Hetlioz (tasimelteon)
Policy Number: C8920-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
4/2016	7/31/2019	7/31/2020
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
J8499 (NOC)	RxPA	Q3 2019 20190828C8920-A

PRODUCTS AFFECTED:
Hetlioz (tasimelteon)

DRUG CLASS:
Selective Melatonin Receptor Agonists

ROUTE OF ADMINISTRATION:
Oral

PLACE OF SERVICE:
Specialty Pharmacy

AVAILABLE DOSAGE FORMS:
Hetlioz CAPS 20MG

FDA-APPROVED USES:
Non-24-hour sleep-wake disorder: For the treatment of non-24-hour sleep-wake disorder (non-24) in patients that are completely blind and have difficulties falling asleep, staying asleep, or who feel drowsy upon wakening.

COMPENDIAL APPROVED OFF-LABELED USES: None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS: Diagnosis of Non-24-Hour Sleep-Wake Disorder

REQUIRED MEDICAL INFORMATION:
A. NON-24 HOUR SLEEP-WAKE DISORDER (N24SWD):

1. Diagnosis of Non-24-Hour Sleep-Wake Disorder [also referred to as free-running disorder (FRD), free-running or non-entrained type circadian rhythm sleep disorder, or hypernychthemeral syndrome] as confirmed by a specialist in sleep medicine based on current practice parameters for the diagnosis of N24SWD. Prescriber submit documentation (i.e. lab tests, clinician-performed evaluations and/or measurements, sleep studies, sleep logs, etc.) confirming diagnosis [NOTE: Diagnosis of insomnia, other circadian rhythm sleep disorders and depression do NOT meet criterion.]
   AND
2. Member is totally blind; defined by the inability to perceive light (completely blind with NO light perception). Documentation confirming member's total blindness
   AND

3. Sleep disturbance is not attributed to concomitant sleep disorder (i.e. sleep apnea, insomnia) medical or neurological disorder, mental disorder, medication use, or substance abuse disorder
   AND
4. History of failure* of at least 6 months of continuous therapy (i.e., uninterrupted daily treatment) or contraindication or intolerance to melatonin or Rozerem
   *Failure defined as: Lack of improvement in overall sleep quality or inadequate results (e.g., entrainment, clinically meaningful or significant increases in nighttime sleep, clinically meaningful or significant decreases in daytime sleep)
   AND
6. Hetlioz (tasimelteon) will not be used concurrently with melatonin or ramelteon (Rozerem), Strong CYP1A2 inhibitors (e.g., fluvoxamine) OR Strong CYP3A4 inducers (e.g., rifampin) melatonin

DURATION OF APPROVAL: Initial authorization: 6 months, Continuation of therapy: 6 months

QUANTITY:
Quantity limit: Dose does not exceed 20 mg daily (1 capsule per day)
Dispensing limit: Only a 1-month supply may be dispensed at a time (30 capsules per 30 days)

PRESCRIBER REQUIREMENTS: Prescribed by, or in consultation with, a board certified sleep medicine specialist OR physician who specializes in the treatment of sleep disorders. Submit consultation notes if applicable.

AGE RESTRICTIONS:
18 years of age or older

GENDER:
Male and female

CONTINUATION OF THERAPY:
1. Adherence to therapy at least 95% of the time [must be continuous without any gaps in treatment and must fill the prescription to have enough medication at least 28.5 days or more for each month] as verified by Prescriber and member's medication fill history (review Rx history for compliance)
   AND
2. Positive response or improvement on therapy: Objective evaluation of the patient's sleep quality. Documentation of an improvement in overall sleep quality while taking Hetlioz required, including but not limited to entrainment, significant increase in nighttime sleep, and/or significant decreases in daytime sleep

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Hetlioz (tasimelteon) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

OTHER SPECIAL CONSIDERATIONS:

BACKGROUND:

Non-24-Hour Sleep-Wake Rhythm Disorder (**N24SWD)** (*also known as free-running disorder, free-running or non-entrained type circadian rhythm sleep disorder, or hypernychthemeral syndrome*) is a chronic primary circadian rhythm sleep disorder (CSRD) that alters sleep patterns, causes daytime sleepiness, and results in impaired social and occupational functioning. Non-24 occurs primarily among blind individuals, though some sighted persons have the disorder also. Most blind individuals perceive enough light to prevent non-24; however, some have no light perception. Since light cannot enter their eyes, people with N24SWD cannot synchronize or "entrain" the suprachiasmatic nucleus. The presence of light in the daytime stimulates the SCN to inhibit melatonin secretion from the pineal gland, while the absence of light at night stimulates melatonin secretion. Thus, in absence of any light, the SCN cannot set the circadian "body clock" to a 24-hour light-dark cycle.

