approval criteria or the Continuity of Care Policy, PA.PHARM.01, applies;
2. Documentation of positive response to therapy as evidenced by, but not limited to, improvement in <u>any</u> 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 per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care Policy, PA.PHARM.01, applies; or

2. Refer to PA.CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

Approval duration: 12 months

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 – PA.CP.PMN.53 or evidence of coverage documents

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CNS: central nervous system
CSF: cerebrospinal fluid
EDS: excessive daytime sleepiness
ESS: Epworth Sleepiness Scale
FDA: Food and Drug Administration
IH: idiopathic hypersomnia
IHSS: Idiopathic Hypersomnia Severity Scale
IR: 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
Sunosi™ (solriamfetol)	Initiate at 75 mg PO once a day; dose may be doubled at intervals of at least 3 days	150 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) amphetamine/ dextroamphetamine (Adderall®)† dextroamphetamine ER (Dexedrine® Spansule®)† dextroamphetamine IR (Zenzedi®, Procentra®)†	5 to 60 mg/day PO in divided doses	60 mg/day

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.
**Non-indication specific (maximum dose for the drug)*
†Off-label indication

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: respiratory depression can occur

- Abuse and misuse: Xyrem/generic Xyrem, Xywav and Lumryz are sodium salts 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.
- Xywav and Xyrem/generic Xyrem are available only through a restricted program called the Xywav and Xyrem REMS (*Xywav and Xyrem/generic Xyrem only*).
- Lumryz is available only through a restricted program called Lumryz REMS (*Lumryz only*).

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	**Sodium oxybate (Xyrem), Xywav:** Adults: The recommended starting dose is 4.5 grams (g) per night administered orally 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 orally 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 orally • *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 orally • ≥ *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 orally **Lumryz:** Adults: The recommended starting dosage is 4.5 g per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the recommended dosage range of 6 g to 9 g once per night orally Pediatrics: Dosing is weight-based as follows: • < *45 kg*: Because the recommended starting dosage cannot be achieved with the available strengths of Lumryz, use another sodium oxybate product to initiate treatment. The maximum recommended dosage for patients weighing 20 kg to < 30 kg is 6 g once per night orally, and the maximum recommended dosage for patients weighing 30 kg to < 45 kg is 7.5 g once per night orally • ≥ *45 kg*: The recommended starting dosage is 4.5 g once per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the maximum recommended dosage of 9 g once per night orally	9 g/ night

Indication	Dosing Regimen	Maximum Dose
IH	**Xywav:** 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

IV. Product Availability

Drug Name	Availability
sodium oxybate (Xyrem)	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
Lumryz (sodium oxybate)	Extended-release oral suspension: 4.5 g, 6 g, 7.5 g, 9 g powder in packets

V. References

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Reviews, Revisions, and Approvals	Date
2Q 2018 annual review: added age requirement as safety and effectiveness in pediatric patients have not been established per PI; modified initial approval duration from 3 to 6 months; references reviewed and updated.	01/2018
2Q 2019 annual review: Updated policy to reflect new pediatric indication expansion for patients aged 7 years and older for both cataplexy and EDS of narcolepsy; references reviewed and updated.	04/2019
2Q 2020 annual review: expanded initial approval durations from 6 months to 12 months; added atomoxetine as a potential redirection for narcolepsy with cataplexy; references reviewed and updated.	04/2020
Updated policy to only require 1 month T/F of armodafinil/modafinil for narcolepsy with EDS if member is ≥ 17 years given lack of evidence	09/2020

Reviews, Revisions, and Approvals	Date
supporting use of armodafinil/modafinil in pediatric populations; references reviewed and updated.	
2Q 2021 annual review: added new salt formulation Xywav to policy; 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; references reviewed and updated.	04/2021
Allowed members 65 years old or older to bypass redirections to any TCA throughout the policy; 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.	07/2021
For narcolepsy with cataplexy added redirection to Xyrem for Xywav requests; for narcolepsy with EDS added redirection to Xyrem for Xywav requests; added idiopathic hypersomnia criteria, added need for UDS, PDMP check and substance abuse diversion criteria; references updated	01/2022
2Q 2022 annual review: no significant changes; references reviewed and updated.	04/2022
2Q 2023 annual review: no significant changes; references reviewed and updated.	04/2023
RT4: added new extended-release oral suspension formulation Lumryz to policy; for narcolepsy with cataplexy and narcolepsy associated with EDS, updated age requirement in initial criteria to reflect minimum age Lumryz use per PI; removed “antidepressant” classification for redirected agents for narcolepsy with cataplexy initial criteria since atomoxetine (although a SNRI) is not considered an antidepressant; per SDC: for narcolepsy with cataplexy and narcolepsy with EDS, added requirement for redirection to Xyrem for Lumryz requests in a step-wise fashion.	07/2023
2Q 2024 annual review: for Narcolepsy with Cataplexy, revised antidepressant redirection criteria by adding “unless member’s age is ≥ 65” to align with Wakix criteria; for boxed warnings, updated central nervous system depression description to “respiratory depression can occur” and added “available only through a restricted REMS program” per prescriber information; references reviewed and updated.	04/2024
Per SDC: for narcolepsy with cataplexy and narcolepsy with EDS, added redirection to generic Xyrem for brand Xyrem requests and “for Xywav or Lumryz requests” modified failure of “Xyrem” to failure of “sodium oxybate (Xyrem)”; added generic Xyrem to criteria and Xyrem to REMS program information in Appendix C.	07/2024
RT4: updated criteria to reflect newly approved pediatric extension for Lumryz.	11/2024