# PRIOR AUTHORIZATION POLICY

**POLICY:** Tasimelteon Products Prior Authorization Policy
- Hetlioz™ (tasimelteon capsules – Vanda, generic)
- Hetlioz LQ™ (tasimelteon oral suspension – Vanda)

**REVIEW DATE:** 01/17/2024

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## 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 who reported no light perception with Non-24 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 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 of 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) 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.

## POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tasimelteon capsules. 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.

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

**Automation:** None.

## RECOMMENDED AUTHORIZATION CRITERIA

**I.** Coverage of tasimelteon capsule is recommended in those who meet the following criteria:

### 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 conditions (A or B):

**A)** Initial Therapy. Approve for 6 months if the patient meets all of the following (i, ii, iii, iv, and v):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient is totally blind with no perception of light; AND
- **iii.** Diagnosis of Non-24 is confirmed by meeting ONE of the following conditions (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 conditions (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 according to the prescriber; 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.

**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; AND
- **iii.** Patient meets both of the following conditions (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 sleep disorders; AND
  - **b)** Patient had inadequate efficacy with melatonin therapy according to the prescriber; 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 conditions (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 1 (initial therapy).
  - **b)** Patient has achieved adequate results with tasimelteon capsules therapy according to the prescriber; 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.

**II.** Coverage of Hetlioz LQ is not recommended.

## CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of tasimelteon /Hetlioz LQ is not recommended in the following situations:

1. **Insomnia, Primary.** Many other agents are available.[10] 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).** Efficacy data for Hetlioz/Hetlioz LQ supporting benefits for nighttime sleep disturbances in SMS are underwhelming.[1,17]

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 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.[6] 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.[13]

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.[14] Further studies are needed to establish the efficacy and safety of Hetlioz in patients with other types of sleep-related disorders.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## REFERENCES

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