N24SWD is a circadian rhythm disorder occurs most commonly in blind patients with no light perception. It occurs when the individual's own biologic circadian period is not aligned to the external 24-hour environment. External cues, primarily the light/dark cycle which normally entrains the circadian rhythm to the 24-hour clock is absent in individuals with no light perception. Due to absence of input from environmental light to the eyes in patients with no light perception, it causes a constant gradual shifting of the sleep-wake cycle approximately 30 minutes each day thus returning to re-alignment with the 24-hour clock only once every 48 days. Due to the lack of entrainment of the circadian rhythm, patients with no light perception suffer from sleep deprivation resulting in long periods of excessive daytime sleepiness, nighttime insomnia, alterations in secretion of melatonin and cortisol, and impairment of social and occupational functioning.

There are approximately 1,300,000 blind people in the United States. Ten percent of these individuals have no light perception.[H] The estimated prevalence of non-24 in the totally blind is approximately 100,000 individuals in the U.S. Disturbances in people who are blind are common, and approximately 50% may have Non-24 according to the American Academy of Neurology. [C]

Diagnosis

The American Academy for Sleep Medicine CSRD practice parameters recommend (based on consensus) sleep logs to determine sleep patterns and also recommend measurement of circadian phase markers (including the urinary biomarker 6-sulfatoxy-melatonin or aMT6s) to determine the circadian phase (τ) and confirm the diagnosis.

- Entrainment is a measure of synchronization of an individual's intrinsic master clock (τ) to the 24-hour day. Entrainment can be measured by 2 distinct circadian rhythms: melatonin (or aMT6s in urine), and cortisol.
- For aMT6s measurement, urine is collected every 4 hours (every 8 hours overnight) over a 48-hour period and the acrophase, or peak timing of analyte secretion, determined. Quartile-nighttime Total Sleep Time (LQ-nTST), Upper Quartile-daytime Total Sleep Duration (UQ-dTSD), Midpoint of Sleep Time (MoST), and Clinician Global Impression- Change (CGI-C) assessments. Q-nTST and UQ-dTSD correlate with the most symptomatic phases of circadian cycle (maximum misalignment), reflecting the 25% most symptomatic days of nighttime sleeplessness or daytime sleepiness, respectively.
- The CGI-C is a 7-point clinician-performed evaluation of global functioning ranging from 1 (very much improved) to 7 (very much worse). Each assessment on the scale is scored as a 1 or 0 depending on whether the prespecified threshold was achieved or not. The score for each assessment is summarized with a range of 0 to 4.

Pivotal Trials

Efficacy for tasimelteon consists of 2 distinct pivotal trials called SET (N=84) and RESET (N=20). Both were randomized, placebo-controlled, double-blind trials with an overlapping patient population in totally blind patients with a diagnosis of Non-24.[a]

Study 1 and Study 2 evaluated the duration and timing of nighttime sleep and daytime naps via patient-recorded diaries.

Because symptoms of nighttime sleep disruption and daytime sleepiness are cyclical in patients with Non-24, with severity varying according to the state of alignment of the individual patient's circadian rhythm with the 24-hour day (least severe when fully aligned, most severe when 12 hours out of alignment), efficacy endpoints for nighttime total sleep time and daytime nap duration were based on the 25% of nights with the least nighttime sleep, and the 25% of days with the most daytime nap time.

Treatment with tasimelteon resulted in an improvement, compared with placebo, for both of these end points in both SET and RESET.

Tasimelteon was generally well-tolerated in SET and RESET. Adverse effects that occurred in at least 5% of patients in the tasimelteon group and at a two-fold higher rate than placebo were headache (17% vs. 7%), increased alanine aminotransferase (10% vs. 5%), nightmare/abnormal dreams (10% vs. 0%), upper respiratory tract infection (7% vs. 0%), and urinary tract infection (7% vs. 2%). There were no withdrawal symptoms, next day residual effect, or increase in suicidality observed in patients receiving tasimelteon.

