

pitolisant (Wakix[®])

Policy # 00700

Original Effective Date: 03/09/2020

Current Effective Date: 01/13/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member’s contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider pitolisant (Wakix[®])[‡] for the treatment of excessive daytime sleepiness or cataplexy in patients with narcolepsy to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for pitolisant (Wakix) will be considered when the following criteria are met:

- Patient meets ONE of the following:
 - Patient is > 18 years of age; AND
 - Patient has a diagnosis of excessive daytime sleepiness associated with narcolepsy or cataplexy associated with narcolepsy; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) GENERIC modafinil or armodafinil for at least 1 month unless there is clinical evidence or patient history that suggests the use of the generic alternatives will be ineffective or cause an adverse reaction to the patient; AND
*(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
 - Patient has tried and failed (e.g., intolerance or inadequate response) at least TWO generic stimulant medications for 1 month EACH unless there is clinical evidence or patient history that suggests the use of the generic stimulants will be ineffective or cause an adverse reaction to the patient. Generic stimulants include methylphenidate, dexamethylphenidate, methamphetamine, and dextroamphetamine-amphetamine; AND
*(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

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- Patient does NOT have a diagnosis of a substance use disorder; OR
*(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility based on clinical trial exclusion criteria and will be denied as not medically necessary** if not met.)*
- Patient is between 6 years and 17 years of age; AND
 - Patient has a diagnosis of excessive daytime sleepiness associated with narcolepsy; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) at least TWO generic stimulant medications for 1 month EACH unless there is clinical evidence or patient history that suggests the use of the generic stimulants will be ineffective or cause an adverse reaction to the patient. Generic stimulants include methylphenidate, dexamethylphenidate, methamphetamine, and dextroamphetamine-amphetamine.
*(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the company considers the use of pitolisant (Wakix) for the treatment of excessive daytime sleepiness or cataplexy in adult patients with narcolepsy when patients have a substance use disorder or have not tried and failed generic modafinil or armodafinil AND two generic stimulants to be **not medically necessary**.**

Based on review of available data, the company considers the use of pitolisant (Wakix) for the treatment of excessive daytime sleepiness in pediatric patients 6 years of age and older with narcolepsy when patients have not tried and failed two generic stimulants to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of pitolisant (Wakix) for indications other than excessive daytime sleepiness in adults or pediatric patients 6 years of age and older with narcolepsy, or cataplexy associated with narcolepsy in adults to be **investigational**.*



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Background/Overview

Wakix is a wakefulness-promoting agent indicated for the treatment of excessive daytime sleepiness and cataplexy in adults with narcolepsy. It is a histamine-3 receptor antagonist/inverse agonist, which represents a novel mechanism of action compared to other wakefulness-promoting agents. The action on these histamine-3 receptors is thought to increase wakefulness and decrease narcolepsy episodes. Wakix is available as 4.45 mg and 17.8 mg tablets and should be dosed in adults as 17.8 mg to 35.6 mg once daily in the morning upon waking. In pediatric patients, dosing is titrated over several weeks to a maximum dose of 17.8 mg per day in patients weighing less than 40 kg and 35.6 mg in those weighing 40 kg or more. It may take up to 8 weeks for some patients to achieve a clinical response. Of note, the majority of patients in the clinical trials received the highest dose. Wakix is not a controlled substance. However, patients with a history of substance use disorder were specifically excluded from the clinical trials, so efficacy and safety cannot be confirmed in this population.

Narcolepsy is a rare, chronic neurologic disorder that affects the brain's ability to control sleep-wake cycles. Affected individuals typically feel rested after waking, but then feel very sleepy throughout much of the day. The most typical symptoms are excessive daytime sleepiness, cataplexy, sleep paralysis, and hallucinations. If left undiagnosed or untreated, narcolepsy can interfere with psychological, social, and cognitive function and development and can inhibit academic, work, and social activities.

