Subject: Hetlioz (tasimelteon)	Original Effective Date: 4/26/2016
Policy Number: MCP-273	Revision Date(s):
Review Date(s):	

DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION STATEMENTS

This policy addresses the coverage of Hetlioz (tasimelteon) for the treatment of non-24-hour sleep-wake disorder (non-24) when appropriate criteria are met.

The intent of this policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies.

- Tasimelteon is a melatonin receptor agonist and is indicated to treat non-24-hour sleep-wake disorder ("non-24") in totally blind individuals. Non-24-hour sleep-wake disorder ("non-24") is a chronic circadian rhythm disorder that causes problems with the timing of sleep and sleep patterns of people who are totally blind. Tasimelteon (Hetlioz) is an agonist of melatonin receptors MT1 and MT2 (greater affinity for the MT2 receptor than the MT1 receptor). Agonism of MT1 is thought to preferentially induce sleepiness, while MT2 receptor activation preferentially influences regulation of circadian rhythms.

- In January 2014, Hetlioz (tasimelteon) became the first drug approved by the FDA for the treatment of non-24. Tasimelteon is a melatonin agonist, which activates both MT1 and MT2 receptors. Entrainment of an individual's circadian clock allows sleep at the same time every night, leading to daytime wakefulness that corresponds to family members and caregivers they may be dependent upon. This ideally leads to an improvement in quality of life; however, this was not assessed in the clinical trials supporting tasimelteon's approval. **Due to the lack of active comparators in clinical trials, the value of tasimelteon is unknown compared with other available sleep aids.**

- The evidence was established from two small (n= 84, n=20), unpublished, randomized, placebo controlled trials (RCTs) in blind individuals that tasimelteon increases nighttime sleep on the worst 25% of nights by of 50 minutes and decreased daytime sleep on the worst 25% of days by 49 minutes.[j]

- **No head-to-head studies of tasimelteon vs. ramelteon or melatonin has been conducted.**

- The melatonin agonist, ramelteon (Rozerem), may be recommended in the treatment of Non-24 is due to its pharmacological and pharmacokinetic similarity to tasimelteon, in addition to its cost-effectiveness compared to the to Tasimelteon (Hetlioz), a specialty drug. However, ramelteon has never been studied in patients with Non-24.

  Melatonin Agonists
  There are two melatonin agonists currently available on the market, ramelteon (Rozerem) and tasimelteon (Hetlioz). Both drugs were approved after the most recent AASM guidelines were released.[B]

  Ramelteon (Rozerem): Ramelteon is currently only FDA-approved for the treatment of insomnia and has not been studied in patients with Non-24. Common side effects include somnolence, dizziness, fatigue, nausea, and exacerbated insomnia.[k]

  Ramelteon has a high affinity for melatonin receptors 1 and 2 (MT1 and MT2) with full agonistic activity at these receptors.[k] MT1 and MT2 receptors are thought to play a significant role in regulating the circadian rhythm and sleep-wake cycle. Ramelteon's major metabolite, M-II, also has activity at the M1 and M2 receptors but at a significantly lower binding affinity than the parent drug. M-II is also much less potent than ramelteon but circulates at higher concentrations, providing greater systemic exposure than ramelteon. After fasting administration, ramelteon peaks in 30 minutes to 1.5 hours with an elimination half-life of 1 to 2.6 hours.

  Tasimelteon (Hetlioz): In January 2014, the FDA approved tasimelteon specifically for the treatment of Non-24 in adults.[a]

  Tasimelteon is also an MT1 and MT2 receptor agonist with higher affinity for the MT2 receptor.20 In January 2014, the FDA approved tasimelteon specifically for the treatment of Non-24 in adults.21 Metabolites of tasimelteon have some affinity for the MT1 and MT2 receptors but at less than one-tenth the affinity of the parent drug. After fasting administration, tasimelteon peaks in 30 minutes to 3 hours with a mean elimination half-life of 1.3 hours. Tasimelteon should only be taken immediately before bedtime.[a]

CLASSIFICATION: Melatonin Receptor Agonist

FDA INDICATIONS

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.