Study1:SET(SafetyandEfficacyofTesimelteon)

Randomized, double-blind, placebo-controlled, multicenter, phase 3 study

The SET trial evaluated Hetlioz in 84 patients with non-24 compared tasimelteon and placebo for 6 months.; 84 patients (n=84) with non-24-hour sleep-wake disorder (median age, 54 years) were randomized to receive tasimelteon 20 mg or placebo, one hour prior to bedtime, at the same time every night for up to 6 months.[a]

Design: Phase III, multicenter, randomized, double-masked, placebo-controlled trial conducted between August 2010 and October 2012. Patients ineligible for randomization or unable to complete the trial could elect to participate in the open-label extension phase.

Objective: To investigate the safety and efficacy of tasimelteon in patients with Non-24

Population: 84 totally blind patients, 18 to 75 years of age, with confirmed Non-24 6-sulfatoxymelatonin rhythms (tau at least 24.25 hours) and history of sleep disturbance. Mean age was 50.7 years (range, 23 to 74 years), 83% were white, and 58% were male. Mean tau was 24.47 hours (circadian cycle lengths ranged from 30 to 114 days corresponding to tau 24.21 to 24.8 hours). Average nighttime sleep time was 3.25 hours in the worst 25% of nights (lower quartile of nighttime total sleep time [LQ-nTST]) and 5.33 hours overall and average daytime sleep time was 2.41 hours in the worst 25% of days (upper quartile of daytime total sleep duration [UQ-dTSD]) and 0.92 hours overall.

Primary endpoint: Significantly more patients treated with tasimelteon 20mg (8/40) compared to placebo (1/38) achieved entrainment measured by aMT6s in one month (20% vs 2.6%, p=0.0171)

Result: Significantly more tasimelteon-treated patients (20% vs. 3%) achieved entrainment (synchronization) of the circadian rhythm as measured by urine levels of a melatonin metabolite. Mean total nighttime sleep was 28 minutes longer and daytime nap time was 27 minutes shorter in patients taking tasimelteon than in patients taking placebo.[1]

In totally blind patients, tasimelteon, compared with placebo, significantly increased nighttime sleep (50 vs. 22 minutes) and significantly decreased daytime napping (49 vs. 22 minutes) compared with baseline.

The duration and timing of night-time sleep and daytime naps were evaluated using patient-recorded diaries. At month 1, more patients receiving Hetlioz were entrained (20%) compared with patients randomized to placebo (2.6%, p=0.0171).

Twenty-two patients did not complete the study: adverse events (n=6), protocol deviation (n=1), withdrawal of consent (n=5), and unsatisfactory response (n=1); travel issues (n=1); study closed by sponsor but patients had adequate data for primary and secondary endpoints in the double-masked phase (n=8; 4-tasimelteon; 4 placebo).

Adverse reactions with tasimelteon compared with placebo included headache (17% vs. 7%), increased ALT (10% vs. 5%), abnormal dreams (10% vs. 0%), upper respiratory tract infection (7% vs. 0%), and urinary tract infection (7% vs. 2%).

Conclusions

Entrainment of the circadian rhythm to a 24-hour day was achieved in 20% of the patients taking tasimelteon compared to 2.6% with placebo as measured by aMT6s by the first month. Assessing entrainment early per trial design may underestimate the entrainment rate effect.

Entrainment of the circadian rhythm to a 24-hour day was achieved in 17.5% of the patients taking tasimelteon compared to 2.6% with placebo as measured by cortisol by the first month.

Tasimelteon had a clinically meaningful improvement as measured by the assessment of clinical response and the Non-24 Clinical Response Scale

Tasimelteon once daily was generally well-tolerated and safe in the studied population. The majority of adverse events were mild or moderate and discontinuation due to adverse events was similar between treatment groups.

Study2:RESET(RandomizedwithdrawalstudyoftheEfficacyandSafEtyofTesimelteon)

Randomized, double-blind, placebo-controlled, multicenter, phase 3 study

Design: Phase III, multicenter, randomized withdrawal, double-masked, placebo-controlled, parallel group designed to determine the long-term maintenance effect and safety of tasimelteon 20 mg in patients with Non-24. The study consisted of two phases: 1) open label pre-randomization phase (~12 weeks), and 2) placebo-controlled randomized withdrawal phase (~8 weeks).

Objective: Demonstrate effectiveness and safety of tasimelteon 20mg in maintaining entrainment when treatment was withdrawn.

Population: Patients meeting inclusion criteria and who had previously participated in, or were screened for SET trial, were eligible to participate. Twenty entrained totally blind individuals (as defined by aMT6 rhythms) were randomized (aged 27-68 years; (mean age 51.7years; 60% male; 90% Caucasian, 5% African American, mean BMI 28.64 kg/m2; mean circadian rhythm= 24.0 hours). No demographic or patient characteristics differences between the two groups exist.

