BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/22/15**
SECTION: DRUGS	**LAST REVIEW DATE: 1/18/18**
	LAST CRITERIA REVISION DATE: 1/18/18
	ARCHIVE DATE:

HETLIOZ™ (tasimelteon) oral capsule

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

HETLIOZ™ (tasimelteon) oral capsule (cont.)

Description:

Hetlioz (tasimelteon) is a melatonin receptor agonist indicated for the treatment of non-24-hour sleep-wake disorder (Non-24). Non-24 is also known as free-running disorder, free running type or non-entrained type circadian rhythm sleep disorder, hypernychthemeral syndrome, and Non-24-hour circadian sleep disorder.

Tasimelteon is an agonist of melatonin receptors MT1 and MT2; it has greater affinity for the MT2 receptor than the MT1 receptor. Stimulation of MT1 receptors is thought to preferentially induce sleepiness, while MT2 receptor activation preferentially influences regulation of circadian rhythms. Because of individual differences in circadian rhythms the effect of tasimelteon may not be seen for weeks or months.

Background:

- Non-24 is characterized by excessive daytime sleepiness and nighttime insomnia
- The International Classification of Sleep Disorders defines non-24-hour sleep wake disorder as a circadian rhythm sleep disorder characterized by complaints of insomnia or excessive sleepiness related to abnormal synchronization between the 24-hour light–dark cycle and the endogenous circadian rhythms of sleep and wake tendency
    - Non-24 is a chronic disorder of the biological circadian rhythm where an individual's biological clock fails to synchronize to a 24-hour day
    - The intrinsic circadian timekeeping system oscillates with a period slightly longer than 24 hours: about 24.2 hours in adults and 24.3 hours in adolescents.
    - To maintain alignment with the 24-hour day, the circadian system must adjust, or phase shift, each day via time cues, called zeitgebers.
        - The most potent zeitgeber is the environmental light-dark cycle
- Patients with Non-24 experience a steady pattern of 1-2-hour daily delays in sleep onset and wake times
- It is estimated that 20% of legally blind individuals have little or no light perception and are considered totally blind
    - More than half of all totally blind individuals have Non-24
- The lack of sight and the loss of light cues to the brain prevent synchronization of the sleep-wake cycle by the suprachiasmatic nucleus of the hypothalamus in the brain
- Circadian sleep-wake rhythm disorders are predominantly a clinical diagnosis
    - But various self-reported and objective measures, including sleep diaries, actigraphy, and melatonin sampling, are beneficial in establishing the diagnosis
    - A sleep diary is a key component of the evaluation of patients with suspected circadian disorders
    - Actigraphy can supplement subjective data from sleep diaries, or it may be the sole source of data on patients who cannot complete a sleep diary
        - Actigrpahy is a noninvasive method of monitoring rest & activity cycles
    - Melatonin secretion follows a circadian rhythm:
        - Plasma and urine concentrations are low during daylight
        - Levels increase after the onset of darkness
            - Peaking in the middle of the night between 11 PM and 3 AM

        - Levels fall before the onset of daylight
    - The nocturnal rise in melatonin secretion plays an important role in the initiation and maintenance of sleep.
        - The normal day/night melatonin rhythm regulates the timing of other 24-hour rhythms
        - Exposure to light suppresses the normal nocturnal rise in plasma melatonin concentrations
    - Objective determination of an individual's circadian phase is most easily accomplished by assessment of the 24-hour rhythm of the hormone melatonin. The circadian system signals the pineal gland to produce melatonin typically 90-120 minutes prior to habitual bedtime
    - Time spent in nighttime sleep and time spent in daytime naps are also used to establish the diagnosis and evaluate treatments

- The patient's circadian rhythm can be calculated by various measures, the most common of which includes assessing a melatonin metabolite in the urine
    - Circadian period is the time taken to complete one cycle of a circadian rhythm and is around 24 hours in healthy individuals
        - It is measured from a fixed point within a single cycle (peak or trough), to the same fixed point of the next cycle
    - The circadian period is calculated by reviewing the peak production of 6-sulfatoxymelatonin (aMT6, a major urinary metabolite of melatonin) and cortisol in urine
    - Determination of circadian period requires numerous sequential urine samples every 4-8 hours for a total of 48 hours
    - For each collection time the aMT6 and cortisol in the urine are measured and expressed as a rate of secretion (nanograms) per hour
    - The circadian period can predict when a subject was in phase with their preferred sleep time

- Entrainment is a term used to describe the synchronization to a normal 24-hour light-dark cycle
    - Entrainment is defined as alignment of a circadian period to an external or endogenous rhythm
    - Entrainment in clinical studies was determined from an analysis of 4 separate peak times of urinary aMT6 specimen collections in 4-8 hour intervals for 48 hours/week for at least 4 weeks beginning 2 weeks after treatment initiation

- The American Academy of Sleep Medicine Practice Parameters recommends timed melatonin administration and scheduled social and physical activities for blind individuals with Non-24

HETLIOZ™ (tasimelteon) oral capsule (cont.)

