Drug Coverage Policy

Effective Date.....3/1/2025
Coverage Policy Number.....IP0292
Policy Title.....Wakix

Wakefulness-Promoting Agents – Wakix

- Wakix® (pitolisant tablets – Harmony)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

OVERVIEW
Wakix, an antagonist/inverse agonist of the histamine-3 receptor, is indicated for the following uses:[1]

- **Excessive daytime sleepiness in adults and pediatric patients ≥ 6 years of age with narcolepsy**.
- **Cataplexy in adults with narcolepsy**.

Wakix is the only wakefulness-promoting agent that is not a controlled substance.[1-4]

Armodafinil and modafinil are wakefulness-promoting agents with actions similar to sympathomimetic agents (e.g., amphetamine and methylphenidate).[2,3] They are indicated to

improve wakefulness in adults with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA), or shift work disorder. Sunosi® (solriamfetol tablets), a dopamine and norepinephrine reuptake inhibitor, is indicated to improve wakefulness in adults with excessive daytime sleepiness associated with narcolepsy or OSA.[4] Armodafinil, modafinil, and Sunosi are Schedule IV controlled substances.[2-4] Armodafinil, modafinil, and Sunosi are not indicated for the treatment of cataplexy.

Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy.[7] Polysomnogram is an overnight recording of brain and muscle activity, breathing, and eye movements. The multiple sleep latency test assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter rapid eye movement (REM) sleep. On the day after polysomnogram, the patient is asked to take five short naps separated by two hours over the course of a day. If an individual falls asleep in < 8 minutes on average over the five naps, this indicates excessive daytime sleepiness. However, patients with narcolepsy also have an abnormally quick start to REM sleep. If REM sleep happens within 15 minutes at least two times out of the five naps and the sleep study the night before, this is likely an abnormality caused by narcolepsy.

Guidelines

Narcolepsy and Cataplexy

The American Academy of Sleep Medicine (AASM) practice parameters for the treatment of central disorders of hypersomnolence were updated in 2021.[5,6]

- Modafinil, Wakix, Xyrem® (sodium oxybate oral solution), and Sunosi are recommended as effective treatments for daytime sleepiness due to narcolepsy and reducing disease severity in adults (Strong Recommendation for each).
- Wakix and Xyrem have also demonstrated efficacy for the treatment of cataplexy in patients with narcolepsy (Strong Recommendation for each).
- Xyrem and armodafinil have Conditional Recommendations for the treatment of narcolepsy, showing efficacy for daytime sleepiness due to narcolepsy and reducing disease severity.
- Dextroamphetamine has a Conditional Recommendation for the treatment of narcolepsy, showing efficacy for excessive daytime sleepiness and cataplexy.
- Methylphenidate has a Conditional Recommendation for the treatment of narcolepsy, showing efficacy in reducing disease severity.
- There was insufficient and inconclusive evidence to make recommendations for l-carnitine, scheduled naps, selegiline, triazolam, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors.
- Modafinil and Xyrem have Conditional Recommendations for the treatment of narcolepsy in pediatric patients.
- A Strong Recommendation should be followed by clinicians under most circumstances. A Conditional Recommendation requires that the clinician use clinical knowledge and experience and strongly consider the individual patient's values and preferences to determine the best course of action.

Cigna Healthcare Coverage Policy

Documentation: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, claims records, and/or other information.

Wakix is considered medically necessary when ONE of the following is met:

FDA-Approved Indications

1. **Cataplexy Treatment in a Patient with Narcolepsy**. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Documentation that the patient has been evaluated using polysomnography and a multiple sleep latency test; AND
   - **C)** Documented diagnosis of narcolepsy has been confirmed,; AND
   - **D)** The medication is prescribed by or in consultation with a sleep specialist physician or a neurologist; AND
   - **E)** Documentation that the patient meets ONE of the following (i or ii):
     - **i.** Patient has tried dextroamphetamine; OR
     - **ii.** Patient has a contraindication or intolerance to dextroamphetamine.
       Note: Contraindications to dextroamphetamine include a history of substance use disorder; advanced arteriosclerosis, symptomatic cardiovascular disease, and/or moderate to severe hypertension; hyperthyroidism; known hypersensitivity to sympathomimetic amines; glaucoma; agitated states; concomitant administration with monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs.

