PRIOR AUTHORIZATION POLICY

POLICY: Hetlioz Prior Authorization Policy
- Hetlioz™ (tasimelteon capsules – Vanda Pharmaceuticals)
- Hetlioz LQ™ (tasimelteon oral suspension – Vanda Pharmaceuticals)

REVIEW DATE: 01/27/2021

OVERVIEW

Hetlioz/Hetlioz LQ, melatonin receptor agonists, are indicated for the following uses:[1]
- Hetlioz is indicated for the treatment of:
  - **Non-24-Hour Sleep-Wake Disorder** (Non-24).
  - **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 and the prevalence of non-entrained rhythms in totally blind patients is 55% to 70%.[2-7] It has been estimated that of the 1.3 million people in the US who are blind, 10% of people have no light perception, a risk factor for this disorder, and reports suggest that as many as one-half to three-quarters of totally blind patients have Non-24, which is approximately 65,000 to 95,000 Americans.[6] 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).[2,7-8] Alternative forms of diagnosis include actigraphy and assessment of sleep logs (sleep diaries).[2,7-8] 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.[7-8]

SMS is a rare disorder identified by an array of physical, neurobehavioral, and developmental characteristics.[14] In the United States, the incidence is estimated to be 1 in 15,000 to 25,000 people in the general population. Predominately cases of SMS are related to either a deletion or mutation in the *RAI1* gene. It affects males and females equally and is found in ethnic groups all over the world. Common symptoms comprise of distinctive facial features, skeletal malformations, varying degrees of intellectual disability, speech and motor delays, sleep disturbances, and self-injurious/attention-seeking behaviors. 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.[1-2] Patients were ≥ 18 years of age and could be enrolled if they had a non-24-hour tau of 24.25 hours or longer as calculated from the rhythm of urinary 6-sulphatoxymelatonin (aMT6s), the major melatonin metabolite. At Month 1, more patients receiving Hetlioz (20%, n = 8/40) were entrained compared with patients randomized to placebo (3%, n = 1/38) [P = 0.0171].[2] Entrainment is defined as the synchronization of the circadian rhythm of the body to the 24-hour day.[2-5] 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 compared with 20% of patients randomized to receive placebo (n = 2/10) [P = 0.0026].[2-3]

The role of Hetlioz and Hetlioz LQ for nighttime sleep disturbances in SMS is extremely limited.[1] Data supporting benefits with these agents are lacking and underwhelming. The pivotal trial for SMS is unpublished, 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 (AASM) that addresses non-24-hour sleep-wake rhythm disorder (N24SWD).[5] The guidelines state the N24SWD occurs when the hypothalamic circadian pacemaker does not entrain (synchronize) to the 24 hour day. Patients may experience periodic nighttime insomnia and daytime somnolence as the circadian rhythms of sleep propensity and alertness drift in and out of synchrony with the usual 24-hour day. The condition mainly occurs in patients who are blind. The Task Force state that there is no evidence to support the use of sleep-promoting medications in patients with N24SWD. Data suggests that melatonin entrainment occurs with melatonin at a greater rate than placebo and melatonin can be an effective treatment for N24SWD. The Task Force recommendation was that clinicians use strategically timed melatonin for the treatment of N24SWD in adults who are blind (versus no treatment). There are insufficient data to support use of melatonin among sighted patients with N24SWD (versus no treatment).

The Parents and Researchers Interested in Smith-Magenis Syndrome (PRISMS) created medical management guidelines for the diagnosis, treatment of manifestations, and ongoing surveillance of SMS.[15] The guidelines do not address Hetlioz/Hetlioz LQ. Multidisciplinary treatment with multimodal options provided by practitioners from different disciplines are 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 Hetlioz/Hetlioz LQ. 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 Hetlioz/Hetlioz LQ as well as the monitoring required for adverse events and long-term efficacy, approval requires Hetlioz/Hetlioz LQ to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Hetlioz capsules are recommended in those who meet the following criteria:

FDA-Approved Indications

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 criteria (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 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 Hetlioz. Approve for 1 year if the patient meets all of the following criteria (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 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 conditions (a and b):

a) Patient has received at least 6 months of continuous therapy (i.e., 6 consecutive months of daily treatment) with Hetlioz under the guidance of a physician who specializes in the treatment of sleep disorders; AND
Note: Patients who have not received at least 6 months of continuous Hetlioz therapy, or if the therapy has not been continuous (i.e., 6 consecutive months of daily treatment), should follow criteria 1 (initial therapy).

b) Patient has achieved adequate results with Hetlioz therapy according to the prescriber; AND
Note: Examples of adequate results with Hetlioz 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Hetlioz/Hetlioz LQ is not recommended in the following situations:

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).** Efficacy data for Hetlioz/Hetlioz LQ for nighttime sleep disturbances in SMS supporting benefits with these agents are lacking and underwhelming.[1] The pivotal trial included few patients and is unpublished (limited to the prescribing information).

3. **Ramelteon tablets (Rozerem™, generics), Concomitant Therapy.** Ramelteon tablets, a melatonin receptor agonist, are 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). Rozerem 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.

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

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