Clinical Policy: Central Nervous System (CNS) Agents: Narcolepsy

Reference Number: OH.PHAR.PPA.102
Effective Date: 06.22
Last Review Date: N/A
Line of Business: Medicaid

Coding Implications
Revision Log

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

Description:
Solriamfetol (Sunosi™) is a dopamine and norepinephrine reuptake inhibitor approved to improve wakefulness in adults with excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA).

Pitolisant (Wakix®) is an oral histamine-3 (H3) receptor antagonist/inverse agonist indicated for the treatment of excessive daytime sleepiness or cataplexy in adult patients with narcolepsy.

Sodium Oxybate (Xyrem®) is a central nervous system (CNS) depressant used for the treatment of cataplexy or excessive daytime sleepiness in patients with narcolepsy.

Calcium, Magnesium, Potassium, & Sodium Oxybates (Xywav™) is a central nervous system (CNS) depressant approved for the treatment of cataplexy or excessive daytime sleepiness in adult and pediatric patients 7 years of age and older with narcolepsy.

CNS AGENTS: NARCOLEPSY

NO PA REQUIRED "PREFERRED"	PA REQUIRED "NON-PREFERRED"
AMPHETAMINE/DEXTROAMPHETAMINE ARMODAFINIL (generic of Nuvigil®) DEXTROAMPHETAMINE ER METHYLPHENIDATE ER METHYLPHENIDATE TAB MODAFINIL (generic of Provigil®)	SUNOSI™ (solriamfetol) WAKIX® (pitolisant) XYREM® (sodium oxybate) XYWAV™ (calcium, magnesium, potassium, & sodium oxybates)

FDA Approved Indication(s)
Sunosi is indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA).

Wakix is indicated for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy.

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

Limitation(s) of use:
- Sunosi is not indicated to treat the underlying airway obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure

(CPAP)) for at least one month prior to initiating Sunosi for excessive daytime sleepiness. Modalities to treat the underlying airway obstruction should be continued during treatment with Sunosi. Sunosi is not a substitute for these modalities.

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 Buckeye Health Plan, an affiliate of Centene Corporation®, that Sunosi, Wakix, Xyrem, and Xywav are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. For Sunosi (solriamfetol) (must meet all)**:**

1. Diagnosis of narcolepsy with excessive daytime sleepiness OR obstructive sleep apnea with excessive daytime sleepiness;
2. Age ≥ 18 years;
3. Documentation that there has been an inadequate response to or inability to tolerate a 30-day course of treatment with a preferred methylphenidate or amphetamine product UNLESS there is a reason the member cannot be changed to a preferred methylphenidate or amphetamine product. Acceptable reasons include:
   - Allergies to all medications not requiring prior approval.
   - Contraindication to or drug-to-drug interaction with medications not requiring prior approval.
   - History of unacceptable/toxic side effects to medications not requiring prior approval;
4. Documentation that there has been an inadequate response to or inability to tolerate a 30-day course of treatment with modafinil or armodafinil UNLESS there is a reason the member cannot be changed to a preferred medication. Acceptable reasons include:
   - Allergies to all preferred medications/medications not requiring prior approval.
   - Contraindication to or drug-to-drug interaction with preferred medications/medications not requiring prior approval.
   - History of unacceptable/toxic side effects to preferred medications/medications not requiring prior approval;
5. Dose does not exceed 150 mg (1 tablet) per day.

Approval duration: 12 months.

B. For Wakix (pitolisant) (must meet all)**:**

1. Age ≥ 18 years;
2. The member meets one of the following (a or b):
   a. Diagnosis of narcolepsy with cataplexy OR;
   b. Diagnosis of narcolepsy with excessive daytime sleepiness AND all of the following are met (i and ii):
      i. Documentation that there has been an inadequate response to or inability to tolerate a 30-day course of treatment with a preferred methylphenidate or amphetamine product UNLESS there is a reason the member cannot be changed to a preferred methylphenidate or amphetamine product. Acceptable reasons include:

- Allergies to all medications not requiring prior approval.
- Contraindication to or drug-to-drug interaction with medications not requiring prior approval.
- History of unacceptable/toxic side effects to medications not requiring prior approval;

ii. Documentation that there has been an inadequate response to or inability to tolerate a 30-day course of treatment with modafinil or armodafinil UNLESS there is a reason the member cannot be changed to a preferred medication. Acceptable reasons include:

- Allergies to all preferred medications/medications not requiring prior approval.
- Contraindication to or drug-to-drug interaction with preferred medications/medications not requiring prior approval.
- History of unacceptable/toxic side effects to preferred medications/medications not requiring prior approval;

3. Dose does not exceed 35.6 mg (two 17.8 mg tablets) per day.

Approval duration: 12 months.