2. **Excessive Daytime Sleepiness Associated with Narcolepsy.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 6 years of age; AND
   - **B)** Documentation that the patient has been evaluated using polysomnography and a multiple sleep latency test; AND
   - **C)** Documented diagnosis of narcolepsy has been confirmed; AND
   - **D)** The medication is prescribed by or in consultation with a sleep specialist physician or a neurologist; AND
   - **E)** Documentation that the patient meets ONE of the following (i or ii):
     - **i.** Patient has tried at least ONE of the following treatments: a central nervous system (CNS) stimulant, generic modafinil or generic armodafinil; OR
       Note: Examples of CNS stimulants include methylphenidate, dexmethylphenidate, and dextroamphetamine. An exception to this requirement is allowed if the patient has previously tried brand Provigil or brand Nuvigil.
     - **ii.** Patient has a history of substance use disorder and a wakefulness-promoting agent that is not a controlled substance is necessary.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Concomitant Use of Wakix with an Oxybate Product and/or Sunosi (solriamfetol tablets).** Wakix, an antagonist/inverse agonist of the histamine-3 receptor, is indicated for excessive daytime sleepiness and cataplexy in adults with narcolepsy.[1] Oxybate products include Xyrem (sodium oxybate oral solution), Lumryz (sodium oxybate extended-release oral suspension), and Xywav (calcium, magnesium, potassium, and sodium oxybates oral solution).[8-10] These products have the same active ingredient (oxybate, a central nervous system depressant) and have not been studied for use in combination or as alternating treatments.

Sunosi, a dopamine and norepinephrine reuptake inhibitor, is indicated to improve wakefulness in adults with excessive daytime sleepiness due to narcolepsy or obstructive sleep apnea.[2] Currently, there are no published studies evaluating combination use of these medications.

References

1. Wakix® tablets [prescribing information]. Plymouth Meeting, PA: Harmony Biosciences; June 2024.
2. Sunosi® tablets [prescribing information]. New York, NY: Axsome; June 2023.
3. Provigil® tablets [prescribing information]. Parsippany, NJ: Teva; December 2022.
4. Nuvigil® tablets [prescribing information]. Parsippany, NJ: Teva; December 2022.
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;17(9):1881–1893.
6. Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med*. 2021;17(9):1895-1945.
7. National Institutes of Health. Narcolepsy. National Institute of Neurological Disorders and Stroke. Last reviewed on November 28, 2023. Available at: Narcolepsy | National Institute of Neurological Disorders and Stroke (nih.gov). Accessed on June 26, 2024.
8. Xyrem® oral solution [prescribing information]. Palo Alto, CA: Jazz; April 2023.
9. Lumryz™ extended-release oral suspension [prescribing information]. Chesterfield, MO: Avadel; May 2023.
10. Xywav® oral solution [prescribing information]. Palo Alto, CA: Jazz; April 2023.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	**Policy Title:** **Updated from** "Pitolisant" **to** "Wakefulness Promoting Agents – Wakix" **Cataplexy Treatment in a Patient with Narcolepsy**. **Updated from** "Narcolepsy Type 1 (Narcolepsy with Cataplexy)" **to** "Cataplexy Treatment in a Patient with Narcolepsy" **Removed "**Daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months" **Removed** "Cataplexy" **Updated** "Documentation of **ONE** of the following: (i) Mean Sleep Latency Test (MSLT) performed according to standard techniques, showing a mean sleep latency of less than or equal to 8 minutes and two or more sleep-onset rapid eye movement periods (SOREMPs) following a nocturnal polysomnogram (PSG) that rules out other causes of excessive daytime sleepiness, (ii) A SOREMP (within 15 minutes of sleep onset) on a nocturnal PSG' TO 'Patient has been evaluated using polysomnography and a multiple sleep latency test"	10/15/2024

	Removed "The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal" **Updated "**Documentation of **ONE** of the following: (i) Treatment of Cataplexy and failure, contraindication or intolerance to **ONE** of the following: dextroamphetamine, a tricyclic antidepressant (TCA) [for example, amitriptyline, desipramine, imipramine], a selective serotonin reuptake inhibitor (SSRI) [for example, fluoxetine, sertraline, paroxetine], venlafaxine; (ii) Treatment of Excessive Daytime Sleepiness and **ONE** of the following: (1) Failure, contraindication, or intolerance to modafinil OR armodafinil , (2) Failure, contraindication, or intolerance to dextroamphetamine, dexmethylphenidate OR methylphenidate, (3) History of substance abuse and, according to the prescriber, a wakefulness-promoting agent that is not a controlled substance is necessary' TO 'Patient meets ONE of the following (i or ii): (i) Patient has tried dextroamphetamine; OR (ii) Patient has a contraindication or intolerance to dextroamphetamine, according to the prescriber, Note: Contraindications to dextroamphetamine include a history of substance use disorder; advanced arteriosclerosis, symptomatic cardiovascular disease, and/or moderate to severe hypertension; hyperthyroidism; known hypersensitivity to sympathomimetic amines; glaucoma; agitated states; concomitant administration with monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs" **Removed** pulmonologist **from** 'Medication is prescribed by, or in consultation with" **Excessive Daytime Sleepiness Associated with Narcolepsy.** **Updated from** "Narcolepsy Type 2 (Narcolepsy without Cataplexy)" **to** "Excessive Daytime Sleepiness Associated with Narcolepsy'" **Updated from** "18 years of age or older" **to** "6 years of age or older" **Updated** "Documentation of a Mean Sleep Latency Test (MSLT) performed according to standard techniques, showing a mean sleep latency of less than or equal to 8 minutes and two or more sleep-onset rapid eye movement periods (SOREMPs) following a nocturnal polysomnogram (PSG) that rules out other causes of excessive daytime sleepiness. A SOREMP (within 15 minutes of sleep onset) on a nocturnal PSG may replace one of the	

