Clinical Policy: Pitolisant (Wakix)

Reference Number: CP.PMN.221
Effective Date: 03.01.20
Last Review Date: 05.25
Line of Business: Commercial, HIM, Medicaid

Revision Log

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

Description

Pitolisant (Wakix®) is a selective histamine 3 (H_3) receptor antagonist/inverse agonist.

FDA Approved Indication(s)

Wakix is indicated for the treatment of:

- Excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy
- EDS in pediatric patients 6 years of age and older with 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 health plans affiliated with Centene Corporation® that Wakix 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. Prescribed by or in consultation with a neurologist or sleep medicine specialist;
3. Age ≥ 18 years;
4. Documentation of one of the following (a or b):
   a. EDS associated with narcolepsy as confirmed by documented multiple sleep latency test (MSLT) 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;
5. Failure of 2 of the following agents, each used for ≥ 1 month, unless member's age is ≥ 65, clinically significant adverse effects are experienced, or all are contraindicated: venlafaxine, fluoxetine, atomoxetine, clomipramine*, protriptyline*;
   **If member's age is ≥ 65 years, tricyclic antidepressants are not required for trial.*
6. Dose does not exceed both of the following (a and b):
   a. 35.6 mg per day;
   b. 2 tablets per day.

Approval duration:

Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Narcolepsy with Excessive Daytime Sleepiness (must meet all)**:**
1. Diagnosis of narcolepsy with EDS;
2. Prescribed by or in consultation with a neurologist or sleep medicine specialist;
3. Age ≥ 6 years;
4. Documentation of both of the following (a and b):
   a. EDS associated with narcolepsy as confirmed by documented MSLT and one of the following (i or ii):
      i. Mean sleep latency ≤ 8 minutes with evidence of two or more SOREMPs;
      ii. At least one SOREMP on MSLT and a SOREMP (less than 15 minutes) on the preceding overnight PSG;
   b. Member has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months;
5. Failure of a 1-month trial of one of the following generic central nervous system stimulant-containing agents 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*
6. If age ≥ 17 years: Failure of a 1-month trial of armodafinil or modafinil at up to maximally indicated doses, unless clinically significant side effects are experienced or both are contraindicated;
   **Prior authorization may be required for armodafinil and modafinil*
7. If age ≥ 18 years, both of the following (a and b):
   a. 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*
   b. If request is for concomitant therapy with other antinarcoleptic agents (e.g., Xyrem®, Xywav®, Sunosi), failure of combination therapy with modafinil or armodafinil and Sunosi, unless contraindicated or clinically significant adverse effects are experienced;
8. Dose does not exceed both of the following (a and b):
   a. One of the following (i or ii):
      i. Adults and pediatric members weighing ≥ 40 kg: 35.6 mg per day;
      ii. Pediatric members weighing < 40 kg: 17.8 mg per day;
   b. 2 tablets per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy as evidenced by, but not limited to, improvement in any 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 one of the following (a or b):
   a. Adults and pediatric members weighing ≥ 40 kg (i and ii):
      i. 35.6 mg per day;
      ii. 2 tablets per day;
   b. Pediatric members weighing < 40 kg (i and ii):
      i. 17.8 mg per day;
      ii. 1 tablet per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for 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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for 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
H_3: histamine-3
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 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/ dextroamphetamine (Adderall®)	Age ≥ 6 years: 5 to 60 mg PO QD in divided doses	60 mg/day
dextroamphetamine (Dexedrine®, ProCentra®,		

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Spansule®, Zenzedi®) amphetamine (Evekeo®)		
methylphenidate (Ritalin® (LA, SR), Concerta®, Metadate® (CD, ER), Methylin® (ER), Daytrana®)	Age ≥ 6 years: Dosing varies; 10 to 60 mg PO divided 2 to 3 times daily 30 to 45 min before meals	60 mg/day
armodafinil (Nuvigil®)	Age ≥ 17 years: 150 mg PO QD in the morning	250 mg/day
modafinil (Provigil®)	Age ≥ 17 years: 200 mg PO QD in the morning	400 mg/day
Sunosi™ (solriamfetol)	Age ≥ 18 years: Initiate at 75 mg PO once a day; dose may be doubled at intervals of at least 3 days	150 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): hypersensitivity, severe hepatic impairment
- Boxed warning(s): none reported

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Narcolepsy	Dose range is 17.8 to 35.6 mg PO once daily in the morning upon wakening. Titrate dosage as follows: **Adults (EDS or cataplexy)**: • 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 **Pediatric patients (EDS only):** • Week 1: Initiate with a dosage of 4.45 mg once daily • Week 2: Increase dosage to 8.9 mg once daily • Week 3: Increase dosage to 17.8 mg once daily, the maximum recommended dosage for patients weighing < 40 kg • Week 4: For patients weighing ≥ 40 kg, may increase to the maximum recommended dosage of 35.6 mg once daily	Adults and pediatric patients weighing ≥ 40 kg: 35.6 mg/day Pediatric patients weighing < 40 kg: 17.8 mg/day

VI. Product Availability

Tablets: 4.45 mg, 17.8 mg

VII. References

1. Wakix Prescribing Information. Plymouth Meeting, PA: Harmony Biosciences, LLC; June 2024. Available at: https://www.wakix.com. Accessed January 27, 2025.
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. *Sleep*. 2007;30(12):1705-1711.
3. Epstein LJ, Kristo D, Strollo PJ Jr, et al. Clinical guideline for the evaluation, management, and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med*. 2009; 15;5(3):263-76.
4. Bassetti CL, Kallweit U, Vignatelli, et al. European guideline and expert statements on the management of narcolepsy in adults and children. J Sleep Res. 2021;00:e13387. DOI: 10.1111/jsr.13387.
5. Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021 Sep 1;17(9):1881-1893. doi: 10.5664/jcsm.9328.
6. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2025. Available at: https://www.clinicalkey.com/pharmacology. Accessed January 27, 2025.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2021 annual review: added diagnostic criteria for narcolepsy with cataplexy and narcolepsy associated with excessive daytime sleepiness; for narcolepsy with excessive daytime sleepiness, added requirement for combination use of preferred agents if request is for concomitant use; references reviewed and updated.	04.13.21	05.21
Consolidated with legacy WCG Medicaid version and increased initial approval duration from 3 months to 12 months (WCG.CP.PMN.221 to be retired); revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less.	09.10.21	02.22
2Q 2022 annual review: no significant changes; references reviewed and updated.	01.31.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.06.22	
2Q 2023 annual review: no significant changes; references reviewed and updated.	02.06.23	05.23
2Q 2024 annual review: for Narcolepsy with Excessive Daytime Sleepiness, removed brand names Provigil and Nuvigil in criteria to clarify redirection is to generic product only; references reviewed and updated.	01.12.24	05.24
RT4: added pediatric extension for EDS with narcolepsy.	06.27.24	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2025 annual review: for narcolepsy with cataplexy, clarified if member is ≥ 65 years then trial of tricyclic antidepressants are not required apply to clomipramine and protriptyline only and removed "antidepressant" classification for redirected agents atomoxetine (although a SNRI) is not considered an antidepressant; references reviewed and updated.	01.23.25	05.25

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.