Drug Coverage Policy

Effective Date.....5/1/2026
Coverage Policy Number.....IP0428
Policy Title..... Tasimelteon Products

Tasimelteon Products

- **Hetlioz™ (tasimelteon capsules – Vanda, generic)**
- **Hetlioz LQ™ (tasimelteon oral suspension – Vanda)**

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 where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. 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

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. 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.

Coverage Policy

POLICY STATEMENT

Prior Authorization is required for benefit coverage of tasimelteon capsules (Hetlioz, generic). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with tasimelteon capsules as well as the monitoring required for adverse events and long-term efficacy, approval requires tasimelteon capsules to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. All documentation must include patient-specific identifying information.

Due to insufficient clinical efficacy data for its FDA-approved use, **approval is not recommended** for Hetlioz LQ.

I. Tasimelteon capsule (Hetlioz, generic) is considered medically necessary when ONE of the following are met:

FDA-Approved Indication

1. Non-24-Hour Sleep-Wake Disorder (Non-24). Approve for the duration noted if the patient meets ONE of the following (A or B):

A. Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v and vi):

i. Patient is ≥ 18 years of age; AND

ii. Patient is totally blind with no perception of light **[documentation required]**; AND

iii. Diagnosis of Non-24 is confirmed by meeting ONE of the following (a or b):

a) Assessment of at least one physiologic circadian phase marker; OR
Note: Examples of physiologic circadian phase markers include measurement of urinary melatonin levels, dim light melatonin onset (as measured in blood or saliva), and assessment of core body temperature.

b) If assessment of at least one physiologic circadian phase marker cannot be done, the diagnosis must be confirmed by actigraphy performed for ≥ 1 week plus evaluation of sleep logs recorded for ≥ 1 month; AND

iv. Patient meets BOTH of the following (a and b):
   a) Patient 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; AND
   b) Patient had inadequate efficacy with melatonin therapy **[documentation required]**; AND

   Note: 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.

v. The medication is prescribed by or in consultation with a physician who specializes in the treatment of sleep disorders.

vi. Preferred product criteria is met for the product(s) as listed in the below table(s);OR

B. Patient is Currently Receiving Tasimelteon Capsules. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, v and vi):

i. Patient is ≥ 18 years of age; AND

ii. Patient is totally blind with no perception of light **[documentation required]**; AND

iii. Patient meets BOTH of the following (a and b):
   a) Patient 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; AND
   b) Patient had inadequate efficacy with melatonin therapy **[documentation required]**; AND

   Note: 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.

iv. Patient meets BOTH of the following (a and b):
   a) Patient has received at least 6 months of continuous therapy (i.e., 6 consecutive months of daily treatment) with tasimelteon capsules under the guidance of a physician who specializes in the treatment of sleep disorders; AND

   Note: A patient who has not received at least 6 months of continuous tasimelteon capsules therapy, or if the therapy has not been continuous (i.e., 6 consecutive months of daily treatment), should follow criterion 1A (initial therapy).
   b) Patient has achieved adequate results with tasimelteon capsules therapy **[documentation required]**; AND

   Note: Examples of adequate results with tasimelteon capsules therapy include entrainment, clinically meaningful or significant increases in nighttime sleep, clinically meaningful or significant decreases in daytime sleep.

v. The medication is prescribed by or in consultation with a physician who specializes in the treatment of sleep disorders.

vi. Preferred product criteria is met for the product(s) as listed in the below table(s).

Employer Plans:

Product	Criteria
Hetlioz (tasimelteon capsules)	The patient has tried **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] **[documentation required]**

Individual and Family Plans:

Product	Criteria
Hetlioz (tasimelteon capsules)	The patient has tried **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] **[documentation required]**

II. Hetlioz LQ is considered to be experimental, investigational, or unproven for nighttime sleep disturbances in SMS in pediatric patients 3 years to 15 years of age due to insufficient data establishing safety, efficacy, and improved health outcomes for any condition, regardless of U.S. Food and Drug Administration (FDA) approval status. Criteria will be updated as newly published data are available.

Conditions Not Covered

Tasimelteon capsules (Hetlioz, generic)/ Hetlioz LQ for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Insomnia, Primary.** American Academy of Sleep Medicine guidelines for pharmacologic treatment of chronic insomnia in adults were updated in 2017 and do not address tasimelteon; many other agents are available.[13] Only limited data have investigated use of tasimelteon capsules in patients with primary insomnia.[14,15] Further data are needed to establish the safety and efficacy of tasimelteon capsules.

2. **Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS).** Efficacy data for tasimelteon capsules/Hetlioz LQ supporting benefits for nighttime sleep disturbances in SMS are underwhelming.[1,11]

3. **Ramelteon Tablets (Rozerem®, generic), Concomitant Therapy.** Ramelteon, a melatonin receptor agonist, is indicated for the treatment of insomnia characterized by difficulty with sleep onset.[12] The safety and efficacy of concomitant use of ramelteon tablets and tasimelteon capsules 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 tasimelteon capsules, patients were not permitted to use medications that could interfere with the assessment of circadian rhythms.[17]

4. **Sedative Hypnotic Medications or Other Medications for Insomnia or Other Sleep-Related Disorders, Concomitant Therapy**. There are no data to support the safety and efficacy of hypnotic medications in patients with Non-24.[6] Also, there are no data to

determine the safety and efficacy of tasimelteon capsules when used with other sedative hypnotic medications or other medications for insomnia or sleep-related disorders.[18]
Note: Examples include benzodiazepines (triazolam, temazepam), nonbenzodiazepine hypnotics (e.g., zolpidem, zaleplon), chloral hydrate.

5. **Sleep-Related Disorders, Other Types**. A published investigation details a Phase II study (n = 29) and a Phase III study (n = 411) assessing tasimelteon capsules treatment in adults with transient insomnia associated with shifted sleep and wake time.[14] Further studies are needed to establish the efficacy and safety of tasimelteon capsules in patients with other types of sleep-related disorders.
Note: Examples include shift work disorder, jet lag disorder, advanced sleep phase disorder, delayed sleep phase disorder, irregular sleep-wake rhythm disorder.

References

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Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes.	4/1/2025
Early Annual Revision	**Updated Coverage Policy Title:** Changed from "*Tasimelteon*" to "*Tasimelteon Products*." **Non-24-Hour Sleep-Wake Disorder (Non-24):** Removed Hetlioz LQ. **Employer Plans:** **Added** *Preferred Products* box table with medical necessity criteria for coverage of brand Hetlioz.	1/1/2026
Annual Revision	**Sedative Hypnotic Medications or Other Medications for Insomnia or Other Sleep-Related Disorders, Concomitant Therapy:** In this Condition Not Recommended for Approval, examples of applicable medications were moved to a Note. **Sleep-Related Disorders, Other Types:** In this Condition Not Recommended for Approval, examples of applicable disorders were moved to a Note.	5/1/2026

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