tasimelteon (Hetlioz®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO215

Description

Tasimelteon (Hetlioz, Hetlioz LQ) is an agonist of melatonin MT1 and MT2 receptors which are thought to be involved in the control of circadian rhythms.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tasimelteon (Hetlioz)	20 mg capsules	Non 24-Hour Sleep-Wake Disorder; Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)	30 capsules/30 days
tasimelteon (Hetlioz LQ)	4 mg/mL oral suspension	Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)	0.7 mg/kg*
			158 ml bottle**

* for members weighing 28kg or less

** for members weighing more than 28kg

Initial Evaluation

I. Tasimelteon (Hetlioz, Hetlioz LQ) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a neurologist, sleep specialist, or psychiatrist; **AND**
   B. Treatment with melatonin (for at least three months continuously) has been ineffective, contraindicated, or not tolerated; **AND**
   C. A diagnosis of **Non-24-hour sleep-wake disorder (N24HSWD)** when the following are met:
      1. Member is 18 years of age or older; **AND**
      2. Member has a diagnosis of total blindness in both eyes without light perception; **AND**
      3. Provider has documented progressively shifting sleep-wake times with sleep diaries and/or actigraphy for at least 14 days; **AND**
      4. Treatment with at least TWO of the following groups has been ineffective or not tolerated, or **all** are contraindicated:
         i. benzodiazepines (eg. flurazepam, lorazepam, temazepam)

ii. non-benzodiazepines (eg. doxepin, eszopiclone, zaleplon)
iii. melatonin agonist (eg. ramelteon); **OR**

D. A diagnosis of **Nighttime sleep disturbances in Smith-Magenis Syndrome (SMS)** when the following are met:
1. Genetic testing has identified a heterozygous deletion of 17p11.2; **OR**
i. A heterozygous pathogenic variant involving RAI1; **AND**
2. Request is for tasimelteon (Hetlioz) capsules; **AND**
i. Member is 16 years of age or older; **OR**
3. Request is for tasimelteon (Hetlioz LQ) oral solution; **AND**
i. Member is between three and 15 years of age; **AND**
ii. Current weight provided in documentation

II. Tasimelteon (Hetlioz, Hetlioz LQ) is considered investigational when used for all other conditions, including but not limited to:
A. Sighted individuals with non-24-hour sleep-wake disorder
B. Non-24-hour sleep-wake disorder in blind individuals with light perception
C. Jet lag disorder
D. Major depressive disorder

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [e.g. longer duration of nighttime sleep, more alert during the day]

Supporting Evidence

I. The safety and efficacy of tasimelteon (Hetlioz) has been established in two phase III, placebo-controlled, randomized, double-blind studies (SET and RESET) in totally blind adult patients without light perception in both eyes and with a diagnosis of non-24-hour sleep-wake disorder.
- Patients were randomized to receive tasimelteon 20mg or placebo every 24 hours at a fixed clock time one hour before target bedtime.
- Primary outcome measure for the SET study of the proportion of entrained patients assessed in the intention-to-treat population assessed from 6-sulphatoxymelatonin

(aMT6s) rhythms for 4 weeks starting from day 14, was met by eight (20%) of 40 patients in the tasimelteon group, compared with one (3%) of 38 patients in the placebo group.
    - Primary outcome measure for the RESET study of the proportion of maintenance of entrainment (aMT6s) has been met by nine (90%) of ten patients in the tasimelteon group, whereas only two (20%) of ten patients withdrawn to placebo, maintained entrainment.
    - Entrained is the synchronization or alignment of the internal biological clock rhythm, including its phase and period, to external time cues, such as the natural dark-light cycle.
    - Duration of nighttime sleep was improved by 28 minutes and the duration of daytime napping was reduced by 27 minutes, while each worsened when treatment was withdrawn.

II. There is a lack of randomized clinical trial data to show safety and efficacy of tasimelteon (Hetlioz) in pediatric patients with the diagnosis of N24SWD. Although the SMS indication is approved in pediatric patients – very few pediatric patients (N=11) have actually received the medication, thus, use for N24HSWD in those under 18 years of age would be considered experimental.

III. Per the American Academy of Sleep Medicine Clinical Practice Guideline, a diagnosis of N24SWD requires at least 14 days of documentation of progressively shifting sleep-wake times with sleep diaries and/or actigraphy.

IV. The exogenous melatonin (0.5-10 mg) has been shown to entrain the free-running circadian rhythms of some blind subjects. The American Academy of Sleep Medicine has identified three studies in their guideline. Melatonin was administered either one hour prior to preferred bedtime, or at a fixed clock hour (21:00), for a period of 26–81 days (one to three months). The entrainment rate (12 of 18) found in the current meta-analysis of melatonin treatment in N24SWD was 67%. Due to the lack of head-to-head trials there is no clinical trial data to show that one therapy is superior to the other.

V. The safety and efficacy of tasimelteon (Hetlioz) for Nighttime Sleep Disturbances in SMS has been established a pivotal phase 2/3, nine-week, double-blind, randomized, placebo-controlled, two-period crossover study in 14 adults and 11 pediatric patients.
    - Patients 16 years of age and older received 20 mg capsules, and pediatric patients three years to 15 years of age received a weight-based dose of oral suspension.
    - The primary endpoints in were nighttime total sleep time [assessed via daily diary total nighttime sleep duration (DDTST)] and nighttime sleep quality from a parent/guardian-recorded diary (DDSQ). 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.

- Compared to placebo, treatment with tasimelteon (Hetlioz) 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 (Hetlioz) treatment, the difference was not statistically significant.

