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# PHARMACY POLICY – 5.01.552

# Hetlioz (tasimelteon)

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| Effective Date: | Mar. 1, 2025 | RELATED MEDICAL POLICIES: |
| Last Revised: | Feb. 24, 2025 | 5.01.605 Medical Necessity Criteria for Pharmacy Edits |
| Replaces: | N/A | |

**Select a hyperlink below to be directed to that section.**

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## Introduction

The circadian rhythm is the body's natural sleep/wake cycle. For most people, the natural clock that guides sleeping and waking runs just a little longer than 24 hours. The amount of light during the day informs the brain about the time of day: morning, midday, or evening. The light coming into the eyes helps the brain reset the sleep/wake cycle every day. But for those who can't sense light due to total blindness, the brain doesn't get information to help it reset to the 24-hour cycle. This eventually results in being awake during the night and feeling extremely sleepy during the day. Smith-Magenis Syndrome (SMS) is a developmental disorder that affects many parts of the body and can result in significant sleep disturbances. These sleep disturbances appear due to inversion of melatonin secretion which is involved in the circadian rhythm. Hetlioz (tasimelteon) is a drug known as a hypnotic and is used to counteract the effects of non-24-hour sleep-wake disorder and SMS. This policy describes when this medication may be considered medically necessary.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

| Drug | Medical Necessity |
|---|---|
| **Hetlioz (tasimelteon) capsules** | **Hetlioz (tasimelteon) may be considered medically necessary for treatment of non-24-hour sleep-wake disorder when ALL the following conditions have been met:**<br>• The individual is aged 18 years or older<br>**AND**<br>• Diagnosis of non-24-hour sleep-wake disorder by a sleep specialist<br>**OR**<br>• Documentation in the medical record of full International Classification of Sleep Disorders diagnostic criteria for non-24-hour sleep-wake disorder<br>**AND**<br>• For use over 6 months, documented evidence of objective response after 6 months and annually thereafter<br>**AND**<br>• Has tried and failed or is intolerant to generic tasimelteon<br>**AND**<br>• Dose prescribed is limited to 20 mg per day<br><br>**Hetlioz (tasimelteon) may be considered medically necessary for treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) when ALL the following conditions have been met:**<br>• The individual is aged 16 years or older<br>**AND**<br>• Diagnosed with SMS as confirmed by genetic testing that documents deletions or mutations to the retinoic acid-induced 1 (RAI1) gene (located on chromosomal region 17p.11.2).<br>**AND**<br>• For use over 3 months, documented evidence of improved nighttime sleep quality after 3 months and annually thereafter<br>**AND**<br>• Hetlioz (tasimelteon) is prescribed by or in consultation with a sleep specialist<br>**AND** |

| Drug | Medical Necessity |
|---|---|
| | • Has tried and failed or is intolerant to generic tasimelteon<br>**AND**<br>• Dose prescribed is limited to 20 mg per day |
| **Generic tasimelteon capsules** | **Generic tasimelteon may be considered medically necessary for treatment of non-24-hour sleep-wake disorder when ALL the following conditions have been met:**<br>• The individual is aged 18 years or older<br>**AND**<br>• Diagnosis of non-24-hour sleep-wake disorder by a sleep specialist<br>**OR**<br>• Documentation in the medical record of full International Classification of Sleep Disorders diagnostic criteria for non-24-hour sleep-wake disorder<br>**AND**<br>• For use over 6 months, documented evidence of objective response after 6 months and annually thereafter<br>**AND**<br>• Dose prescribed is limited to 20 mg per day<br><br>**Generic tasimelteon may be considered medically necessary for treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) when ALL the following conditions have been met:**<br>• The individual is aged 3 years or older<br>**AND**<br>• Diagnosed with SMS as confirmed by genetic testing that documents deletions or mutations to the retinoic acid-induced 1 (RAI1) gene (located on chromosomal region 17p.11.2).<br>**AND**<br>• For use over 3 months, documented evidence of improved nighttime sleep quality after 3 months and annually thereafter<br>**AND**<br>• Generic tasimelteon is prescribed by or in consultation with a sleep specialist<br>**AND** |

