# tasimelteon (Hetlioz®, Hetlioz LQ™, generics)

**Policy #** 00431
Original Effective Date: 09/17/2014
Current Effective Date: 06/10/2024

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

# When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider tasimelteon (Hetlioz®, Hetlioz LQ™, generics)‡ for the treatment of certain sleep disturbances to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for tasimelteon (Hetlioz, Hetlioz LQ, generics) will be considered when the following criteria are met:

- If the request is for Non-24-Hour Sleep-Wake Disorder (Non-24):
    - Drug requested is brand Hetlioz or generic tasimelteon; AND
    - Patient is totally blind without light perception; AND
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
    - Patient has a diagnosis of Non-24, defined as meeting all of the following:
        - Patient has a history of insomnia, excessive daytime sleepiness, or both, which alternate with asymptomatic episodes, due to misalignment of the 24-hour light-dark cycle and the non-entrained endogenous circadian rhythm of sleep-wake propensity; AND
        - Patient's symptoms persist over the course of at least 3 months; AND
        - Patient sleep logs are submitted (at least 14 days) that demonstrate a pattern of sleep and wake times that typically delay each day, with a circadian period that is usually longer than 24 hours; AND
        - Patient's sleep disturbance is not attributed to another current sleep disorder or other disorder (i.e., substance abuse, medications, etc.); AND

- Patient has tried and failed (e.g., intolerance or inadequate response) another sleep medication after at least 3 months of use unless there is clinical evidence or patient history that suggests the use of these agents will be ineffective or cause an adverse reaction to the patient; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- If the request is for brand Hetlioz, patient has tried and failed (e.g., intolerance or inadequate response) generic tasimelteon unless there is clinical evidence or patient history that suggests the use of generic tasimelteon will be ineffective or cause an adverse reaction to the patient; OR
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

- If the request is for Smith-Magenis Syndrome:
  - Patient has a diagnosis of Smith-Magenis Syndrome; AND
    - If the request is for Heltioz LQ: Patient is 3 to 15 years of age; OR
    - If the request is for brand Hetlioz or generic tasimelteon: Patient is 16 years of age or older; AND
  - Patient has nighttime sleep disturbances; AND
  - Patient has a deletion of chromosome 17p11.2 OR *RAI1* gene mutation; AND
  - Patient has tried and failed (e.g., intolerance or inadequate response) therapy with melatonin after at least 3 months of use unless there is clinical evidence or patient history that suggests the use of melatonin will be ineffective or cause an adverse reaction to the patient; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - If the request is for brand Hetlioz, patient has tried and failed (e.g., intolerance or inadequate response) generic tasimelteon unless there is clinical evidence or patient history that suggests the use of generic tasimelteon will be ineffective or cause an adverse reaction to the patient; OR
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

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# When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of tasimelteon (Hetlioz, generics) when a patient has not tried and failed another sleep medication after at least 3 months of use for the treatment of Non-24 to be **not medically necessary.****

Based on review of available data, the Company considers the use of tasimelteon (Hetlioz, generics) when a patient is not totally blind without light perception for the treatment of Non-24 to be **not medically necessary.****

Based on review of available data, the Company considers the use of tasimelteon (Hetlioz) when a patient has not tried and failed generic tasimelteon for the treatment of Non-24 and Smith-Magenis Syndrome to be **not medically necessary.****

Based on review of available data, the Company considers the use of tasimelteon (Hetlioz LQ) when a patient has not tried and failed therapy with melatonin after at least 3 months of use for the treatment of Smith-Magenis Syndrome to be **not medically necessary.****

# When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers the use of tasimelteon (Hetlioz, Hetlioz LQ, generics) when patient selection criteria are not met to be **investigational*** (with the exception of those denoted above as **not medically necessary**).**

# Background/Overview

Hetlioz is a melatonin agonist that is approved for the treatment of Non-24, also known as Non-24-Hour Sleep-Wake Disorder, as well as for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in patients 16 years of age or older. Hetlioz is a capsule formulation dosed at 20 mg by mouth prior to bedtime, at the same time every night, and it should be taken without food. It is also available in a generic formulation. Hetlioz LQ is the oral suspension version of tasimelteon and is approved to treat nighttime sleep disturbances in SMS in pediatric patients 3

years to 15 years of age. The oral suspension is a 4 mg/mL formulation. It is dosed based on weight. Hetlioz LQ is not yet available generically. More detailed dosing instructions for pediatric patients can be found in the package insert.

**Non-24**

Non-24 is a chronic circadian rhythm disorder that occurs when the endogenous circadian pacemaker is not aligned with the 24-hour clock. The major environmental factor that synchronizes the circadian rhythm is the light-dark cycle, which is detected exclusively by the eyes, and signals are then directed to the suprachiasmatic nuclei (SCN). Exposure to light causes adjustments, or phase shifts, in the circadian rhythm via melatonin. Melatonin synthesis, signaled by the SCN, occurs in the pineal gland. Light causes the SCN to inhibit the production of melatonin and darkness has the opposite effect. In an individual entrained to the 24 hour clock, melatonin levels are typically elevated at night and lower during the day. Melatonin affects the initiation of sleep (via the $MT_1$ receptor) as well as entrainment (via the $MT_2$ receptor). In patients without light perception, this "normal" process isn't able to take place. The misalignment causes a gradual shift of the sleep-wake cycle to become out of sync with the 24 hour clock. Hetlioz works in patients with Non-24 to bind to the $MT_2$ and cause entrainment to the 24 hour clock. Hetlioz also has an affinity to the $MT_1$ receptor, however the affinity to the $MT_2$ receptor is much greater.

