

## PRIOR AUTHORIZATION POLICY

**POLICY:** Hetlioz™ (tasimelteon capsules – Vanda Pharmaceuticals)

**TAC APPROVAL DATE:** 04/17/2019

---

### OVERVIEW

Hetlioz, a melatonin receptor agonist, is indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24).<sup>1</sup> 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%.<sup>2-7</sup> 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.<sup>6</sup> 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).<sup>2,7-8</sup> Alternative forms of diagnosis include actigraphy and assessment of sleep logs (sleep diaries).<sup>2,7-8</sup> 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.<sup>7-8</sup> The recommended dosage of Hetlioz is 20 mg once daily (QD) taken before bedtime at the same time every night.<sup>1</sup> Take Hetlioz without food. The most common adverse events (AEs) with Hetlioz include headache (17%), alanine aminotransferase increases (10%), and nightmares or abnormal dreams (10%). Hetlioz has a Warning and Precaution regarding somnolence and that it can potentially impair performance if doing activities that require complete mental alertness.<sup>1</sup>

### Clinical Efficacy

The efficacy of Hetlioz was established in two, Phase III, randomized, placebo-controlled, double-masked, multicenter trials pivotal studies involving totally blind patients who reported no light perception with Non-24. SET (Safety and Efficacy of Tasimelteon) [n = 84] evaluated Hetlioz for up to 6 months and RESET (Randomized withdrawal study of the Safety and Efficacy of Tasimelteon) evaluated the effects of Hetlioz withdrawal.<sup>1-2</sup> Patients in SET were aged 18 to 75 years 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. Upon completion of SET, patients were offered continued participation in RESET.<sup>2</sup> In SET, patient diaries were used for an average of 88 days during screening and 133 days during randomization.<sup>1-2</sup> 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].<sup>2</sup> Entrainment is defined as the synchronization of the circadian rhythm of the body to the 24-hour day.<sup>2-5</sup> The patient's circadian rhythm is calculated by various measures, the most common of which includes assessing a melatonin metabolite in the urine.<sup>3-5</sup> The step down endpoint of the clinical response rate demonstrated that 24% of patients given Hetlioz (n = 9/38) became entrained and reached a Non-24 Clinical Response Scale (N24CRS) score  $\geq 3$  compared with none of the patient given placebo (P = 0.0028).<sup>2</sup> In the Hetlioz group, 29% of patients (n = 12) met responder criteria, defined as patients with both a  $\geq 45$  minute increase in nighttime sleep and a  $\geq 45$  minute decrease in daytime nap time, compared with 12% of patients (n = 5) who received placebo (time of endpoint assessment not stated).<sup>1</sup> The RESET trial (n = 20) involved patients who received Hetlioz for 12 weeks and became entrained.<sup>1-3</sup> 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].<sup>2-3</sup>

### **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).<sup>5</sup> 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).

### **POLICY STATEMENT**

Prior authorization is recommended for prescription benefit coverage of Hetlioz. Because of the specialized skills required for evaluation and diagnosis of patients treated with Hetlioz in Non-24, approval requires Hetlioz to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 12 months in duration unless otherwise noted below.

**Automation:** None.

### **RECOMMENDED AUTHORIZATION CRITERIA**

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

#### **Food and Drug Administration (FDA)-Approved Indications**

- 1. Non-24-Hour Sleep Wake Disorder (Non-24), Initial Therapy.** Approve for 6 months if the patient meets all of the following criteria (A, B, C, D, and E):
  - A)** The patient is  $\geq 18$  years of age; **AND**
  - B)** The patient is totally blind with no perception of light; **AND**
  - C)** The medication is prescribed by, or in consultation with, a physician who specializes in the treatment of sleep disorders; **AND**
  - D)** The diagnosis of Non-24 is confirmed by meeting **ONE** of the following conditions (i or ii):
    - i.** Assessment of at least one physiologic circadian phase marker (e.g., measurement of urinary melatonin levels, dim light melatonin onset [as measured in blood or saliva], assessment of core body temperature); **OR**
    - ii.** If assessment of at least one physiologic circadian phase marker cannot be done, the diagnosis must be confirmed by actigraphy performed for  $\geq 1$  week plus evaluation of sleep logs recorded for  $\geq 1$  month; **AND**
  - E)** The patient meets both of the conditions below (i and ii):
    - i.** The 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**
    - ii.** The patient did not achieve adequate results with melatonin therapy according to the prescribing physician (e.g., entrainment, clinically meaningful or significant increases in nighttime sleep, clinically meaningful or significant decreases in daytime sleep).

- 2. Non-24-Hour Sleep Wake Disorder (Non-24), Continuation Therapy.** Approve for 12 months if the patient meets all of the following criteria (A, B, C, D, and E):
- A) The patient is  $\geq 18$  years of age; AND
  - B) The patient is totally blind with no perception of light; AND
  - C) The medication is prescribed by, or in consultation with, a physician who specializes in the treatment of sleep disorders; AND
  - D) The 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 (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]); AND
  - E) The patient has achieved adequate results with Hetlioz therapy according to the prescribing physician (e.g., entrainment, clinically meaningful or significant increases in nighttime sleep, clinically meaningful or significant decreases in daytime sleep).