| Drug | Medical Necessity |
|---|---|
| | • Dose prescribed is limited to 20 mg per day |
| **Hetlioz LQ (tasimelteon) oral suspension** | **Hetlioz LQ (tasimelteon) may be considered medically necessary for treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) when ALL of the following conditions have been met:**<br>• The individual is aged 3 years to 15 years<br>**AND**<br>• Diagnosed with SMS as confirmed by genetic testing that documents deletions or mutations to the retinoic acid-induced 1 (RAI1) gene (located on chromosomal region 17p.11.2).<br>**AND**<br>• For use over 3 months, documented evidence of improved nighttime sleep quality after 3 months and annually thereafter<br>**AND**<br>• Hetlioz LQ (tasimelteon) is prescribed by or in consultation with a sleep specialist<br>**AND**<br>• Has tried and failed or is intolerant to generic tasimelteon or documentation is provided that the product is medically necessary (e.g., generic cannot provide the dose required or unable to swallow)<br>**AND**<br>• Dose prescribed is limited to:<br>○ ≤ 28 kg: 0.7 mg/kg daily<br>○ > 28 kg: 20 mg daily |

| Drug | Investigational |
|---|---|
| **Hetlioz (tasimelteon), Hetlioz LQ (tasimelteon), generic tasimelteon capsules** | **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**<br><br>**Use of Hetlioz (tasimelteon), generic tasimelteon capsules, and Hetlioz LQ (tasimelteon) for all other indications is considered investigational.** |

| Length of Approval | |
|---|---|
| **Approval** | **Criteria** |
| **Initial authorization** | **Non-formulary exception reviews for Hetlioz (tasimelteon) and generic tasimelteon may be approved for up to 12 months for non-24-hour sleep-wake disorder or Smith-Magenis Syndrome (SMS).**<br><br>**All other reviews for Hetlioz (tasimelteon) and generic tasimelteon may be approved for up to 6 months for non-24-hour sleep-wake disorder.**<br><br>**All other reviews for Hetlioz (tasimelteon) and Hetlioz LQ (tasimelteon) may be approved for up to 3 months for Smith-Magenis Syndrome (SMS).** |
| **Re-authorization criteria** | **Non-formulary exception reviews and all other reviews for Hetlioz (tasimelteon) and generic tasimelteon for non-24-hour sleep-wake disorder may be approved up to 12 months in duration when there is documentation of objective response.**<br><br>**Non-formulary exception reviews and all other reviews for Hetlioz (tasimelteon) and Hetlioz LQ (tasimelteon) for Smith-Magenis Syndrome (SMS) may be approved for up to 12 months in duration when there is documented evidence of improved nighttime sleep quality.** |

| Documentation Requirements |
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| **The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:**<br>• Office visit notes that document the diagnosis of non-24-hour sleep-wake disorder or document the diagnosis of Smith-Magenis Syndrome (SMS). |

## Coding

N/A

## Related Information

### Benefit Application

This policy is managed by the pharmacy benefit.

## Evidence Review

### Description

Non-24-hour sleep-wake disorder (also known as "non-24" or "free-running disorder") is a severe, chronic, circadian sleep rhythm disorder (CSRD) characterized by the inability to entrain (synchronize) the master body clock to the 24-hour day. Individuals with non-24 have prolonged periods of misalignment of circadian rhythms, including the timing of melatonin and cortisol secretion and the sleep-wake cycle, which are associated with significant impairments in social and occupational functioning, or marked subjective distress.

