Clinical Policy: Sodium Oxybate (Xyrem)

Reference Number: PA.CP.PMN.42
Effective Date: 01/18
Last Review Date: 04/19

Coding Implications
Revision Log

Description
Sodium oxybate (Xyrem®) is a central nervous system (CNS) depressant.

FDA approved indication
Xyrem is indicated for the treatment of patients 7 years of age and older with:

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

Limitation(s) of use: Xyrem may only be dispensed to patients enrolled in the Xyrem REMS Program.

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 Pennsylvania Health and Wellness ® that Xyrem is **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. Age ≥ 7 years;
3. Failure of 2 of the following antidepressants, each trialed for ≥ 1 month, unless all are contraindicated or clinically significant adverse effects are experienced: venlafaxine, fluoxetine, tricyclic antidepressant (e.g., protriptyline, clomipramine);
4. Dose does not exceed 9 grams per day (18 mL per day).

Approval duration: 6 months

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

1. Diagnosis of narcolepsy with EDS;
2. Age ≥ 7 years;
3. Failure of a 1-month trial of one of the following CNS stimulants at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced: amphetamine immediate-release (IR), amphetamine; dextroamphetamine IR, dextroamphetamine, methylphenidate IR, or Metadate® ER; **Prior authorization may be required for CNS stimulants.*
4. 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; **Note: Armodafinil and modafinil require prior authorization*
5. Dose does not exceed 9 grams/day.

Approval duration: 6 months

C. 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 (must meet all)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care Policy, PA.LTSS.PHAR.01, applies;
2. Documentation of positive response 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 grams/day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care Policy, PA.LTSS.PHAR.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
EDS: excessive daytime sleepiness
FDA: Food and Drug Administration
IR: immediate release

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 PO BID, or 75–150 mg (extended release) PO QAM	375 mg/day* (IR tablets); 225* mg/day (extended release)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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
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 (Ritalin®, Methylin®)	10 to 60 mg/day PO in 2 to 3 divided doses	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

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 use

Xyrem is 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.

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 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	9 g per night

VI. Product Availability

Oral solution: 0.5 g per mL

VII. References

1. Xyrem Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; November 2017. Available at: https://www.xyrem.com/. Accessed February 26, 2019.
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.
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 Sleep. 2015; 7:159-169.

Reviews, Revisions, and Approvals	Date	P&T Approval 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.	1.23.18	
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.	4.17.19	