### CONDITIONS NOT RECOMMENDED FOR APPROVAL

Hetlioz has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Insomnia, Primary.** Many other agents are available.<sup>9</sup> Only limited data have investigated use of Hetlioz in patients with primary insomnia.<sup>10</sup> Further data are needed to establish the safety and efficacy of Hetlioz.
  2. **Rozerem™ (ramelteon tablets), Concomitant Therapy.** Rozerem is a melatonin receptor agonist indicated for the treatment of insomnia characterized by difficulty with sleep onset.<sup>11</sup> The safety and efficacy of concomitant use of Rozerem and Hetlioz have not been studied and it is suspected that the AEs 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.
  3. **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.<sup>5</sup> Also, there are not 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.<sup>12</sup>
  4. **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.<sup>13</sup> Further studies are needed to establish the efficacy and safety of Hetlioz in patients with other types of sleep-related disorders.
  5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.
-

## REFERENCES

1. Hetlioz™ [prescribing information]. Washington, DC: Vanda Pharmaceuticals; December 2014.
2. Lockley SW, Dressman MA, Licanele L, et al. Tasimelteon for non-24-hour sleep-wake disorder in totally blind people (SET and RESET): two multicenter, randomized, double-masked, placebo-controlled phase 3 trials. *Lancet*. 2015;386:1754-1764.
3. Keating GM. Tasimelteon: a review in non-24-hour sleep-wake disorder in totally blind individuals. *CNS Drugs*. 2016 Mar 22. [Epub ahead of print].
4. American Academy of Sleep Medicine. International Classification of sleep disorders: diagnostic and coding manual. 3<sup>rd</sup> edition. Darien (IL): American Academy of Sleep Medicine; 2014.
5. Auger RR, Burgess HJ, Emens JS, et al. Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: Advanced Sleep-Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Irregular Sleep-Wake Rhythm Disorder (ISWRD). An update for 2015. *J Clin Sleep Med*. 2015;11(10):1199-1236. Available at: <http://www.aasmnet.org/Resources/Clinicalguidelines/CRSWD-intrinsic.pdf> Accessed on April 10, 2019.
6. National Sleep Foundation [Internet]. Non-24-hour Sleep Wake Disorder Facts and Prevalence. Available at: <https://sleepfoundation.org/non-24/content/facts-prevalence>. Accessed on April 10, 2019.
7. Uchiyama M, Lockley SW. Non-24-Hour Sleep-Wake Rhythm Disorder in Sighted and Blind Patients. *Sleep Med Clin*. 2015;10:495-516.
8. Morgenthaler T, Alessi C, Friedman L, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. *Sleep*. 2007;30(4):519-529. Available at: [http://www.aasmnet.org/Resources/PracticeParameters/PP\\_Actigraphy\\_Update.pdf](http://www.aasmnet.org/Resources/PracticeParameters/PP_Actigraphy_Update.pdf). Accessed on April 10, 2019.
9. Winkelman JW. Insomnia disorder. *N Engl J Med*. 2015;373:1437-1444.
10. Feeney J, Birznieks G, Scott C, et al. Melatonin agonist tasimelteon improves sleep in primary insomnia characterized by difficulty falling asleep. *Sleep*. 2009;32(Suppl):43.
11. Rozerem™ tablets [prescribing information]. Deerfield, IL: Takeda; December 2018.
12. No authors listed. Drugs for insomnia. *Treat Guidel Med Lett*. 2012;10(119):57-60.
13. Rajartnam SMW, Polymeropoulos MH, Fisher DM, et al. Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomized controlled multicenter trials. *Lancet*. 2009;373:482-491.

## OTHER REFERENCES UTILIZED

- Emens JS, Eastman CI. Diagnosis and treatment of non-24-h sleep-wake disorder in the blind. *Drugs*. 2017;77:637-650.
- Williams WP, McLin DE, Dressman MA, Neubauer DN. Comparative review of approved melatonin agonists for the treatment of circadian rhythm sleep-wake disorders. *Pharmacotherapy*. 2016;36(9):1028-1041.
- Smith M, McCrae C, Cheung J, et al. Use of actigraphy for the evaluation of sleep disorders and circadian rhythm sleep-wake disorders. *Journal of Clinical Sleep Medicine*. 2018;14(7):1209–1230.

## HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Integrated policy	New policy	04/02/2014
Annual revision	No criteria changes	04/08/2015
Annual revision	No criteria changes.	04/13/2016
Annual revision	No criteria changes.	04/12/2017
Annual revision	No criteria changes.	04/17/2019

TAC – Therapeutic Assessment Committee; \* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>.