Most cases of non-24 occur in blind individuals with no perception of light. As a result of light information failing to reach the suprachiasmatic nucleus (SCN) to synchronize the clock to the 24-hour light-dark cycle, the SCN reverts to an endogenous non-24-hour period. As a result, physiologic processes and behavior that are controlled by the circadian system (e.g., the timing of melatonin and cortisol production, the core body temperature rhythm, metabolic processes, the sleep-wake cycle, and alertness and performance patterns) becomes desynchronized from the 24-hour day, which has consequences for daily functioning. Most blind individuals can perceive enough light to prevent non-24. Entrainment is a measure of synchronization of an individual's intrinsic master clock (τ) to the 24-hour day. Most individuals with non-24 have intrinsic clocks (τ) longer than 24.0 hours.

## Epidemiology and Risk Factors

Most individuals with non-24 are totally blind and without light perception. The estimated prevalence of non-24 in the totally blind is approximately 80,000 to 100,000 individuals in the US.

## Clinical Presentation

Symptoms of non-24 include nighttime sleeplessness and daytime fatigue and sleepiness. Persons with non-24 may have comorbidities of depression or other mood disorders. Individuals with non-24 may not experience the same degree of symptom severity.

## Diagnosis

The International Classification of Sleep Disorders criteria for non-24 include:

- Primary complaint of either difficulty initiating sleep or difficulty in awakening.
- Progressive delays of sleep onset and offset with the inability to maintain stable entrainment to a 24-hour sleep–wake pattern.
- Presence of the sleep pattern for at least 6 weeks.
- Evidence of a progressive sequential delay of the sleep period by polysomnography performed over several consecutive days on a fixed 24-hour bedtime and wake-time schedule, continuous 24-hour temperature monitoring over at least 5 days that shows a progressive delay of the temperature nadir, and the individual does not meet criteria for any other sleep disorder causing inability to initiate sleep or excessive sleepiness.

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, is 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.

## Therapeutic Alternatives

There are no other US Food and Drug Administration (FDA) -approved treatments for non-24 in blind individuals without light perception; however, two other pharmacologic treatment options are available:

- Another oral melatonin receptor agonist, Rozerem (ramelteon) (Takeda) was approved in 2005 for the treatment of insomnia characterized by difficulty with sleep onset in adult individuals ≥18 years of age. There are no published trials or studies of ramelteon for non-24, nor are there any ongoing or completed trials listed at ClinicalTrials.gov, but the similarity in pharmacology suggests that ramelteon would be an effective and much lower cost option.
- Melatonin, which is regulated as a dietary supplement in the US, has been used in the treatment of non-24 and is listed as a guideline-level recommendation in the 2007 American Academy of Sleep Medicine guidelines for the evaluation and treatment of CSRDs. This recommendation was based on several small studies. A 2004 review article cites several issues with using melatonin in the treatment of insomnia and CSRDs, including pharmacokinetic issues such as its short half-life and large first-pass metabolism, as well as nonspecific effect on melatonin subreceptors. However, they generally note the lack of large-scale clinical trials, partially owing to the fact that melatonin cannot be patented. Melatonin is approved as a drug in the EU and in Australia.

## Efficacy: Non-24

The Sponsor submitted to the FDA two randomized, placebo-controlled, double-masked, Phase III trials in support of the new drug application, SET (cited as "Study 1" in PI) and RESET (cited as "Study 2" in PI). SET was a multicenter, randomized, double-masked, placebo-controlled, parallel study designed to evaluate the efficacy and safety of tasimelteon 20 mg versus placebo in 84

totally blind individuals with non-24. SET included a screening phase, a double-blind phase, and an open-label extension phase.

In the Sponsor analysis of the intention-to-treat population of SET, 20% of individuals in the tasimelteon group entrained by aMT6s measurement at 1 month compared with 2.6% in the placebo group (p=0.017). There was also a statistically significant difference the step-down primary end point of entrainment plus a greater than 3-point change in the N24CRS. The Sponsor analysis of RESET showed a higher rate of non-entrainment in individuals who had previously been entrained in on tasimelteon and switched to placebo (80%) than in individuals entrained on tasimelteon and maintained on the drug (10%, p=0.003).