Treatment of narcolepsy includes lifestyle modifications and medications. Lifestyle modifications are a necessary part of treatment and include taking short, regularly scheduled naps, maintaining a regular sleep schedule, avoiding caffeine and alcohol several hours before bedtime, and exercising regularly. Medications used to treat narcolepsy include stimulants such as modafinil and amphetamines for the treatment of daytime sleepiness and sodium oxybate (Xyrem[®])[‡] for the treatment of cataplexy, daytime sleepiness, and disrupted sleep. The American Academy of Sleep Medicine (AASM) practice guidelines for the treatment of central disorders of hypersomnolence were updated in 2021. Medications with Strong Recommendations as effective treatments for daytime sleepiness due to narcolepsy and reducing disease severity in adults include modafinil, Wakix, Xyrem, and solriamfetol (Sunosi[®])[‡]. Wakix and Xyrem have also demonstrated efficacy for the treatment of cataplexy in patients with narcolepsy and are rated as a Strong Recommendation. Modafinil and armodafinil are only approved for use in adults. Tricyclic antidepressants, selective serotonin reuptake inhibitors, and venlafaxine may be effective for the treatment of cataplexy and selegiline may be effective for the treatment of cataplexy and daytime sleepiness.



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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Wakix was approved in August 2019 for the treatment of excessive daytime sleepiness in adults with narcolepsy. In October 2020, the indication was updated to include adults with cataplexy associated with narcolepsy. In June 2024, the approval for the treatment of excessive daytime sleepiness was further expanded to include pediatric patients 6 years of age and older with narcolepsy.

The safety and efficacy of Wakix have not been established for treatment of cataplexy in pediatric patients with narcolepsy.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Excessive Daytime Sleepiness in Adult Patients with Narcolepsy

The efficacy of Wakix for the treatment of excessive daytime sleepiness in adult patients with narcolepsy was evaluated in two multicenter, randomized, double-blind, placebo-controlled studies. Both studies included patients ≥ 18 years of age who met the International Classification of Sleep Disorders (ICSD-2) criteria for narcolepsy and who had an Epworth Sleepiness Scale (ESS) score ≥ 14 . Excessive daytime sleepiness (EDS) was assessed using the ESS, an 8-item questionnaire by which patients rate their perceived likelihood of falling asleep during usual daily life activities. Each of the 8 items is rated from 0 (would never doze) to 3 (high chance of dozing); the maximum score is 24. Both studies included an 8-week treatment period, a 3-week dose titration phase, and a 5-week stable dose phase.

In Study 1, 61 patients were randomized to receive Wakix or placebo. The dose of Wakix was initiated at 8.9 mg once daily and could be increased at weekly intervals to 17.8 mg or 35.6 mg based on efficacy response and tolerability. No dose adjustments were permitted during the 5-week stable-dose phase. 61% of patients reached a stable dose of 35.6 mg. The primary endpoint was least square mean final ESS score compared to placebo at week 8. Wakix demonstrated a statistically significant improvement in this measure with a difference of -3.1 [95% CI -5.73; -0.46].

In Study 2, 95 patients were randomized to receive Wakix or placebo. The dose of Wakix was initiated at 4.45 mg and could be increased at weekly intervals to 8.9 mg or 17.8 mg based on efficacy response and tolerability. No dose adjustments were permitted during this 5-week stable-dose phase. 76% of patients reached a stable dose of 17.8 mg. Wakix demonstrated a statistically significant improvement in the primary endpoint of least square mean final ESS score compared to placebo at week 8 with a treatment difference of -2.2 [95% CI -4.17; -0.22].



