Clinical Policy Title:	oxybate salt products
Policy Number:	RxA.309
Drug(s) Applied:	Xyrem®, XYWAV™
Original Policy Date:	02/07/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

Sodium oxybate (Xyrem®) and calcium, magnesium, potassium, and sodium oxybates (XYWAV™) are central nervous system (CNS) depressants indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

Limitation(s) of use: Because of CNS depression, abuse, and misuse risks, Xyrem® and XYWAV™ are only available through the Xyrem® and XYWAV™ REMS program.

Dosing Information

<table>
<tr><th>Drug Name</th><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>sodium oxybate (Xyrem®); Ca, Mg, K & Na oxybates (XYWAV™)</td><td>Cataplexy and/or EDS in narcolepsy</td><td>Adults: The recommended starting dose is 4.5 gm per night administered orally in two equal, divided doses (2.25 g at bedtime and 2.25 gm taken 2.5 to 4 hours later). Increase the dose by 1.5 gm per night at weekly intervals (additional 0.75 gm at bedtime and 0.75 gm taken 2.5 to 4 hours later) to the effective dose range of 6 to 9 gm per night orally.

Pediatrics (7 years of age and older): Dosing is weight-based.
<table>
<tr><th></th><th colspan="2">Initial Dose</th><th colspan="2">Max Weekly Dose Increase</th><th colspan="2">Max Dose</th></tr>
<tr><th></th><th>HS</th><th>2.5-4 hrs later</th><th>HS</th><th>2.5-4 hrs later</th><th>HS</th><th>2.5-4 hrs later</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>20-29.9 kg</td><td>≤ 1 gm</td><td>≤ 1 gm</td><td>0.5 gm</td><td>0.5 gm</td><td>3 gm</td><td>3 gm</td></tr>
<tr><td>30-44.9 kg</td><td>≤ 1.5 gm</td><td>≤ 1.5 gm</td><td>0.5 gm</td><td>0.5 gm</td><td>3.75 gm</td><td>3.75 gm</td></tr>
<tr><td>45 kg or greater</td><td>≤ 2.25 gm</td><td>≤ 2.25 gm</td><td>0.75 gm</td><td>0.75 gm</td><td>4.5 gm</td><td>4.5 gm</td></tr>
</table>
There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.</td><td>9 gm per night</td></tr>
</table>

Dosage Forms

- Oral solution: 0.5 gm per mL (both products)

Clinical Policy

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

I. Initial Approval Criteria

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

1. Prescribed for the treatment of cataplexy in members with narcolepsy;
2. Diagnosis has been confirmed through sleep lab evaluation [e.g., polysomnography and/or multiple sleep latency test (MSLT)];
3. Prescribed by or in consultation to a sleep specialist or neurologist;
4. Member is 7 years of age or older;
5. Member has tried and failed at least two (2) of the following antidepressants, each used for one-month or longer, unless all are contraindicated or clinically significant adverse effects are experienced: a selective serotonin inhibitor (e.g., fluoxetine, sertraline, paroxetine), tricyclic antidepressant (e.g., clomipramine, protriptyline), or venlafaxine;
6. Dose does not exceed 9 gm per day (18 mL per day).

Approval duration
Commercial: 12 months
Medicaid: 12 months

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

1. Prescribed for the treatment of EDS in members with narcolepsy;
2. Diagnosis has been confirmed through sleep lab evaluation [e.g., polysomnography and/or multiple sleep latency test (MSLT)];
3. Prescribed by or in consultation to a sleep specialist or neurologist;
4. Member is 7 years of age or older;
5. Member has tried and failed at least a one month trial of one (1) of the following CNS stimulants at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced: amphetamine IR/ER, amphetamine/dextroamphetamine; dextroamphetamine IR, dextroamphetamine, methylphenidate IR/ER;
   **Prior authorization may be required for CNS stimulants*
6. For members 18 years of age or older, the member has tried and failed at least a one-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*
7. For members 18 years of age or older, the member has tried and failed at least a one-month trial of solriamfetol (Sunosi™) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for solriamfetol*
8. Dose does not exceed 9 gm per day (18 mL per day).

