09-J3000-52

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Subject: Pitolisant (Wakix)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Approximately 1 in 2,000 patients are affected by narcolepsy, a sleep disorder characterized by episodes of daytime sleepiness and often in conjunction with disturbed sleep at night, cataplexy, and sleep paralysis. Symptoms usually begin in patients between the ages of 10 and 20 years old. Additionally, sleep disorders such as obstructive sleep apnea, restless legs syndrome, sleep walking, and rapid eye movement sleep behavior disorder are commonly observed in patients with narcolepsy. The International Classification of Sleep Disorders recognizes two forms of narcolepsy: narcolepsy type 1 (formerly called narcolepsy with cataplexy) and narcolepsy type 2 (formerly called narcolepsy without cataplexy). Type 1 is characterized by cataplexy, very low levels of hypocretin 1 in cerebrospinal fluid, and severe loss of hypocretin neurons, while type 2 is characterized by the absence of cataplexy, normal levels of hypocretin 1 in cerebrospinal fluid, and minimal loss of hypocretin neurons (reported in only 10 to 30% of patients).

A diagnosis of narcolepsy should be confirmed with overnight polysomnography followed by a multiple sleep latency test the next day (usually beginning around 8 am and ending at 5 or 6 pm). The overnight sleep study may show fragmented, light sleep and an early transition into REM sleep (<15 minutes after the onset of sleep). During the multiple sleep latency test, the patient is encouraged to nap for 20 minutes every two hours. Patients with narcolepsy will usually fall asleep in less than 8 minutes (vs 15 minutes or more in healthy patients) and will usually have REM sleep during at least two of these daytime naps (known as sleep-onset REM sleep periods), whereas people without narcolepsy rarely have any daytime REM sleep. A positive multiple sleep latency test (defined as a short time to fall asleep plus REM sleep in at least two of the naps) provides strong, objective evidence of excessive sleepiness and poorly regulated REM sleep.

Treatment options for narcolepsy include both behavioral and pharmacologic interventions. All patients should have good quality nighttime sleep and a 20-minute nap in the afternoon. Medications such as modafinil, methylphenidate, dextroamphetamine (and other amphetamines), and sodium oxybate promote wakefulness and reduce the symptoms of excessive daytime sleepiness. Venlafaxine, fluoxetine, clomipramine, and sodium oxybate can be used to manage cataplexy. Response to treatment should be assessed on a regular basis using a validated sleep scale such as the Epworth Sleepiness Scale (ESS).

Pitolisant (Wakix®), an oral histamine-3 (H3) receptor antagonist/inverse agonist, was approved by the U.S. Food and Drug Administration (FDA) in August 2019 for the treatment of excessive daytime sleepiness in adult patients with narcolepsy. Pitolisant works through a novel mechanism of action to increase the synthesis and release of histamine, a wake-promoting neurotransmitter in the brain. Pitolisant also modulates various neurotransmitter systems, increasing acetylcholine, noradrenaline and dopamine release in the brain. The recommended daily dosage range is 17.8 mg to 35.6 mg daily, with a titration schedule outlined in the labeling.

The safety and efficacy of pitolisant were evaluated in two randomized, double-blind, placebo-controlled trials of patients with narcolepsy with or without cataplexy.

HARMONY-CTP enrolled adult patients 18 years of age and older who were diagnosed with narcolepsy with cataplexy, experienced at least three cataplexies per week, and had excessive daytime sleepiness based on an ESS score of 12 or more. Patients were randomized to receive either pitolisant or placebo. Treatment lasted for 7 weeks, with 3 weeks of flexible dosing based on response/efficacy (5 mg, 10 mg, 20 mg, or 40 mg), followed by 4 weeks of stable dosing. The primary endpoint was the change in the average number of cataplexy attacks per week as recorded in patient diaries (weekly cataplexy rate [WCR]) between the 2 weeks of baseline and the 4 weeks of stable dosing period.

The WCR during the stable dosing period compared with baseline was decreased by 75% (WCR_{final}=2.27; $WCR_{baseline}$=9.15; $WCR_{final/baseline}$=0.25) in patients who received pitolisant and 38% (WCR_{final}=4.52; $WCR_{baseline}$=7.31; $WCR_{final/baseline}$=0.62) in patients who received placebo (rate ratio 0.512; 95% CI 0.43–0.60, p<0.0001). Treatment-related adverse events were significantly more common in the pitolisant group than in the placebo group (15 [28%] of 54 *vs* 6 [12%] of 51; p=0.048). There were no serious adverse events, but one case of severe nausea in the pitolisant group. The most frequent adverse events in the pitolisant group (headache, irritability, anxiety, and nausea) were mild or moderate except one case of severe nausea. No withdrawal syndrome was detected following pitolisant treatment; one case was detected in the placebo group.

