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Tasimelteon

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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. 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

This policy supports medical necessity review for the following products:

- **Hetlioz™ (tasimelteon capsules)**
- **Hetlioz LQ™ (tasimelteon oral suspension)**
- **Tasimelteon capsules**

Medical Necessity Criteria

Tasimelteon (Hetlioz, Hetlioz LQ) is considered medically necessary when the following are met:

1. **Non-24-Hour Sleep-Wake Disorder (Non-24).** Individual meets **ALL** of the following criteria:
   A. Age 18 years of age or older
   B. Documented diagnosis of non-24 hour sleep-wake disorder (N24SWD) is confirmed by **ONE** of the following:

i. Assessment of at least **ONE** physiologic circadian phase marker (for example measurement of urinary melatonin levels, dim light melatonin onset [as measured in blood or saliva], assessment of core body temperature)
ii. If assessment of at least one physiologic circadian phase marker cannot be done, the diagnosis must be confirmed by the evaluation of sleep logs recorded for at least 1 month

C. Documentation that the individual is totally blind with no perception of light
D. Documentation of **BOTH** of the following:
i. Individual has received at least 6 months of continuous therapy (i.e., 6 consecutive months of daily treatment) with melatonin under the guidance of a physician who specializes in the treatment of sleep disorders
ii. Individual had inadequate efficacy with melatonin therapy according to the prescriber Examples of efficacy with melatonin therapy include entrainment, clinically meaningful or significant increases in nighttime sleep, and clinically meaningful or significant decreases in daytime sleep.
E. Medication is prescribed by, or in consultation with, a neurologist or physician who specializes in the treatment of sleep disorders
F. Preferred product criteria is met for the products listed in the below table(s)

Individual and Family Plans:

Product	Criteria
Hetlioz (tasimelteon capsules)	Documented trial of **tasimelteon capsules** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction [may require prior authorization]

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.

Reauthorization Criteria

Continuation of Tasimelteon (Hetlioz, Hetlioz LQ) is considered medically necessary for Non-24-Hour Sleep-Wake Disorder when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration: up to 6 months.
Reauthorization approval duration: up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Insomnia, Primary.** Many other agents are available.[9] Only limited data have investigated use of Hetlioz in patients with primary insomnia.[10] Further data are needed to establish the safety and efficacy of Hetlioz.

2. **Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS).** There is insufficient and underwhelming clinical efficacy data for Hetlioz/Hetlioz LQ supporting benefits for nighttime sleep disturbances in SMS.[1,16]

3. **Ramelteon Tablets (Rozerem™), Concomitant Therapy.** Ramelteon, a melatonin receptor agonist, is indicated for the treatment of insomnia characterized by difficulty with sleep onset.[11] The safety and efficacy of concomitant use of ramelteon tablets and Hetlioz have not been studied and it is suspected

that the adverse events with use of these agents with a similar mechanism of action taken together may be additive (e.g., central nervous system effects [somnolence], hepatic impairment). Ramelteon has not been studied in Non-24. In the clinical trials with Hetlioz, patients were not permitted to use medications that could interfere with the assessment of circadian rhythms.

4. **Sedative Hypnotic Medications or Other Medications for Insomnia or Other Sleep-Related Disorders, Concomitant Therapy** (e.g., benzodiazepines [triazolam, temazepam], nonbenzodiazepine hypnotics [e.g., zolpidem, zaleplon], chloral hydrate). There are no data to support the safety and efficacy of hypnotic medications in patients with Non-24.[5] Also, there are no data to determine the safety and efficacy of Hetlioz when used with other sedative hypnotic medications or other medications for insomnia or sleep-related disorders.[12]

5. **Sleep-Related Disorders, Other Types** (e.g., shift work disorder, jet lag disorder, advanced sleep phase disorder, delayed sleep phase disorder, irregular sleep-wake rhythm disorder). A published investigation details a Phase II study (n = 29) and a Phase III study (n = 411) assessing Hetlioz treatment in adults with transient insomnia associated with shifted sleep and wake time.[13] Further studies are needed to establish the efficacy and safety of Hetlioz in patients with other types of sleep-related disorders.

Background

OVERVIEW

Tasimelteon products are melatonin receptor agonists indicated for the following uses:[1,2]

- Tasimelteon capsule is indicated for the treatment of:
  - **Non-24-Hour Sleep-Wake Disorder** (Non-24) in adults.
  - **Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)**, in patients ≥ 16 years of age.
- Hetlioz LQ is indicated for the treatment of **nighttime sleep disturbances in SMS**, in patients 3 to 15 years of age.

