Hetlioz (tasimelteon) Prior Authorization with Quantity Limit Program Summary

This program applies to Medicaid.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
06-01-2024	01-01-2019

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Hetlioz® (tasimelteon) Capsules*	Treatment of Non-24-Hour Sleep-Wake Disorder (Non-24 SWD) in adults Treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in patients 16 years of age and older	*generic available	1
Hetlioz LQ™ (tasimelteon) Oral suspension	Treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in pediatric patients 3 to 15 years of age		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Non-24 Hour Sleep-Wake Disorder	Non-24 hour sleep-wake disorder (Non-24) is a circadian rhythm sleep disorder that is due to the failure of the biological clock to synchronize to a 24-hour day.(2) Numerous biological processes require an endogenous, entrainable oscillation with a period of about 24 hours, also known as the circadian rhythm. Retinal rods, cones, and ganglion cells that express the photopigment melanopsin play a key role in circadian photoentrainment. Light that reaches the photoreceptors activates the suprachiasmatic nuclei (SCN), which contains the master biological clock, activating a regulatory feedback loop that inhibits melatonin synthesis. In totally blind patients, the circadian process can become desynchronized due to the absence of light input into the master biological clock.(5) Patients with Non-24 typically find their sleep time gradually delaying by minutes to hours every day, rather than sleeping at roughly the same time every day. Cycles of body temperature and hormone rhythms also follow a non-24 hour rhythm. If Non-24 is not detected and addressed, and the person attempts to stay on a 24-hour schedule, the symptoms of chronic sleep deprivation will accumulate, such as excessive daytime sleepiness, fatigue, depression, difficulty concentrating, and memory problems. Non-24 hour sleep-wake disorder can be severely disabling as it causes extreme difficulty for the individual attempting to maintain social and career obligations.(2) The condition primarily occurs in blind individuals, and at least 50% of the totally blind (i.e., those with no light perception) are thought to suffer from the disorder.(3) The American Academy of Sleep Medicine (AASM) guidelines on treatment of circadian rhythm disorders recommends clinicians use strategically timed administration of melatonin for treatment of Non-24-Hour Sleep-Wake Disorder in blind adults (vs. no treatment). The suggestion carried a "Weak" recommendation, as there were only 3 studies that met the task force's inclusion criteria for analysis, and the level of evidence from these small trials was low. The task force states that no serious adverse reactions

	to melatonin have been described to date and therefore benefits of use appear to outweigh any potential harm.(3)
Efficacy	The effectiveness of Hetlioz in the treatment of Non-24-Hour Sleep-Wake Disorder(Non-24) was established in two randomized double-masked, placebo-controlled, multicenter, parallel-group studies (Studies 1 and 2) in totally blind patients with Non-24. In study 1, 84 patients with Non-24 (median age 54 years) were randomized to receive Hetlioz 20 mg or placebo, one hour prior to bedtime, at the same time every night for up to 6 months. Study 2 was a randomized withdrawal trial in 20 patients with Non-24 (median age 55 years) that was designed to evaluate the maintenance of efficacy of Hetlioz after 12 weeks. Patients were treated for approximately 12 weeks with Hetlioz 20 mg one hour prior to bedtime, at the same time every night.(1) 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 Hetlioz resulted in a significant improvement, compared with placebo, for both endpoints in Study 1 and Study 2.(1)
Smith-Magenis Syndrome (SMS)	Smith-Magenis Syndrome (SMS) is genetic condition resulting in developmental delays, cognitive impairment, behavioral abnormalities, sleep disturbances, distinctive physical features, and childhood abdominal obesity. SMS is a result of a deletion of the retinoic acid induced 1 (RAI1) gene in chromosome 17p11.2. Most cases are the result of de novo deletions, but rare occurrences of inherited cases have occurred.(7) The diagnosis of SMS is established via a combination of clinical features and genetic testing. Clinical features suspect of SMS include the following:(6) • Subtly distinctive facial appearance that becomes more evident with age • Mild to moderate infantile hypotonia with feeding difficulties and failure to thrive • Some level of developmental delay and/or intellectual disability, including early speech delays with or without associated hearing loss • Distinct neurobehavioral phenotype that includes stereotypic and maladaptive behaviors • Sleep disturbance • Short stature (prepubertal) • Childhood obesity • Minor skeletal anomalies, including brachydactyly • Signs of peripheral neuropathy • Ophthalmologic abnormalities • Otolaryngologic abnormalities The presence of either a heterozygous deletion at chromosome 17p11.2 that includes RAI1 or a heterozygous intragenic RAI1 pathogenic variant are definitive of a SMS diagnosis.(6) Sleep disturbances are a major clinical characteristic of SMS. The sleep disturbances are believed to be attributed to a primary disturbance of the circadian clock, with RAI1 functioning as a positive regulator of the circadian locomotor output cycles kaput (CLOCK) gene transcription. The dysregulation of CLOCK results in dysregulation of other circadian clock components. Patients with SMS also have elevated levels of daytime melatonin resulting in daytime sleepiness. The sleep disturbances manifest as fragmented sleep cycles with a reduction in total sleep time. Patients may complain of frequent nighttime awakenings, parasomnias, and excessive daytime sleepiness.(7) Sleep disturbances contribute to behavioral problems typical to SMS, and normalizing sleep habits, improved both behavior and quality of life for patients and families. There is currently no pharmaceutical standard of care, but melatonin has been used in case reports with some response.(6,7) Hetlioz (tasimelteon) is the first FDA-approved treatment of nighttime sleep disturbance in SMS.(6)