HARMONY I enrolled adult patients 18 years of age and older who had not taken psychostimulants for at least 14 days and had excessive daytime sleepiness based on an ESS score of 14 or more. Patients were randomized to receive either pitolisant, modafinil, or placebo. Treatment lasted for 8 weeks, with 3 weeks of flexible dosing based on response/efficacy (5 mg, 10 mg, 20 mg, or 40 mg of pitolisant; 100 mg, 200 mg, or 400 mg of modafinil), followed by 5 weeks of stable dosing. For the primary analysis, assessed in the intention-to-treat population, we assessed the superiority of pitolisant versus placebo, and the non-inferiority of pitolisant versus modafinil.

Over the 8-week treatment period, mean ESS score reductions were −3.4 (SD 4.2) in the placebo group, −5.8 (6.2) in the pitolisant group, and −6.9 (6.2) in the modafinil group. Primary analysis of between-

group differences in mean ESS score at endpoint (adjusted for baseline) showed pitolisant to be superior to placebo (difference −3.0, 95% CI −5.6 to −0.4; p=0.024), but not non-inferior to modafinil (difference 0.12, 95% CI −2.5 to 2.7; p=0.250). There were 22 adverse events with pitolisant, 26 with modafinil, and 10 with placebo. Six severe adverse events were treatment-related: one with pitolisant (abdominal discomfort) and five with modafinil (abdominal pain, abnormal behavior, amphetamine-like withdrawal symptoms, lymphoadenopathy, and inner ear disorders).

The American Academy of Sleep Medicine is expected to publish updated clinical practice guidelines for the treatment of narcolepsy in Fall 2019.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of pitolisant (Wakix) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member has experienced daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months
2. Member is diagnosed with one of the following conditions and all associated criteria are met:
    a. Narcolepsy Type 1 (narcolepsy with cataplexy)
        i. Member has clear historic evidence of cataplexy
        ii. Member is 18 years of age or older
    b. Narcolepsy Type 2 (narcolepsy without cataplexy)
        i. Alternative causes of excessive daytime sleepiness (e.g., insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal) have been ruled out or adequately addressed
        ii. One of the following:
            - Member has had an inadequate therapeutic response with a trial of at least 8 weeks with either modafinil (generic Provigil) **OR** armodafinil (generic Nuvigil)
            - Member had persistent intolerable adverse effects with or hypersensitivity to either modafinil (generic Provigil) **OR** armodafinil (generic Nuvigil) – the specific adverse effect or hypersensitivity must be specified
            - Member has a contraindication to treatment with **BOTH** modafinil (generic Provigil) **OR** armodafinil (generic Nuvigil)

- Member was previously approved for pitolisant by another health plan – documentation of a recent (within 90 days prior to authorization request) health plan-paid claim for pitolisant must be provided

iii. Member is 6 years of age or older

3. Member's diagnosis has been confirmed by overnight polysomnography (PSG) followed by a multiple sleep latency test (MSLT) the next day* demonstrating **BOTH** of the following – documentation of results of both PSG and MSLT testing must be provided:
    a. Mean sleep latency of less than or equal to 8 minutes
    b. Two or more sleep onset REM periods (SOREMPs) on the MSLT **OR** one SOREMP on the MSLT plus a SOREMP (within 15 minutes of sleep onset) on the preceding overnight PSG

    * For type 1 narcolepsy (narcolepsy with cataplexy), PSG with MSLT is not required if the member has laboratory confirmed hypocretin-1 deficiency defined as a cerebrospinal fluid (CSF) hypocretin-1 level less than or equal to 110 pg/mL or less than one-third of the mean values obtain in normal subjects with the same standardized assay – laboratory documentation must be submitted
4. Pitolisant will **NOT** be started in combination with an oxybate product
5. Pitolisant is prescribed by (or in consultation with) a neurologist, pulmonologist, psychiatrist, or sleep medicine specialist
6. Dose does not exceed 35.6 mg/day – dosage will be achieved using the fewest tablets possible

Approval duration: 12 months

Continuation of pitolisant (Wakix) meets the definition of **medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue in the past two years for treatment of narcolepsy type 1 or narcolepsy type 2 **OR** the member has previously met all indication-specific criteria
2. Member demonstrates a clinically meaningful response to treatment with pitolisant as indicated by the following:
    a. Type 1 Narcolepsy
        i. Reduction in frequency of cataplexy attacks or symptoms of excessive daytime sleepiness compared to baseline – documentation from the medical record must be provided
    b. Type 2 Narcolepsy
        i. Reduction in symptoms of excessive daytime sleepiness compared to baseline – documentation from the medical record must be provided
3. Pitolisant is prescribed by (or in consultation with) a neurologist, pulmonologist, psychiatrist, or sleep medicine specialist
4. Pitolisant will **NOT** be used in combination with an oxybate product **UNLESS** the member has Type 1 narcolepsy with a suboptimal response to either sodium oxybate **OR** calcium,

magnesium, potassium, and sodium oxybate monotherapy – details of the member's treatment history and justification for using combination therapy must be submitted