C. For Xyrem (sodium oxybate) (must meet all)**:**

1. Age ≥ 7 years;
2. The member meets one of the following (a or b):
   a. Diagnosis of narcolepsy with cataplexy OR;
   b. Diagnosis of narcolepsy with excessive daytime sleepiness AND all of the following are met (i and ii):
      i. Documentation that there has been an inadequate response to or inability to tolerate a 30-day course of treatment with a preferred methylphenidate or amphetamine product UNLESS there is a reason the member cannot be changed to a preferred methylphenidate or amphetamine product. Acceptable reasons include:
         - Allergies to all medications not requiring prior approval.
         - Contraindication to or drug-to-drug interaction with medications not requiring prior approval.
         - History of unacceptable/toxic side effects to medications not requiring prior approval;
      ii. Documentation that there has been an inadequate response to or inability to tolerate a 30-day course of treatment with modafinil or armodafinil UNLESS there is a reason the member cannot be changed to a preferred medication. Acceptable reasons include:
         - Allergies to all preferred medications/medications not requiring prior approval.
         - Contraindication to or drug-to-drug interaction with preferred medications/medications not requiring prior approval.
         - History of unacceptable/toxic side effects to preferred medications/medications not requiring prior approval;
3. Dose does not exceed 9 grams (18 mL) per day.

Approval duration: 12 months.

D. For Xywav (calcium, magnesium, potassium, & sodium oxybates) (must meet all)**:**
1. Age ≥ 7 years;
2. The member meets one of the following (a or b):
   a. Diagnosis of narcolepsy with cataplexy and sodium restriction with documented adherence to sodium restricted diet OR;
   b. Diagnosis of narcolepsy with excessive daytime sleepiness and sodium restriction with documented adherence to sodium restricted diet AND all of the following are met (i and ii):
      i. Documentation that there has been an inadequate response to or inability to tolerate a 30-day course of treatment with a preferred methylphenidate or amphetamine product UNLESS there is a reason the member cannot be changed to a preferred methylphenidate or amphetamine product. Acceptable reasons include:
         - Allergies to all medications not requiring prior approval.
         - Contraindication to or drug-to-drug interaction with medications not requiring prior approval.
         - History of unacceptable/toxic side effects to medications not requiring prior approval;
      ii. Documentation that there has been an inadequate response to or inability to tolerate a 30-day course of treatment with modafinil or armodafinil UNLESS there is a reason the member cannot be changed to a preferred medication. Acceptable reasons include:
         - Allergies to all preferred medications/medications not requiring prior approval.
         - Contraindication to or drug-to-drug interaction with preferred medications/medications not requiring prior approval.
         - History of unacceptable/toxic side effects to preferred medications/medications not requiring prior approval;
3. Dose does not exceed 9 grams (18 mL) per day.

Approval duration: 12 months.

E. Other diagnoses/indications:
1. There are no pharmacy and therapeutic committee approved off-label use criteria for the diagnosis;
2. Use is supported by one of the following (a, b, or c):
   a. The National Comprehensive Cancer Network (NCCN) Drug Information and Biologics Compendium level of evidence 1 or 2A;
   b. Evidence from at least two high-quality, published studies in reputable peer-reviewed journals or evidence-based clinical practice guidelines that provide all of the following (i – iv):
      i. Adequate representation of the member's clinical characteristics, age, and diagnosis;
      ii. Adequate representation of the prescribed drug regimen;
      iii. Clinically meaningful outcomes as a result of the drug therapy in question;
      iv. Appropriate experimental design and method to address research questions;
   c. Micromedex DrugDex® with strength of recommendation Class I, IIa, or IIb;
3. Prescribed by or in consultation with an appropriate specialist for the diagnosis;

4. Failure of no less than 30 days each of at least two preferred FDA-approved drugs for the indication and/or drugs that are considered the standard of care, when such agents exist for the same indication at maximum indicated doses, unless no such drugs exist, at maximum indicated doses, unless contraindicated or clinically significant adverse effect are experienced;
5. Dosing regimen and duration are within dosing guidelines recommended by clinical practice guidelines and/or medical literature.