Efficacy	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 crossover study in adults and pediatric patients with SMS (Study 3; NCT 02231008). 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. 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. Compared to placebo, treatment with Hetlioz resulted in a statistically significant improvement in the 50% worst nights' sleep quality.(1)
Safety	Hetlioz and Hetlioz LQ have no FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Hetlioz prescribing information. Vanda Pharmaceuticals Inc. January 2023.
2	Non-24-Hour Sleep-Wake Disorder. National Organization for Rare Disorders (NORD). (2023, November 20) https://rarediseases.org/rare-diseases/non-24-hour-sleep-wake-disorder/
3	Auger, R. R., Burgess, H. J., Emens, J. S., Deriy, L. V., Thomas, S. M., & Sharkey, K. M. (2015). 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, 11(10), 1199–1236. https://doi.org/10.5664/jcsm.5100
4	Reference no longer used.
5	Quera Salva Maria Antonia, Hartley Sarah, Léger Damien, Dauvilliers Yves A. (2017) Non-24-Hour Sleep–Wake Rhythm Disorder in the Totally Blind: Diagnosis and Management. *Frontiers in Neurology*, 8(686), pages 1-7. Doi: 10.3389/fneur.2017.00686.
6	Smith ACM, Boyd KE, Elsea SH, et. al. Smith-Magenis Syndrome. *GeneReviews*. October, 2022; https://www.ncbi.nlm.nih.gov/books/NBK1310/
7	Shayota, B. J., & Elsea, S. H. (2019). Behavior and sleep disturbance in Smith-Magenis syndrome. *Current opinion in psychiatry*, *32*(2), 73–78. https://doi.org/10.1097/YCO.0000000000000474

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Hetlioz	tasimelteon capsule	20 MG	M ; N ; O ; Y	O ; Y		
Hetlioz lq	tasimelteon oral susp	4 MG/ML	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Hetlioz	Tasimelteon Capsule 20 MG	20 MG	30	Capsules	30	DAYS			
Hetlioz lq	Tasimelteon Oral Susp	4 MG/ML	158	mLs	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Hetlioz	tasimelteon capsule	20 MG	Medicaid
Hetlioz lq	tasimelteon oral susp	4 MG/ML	Medicaid

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Hetlioz	Tasimelteon Capsule 20 MG	20 MG	Medicaid
Hetlioz lq	Tasimelteon Oral Susp	4 MG/ML	Medicaid

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   - A. BOTH of the following:
     1. The patient has a diagnosis of Non-24-hour sleep-wake disorder **AND**
     2. The patient is totally blind (i.e., no light perception) **OR**
   - B. BOTH of the following:
     1. The patient has a diagnosis of Smith-Magenis Syndrome (SMS) confirmed by the presence of ONE of the following genetic mutations:
        - A. A heterozygous deletion of 17p11.2 **OR**
        - B. A heterozygous pathogenic variant involving RAI1 **AND**
     2. The requested agent is being used to treat nighttime sleep disturbances associated with SMS **OR**
   - C. The patient has another FDA labeled indication for the requested agent and route of administration **AND**
2. If the patient has an FDA approved indication, then ONE of the following:
   - A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
   - B. There is support for using the requested agent for the patient's age for the requested indication **AND**
3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., sleep specialist, neurologist, psychiatrist) or has consulted with a specialist in the area of the patient's diagnosis **AND**
4. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., sleep specialist, neurologist, psychiatrist) or has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support of therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months