5. Dose does not exceed 35.6 mg/day – dosage will be achieved using the fewest tablets possible

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Administer once daily in the morning upon wakening
- Adults:
    - Week 1: Initiate with 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 (6 years and older):
    - Week 1: Initiate with 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 less than 40 kg
    - Week 4: For patients weight greater than or equal to 40 kg, may increase to the maximum recommended dosage of 35.6 mg once daily

Dose Adjustments

- Moderate hepatic impairment:
    - Adult patients: Initial dosage is 8.9 mg once daily. Titrate to a maximum dosage of 17.8 mg once daily after 14 days
    - Pediatric patients: Initial dosage is 4.45 mg once daily. Titrate to 8.9 mg once daily after 14 days; for patients weighing at least 40 kg, may increase to 17.8 mg once daily after another 14 days
- Moderate and severe impairment:
    - Adult patients: Initial dosage is 8.9 mg once daily. Titrate to maximum dosage of 17.8 mg once daily after 7 days
    - Pediatric patients: Initial dosage is 4.45 mg once daily. Titrate to 8.9 mg once daily after 7 days; for patients weighing at least 40 kg, may increase to 17.8 mg once daily after another 7 days

- End-stage renal disease (ESRD): Not recommended
- Poor Metabolizers of CYP2D6:
    - Adult patients: Maximum recommended dosage is 17.8 mg once daily
    - Pediatric patients: Maximum recommended dosage is 8.9 mg once daily for patients weighing less than 40 kg and 17.8 mg for patients weighing at least 40 kg

Drug Availability

- Tablets: 4.45 mg and 17.8 mg

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Severe hepatic impairment

Precautions/Warnings

- QT Interval Prolongation: Increases in QT interval. Avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval. Monitor patients with hepatic or renal impairment for increased QTc

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

G47.419	Narcolepsy, without cataplexy

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Cataplexy: a condition, often associated with narcolepsy; marked by abrupt attacks of muscular weakness and hypotonia triggered by an emotional stimulus, such as mirth, anger, or fear.

Excessive Daytime Sleepiness: This refers to a condition where a person feels very drowsy during the day, even after getting adequate night time rest, and has a tendency to fall asleep or requires extra effort to avoid sleeping in inappropriate situations, such as at work or driving. This condition is also defined as a score greater than or equal to 10 on the Epworth Sleepiness Scale.

Multiple Sleep Latency Test (MSLT): This is a test used in conjunction with polysomnography (PSG) to determine the presence and severity of sleepiness. During this test, the subject is given the opportunity to take naps at specified time intervals. The test consists of four or five nap opportunities at two hour intervals. Each nap opportunity is 20 minutes in duration. Individuals with excessive daytime sleepiness may fall asleep almost immediately, while those without excessive sleepiness may not fall asleep at all. Severe sleepiness is usually associated with an MSLT mean sleep latency of less than 5 minutes. The presence of sleep onset rapid eye movement (REM) and the number of naps in which sleep REM occurs are also determined.

Narcolepsy: recurrent, uncontrollable, brief episodes of sleep often associated with hallucinations just beforehand or just afterward.

Parasomnias: a category of sleep disorders that involve abnormal and unnatural movements, behaviors, emotions, perceptions, and dreams that occur while falling asleep, sleeping, between sleep stages, or during arousal from sleep.

Type 1 Narcolepsy: narcolepsy with cataplexy in which patients have very low CSF hypocretin/orexin levels resulting from extensive loss of hypothalamic neurons

Type 2 Narcolepsy: narcolepsy without cataplexy in which patients have normal or mildly decrease CSF hypocretin/orexin levels

RELATED GUIDELINES

Sodium oxybate (Xyrem), 09-J1000-06

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/09/25.

GUIDELINE UPDATE INFORMATION:

12/15/19	New Medical Coverage Guideline.
12/15/20	Updated Position Statement to include new FDA approved indication.
05/15/21	Updated Position Statement.
07/15/21	Review and revision to guideline; updated position statement and references.
08/15/24	Review and revision to guideline; updated position statement, dosage, and references.
05/15/25	Review and revision to guideline; updated position statement and references.