Clinical Policy: Sodium Oxybate (Xyrem)

Reference Number: AZ.CP.PMN.42
Effective Date: 09.01.2020
Last Review Date: 08.20
Line of Business: Arizona Medicaid

Revision Log

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

Description

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

FDA Approved Indication(s)

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

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

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.

It is the policy of Arizona Complete Health that Xyrem is **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 as confirmed by supporting documentation of the polysomnography (PSG) and Multiple Sleep latency Test (MSLT) (must meet all):
   a. Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months;
   b. Presence of cataplexy;
   c. Mean sleep latency of ≤ 8 minutes;
   d. Two or more sleep onset REM sleep periods (SOREMPs) **or** CSF hypocretin-1 deficiency (*see Appendix D*);
2. Prescribed by or in consultation with a neurologist or sleep specialist in narcolepsy;
3. Age ≥ 7 years;
4. Member meets both of the following (a and b):
   a. For symptoms of cataplexy (applicable to adults aged ≥ 18 years only): Failure of **one** of the following antidepressants, used for ≥ 1 month, unless member's age is ≥ 65, all are contraindicated, or clinically significant adverse effects are experienced: venlafaxine, fluoxetine, atomoxetine, clomipramine, or protriptyline;
   b. For symptoms of daytime sleepiness: Failure of **one** of the following, used for ≥ 1 month at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced: a CNS stimulant (amphetamine immediate-release (IR), amphetamine, dextroamphetamine IR,

dextroamphetamine, methylphenidate IR, or Metadate® ER), armodafinil or modafinil,;
**Prior authorization may be required for armodafinil and modafinil*

5. Dose does not exceed 9 grams (18 mL) per day.

Approval duration: 6 months

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

1. Diagnosis of narcolepsy with EDS as confirmed by supporting documentation of the polysomnography (PSG) and Multiple Sleep Latency Test (MSLT) (must meet all):
   a. Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months;
   b. Absence of cataplexy;
   c. Mean sleep latency of ≤ 8 minutes;
   d. Two or more sleep onset REM sleep periods (SOREMPs);
   e. Excessive daytime sleepiness and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal (*see Appendix D*);
2. Prescribed by or in consultation with a neurologist or sleep specialist in narcolepsy;
3. Age ≥ 7 years;
4. 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*
5. 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*
6. Dose does not exceed 9 grams (18 mL) per day.

Approval duration: 6 months

C. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona Medicaid.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively 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 (18 mL) per day.

Approval duration: 12 months

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona Medicaid.

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 policies – AZ.CP.PMN.53 for Arizona Medicaid 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
FDA: Food and Drug Administration
IR: immediate-release
MSLT: multiple sleep latency test
PSG: polysomnography
REM: rapid eye movement
SOREMP: sleep-onset rapid eye movement periods

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)
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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
amphetamine/ dextroamphetamine (Adderall®)		
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

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: In clinical trials at recommended doses, obtundation and clinically significant respiratory depression occurred in adult patients treated with Xyrem.
  - Abuse and misuse: 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.

Appendix D: General Information

- The American Academy of Sleep Medicine (AASM) International Classification of Sleep Disorders – Third Edition (ICSD-3), contains diagnostic criteria for sleep disorders, including narcolepsy
- If narcolepsy type 1 is strongly suspected clinically but the MSLT criteria (a mean sleep latency of ≤ 8 minutes and two or more SOREMPs) are not met, a possible strategy is to repeat the MSLT
- In narcolepsy 1, CSF hypocretin-1 deficiency is defiend as 110 pg/mL or less than one-third of the normative values with the same standardized assay
- In narcolepsy 2, either CSF hypocretin-1 levels have not been measured or are above the threshold for narcolepsy type 1

- In narcolepsy 2, if cataplexy develops later, then the disorder should be reclassified as narcolepsy type 1
- If the CSF hypocretin-1 concentration is tested at a later stage and found to be either <110 pg/ml or <1/3 of mean values obtained in normal subjects with the same assay, then the disorder should be reclassified as narcolepsy type 1
- Shift-work and the presence of REM suppressing medications are associated with sleep-onset REM periods (SOREMPs)
- Examples of other sleep disorders associated with SOREMPs include obstructive sleep apnea, or any condition associated with reduced nocturnal REM sleep leading to "REM rebound" during the day
- Stimulants, stimulant-like medications, and REM suppressing medications should ideally be stopped 2 weeks before MSLT. Drug screening may be indicated to ensure that sleepiness on the MSLT is not pharmacologically induced
- Examples of REM suppressant medications may include, but are not limited to the following:
  - Antidepressants
    - Tricyclic medications
    - Serotonin reuptake inhibitors
    - Serotonin/norepinephrine reuptake inhibitors
  - Alcohol
  - Benzodiazepines
  - Barbiturates
- Three features can help distinguish idiopathic hypersomnia from narcolepsy type 2: (1) absence of multiple SOREMPs on MSLT, (2) presence of long habitual sleep periods, long naps, and sleep inertia, and (3) high sleep efficiency on PSG
- Two key findings can help discriminate Insufficient Sleep Syndrome (chronic sleep deprivation) from narcolepsy type 1: (1) longer sleep duration on weekends and holidays compared to weekdays, as assessed by sleep logs or actigraphy; and (2) if SOREMPs occur on the MSLT, they usually follow N2 sleep
- Sleep apnea can co-occur in patients with narcolepsy. However, sleep apnea should be adequately treated with CPAP for a sufficient period of time prior to making a diagnosis of narcolepsy

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:	9 g/night

Indication	Dosing Regimen	Maximum Dose
	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	

VI. Product Availability

Oral solution: 0.5 g per mL in 180 mL bottle

VII. References

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11. Pagel JF. Pharmacological Alteration of Sleep and DreamsA Clinical Framework for Utilizing the Electrophysiological and Sleep Stage Effects of Psychoactive Medications. Human Psychopharmacology. 1996;11(3):217-223.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	08.15.20	10.20

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.