Medical Policy

BlueCross BlueShield of Kansas
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Title: Circadian Rhythm Disorder

- **Prime Therapeutics will review Prior Authorization requests**

Prior Authorization Form:
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6341KS-HETL.pdf

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

Professional
Original Effective Date: September 1, 2015
Revision Date(s): September 1, 2015; June 1, 2016
Current Effective Date: June 1, 2016

Institutional
Original Effective Date: September 1, 2015
Revision Date(s): September 1, 2015; June 1, 2016
Current Effective Date: June 1, 2016

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

The intent of the Circadian Rhythm Disorder prior authorization criteria is to appropriately select patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies and according to dosing recommended in product labeling. Tasimelteon will be approved for use in blind patients (i.e. no light perception) with Non-24-Hour

Sleep-Wake Disorder (Non-24), or another FDA approved indication. Requests for tasimelteon will be reviewed when patient-specific documentation is provided.

Target Drugs

- **Hetlioz™** (tasimelteon)

FDA Approved Indications and Dosage[1]

- **FDA Indication:** for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24).
- **Dosing:** the recommended dosage is 20 mg per day taken before bedtime, at the same time every night. Hetlioz should be taken with food.

POLICY

Prior Authorization and Quantity Limits Criteria for Approval

Hetlioz will be approved when **ALL** of the following is met:

1. ONE of the following:
   a. ALL of the following for Non-24-hour sleep wake disorder:
      i. The patient is totally blind (i.e. no light perception)
      AND
      ii. The patient has a diagnosis of Non-24-hour sleep-wake disorder
      AND
      iii. The prescriber is a sleep specialist or has consulted with a sleep specialist
   OR
   b. ALL of the following:
      i. The patient has another FDA labeled indications
      AND
      ii. The prescriber is a specialist in the area of the patient's diagnosis or has consulted with a specialist in the area of the patient's diagnosis

   AND
2. The patient does not have any FDA labeled contraindications to the requested agent
   AND
3. The patient does not have severe hepatic impairment (Child-Pugh Class C)
   AND
4. ONE of the following:
   a. The quantity requested is less than or equal to the program quantity limit
   OR
   b. The quantity (dose) requested is above the program limit, less than or equal to the maximum dose recommended in FDA approved labeling and the prescribed dose cannot be achieved using a lesser quantity of a higher strength
   OR

c. The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis

Length of Approval: 12 months

FDA Labeled Contraindications	
Agent	**Contraindications**
Hetlioz (tasimelteon)	None

Program Quantity Limits	
Brand (generic)	**Quantity Limit Per Day**
Hetlioz (tasimelteon)	
20 mg capsule	1 capsule

RATIONALE

Tasimelteon (Hetlioz) is a melatonin receptor agonist indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24). Non-24 is a rare, chronic circadian rhythm disorder characterized by the inability to synchronize (entrain) the master body clock with the 24 hour day-night cycle, resulting in significant disruption of the sleep-wake cycle which affects nighttime sleep patterns and causes excessive daytime sleepiness. According to the American Academy of Neurology "disturbances in people who are blind are common, and approximately 50% may have Non-24."[3] The FDA review states that "There are approximately 1,300,000 blind people in the United States. Ten percent of these individuals have no light perception. The Applicant cites an estimated prevalence of Non-24 in the totally blind as being approximately 100,000 individuals in the United States."[6] Totally blind is defined as when there is no light perception.[7-9]

Non-24 occurs almost exclusively in people who are deprived of light, which is needed to synchronize the body's internal clock. When light does not enter the eyes, the body cannot synchronize to the 24 hour light-dark cycle. Those affected may have difficulty falling asleep or staying asleep and may wake up feeling as if they need more sleep. Many people may have their sleep patterns reversed, needing to sleep during the day and to be awake at night. Those individuals with Non-24 may experience severe disruptions to essential activities such as school, work, and parenting due to the condition.[2,3]

Guidelines, Reviews

The American Academy of Sleep Medicine guidelines on treatment of circadian rhythm disorders (AASM, 2015) recommends clinicians use strategically timed administration of melatonin for treatment of Non-24-Hour Sleep-Wake Disorder in blind adults (vs. no treatment) [Weak]. No serious adverse reactions to melatonin have been described to date and therefore benefits of use appear to outweigh any potential harm.[4]

A review on circadian rhythm disorders (American Academy of Neurology, 2013) suggests that melatonin is the therapeutic mainstay in blind patients with Non-24-Hour Sleep-Wake Disorder,

together with strong structured behavioral and social cues (e.g., timing of meals, planned activities, and regular physical exercise). 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-Hour Sleep-Wake Disorder 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.[3]

