OVERVIEW

Hetlioz, a melatonin receptor agonist, is indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24). 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. 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. The recommended dosage of Hetlioz is 20 mg once daily (QD) taken before bedtime at the same time every night. 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.

The efficacy of Hetlioz was established in two pivotal studies involving totally blind patients with Non-24. The SET (Safety and Efficacy of Tesimelteon) trial (unpublished) [n = 84] evaluated Hetlioz for up to 6 months. At Month 1, more patients receiving Hetlioz were entrained compared with patients randomized to placebo (P = 0.0171). Entrainment is defined as the synchronization of the circadian rhythm of the body to the 24-hour day. The patient’s circadian rhythm is calculated by various measures, the most common of which includes assessing a melatonin metabolite in the urine. 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). The RESET (Randomized withdrawal study of the Efficacy and Safety of Tesimelteon) trial (unpublished) [n = 20] involved patients who received Hetlioz for 12 weeks and became entrained. 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].

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.

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 ≥ 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 ≥ 1 week plus evaluation of sleep logs recorded for ≥ 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 ≥ 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 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).

Approval Duration

Initial Approval = 180 Days
Re-authorization = 365 Days

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. Only limited data have investigated use of Hetlioz in patients with primary insomnia. 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. 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 evaluate the safety and efficacy of hypnotic medications in patients who are blind with Non-24. 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.

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. 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**

- Rozerem™ tablets [prescribing information]. Deerfield, IL: Takeda; November 2010.