Approval duration: 112 days.

II. Continued Therapy

A. Narcolepsy with excessive daytime sleepiness, obstructive sleep apnea with excessive daytime sleepiness, or narcolepsy with cataplexy (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Attestation that condition improved while taking the requested medication;
3. If request is for a dose increase, new dose does not exceed (a, b, or c);
   a. For Sunosi: 150 mg (1 tablet) per day;
   b. For Wakix: 35.6 mg (two 17.8 mg tablets) per day;
   c. For Xyrem and Xywav: 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 attestation that condition improved while taking the requested medication; 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): CP.PMN.53 for Medicaid.

Approval duration: Duration of request or 12 months (whichever is less).

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

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 – CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
CNS: Central Nervous System
CPAP: Continuous Positive Airway Pressure
EDS: Excessive Daytime Sleepiness
FDA: Food and Drug Administration
OSA: Obstructive Sleep Apnea
PA: Prior Authorization

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
amphetamine/ dextroamphetamine (Adderall®)	**Narcolepsy** 5 to 60 mg/day PO in divided doses	60 mg/day
dextroamphetamine (Dexedrine®)		
methylphenidate (Ritalin® LA or SR, Concerta®, Metadate® CD or ER, Methylin® ER)	**Narcolepsy** Dosing varies; 10-60 mg PO divided 2 to 3 times daily 30-45 min before meals	60 mg/day
armodafinil (Nuvigil®)	**Narcolepsy/OSA** 150 mg to 250 mg PO once a day in the morning	250 mg/day
modafinil (Provigil®)	**Narcolepsy/OSA** 200 mg PO once a day in the morning	400 mg/day
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*

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):
  - For Sunosi: concomitant treatment with MAOIs, or within 14 days following discontinuation of MAOI;
  - For Wakix: hypersensitivity, severe hepatic impairment;
  - For Xyrem and Xywav: 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.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Narcolepsy (Sunosi)	Initiate at 75 mg PO once a day; dose may be doubled at intervals of at least 3 days	150 mg/day
OSA (Sunosi)	Initiate at 37.5 mg PO once a day; dose may be doubled at intervals of at least 3 days	150 mg/day
Narcolepsy (Wakix)	Dose range is 17.8 to 35.6 mg PO once daily in the morning upon wakening. Titrate dosage as follows: • Week 1: Initiate with a dosage of 8.9 mg once daily • Week 2: Increase dosage to 17.8 mg once daily Week 3: May increase to the maximum recommended dosage of 35.6 mg once daily	35.6 mg/day
Cataplexy in narcolepsy (Xyrem and Xywav) EDS in narcolepsy (Xyrem and 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	9 g/night

VI. Product Availability

Drug Name	Availability
Sunosi (solriamfetol)	Tablets: 75 mg, 150 mg
Wakix (pitolisant)	Tablets: 4.45 mg, 17.8 mg
Xyrem (sodium oxybate)	Oral solution: 0.5 g per mL in 180 mL bottle

Drug Name	Availability
Xywav (calcium, magnesium, potassium, and sodium oxybates)	Oral solution: 0.5 g per mL

VII. References

1. Sunosi Prescribing Information. Palo Alto, CA: Jazz Pharma, Inc.; June 2019. Available at: www.sunosi.com. Accessed February 25, 2020.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: http://www.clinicalpharmacology-ip.com/.
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4. Thorpy MJ, Dauvilliers Y. Clinical and practical considerations in the pharmacologic management of narcolepsy. Sleep Medicine. 2014;16(1):9-18. doi:10.1016/j.sleep.2014.10.002.
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7. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed October 16, 2020.
8. Xyrem Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; October 2018. Available at: https://www.xyrem.com/. Accessed February 25, 2020.
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10. 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.
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12. Swick TJ. Treatment paradigms for cataplexy in narcolepsy: past, present, and future. Nat Sci Sleep. 2015; 7:159-169.
13. Billiard M. Narcolepsy: current treatment options and future approaches. Neuropsychiatric Disease and Treatment. 2008;4(3):557-566.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
New policy created.	07.21	N/A
Annual review – no changes deemed necessary.	06.22	N/A

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.