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Excessive Daytime Sleepiness in Pediatric Patients (6 years of age and older) with Narcolepsy

The efficacy of Wakix for the treatment of excessive daytime sleepiness in pediatric patients 6 years of age and older with narcolepsy was evaluated in one multicenter, randomized, double-blind, placebo-controlled study. Pediatric patients 6 to 17 years who met the International Classification of Sleep Disorders (ICSD-3) criteria for narcolepsy (with or without cataplexy) and who had a Pediatric Daytime Sleepiness Scale (PDSS) score ≥ 15 were eligible to enroll in the study. EDS was assessed with the PDSS, an 8-item questionnaire in which patients report their frequency of EDS-related symptoms. Each of the 8 items on the PDSS is rated from 0 (never) to 4 (very often, always); the maximum score is 32, with higher scores representing greater severity of symptoms. The study included an 8-week treatment period: a 4-week dose titration phase followed by a 4-week stable dose phase.

In Study 4, 110 pediatric patients 6 to 17 years were randomized to receive Wakix or placebo. The dose of Wakix was initiated at 4.45 mg once daily and could be increased at weekly intervals to 17.8 mg for patients weighing < 40 kg or 35.6 mg for patients weighing ≥ 40 kg, based on clinical response and tolerability. No dose adjustments were permitted during the 4-week stable dose phase. 69% of patients weighing < 40 kg reached a stable dose of 17.8 mg and 72% of patients weighing ≥ 40 kg reached a stable dose of 35.6 mg. Wakix demonstrated statistically significantly greater improvement on the least square mean change from baseline to the end of treatment in final PDSS total score compared to placebo, of -3.41 points (95% CI: -5.52, -1.31).

Cataplexy in Patients with Narcolepsy

The efficacy of Wakix for the treatment of cataplexy in adult patients with narcolepsy was evaluated in two multicenter, randomized, double-blind, placebo-controlled studies (Study 3 and Study 1 [described above]). Both studies included patients ≥ 18 years of age. Study 3 required patients to meet the ICSD-2 criteria for narcolepsy with cataplexy with at least 3 cataplexy attacks per week and an ESS score of ≥ 12 .

Study 3 included a 7-week treatment period that consisted of a 3-week dose titration phase followed by a 4-week stable dose phase. A total of 105 patients were randomized to receive Wakix or placebo. The dose of Wakix was initiated at 4.45 mg once daily for the first week, increased to 8.9 mg for the second week, and could remain the same or be decreased or increased at the next two weekly intervals to a maximum of 35.6 mg based on clinical response and tolerability. No dose adjustments were permitted during the 4-week stable dose phase during which 65% of patients reached a stable dose of 35.6 mg.

The primary endpoint of Study 3 was the change in geometric mean number of cataplexy attacks per week from baseline to the average of the 4-week stable dosing period for Wakix compared to placebo. On this endpoint, Wakix demonstrated statistically significantly greater improvement with a decrease from 9.1 weekly attacks at baseline to 2.3 attacks during the 4-week stable dosing period. The placebo group had a decrease from 7.3 attacks at baseline to 4.5 during the stable dosing period.



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References

1. Wakix [package insert]. Harmony Biosciences, LLC. Plymouth Meeting, PA. Updated June 2024.
2. Wakix Drug Evaluation. Express Scripts. Updated August, 28, 2019.
3. 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.
4. 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.

Policy History

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02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. New policy.
02/04/2021	Medical Policy Committee review
02/10/2021	Medical Policy Implementation Committee approval. Criteria updated to include cataplexy in patients with narcolepsy based on expanded FDA indication.
02/03/2022	Medical Policy Committee review
02/09/2022	Medical Policy Implementation Committee approval. Criteria eligibility unchanged.
02/02/2023	Medical Policy Committee review
02/08/2023	Medical Policy Implementation Committee approval. Criteria eligibility unchanged.
02/01/2024	Medical Policy Committee review
02/14/2024	Medical Policy Implementation Committee approval. Criteria eligibility unchanged.
12/05/2024	Medical Policy Committee review
12/11/2024	Medical Policy Implementation Committee approval. Updated the age requirement for the treatment of EDS in patients with narcolepsy to include pediatric patients 6 years of age and older per the updated FDA package insert.

Next Scheduled Review Date: 12/2025

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and



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whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