Primary End Point(s):

The primary endpoint of the RESET to treat N24SWD was the proportion of patients who did not maintain entrainment of an aMT6s rhythm to 24 hours after therapy was withdrawn.

Twenty blind patients (median age 54 years) with N24SWD were randomized.

The discontinuation of therapy following achievement of entrainment caused a loss in circadian rhythm synchronization in 80% of patients within 8 weeks.

In totally blind patients treated with tasimelteon, continued maintenance therapy with tasimelteon, compared with placebo, produced significant differences in nighttime sleep (-7 vs. -74 minutes) and daytime napping (-9 vs. +50 minutes) compared with baseline.

Conclusion

Discontinuation of tasimelteon therapy resulted in a loss of entrainment that corresponded with an approximately 50 minute decrease in nighttime sleep and 60 minute increase in daytime napping.
Chronic therapy with tasimelteon is required to maintain entrainment in totally blind patients with Non-24

GUIDELINES

The International Classification of Sleep Disorders defines non-24-hour sleep wake disorder as a circadian rhythm sleep disorder characterized by complaints of insomnia or excessive sleepiness related to abnormal synchronization between the 24-hour light–dark cycle and the endogenous circadian rhythms of sleep and wake propensity. Patients with non-24 experience a steady pattern composed of 1- to 2-hour daily delays in sleep onset and wake times. More than half of all totally blind individuals have non-24. The lack of sight and the ability of light cues to be given to the brain prevent synchronization of the sleep-wake cycle by the suprachiasmatic nucleus of the hypothalamus in the brain.[A]

The National Organization for Rare Disorders (NORD) states that the condition is characterized by the failure of a person's biological clock to synchronize to a 24-hour day light-dark cycle because light does not enter their eyes. Those with the disorder may have difficulty falling or staying asleep, and may wake up feeling as if they need more rest. People with non-24 may find their sleep patterns reversed (e.g., needing to sleep during the day and to be awake at night). Due to differences in circadian rhythms, it can take weeks or months of daily use of tasimelteon before the patient experiences any benefit.

Melatonin

American Academy of Neurology (2013) review on circadian rhythm disorders suggests that melatonin is the therapeutic mainstay in blind patients with Non-24, together with strong structured behavioral and social cues (e.g., timing of meals, planned activities, and regular physical exercise).[C] This same approach is recommended for sighted persons, with the additional option of bright light exposure in the morning shortly after awakening.

Although the dose of melatonin for the treatment of Non-24 varies among studies, a practical recommendation is to start with a higher dose (3 mg to 10 mg) 1 hour before bedtime or a few hours before predicted melatonin onset measured in a dim light environment for the first month. Entrainment usually occurs within 3 to 9 weeks but must be maintained by regular low-dose (0.5 mg) melatonin to prevent a relapse. If the initiation dose fails, an alternate method is a 0.5-mg dose over a period of several months. Most blind patients whose circadian period is close to 24 hours can maintain entrainment with very low nightly doses of 20 µg to 300 µg. Evidence from case reports suggests that a combination of timed melatonin doses of 0.5 mg to 5.0 mg taken nightly at 9:00 PM, exposure to bright light, and a regular sleep-wake schedule is successful in entraining these patients.

The American Sleep Disorder Association considers melatonin an experimental drug and does not recommend its use without medical supervision. Melatonin has been classified as an orphan drug by the US FDA since 1993 for circadian rhythm sleep disorders in blind patients who have no light perception. Melatonin is also available over the counter (OTC) in the US, and products are marketed under the Dietary Supplement and Health Education Act of 1994 (DSHEA). In Europe melatonin is available by prescription only.[F,G]

A meta-analysis with the critical outcome of entrainment using melatonin was included in the recent American Academy of Sleep Medicine Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders.[3]

Three placebo-controlled, crossover studies using timed oral melatonin for patients with N24SWD (n=36) were included in the meta-analysis. The dose of melatonin studied included 0.5mg, 5 mg, and 10mg and the duration of melatonin treatment ranged from 26-81 days. The odds ratio for entrainment was 21.18 (95% CI 3.22-139.17) in favor of melatonin.

Although the quality of evidence was low and the strength of the recommendation was weak for, the recommendation that clinicians use strategically timed melatonin for the treatment of N24SWD in blind adults (versus no treatment) was made based on the assessment of evidence, benefits versus harms analyses, and patient values and preferences.

APPENDIX:

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