Non-24 is common in individuals that are totally blind without light perception. Studies have found that 57-70% of blind patients without light perception have Non-24. In totally blind patients without light perception, the endogenous circadian rhythm can range from 24.2-24.5 hours. The diagnosis of Non-24 is mainly clinical, but the International Classification of Sleep Disorders, which is published by the American Academy of Sleep Medicine (AASM), gives guidance on characteristics of the diagnosis. The AASM also released a guideline document that concluded that the use of appropriately timed melatonin has been shown to entrain totally blind patients with Non-24. It should also be noted that clinical studies for Hetlioz for Non-24 were only studied in totally blind patients.

**Smith-Magenis Syndrome**

Smith-Magenis Syndrome is a developmental disorder that impacts many parts of the body. Common features include intellectual disability, delayed speech and language skills, sleep disturbances, and behavioral problems (e.g., frequent tantrums, aggression, anxiety, impulsiveness, repetitive self-hugging). The cause of Smith-Magenis Syndrome has been linked to a deletion of genetic material from chromosome 17p11.2, in particular the *RAI1* gene in most cases. The sleep

problems associated with this condition are significant. They include difficulty falling asleep, shortened sleep cycles, frequent and prolonged nocturnal awakenings, excessive daytime sleepiness, daytime napping, and snoring. The sleep problems are likely due to an inversion of melatonin secretion.

# FDA or Other Governmental Regulatory Approval

**U.S. Food and Drug Administration (FDA)**

Hetlioz was approved in January of 2014 by the FDA for the treatment of Non-24. In late 2020, Hetlioz's indication was expanded to include the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome in patients 16 years of age and older. At this time, Hetlioz LQ, an oral suspension, was approved for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome in patients 3 years to 15 years of age.

# Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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**Non-24**

The efficacy of Hetlioz was studied in two randomized double-masked, placebo-controlled, multicenter, parallel group studies in totally blind patients with Non-24. In Study 1 (n=84), patients with Non-24 were randomized to receive Hetlioz 20mg or placebo one hour prior to bedtime. The duration and timing of nighttime 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). Entrainment is defined as the synchronization of the

circadian rhythm of the body to the 24 hour day. In the Hetlioz group, 29% of patients 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 who received placebo.

Study 2 involved patients who received Hetlioz for 12 weeks and became entrained during Study 1. The patients were then randomized to either continue Hetlioz or switch to placebo. Ninety percent of patients who continued Hetlioz remained entrained compared with 20% of patients that were randomized to placebo.

**Smith-Magenis Syndrome**

The effectiveness of Hetlioz 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 patients with SMS (Study 3). Patients 16 years of age and older received Hetlioz 20 mg capsules, and pediatric patients 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. Patients were randomized to a treatment sequence of Hetlioz in the first period and placebo in the second period, or placebo in the first period and Hetlioz in the second period. Patients 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 patient.

A total of 25 patients 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 Hetlioz resulted in a statistically significant improvement in the 50% worst nights' sleep quality (score of 2.8 vs. 2.4, difference of 0.4 [95% CI, 0.1, 0.7]). Although improvement on the 50% worst total nighttime sleep

time numerically favored Hetlioz treatment, the difference was not statistically significant (7.0 hours vs. 6.7 hours (difference of 0.3 [95% CI, -0.0, 0.6]).

# References

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# Policy History

Original Effective Date: 09/17/2014
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| 09/04/2014 | Medical Policy Committee review |
| 09/17/2014 | Medical Policy Implementation Committee approval. New policy. |
| 09/03/2015 | Medical Policy Committee review |
| 09/23/2015 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 09/08/2016 | Medical Policy Committee review |
| 09/21/2016 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 09/07/2017 | Medical Policy Committee review |
| 09/20/2017 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 09/06/2018 | Medical Policy Committee review |
| 09/19/2018 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 09/05/2019 | Medical Policy Committee review |

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| 09/11/2019 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 09/03/2020 | Medical Policy Committee review |
| 09/09/2020 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 08/05/2021 | Medical Policy Committee review |
| 08/11/2021 | Medical Policy Implementation Committee approval. Added new criteria and background information for the newly FDA approved indication, Smith-Magenis Syndrome. |
| 08/04/2022 | Medical Policy Committee review |
| 08/10/2022 | Medical Policy Implementation Committee approval. NMN statement added for the use of tasimelteon (Hetlioz) when a patient is not totally blind without light perception for the treatment of Non-24. This criterion was already present in the policy. |
| 05/04/2023 | Medical Policy Committee review |
| 05/10/2023 | Medical Policy Implementation Committee approval. Added generic tasimelteon to policy. Changed title from "tasimelteon (Hetlioz, Hetlioz LQ)" to "tasimelteon (Hetlioz, Hetlioz LQ, generics)." |
| 05/02/2024 | Medical Policy Committee review |
| 05/08/2024 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |

Next Scheduled Review Date: 05/2025

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

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B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.