In the FDA analysis of SET (cited as Study 1 in the package insert), individuals in the tasimelteon group had at baseline, an average 195 minutes of nighttime sleep and 137 minutes of daytime nap time on the 25% of most 10 symptomatic nights and days, respectively. Treatment with tasimelteon resulted in a significant improvement, compared with placebo, for both of these end points in both SET and RESET. A responder analysis of individuals with both ≥45 minutes increase in nighttime sleep and ≥45 minutes decrease in daytime nap time was conducted in SET (Study 1): 29% (n=12) of individuals treated with tasimelteon, compared with 12% (n=5) of individuals treated with placebo met the responder criteria. There is no evidence to assess real world comparative effectiveness. No head-to-head studies vs. ramelteon or melatonin were performed.

Tasimelteon was generally well tolerated in SET and RESET. Adverse effects that occurred in at least 5% of individuals 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 individuals receiving tasimelteon.

## Efficacy: SMS

The effectiveness of tasimelteon in the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) was established in a 9-week, double-blind, placebo- controlled cross-over study in adults and pediatric individuals with SMS (Study 3; NCT 02231008). Individuals 16 years of age and older received tasimelteon 20 mg capsules, and pediatric individuals 3 years to 15 years of age received a weight-based dose of oral suspension.

Study 3 had two 4-week periods, separated by a 1-week washout interval. Individuals were randomized to a treatment sequence of tasimelteon in the first period and placebo in the

second period, or placebo in the first period and tasimelteon in the second period. Individuals were to take the study drug one hour prior to bedtime.

The primary endpoints in Study 3 were nighttime total sleep time and nighttime sleep quality from a parent/guardian-recorded diary. Nighttime total sleep time was reported as a time unit in hours and minutes. Nighttime sleep quality was rated as follows: 5 = excellent; 4 = good; 3 = average; 2 = fair; 1 = poor. The efficacy comparisons for nighttime sleep quality and total sleep time were based on the 50% of nights with the worst sleep quality and the 50% of nights with the least nighttime sleep in each 4- week period. In accordance with the cross-over design, the efficacy comparisons were within individual.

A total of 25 individuals were randomized in Study 3. During screening, the mean quality score of the 50% of nights with the worst sleep quality was 2.1, and the total sleep time of 50% of nights with the least nighttime sleep was 6.4 hours. Compared to placebo, treatment with tasimelteon resulted in a statistically significant improvement in the 50% worst nights' sleep quality. Although improvement on the 50% worst total nighttime sleep time numerically favored tasimelteon treatment, the difference was not statistically significant.

## 2015 Update

A literature search from July 1, 2014, through June 28, 2015, was conducted. No studies were found that would indicate the need to revise this policy. References updated.

## 2016 Update

A literature search from January 1, 2015, through December 6, 2016, was conducted. No studies were found that would indicate the need to revise this policy. References updated.

## 2017 Update

A literature search from July 1, 2016, through November 1, 2017, was conducted. No studies were found that would indicate the need to revise this policy. References updated.

## 2018 Update

A literature search from November 1, 2017, through October 31, 2018, was conducted. No studies were found that would indicate the need to revise this policy. References updated.

## 2019 Update

Reviewed Hetlioz (tasimelteon) prescribing information and conducted a literature search from November 1, 2018, through November 30, 2019. No new information was identified that would require changes to this policy.

## 2020 Update

Reviewed Hetlioz (tasimelteon) prescribing information and conducted a literature search from December 1, 2019, through September 30, 2020. No new information was identified that would require changes to this policy. Added a separate investigational table to the policy.

## 2021 Update

Reviewed Hetlioz (tasimelteon) prescribing information and added a new indication for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS). Added Hetlioz LQ (tasimelteon) to the policy which is an oral suspension. Per prescribing information Hetlioz capsules and Hetlioz LQ oral suspension are not substitutable. Added a daily dose limit to coverage criteria for non-24 and SMS following the recommended dosage.