	SOREMPs on the MSLT.' TO 'Patient has been evaluated using polysomnography and a multiple sleep latency test" **Removed** "Daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months" **Added "**Diagnosis of narcolepsy has been confirmed, according to the prescriber" **Removed** pulmonologist **from** "Medication is prescribed by, or in consultation with" **Updated** "Documentation of **ONE** of the following: (i) Failure, contraindication, or intolerance to modafinil OR armodafinil, (2) Failure, contraindication, or intolerance to dextroamphetamine, dexmethylphenidate OR methylphenidate, (3) History of substance abuse and, according to the prescriber, a wakefulness-promoting agent that is not a controlled substance is necessary" **Conditions Not Covered.** **Added** "Concomitant Use of Wakix with an Oxybate Product and/or Sunosi (solriamfetol tablets)"	
Selected Revision	**Cataplexy Treatment in a Patient with Narcolepsy.** The criteria were updated to include central nervous system (CNS) stimulants as an option for patients who are ≥ 18 years of age to have tried prior to approval of Wakix. Now a patient who is ≥ 18 years of age needs to have tried a central nervous system (CNS) stimulant, generic modafinil, or generic armodafinil OR have a history of substance use disorder prior to approval of Wakix. Previously, a patient who is ≥ 18 years of age had to have tried one of generic modafinil or generic armodafinil. Additionally, examples CNS stimulants were added to the Note.	11/01/2024
Selected Revision	**Added "<u>Documentation</u>**: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, claims records, and/or other information." **Cataplexy Treatment in a Patient with Narcolepsy** **Updated** criteria **from** "Patient has been evaluated using polysomnography and a multiple sleep latency test" **to** "Documentation that the patient has been evaluated using polysomnography and a multiple sleep latency test." **Updated** criteria **from** "Diagnosis of narcolepsy has been confirmed, according to the prescriber" **to**	3/1/2025

	"Documented diagnosis of narcolepsy has been confirmed." **Updated** criteria **from** "Patient meets ONE of the following (i or ii): i. Patient has tried dextroamphetamine; OR ii. Patient has a contraindication or intolerance to dextroamphetamine, according to the prescriber." **to** "Documentation that the patient meets ONE of the following (i or ii): i. Patient has tried dextroamphetamine; OR ii. Patient has a contraindication or intolerance to dextroamphetamine." **Excessive Daytime Sleepiness Associated with Narcolepsy** **Updated** criteria **from "**Patient has been evaluated using polysomnography and a multiple sleep latency test" **to** "Documentation that the patient has been evaluated using polysomnography and a multiple sleep latency test." **Updated** criteria **from** "Diagnosis of narcolepsy has been confirmed, according to the prescriber" **to "**Documented diagnosis of narcolepsy has been confirmed." The criteria were updated to remove the restriction to patients who are ≥ 18 years of age when requiring a patient to have tried a central nervous system (CNS) stimulant, generic modafinil, or generic armodafinil OR have a history of substance use disorder prior to approval of Wakix. **Updated** criteria **from** "If the patient is ≥ 18 years of age, then the patient meets ONE of the following (i or ii): i. Patient has tried at least ONE of the following treatments: a central nervous system (CNS) stimulant, generic modafinil or generic armodafinil; OR ii. Patient has a history of substance use disorder and a wakefulness-promoting agent that is not a controlled substance is necessary, per the prescriber" **to** "Documentation that the patient meets ONE of the following (i or ii): "i. Patient has tried at least ONE of the following treatments: a central nervous system (CNS) stimulant, generic modafinil or generic armodafinil; OR ii. Patient has a history of substance use disorder and a wakefulness-promoting agent that is not a controlled substance is necessary."	

The policy effective date is in force until updated or retired.