Primary Efficacy Measures	Treatment Group	LS Meana (SE)	Placebo-subtracted Difference (95% CI)
Average of 50% Worst Daily Nighttime Sleep Quality*	HETLIOZ (n=25)	2.8 (0.15)	0.4 (0.1, 0.7)
	Placebo (n=25)	2.4 (0.15)	-
Average of 50% Worst Daily Nighttime Total Sleep Time, hours	HETLIOZ (n=25)	7.0 (0.26)	0.3 (-0.0, 0.6)
	Placebo (n=25)	6.7 (0.26) -	-

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval unadjusted for multiplicity.

[a] LS Means are the model-based averages based on the 50% worst days per 4-week period.

[b] Difference (drug minus placebo) in least-squares means.

* Endpoint on which HETLIOZ was statistically significant different from placebo after controlling for multiple comparisons.

VI. The recommended dosage of tasimelteon (Hetlioz LQ) oral suspension for the treatment of nighttime sleep disturbance in SMS pediatric patients three to 15 years of age is by body weight. For patients with 28 kg or less the recommended dose is 0.7 mg/kg and for patients who weigh more than 28kg the recommended dose is 20 mg one hour before bedtime.

VII. Smith-Magenis syndrome (SMS) is a developmental disorder that affects many parts of the body. The major features of this condition include mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioral problems. Most people with SMS have a deletion of genetic material in each cell from a specific region of chromosome 17. Although this region contains multiple genes, researchers believe that the loss of one particular gene, RAI1, is responsible for most of the features of the condition. In most of these cases, the deletion is not inherited, occurring randomly during the formation of eggs or sperm, or in early fetal development.

- The diagnosis of SMS is established in a proband with suggestive clinical features and one of the following on molecular genetic testing: A heterozygous deletion of 17p11.2 or heterozygous pathogenic variant involving RAI1. When the phenotypic findings suggest the diagnosis of SMS, molecular genetic testing approaches can include chromosomal microarray analysis, single-gene testing, or use of a multigene panel.

VIII. Recent studies have attributed the sleep disturbance in SMS to a primary disturbance of the circadian clock, with RAI1 functioning as a positive regulator of Circadian Locomotor Output Cycles Kaput (CLOCK) transcription, a key component of the mammalian circadian oscillator.

Additionally, disrupted melatonin secretion has been noted with moderate to high levels of daytime salivary melatonin observed in SMS patients.

IX. As patients with SMS typically display a diurnal rather than nocturnal peak in melatonin secretion, exogenous melatonin has been used nocturnally to supplement the typical biological melatonin secretion. By adding an exogenous melatonin dose prior to bedtime, a nocturnal rise in melatonin levels can assist in increasing the biological propensity to sleep. Given the very limited experience of tasimelteon (Hetlioz) in pediatric populations, the safety and efficacy profile are largely unknown. Melatonin has a more established safety and efficacy profile and should be considered for use prior to tasimelteon (Hetlioz).

Investigational or Not Medically Necessary Uses

I. Tasimelteon (Hetlioz) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Sighted individuals with non-24-hour sleep-wake disorder and non-24-hour sleep-wake disorder in blind individuals with light perception
      i. There no published clinical trial data to show safety and efficacy and support the use of tasimelteon (Hetlioz) in these patient populations.
   B. Jet lag disorder
      i. A phase II, randomized, double blind proof of concept study to evaluate the effects of tasimelteon and placebo in travelers with jet lag disorder with the primary outcome measure of changes in sleep after transmeridian travel measured by nighttime sleep parameters
      ii. A randomized, double-blind, placebo-controlled, parallel design study evaluating the effects of tasimelteon compared to placebo on jet lag type insomnia enrolled 320 healthy adult patients. Tasimelteon treatment increased Total Sleep Time in the first 2/3 of the night (primary endpoint) by 60.3 min (95%CI 44.0 to 76.7, $P < 0.0001$) and whole night TST by 85.5 min (95% CI 64.3 to 106.6, $P < 0.0001$), improved next day alertness, next day sleepiness, and shortened latency to persistent sleep by −15.1 min (95% CI −26.2 to −4.0, $P = 0.0081$).
      iii. Jet Lag was induced by an immediate phase advance of the sleep-wake cycle in a sleep clinic, rather than jet travel in the eastward direction.
      iv. There isn't robust safety and efficacy data to support the use of tasimelteon (Hetlioz) in the treatment of the jet lag disorder.
   C. Major Depressive Disorder (MDD)
      i. A randomized, parallel, double-masked, placebo-controlled, multicenter outpatient study comparing tasimelteon with placebo with 507 enrolled participants (MAGELLAN) followed by a 52-week open label extension.

- The primary outcome measure was change from baseline to endpoint at week 8 using the total score of Hamilton Depression Rating Scale (HAM-D) was not met.
- The clinical trial showed insufficient efficacy and limited safety data.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
• Added new indication of Nighttime Sleep Disturbances in SMS • Added a new formulation, the tasimelteon (Hetlioz LQ) oral solution • New criteria added for the indication of N24HSWD:	12/2020

○ Treatment with melatonin (for at least three months continuously) has been ineffective, contraindicated or not tolerated ○ Member has a diagnosis of total blindness in both eyes without light perception ○ Provider has documented progressively shifting sleep-wake times with sleep diaries and/or actigraphy for at least 14 days ○ Treatment with at least TWO alternatives has been ineffective or not tolerated, or all are contraindicated: benzodiazepines (eg. flurazepam, lorazepam, temazepam), or non-benzodiazepines (eg. doxepin, eszopiclone, zaleplon) or melatonin agonist (eg. ramelteon) • Criteria removed from the indication of N24HSWD: ○ Member has no hepatic impairment or mild to moderate hepatic impairment ○ Member is not on concurrent strong CYP3A4 inducers or CYP1A2 inhibitors Criteria updated to policy format	
Criteria created	04/2014