Circadian Rhythm Disorder
Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, Health Insurance Marketplace, FocusRx and KeyRx.

This is a FlexRx standard and GenRx standard prior authorization program.

FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosing and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hetlioz®</td>
<td>Treatment of Non-24-Hour Sleep-Wake Disorder (Non-24)</td>
<td>20 mg prior to bedtime, at same time every night</td>
</tr>
<tr>
<td>capsules</td>
<td></td>
<td>Take without food</td>
</tr>
</tbody>
</table>

CLINICAL 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.

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. Totally blind is defined as when there is no light perception. 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.

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. 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). 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.
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.\(^5\)

Tasimelteon is a melatonin receptor agonist indicated for the treatment of Non-24-Hour-Sleep-Wake Disorder. In the Safety and Efficacy of Tasimelteon (SET) trial, 84 patients were randomized to 20mg of tasimelteon or placebo. Patients assigned to the tasimelteon were more likely to be entrained at one month (20% versus 3%). Entrainment rates improved to 50% in individuals assessed at 6 weeks.\(^9\)

REFERENCES

Circadian Rhythm Disorder Prior Authorization with Quantity Limit

TARGET AGENTS
Hetlioz® (tasimelteon)

PROGRAM PRIOR AUTHORIZATION AND QUANTITY LIMIT

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hetlioz (tasimelteon)</td>
<td>60250070000130</td>
<td>M, N, O, or Y</td>
<td>1 capsule</td>
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</tbody>
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PRIOR AUTHORIZATION AND QUANTITY LIMIT CRITERIA FOR APPROVAL

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

1. ONE of the following:
   a. BOTH of the following:
      i. The patient has a diagnosis of Non-24-hour sleep-wake disorder AND
      ii. The patient is totally blind (i.e. no light perception)
   OR
   b. The patient has another FDA labeled indication AND

2. The prescriber is a specialist in the area of the patient’s diagnosis (e.g. sleep specialist for Non-24-hour sleep-wake disorder) or has consulted with a specialist in the area of the patient’s diagnosis AND

3. The patient does NOT have any FDA labeled contraindications to the requested agent AND

4. ONE of the following:
   a. The requested quantity (dose) does not exceed the program quantity limit OR
   b. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit AND
      ii. The requested quantity (dose) does not exceed the maximum FDA labeled dose for the requested indication AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit OR
   c. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit AND
      ii. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication AND
      iii. The prescriber has submitted documentation in support of therapy with a higher dose for the requested indication

Length of Approval: 12 months