Approval duration
Commercial: 12 months
Medicaid: 12 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy (e.g., 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 gm per day (18 mL per day).

Approval duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
CNS: Central Nervous System
EDS: Excessive Daytime Sleepiness
ER: Extended-Release
FDA: Food and Drug Administration
IR: Immediate-Release
MSLT: Multiple Sleep Latency Test
PO: By Mouth

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 for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Cataplexy		
venlafaxine (Effexor®)†	75–150 mg IR PO twice daily or 75–150 mg ER PO every morning	375 mg/day* (IR tablets); 225* mg/day (extended release)
fluoxetine (Prozac®)†	20 to 80 mg PO every morning	80 mg/day
clomipramine (Anafranil®)†	25 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
Excessive daytime sleepiness		
Evekeo® (amphetamine)	5 to 60 mg/day PO in divided doses	60 mg/day
amphetamine/ dextroamphetamine (Adderall®)		
dextroamphetamine ER (Dexedrine® spansule)		
dextroamphetamine IR (Zenzedi®, Procentra®)		
methylphenidate IR	10 to 60 mg/day PO in 2 to 3 divided doses	60 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
(Ritalin®, Methylin®)		
armodafinil (Nuvigil®)	150 mg to 250 mg PO once daily	250 mg/day
modafinil (Provigil®)	200 mg PO once daily	400 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):
  - Respiratory depression can occur with Xyrem® and XYWAV™ use
  - Xyrem® and XYWAV™ 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.

APPENDIX D: General Information

- Use caution when using oxybate salt products in combination with other CNS depressants.
- Monitor patients for emergent or increased depression or suicidality.
- Evaluate patients for sleepwalking.
- For Xyrem®, monitor patients with heart failure, hypertension, or impaired renal function due to high sodium content.

References

1. Xyrem Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; September, 2020. Available at: https://pp.jazzpharma.com/pi/xyrem.en.USPI.pdf. Accessed January 29, 2021.
2. Morgenthaler TI, Kapur VK, Brown T, et al. Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin an American Academy of Sleep Medicine Report: An American Academy of Sleep Medicine Report. Sleep. 2007; 30(12): 1705-1711. https://aasm.org/resources/practiceparameters/pp_narcolepsy.pdf
3. Wise MS, Arand DL, Auger RR, Brooks SN, Watson NF. Treatment of Narcolepsy and other Hypersomnias of Central Origin: An American Academy of Sleep Medicine Review. Sleep. 2007;30(12):1712-1727.
4. Scammell TE. The neurobiology, diagnosis, and treatment of narcolepsy. Ann Neurol 2003; 53: 154 –166.
5. Swick TJ. Treatment paradigms for cataplexy in narcolepsy: past, present, and future. Nat Sci
6. Billiard M. Narcolepsy: current treatment options and future approaches. Neuropsychiatric Disease and Treatment. 2008; 4(3): 557-566
7. Moldofsky H, Inhaber NH, Guinta DR, et al. Effects of sodium oxybate on sleep physiology and sleep/wakerelated symptoms in patients with fibromyalgia syndrome: a double-blind, randomized, placebo-controlled study. J Rheumatol. 2010; 37(10): 2156-2166
8. Scharf MB, et al. The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia. J Rheumatol. 2003; 30(5): 1070-1074

9. Xywav Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; October, 2020. Available at: https://pp.jazzpharma.com/pi/xyrem.en.USPI.pdf. Accessed January 29, 2021.
10. Sunosi Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; July, 2019. Available at: https://pp.jazzpharma.com/pi/sunosi.en.USPI.pdf. Accessed January 29, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Clinical Policy Title and lines of business updated. 2. Continued therapy II.A.1. was rephrased to "Currently receiving medication that has been authorized by RxAdvance….". 3. Initial and continued therapy approval duration was updated from "Length of benefit" to 12 months for Commercial and included Medicaid & HIM approval duration. 4. References were reviewed and updated.	06/26/2020	09/14/2020
Policy reviewed and updated. 1. Xywav added to the policy. 2. Initial criteria for approval and duration of approval updated. 3. Updated Appendix D. 4. References updated.	01/29/2021	03/09/2021