Non-24 is a chronic circadian rhythm disorder that occurs in blind patients because they cannot synchronize their circadian rhythms to a light-dark cycle.

Note: Efficacy was established in totally blind patients with non-24-hour sleep-wake disorder.

Available as: 20mg capsule

FDA Approved: January 2014: The first product approved for the indication of non-24-hour sleep-wake disorder (non-24)
Tasimelteon has been designated an orphan drug by the FDA for this use.[b,l]

Black Box Warnings: *None at the time of this writing*
REMS: *None at the time of this writing*

RECOMMENDATIONS/COVERAGE CRITERIA

Hetlioz (tasimelteon) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ 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.
  NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ALL]

- ❒ 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.

  Note:
  - ➢ *The Diagnostic and Statistical Manual (DSM)-5 criteria for the diagnosis of N24SWD is based on a history of symptoms, daily sleep logs, and ruling out other medical or substance use disorders.*
  - ➢ *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.*

3. Age/Gender/Restrictions [ALL]

- ❒ 18 years of age or older
  - ➢ *The safety and effectiveness of the use of tasimelteon in children and adolescents under the age of 18 years of age has not been established.*

- ❒ Member is totally blind; defined by the inability to perceive light (completely blind with NO light perception). Documentation confirming member's total blindness.
  NOTE: Non-24 is a chronic circadian rhythm disorder that only affects totally blind individuals without light perception; therefore tasimelteon will <u>not</u> be authorized in sighted individuals or blind individuals with light perception. Tasimelteon has not been evaluated for the treatment of FRD in sighted individuals or blind individuals with light perception.

- ❒ Sleep disturbance is **<u>not</u>** attributed to concomitant sleep disorder (i.e. sleep apnea, insomnia) medical or neurological disorder, mental disorder, medication use, or substance abuse disorder

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ❒ Melatonin therapy is documented by ONE (1) of the following: [ONE]
  - ❍ History of contraindication or intolerance to **melatonin or Rozerem** therapy [C,F,G]
  - ❍ History of failure* of at least 6 months of ***continuous*** therapy (i.e., uninterrupted daily treatment) with **melatonin or Rozerem** under the ***policy of a specialist*** in sleep disorders.[C,F,G]
    *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)
- ❒ Hetlioz (tasimelteon) will not be used concurrently with melatonin or ramelteon (Rozerem)
  - ➢ *Due to pharmacologic similarities in action as melatonin-receptor agonists, tasimelteon should likely not be co-administered with melatonin or ramelteon. The actions would be expected to be duplicative, and might result in additive side effects. In a clinical trial, there was clear evidence for a transitory pharmacodynamic interaction between melatonin and another hypnotic agent one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and coordination compared to the hypnotic agent alone. Use of more than one agent for hypnotic purposes may increase the risk for over-sedation, CNS effects, or sleep-related behaviors.*

5. Contraindications*/Exclusions/Discontinuations

The FDA-approved prescribing information lists no contraindications to tasimelteon use.[a] However, coadministration of tasimelteon with strong inhibitors of CYP1A2 and strong inducers of CYP3A4 should be avoided.[a]

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to tasimelteon or any of its components

Exclusions [ANY]

- ❒ Severe hepatic impairment (Child-Pugh Class C)
  - ➢ *Use is not recommended in patients with severe hepatic impairment.[a]*
- ❒ Concomitant use with ANY of the following
  - ❍ Strong CYP1A2 inhibitors (e.g., fluvoxamine)
    - ➢ *Avoid co-administration of tasimelteon with a strong CYP1A2 inhibitor. Concomitant use of tasimelteon (a CYP1A2 substrate) with a strong CYP1A2 inhibitor may result in a potentially large increase in tasimelteon exposure and greater risk of related adverse events.*
  - ❍ Strong CYP3A4 inducers (e.g., rifampin)
  - ❍ melatonin
  - ❍ ramelteon (Rozerem)