Disease Overview

Non-24 is a chronic circadian rhythm disorder that is due to the misalignment of the endogenous master body clock to the 24-hour day which disrupts the sleep-wake cycle and commonly is thought to be caused by the failure of light to reach the suprachiasmatic nuclei. Patients who are completely blind are particularly susceptible to this condition; as many as one-half to three-quarters of totally blind patients have Non-24, which is approximately 65,000 to 95,000 Americans.[3-8] Patients can be diagnosed using circadian phase markers (e.g., measurement of urinary melatonin levels, dim light melatonin onset [assessed in blood or saliva], or assessing core body temperature).[3,8,9] Alternative forms of diagnosis include actigraphy and assessment of sleep logs (sleep diaries).[3,8,9] Actigraphy is a non-invasive method of monitoring human rest and activity cycles and involves the use of a portable device to document movement. Other reviews confirm these diagnostic methods.[8,9]

SMS is a rare disorder identified by an array of physical, neurobehavioral, and developmental characteristics.[15] In the United States, the incidence is estimated to be 1 in 15,000 to 25,000 people in the general population. Cases of SMS are predominantly related to either a deletion or mutation in the RAI1 gene. Sleep disturbances start as early as one year of age and continue into adulthood and include shortened sleep cycles with multiple awakenings during the night, early morning arousal from sleep, and increased somnolence during daytime hours. Inability to achieve a normal sleeping pattern appears to aggravate behavioral issues such as impulsivity, aggression, hyperactivity and frequent temper tantrums. Sleep issues in SMS have been attributed to a primary disturbance of the circadian clock disruption and instabilities in melatonin secretion. Physical traits such as muscle weakness, obesity-related breathing difficulties, and facial composition can be underlying factors that affect sleep.

Clinical Efficacy

The efficacy of Hetlioz for Non-24 was established in two Phase III pivotal studies involving totally blind patients with Non-24 who reported no light perception for up to 6 months and evaluated the effects of Hetlioz withdrawal.[1,3] In the Hetlioz group, 29% of patients (n = 12) met responder criteria, defined as patients with both a ≥ 45 minute increase in nighttime sleep and a ≥ 45 minute decrease in daytime nap time, compared with 12% of patients (n = 5) who received placebo (time of endpoint assessment was not stated).[1] During the withdrawal period of the trial, which lasted 8 weeks, 90% of patients who continued Hetlioz (n = 9/10) remained entrained (circadian rhythm synchronized to 24-hour day) compared with 20% of patients randomized to receive placebo (n = 2/10).[3,4]

The data for Hetlioz and Hetlioz LQ supporting benefits for nighttime sleep disturbances in SMS are underwhelming.[1,17] The pivotal trial for SMS included very few patients and was relatively short-term; this condition would likely require long-term therapy. Only one of the two primary efficacy endpoints was statistically significant after controlling for multiple comparisons.

Guidelines

In 2015, clinical practice guidelines were published by the American Academy of Sleep Medicine that address Non-24.[6] The condition mainly occurs in patients who are blind. The Task Force states that there is no evidence to support the use of sleep-promoting medications in patients with Non-24. Data suggest that melatonin entrainment occurs with melatonin at a greater rate than placebo and melatonin can be an effective treatment for Non-24. The Task Force recommendation was that clinicians use strategically timed melatonin for the treatment of Non-24 in adults who are blind (versus no treatment). There are insufficient data to support use of melatonin among sighted patients with Non-24 (versus no treatment).

The Parents and Researchers Interested in SMS (PRISMS)[2018] created medical management guidelines for the diagnosis, treatment of manifestations, and ongoing surveillance of SMS.[16] The guidelines do not address Hetlioz/Hetlioz LQ. Multidisciplinary treatment is recommended. The guidelines recognize sleep management is a challenge and no well-controlled treatment trials have been reported. The first suggestion is to incorporate a good sleep routine (e.g., consistent bedtime and bedtime routine, quiet/non-stimulating activities, use of white noise or a rhythmic sound, and a comfortably cool/dark room). Concerns for sleep apnea should be addressed. Melatonin is endorsed as monotherapy for sleep management. The concomitant use of a morning beta-blocker (acebutolol) with an evening dose of melatonin for 6 to 8 weeks could be beneficial to restore circadian plasma melatonin rhythmicity, decrease daytime sleepiness, improve daytime behavior, and enhance sleep in children with SMS.

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Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes	4/1/2025

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