## 2022 Update

Reviewed Hetlioz (tasimelteon) and Hetlioz LQ (tasimelteon) prescribing information and conducted a literature search from April 31, 2021, through February 28, 2022. No new information was identified that would require changes to this policy. References reviewed.

## 2023 Update

Reviewed Hetlioz (tasimelteon) and Hetlioz LQ (tasimelteon) prescribing information. Updated Hetlioz (tasimelteon)'s criteria to have trial and failure of generic tasimelteon first for the indication of non-24-hour-sleep-wake disorder. Added criteria for generic tasimelteon capsule similar to brand Hetlioz (tasimelteon) capsule for the indication of non-24-hour-sleep wake disorder.

## 2024 Update

Reviewed Hetlioz (tasimelteon) and Hetlioz LQ (tasimelteon) prescribing information. Updated Hetlioz (tasimelteon) coverage criteria to require trial with generic tasimelteon for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS). Updated Hetlioz LQ (tasimelteon) coverage criteria to require trial with generic tasimelteon. Updated generic tasimelteon to include coverage criteria for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS).

## 2024 Update

Reviewed the prescribing information for the drugs listed in this policy. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

# References


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3. US Food and Drug Administration. Center for Drug Evaluation and Research. Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. Briefing Materials. Tasimelteon (melatonin agonist). For the treatment of Non-24-hour

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## History

| Date | Comments |
|---|---|
| 06/09/14 | New policy, add to Prescription Drug section. Tasimelteon (Hetlioz) may be considered medically necessary for treatment of non-24-hour sleep-wake disorder when criteria are met and documentation of the diagnosis including appropriate sleep studies must be submitted with the request. All other uses are considered investigational. Approved by P&T Committee on May 22, 2014. |
| 07/14/15 | Annual Review. Policy updated with literature review; no change to policy statement. References updated. |
| 01/01/17 | Annual Review, approved December 13, 2016. Policy updated with literature review; no change to policy statement. References updated. |
| 12/01/17 | Annual Review, approved November 21, 2017. No change to policy statement. No new literature was found. |
| 12/01/18 | Annual Review, approved November 21, 2018. No change to policy statement. References updated to 10/31/18. |
| 05/01/19 | Interim Review, approved April 9, 2019. Updated criteria to include International Classification of Sleep Disorders documentation and removed requirement to use ramelteon first. |
| 01/01/20 | Annual Review, approved December 10, 2019. No changes to policy statement. |
| 12/01/20 | Annual Review, approved November 3, 2020. No changes to policy statement. |
| 05/01/21 | Annual Review, approved April 1, 2021. Updated Hetlioz criteria for non-24-hour sleep-wake disorder adding an age limitation and daily dose limit. Added coverage criteria for Hetlioz and Hetlioz LQ for the treatment of nighttime sleep disturbances in SMS. |
| 04/01/22 | Annual Review, approved March 21, 2022. No changes to policy statement. |
| 06/01/23 | Annual Review, approved May 9, 2023. Reviewed Hetlioz (tasimelteon) and Hetlioz LQ (tasimelteon) prescribing information. Updated Hetlioz (tasimelteon)'s criteria to have trial and failure of generic tasimelteon first for the indication of non-24-hour-sleep- |

| Date | Comments |
|---|---|
| | wake disorder. Added criteria for generic tasimelteon capsule similar to brand Hetlioz (tasimelteon) capsule for the indication of non-24-hour-sleep wake disorder. Changed the wording from "patient" to "individual" throughout the policy for standardization. |
| 12/01/24 | Annual Review, approved November 25, 2024. Updated Hetlioz (tasimelteon) coverage criteria to require trial with generic tasimelteon for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS). Updated Hetlioz LQ (tasimelteon) coverage criteria to require trial with generic tasimelteon. Updated generic tasimelteon to include coverage criteria for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS). |
| 03/01/25 | Annual Review, approved February 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. |



**Scope**: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.