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP are included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Hetlioz (tasimelteon) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria

- ❑ Member currently meets ALL initial coverage criteria
- ❑ Subsequent authorizations will require the Member to have an office visit and re-assessement for this condition annually to determine if continuation of treatment with requested medication is medically necessary. Chart notes or consultation notes (if applicable) must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Compliance

- ❑ 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), including:
  - ❍ Adherent to the prescribed regimen, including taking medication at the same time every night
  - ❍ Tolerance to therapy; no severe adverse reactions or drug toxicity

NOTE: Due to individual difference in circadian rhythms, daily use for several weeks or months may be necessary before entrainment of circadian rhythm is achieved. **Daily use is required to maintain entrainment of circadian rhythms.**
NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 95% has been demonstrated in at least two months during the course of therapy.
NOTE: History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile may result in continuation of therapy request not being authorized. [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY

3. Labs/Reports/Documentation required [ALL APPLICABLE]

- ❒ 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

4. Discontinuation of Treatment [ANY]
Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or drug toxicity
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❑ Contraindications/Exclusions to therapy
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to tasimelteon or any of its components
- ❒ Exclusions [ANY]
  - ❍ Severe hepatic impairment (Child-Pugh Class C)
  - ❍ Concomitant use with ANY of the following
    - o Strong CYP1A2 inhibitors (e.g., fluvoxamine)
    - o Strong CYP3A4 inducers (e.g., rifampin)
    - o melatonin or ramelteon (Rozerem)

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

1. Recommended Dosage [ALL]

- ❒ 20 mg (1 capsule) orally daily at bedtime, at the same time every night; take without food
  - ➢ *Due to individual differences in circadian rhythms, daily use for several weeks or months may be necessary before benefit from tasimelteon is observed.*

2. Authorization Limit [ALL]

- ❒ 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)
- ❒ Duration of initial authorization: **6 months**
  NOTE: An initial course of at least 6 months is recommended to determine efficacy in individuals. Discontinuation of therapy following achievement of entrainment causes a loss in circadian rhythm synchronization in 80% of patients within 8 weeks.[2]
- ❒ Continuation of treatment: Re-authorization for continuation of treatment is required every **6 months** to determine continued need based on documented positive clinical response

3. Route of Administration [ALL]

- ❒ Hetlioz (tasimelteon) is an oral, **self-administered** medication or administration by a caregiver (i.e., not a healthcare professional)..
- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.

COVERAGE EXCLUSIONS

This policy only addresses the indication of treatment of non-24-hour sleep-wake disorder (non-24) when appropriate criteria are met.

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.

SUMMARY OF EVIDENCE/POSITION STATEMENTS

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.

Study 1: SET (Safety and Efficacy of Tesimelteon)

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.

Study 2: RESET (Randomized withdrawal study of the Efficacy and SafEty of Tesimelteon)
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.

DEFINITIONS

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.

Melatonin (or aMT6s in urine): 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.

APPENDIX

N/A

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
NA	

HCPCS	Description
J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

REFERENCES

Package Insert, FDA, Drug Compendia

a. Hetlioz (tasimelteon) [prescribing information]. Washington, DC: Vanda Pharmaceuticals; December 2014.
b. American Hospital Formulary Service (AHFS). Drug Information 2016. [STAT!Ref Web site]. Available via subscription only.
c. Micromedex Healthcare Series. DrugDex. [Micromedex Web site]; 2016. Available via subscription only.
d. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2016. Available from Wolters Kluwer Health, Inc.
e. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2016. URL: http://www.clinicalpharmacology.com.
f. Lexi-Comp Online. (2016). AHFS DI. Retrieved January 2016 from Lexi-Comp Online with UpToDate Online.
g. American Society of Health System Pharmacists, Inc., DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. 906323, Tasimelteon; [updated 2015 Jan 13, cited place cited date here]; [about 4 screens]. Available from http://search.ebscohost.com/login.aspx?direct=true&db=dnh&AN=906323&site=dynamed-live&scope=site. Registration and login required.
h. Food and Drug Administration. Center for Drug Evaluation and Research. Medical Review. NDA 205677. Tasimelteon (Hetlioz). November 29, 2013. Accessed April 2016 at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205677Orig1s000MedR.pdf.