An evidence base review suggested appropriately timed melatonin, in doses from 0.5 mg to 10 mg, have been shown to entrain totally blind people who have Non-24-Hour Sleep-Wake Disorder. The effective dose may be even less than 0.5 mg (the dose that approximates a physiological plasma concentration). Treatment must be sustained or relapse will occur. Entrainment may not occur for weeks or months after initiating treatment, depending on the phase of the patient's rhythm when treatment is started and the period of the patient's free-running rhythm.[6]

Efficacy

The efficacy of tasimelteon was evaluated in two randomized double-blind, placebo-controlled, multicenter, parallel-group trials in totally blind patients with a diagnosis of Non-24-Hour Sleep-Wake Disorder.[1]

In study 1 (also known as the SET Study), 84 patients 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.[1]

Study 2 (also known as the RESET Study) was a randomized withdrawal trial in 20 patients with Non-24-Hour Sleep-Wake Disorder (median age 55 years) that was designed to evaluate the maintenance of efficacy of tasimelteon after 12-weeks. Patients were treated for approximately 12 weeks with tasimelteon 20 mg one hour prior to bedtime, at the same time every night. Patients in whom the calculated time of peak melatonin level (melatonin acrophase) occurred at approximately the same time of day (in contrast to the expected daily delay) during the run-in phase were randomized to receive placebo or continue treatment with tasimelteon 20 mg for 8 weeks.[1]

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-Hour Sleep-Wake Disorder, 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. In Study 1, patients in the tasimelteon group had, at baseline, an average 195 minutes of nighttime sleep and 137 minutes of daytime nap time on 25% of most symptomatic nights and days, respectively.

Treatment with tasimelteon resulted in a significant improvement, compared with placebo, for both of these endpoints in Study 1 and Study 2.[1]

Table 2: Effects of HETLIOZ 20 MG on Nighttime Sleep Time and Daytime Nap Time in Study 1 and Study 2

	Study 1		Study 2	
Change from Baseline	**HETLIOZ 20 MG N=42**	**Placebo N=42**	**HETLIOZ 20 MG N=20**	**Placebo N=20**
Nighttime sleep time on 25% most symptomatic nights (minutes)	50	22	-7	-74
Daytime nap time on 25% most symptomatic days (minutes)	-49	-22	-9	50

Safety

The package labeling for Hetlioz states that after taking it patients should limit their activity to preparing for going to bed as tasimelteon can potentially impair the performance of activities requiring complete mental alertness.[1]

The most commonly reported adverse reactions during clinical trials were headache, increased ALT, nightmares or unusual dreams, and upper respiratory or urinary tract infections. Tasimelteon has not been studied in those with severe liver impairment and is not recommended in these patients. The risk of adverse reactions may be greater in elderly (>65 years) patients than younger patients because exposure to tasimelteon is increased by approximately 2-fold compared with younger patients.[1]

Use of tasimelteon with fluvoxamine or other strong CYP1A2 inhibitors should be avoided due to a potentially large increase in tasimelteon exposure and a greater risk of adverse effects. Smoking induces CYP1A2 and exposure of tasimelteon was lower in smokers than in non-smokers which may lower the efficacy. Tasimelteon should also not be used in combination with rifampin or other CYP3A4 inducers because of a potentially large decrease in tasimelteon exposure and reduced efficacy.[1]

REVISIONS

09-01-2015	Policy added to bcbsks.com on 08-25-2015 and effective 09-01-2015.
06-01-2016	Policy title change to “Circadian Rhythm Disorder” from “Hetlioz (tasimelteon)”
	Description section updated
	In Policy section: ▪ Added Item 1 added “ONE of the following:” ▪ Removed “The patient is greater than or equal to 18 years of age” ▪ Added Item 1 a “ALL of the following for Non-24-hour sleep wake disorder:” ▪ In Item 1 a i added “totally” and “(i.e. no light perception)” and removed

	"legally" to read "The patient is totally blind (i.e. no light perception)" ▪ Added b. "ALL of the following: i. The patient has another FDA labeled indications AND ii. The prescriber is a specialist in the area of the patient's diagnosis or has consulted with a specialist in the area of the patient's diagnosis" ▪ In Item 2 added "the requested agent" and removed "therapy with Hetlioz (tasimelteon)" to read "The patient does not have any FDA labeled contraindications to the requested agent" ▪ Added 4 b "The quantity (dose) requested is above the program limit, less than or equal to the maximum dose recommended in FDA approved labeling and the prescribed dose cannot be achieved using a lesser quantity of a higher strength"
	Rationale section updated
	References updated

REFERENCES

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