Definitions:

Diagnostic criteria for non-24-hour sleep-wake rhythm disorder - American Academy of Sleep Medicine. International Classification of Sleep Disorders

Diagnostic criteria A-D must be met:	
A	There is a history of insomnia, excessive daytime sleepiness, or both, which alternate with asymptomatic episodes, due to misalignment between the 24-hour light-dark cycle and the non-entrained endogenous circadian rhythm of sleep-wake propensity.
B	Symptoms persist over the course of at least three months.
C	Daily sleep logs and actigraphy for at least 14 days, preferably longer for blind persons, demonstrate a pattern of sleep and wake times that typically delay each day, with a circadian period that is usually longer than 24 hours.
D	The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Hetlioz (tasimelteon)

Medication class:
Hypnotic, Melatonin Receptor Agonist

FDA-approved indication(s):
- For the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24)

Recommended Dose:
- 20 mg one hour prior to bedtime

Maximum dosage
- Not stated

Available Dosage Forms:
- 20 mg caps

Warnings, Precautions, and other Clinical Information:
- Drug effect may not occur for weeks or months
- Hetlioz has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and is not recommended in these patients
- The absolute bioavailability of Hetlioz is 38.3%
- Hetlioz is metabolized by CYP1A2 & CYP3A4
- Use of CYP1A2 inducers or smoking may decrease Hetlioz efficacy
- Avoid use with fluvoxamine or other strong CYP1A2 inhibitors
- Avoid use with strong rifampin or other CYP3A4 inducers

HETLIOZ™ (tasimelteon) oral capsule (cont.)

- Hetlioz may cause somnolence, use with caution when other drugs that cause are also used
- Efficacy of Hetlioz may be reduced with concurrent use with a beta-adrenergic receptor antagonist
- Hetlioz is not indicated for use in general insomnia, sighted individuals with Non-24-hour sleep wake disorder, blind individuals with Non-24-hour sleep wake disorder who have light perception, obstructive sleep apnea, shift work sleep disorder, jet lag, major depressive disorder, or narcolepsy

Criteria:

- **Criteria for initial therapy:** Hetlioz (tasmelteon) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met :

  1. Request is from a Specialist in Sleep Disorders

  2. Individual is 18 years of age and older

  3. A confirmed diagnosis of Non-24-hour sleep wake disorder in an individual who is totally blind with no light perception
     - Diagnosis is supported by **ONE** of the following:
       - Measurement of urinary melatonin levels
       - Actigraphy performed for ≥ 1 week plus evaluation of sleep logs recorded for ≥ 1 month

  4. Individual has failure, contraindication or intolerance to **ALL** the following preferred step therapy agents:
     - Preferred step therapy agents include: (used nightly at same time, not on an as needed basis)
       - Timed melatonin
       - Timed Rozerem (ramelteon)

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Hetlioz (tasmelteon) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met :

  1. Individual continues to be seen by Specialist in Sleep Disorders

  2. Individual's condition responded while on therapy
     - Response is defined as:
       - 45 minute increase in nighttime sleep and 45 minute decrease in daytime sleep
       - Entrainment to a 24-hour cycle has been achieved

  3. Individual has been adherent with the medication, there must not be any gaps in usage

  4. There are no significant interacting drugs

  Renewal duration: 12 months

HETLIOZ™ (tasimelteon) oral capsule (cont.)

Resources:

Hetlioz. Package Insert. Reference ID: 3627825. Revised by the manufacturer 01/2014. Accessed 12-05-2014.

Hetlioz. Package Insert. Revised by the manufacturer 12/2014. Accessed 12-04-2016, 12-18-2017

Morgenthaler TI, Lee-Chiong T, Alessi C, et al. Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders: An American Academy of Sleep medicine Report. Sleep 2007; 30(11):1445-1459.

Sack RL, Auckley D, Auger R, et. Al. Circadian Rhythm Sleep Disorders: Part II, Advanced Sleep Phase Disorder, Delayed Sleep Phase Disorder, Free-Running Disorder, and Irregular Sleep-Wake Rhythm: An American Academy of Sleep Medicine Review. Sleep 2007; 30(11):1484-1501.

UpToDate: Overview of circadian sleep-wake rhythm disorders. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/overview-of-circadian-sleep-wake-rhythm-disorders?source=search_result&search=non%2024%20hour%20sleep%20wake%20disorder&selectedTitle=1~59

UpToDate: Classification of sleep disorders. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/classification-of-sleep-disorders?source=search_result&search=non%2024%20hour%20sleep%20wake%20disorder&selectedTitle=3~59

UpToDate: Physiology and available preparations of melatonin. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/physiology-and-available-preparations-of-melatonin?sectionName=Circadian%20rhythm&anchor=H14100125&source=see_link#H31

UpToDate: Overview of actigraphy. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/overview-of-actigraphy?source=search_result&search=non%2024%20hour%20sleep%20wake%20disorder&selectedTitle=4~59

UpToDate: Treatment of insomnia in adults. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-insomnia-in-adults?source=search_result&search=non%2024%20hour%20sleep%20wake%20disorder&selectedTitle=2~59

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.