i. FDA News Release on Jan 31, 2014: FDA approves Hetlioz: first treatment for non-24 hour sleep-wake disorder in blind individuals. Available online at: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm384092.htm
j. U.S. Drug Food and Administration. Summary Review: NDA 205,677. 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205677Orig1s000SumR.pdf. Accessed April 2016
k. Rozerem [package insert]. Deerfield, IL: Takeda Pharmaceuticals America Inc; October 2008.
l. Food and Drug Administration. FDA Application: Search Orphan Drug Designations and Approvals. Rockville, MD. From FDA website. Accessed 2014 Apr 23.

Clinical Trials, Definitions, Peer-Reviewed Publications

1. SW Lockley et al. Tasimelteon treatment entrains the circadian clock and demonstrates a clinically meaningful benefit in totally blind individuals with non-24-hour circadian rhythms. The Endocrine Society 95th annual meeting (ENDO), San Francisco, June 15-18, 2013. Poster SUN-134.
2. SW Lockley et al. RESET study demonstrates that tasimelteon maintains entrainment of melatonin and cortisol in totally blind individuals with non-24-hour circadian rhythms. The Endocrine Society 95th annual meeting (ENDO), San Francisco, June 15-18, 2013. Poster SUN-137.
3. Auger RR, Burgess HJ, Emens JS et al. Clinical practice guideline for the treatment of instrinsic circadian rhythm sleep-wake disorders: advance 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;11:1199-1236.

Government Agencies, Professional Societies, and Other Authoritative Publications

A. **International Classification of Sleep Disorders:** Diagnostic & Coding Manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.
B. Morgenthaler TI, Lee-Chiong T, Alessi C, et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders: an **American Academy of Sleep Medicine** report. Sleep 2007;30(11):1445-1459.
C. Zee P, Attarian H, Videnovic A. Circadian rhythm disorders. Continuum (Minneap Minn). **American Academy of Neurology.** 2013;19(1):132-147.
D. **National Sleep Foundation.** Non-24-hour Sleep Wake Disorder Facts and Prevalence. Available at: http://sleepfoundation.org/non-24/facts_prevalence.html. Accessed on April 2016.
E. **Circadian Sleep Disorders Network.** Non-24-Hour Sleep-Wake Disorder Questions and Answers. Available at: http://www.circadiansleepdisorders.org/docs/N24-QandA.php. Accessed on April 2016.
F. Morgenthaler T, Lee-Chiong T, Alessi C, et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An **American Academy of Sleep Medicine** report. Sleep. 2007;30(11):1445-1459.
G. Sack R, Auckley D, Auger R, et al. Circadian rhythm-sleep disorders: part II, advanced sleep phase disorder, delayed sleep phase disorder, free-running disorder, and irregular sleep-wake rhythm. An **American Academy of Sleep Medicine Review.** Sleep. 2007;30(11):1484-1501.
H. Lighthouse International. Prevalence of visual impairment. URL: www.lighthouse.org/research/statistics-on-vision-impairment/prevalence-of-vision-impairment/#national. Accessed on April 2016.
I. **American Academy of Sleep Medicine (AASM).** An American Academy of Sleep Medicine Clinical Practice Guideline: 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. Journal of Clinical Sleep Medicine, Vol. 11, No. 10, 2015. Available at: *http://www.aasmnet.org/Resources/clinicalguidelines/CRSWD-intrinsic.pdf*. Accessed on April 2016.