

Tasimelteon (Hetlioz®)

FDA approved January 2014; Vanda Pharmaceuticals

Indication: Tasimelteon is indicated for the treatment of Non 24-Hour Sleep-Wake Disorder (Non-24 or N24SWD), a circadian sleep-wake rhythm disorder that occurs primarily in completely blind individuals

Mechanism of action

The precise mechanism is not known; however, the efficacy could be mediated through an agonist activity at melatonin MT₁ and MT₂ receptors. These receptors are thought to be involved in the control of circadian rhythms

Dosage	20 mg
Severe hepatic impairment	Not recommended (not studied)
Administration	<ul style="list-style-type: none">• Administer without food prior to bedtime, at same time every night• Skip the dose on a night that the drug cannot be taken at the same time as previous nights
How Supplied	20 mg capsules

Interactions

Concomitant Medication	Effect
Strong CYP1A2 inhibitors (eg. fluvoxamine)	Avoid use (increased exposure)
Strong CYP3A4 inducers (eg. rifampin)	Avoid use (decreased exposure)
Drug-Food Interactions	Administer without food (high-fat meal lowers C _{max} 44% & delays T _{max} ~1.75 hrs)

Adverse Effects

Most frequently reported AEs (≥5% & at least twice of placebo)	Headache, ↑ALT, nightmares or unusual dreams, upper respiratory infection or UTI
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Warnings & precautions

CNS depression: May cause somnolence (can impair the performance of activities requiring complete mental alertness)

Pharmacokinetics

Onset	Weeks to months d/t individual differences in circadian rhythms
Absorption	High-fat meals delay T _{max} & reduce C _{max} by 44%
Bioavailability	~38%

Half-life	~1 to 2 hours
Metabolism	▪ extensive hepatic metabolism; oxidative metabolism primarily through CYP1A2 & CYP3A4
T_{max}	Fasting: ~0.5 to 3 hrs (delayed by ~1.75 hrs with high-fat meal)
Excretion	Urine (80%); feces (~ 4%)

Clinical Studies

Efficacy: The efficacy of tasimelteon was evaluated in 104 patients in 2 randomized, double masked trials of completely blind individuals with N24SWD disorder. Pts were randomized to receive tasimelteon or placebo at the same time every night. Both studies evaluated the duration and timing of night time sleep and daytime naps via patient-recorded diaries

Study 1 - Safety & Efficacy of Tasimelteon (SET)

- 84 patients were randomized to receive tasimelteon 20 mg or placebo for up to 6 months
- at baseline, pts had an average 195 minutes of night time sleep & 137 minutes of daytime nap time on the 25% of most symptomatic nights & days respectively
- treatment with tasimelteon resulted in a significant improvement compared to placebo
 - mean total night time sleep was 28 minutes longer & daytime nap time was 27 minutes shorter in the tasimelteon group
- 80% of the tasimelteon-treated individuals did not entrain, highlighting the challenges in treating this pt population
 - entrainment rates improved to 50% in individuals assessed at 6 rather than 4 weeks indicating that a longer observation period is needed before determining whether a patient is responding to the treatment
- A responder analysis of pts with at least 45 minutes increase in night time sleep and at least 45 minutes decrease in daytime nap time indicates that 29% (n = 12) of tasimelteon treated pts compared with 12% (n = 5) of placebo treated pts met the responder criteria

Study 2 - Randomized Withdrawal Study of the Efficacy and Safety of Tasimelteon (RESET) to evaluate tasimelteon (n = 10) maintenance of efficacy compared to placebo (n = 10). Pts were treated initially for ~ 12 weeks

- Pts in whom the calculated time of peak melatonin level 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 for 8 weeks
- synchronization was maintained in 90% of the tasimelteon group compared to 20% of placebo
- mean total night time sleep was 67 minutes longer & daytime nap time was 59 minutes shorter in the tasimelteon group versus placebo

Safety: The most common AEs observed in the SET study were headache (17 vs 7%), elevated ALT (10 vs 5%), nightmares/abnormal dreams (10 vs 0%), upper respiratory tract infection (7 vs 0%), & UTI (7 vs 2%)

Role in Therapy

- Tasimelteon is the first FDA approved drug for the treatment of non-24-hour sleep-wake disorder. The endogenous circadian rhythm is slightly longer than 24 hours and daily adjustment/entrainment of the circadian clock is required to maintain alignment with the 24-hour environment
 - light serves as one of the primary entraining signals and individuals with N24SWD are unable to maintain appropriate alignment with the 24-hour environment
 - the sleep-wake patterns of Non-24 pts shift daily with respect to external time & they suffer from periodic daytime somnolence and nighttime insomnia as their circadian rhythms drift in and out of synchrony with the 24-hr day
- Tasimelteon can significantly increase nighttime sleep and reduce daytime nap time
 - preferred option in pts who do not respond to melatonin and an alternative for pts not comfortable taking an OTC supplement
- Due to individual differences in circadian rhythms, daily use for several weeks / months may be necessary to achieve clinical benefit
 - higher rates of entrainment were found during longer, open label treatment
- Tasimelteon displays greater affinity for the MT₂ receptor. The MT₁ receptor is considered to regulate sleepiness, whereas the MT₂ receptor is thought to help the body shift between day and night
 - Tasimelteon may therefore act by signaling the body that it is nighttime
 - During clinical trials, 20% of those taking tasimelteon were able to get day-night synchronized compared to 3% taking placebo
- In elderly subjects, tasimelteon exposure increased by ~2-fold; whereas exposure decreased by ~40% in smokers
- Tasimelteon's efficacy may be reduced in pts on concomitant beta-adrenergic receptor antagonists
- Preliminary data suggests that melatonin and melatonin agonists may be useful for improvement of sleep quality and relapse prevention in Bipolar Disorder
- Future studies investigating the role of melatonin and its analogues in other circadian rhythm disorders such as shift-work disorders, jet-lag, "sundowning" associated with Alzheimer's Disease, and depression would be beneficial to produce evidence based therapeutic guidelines
- Non-FDA-approved therapeutic alternatives for non-24 in blind individuals without light perception
- Ramelteon (Rozerem), a melatonin receptor agonist is approved for the treatment of insomnia. Short-term use is associated with improvement in sleep onset in patients with insomnia, but the effect size is relatively small & may not be clinically significant

- Findings of a 2014 meta-analysis (over 5700 patients) suggest that ramelteon was associated with significant improvement in sleep latency (-4.6 minutes) & total sleep time (7.3 minutes) compared to placebo
- Although not studied in patients with N24SWD, has been shown to shift circadian phase in individuals with jet lag and might be expected to have similar effects as tasimelteon in treating N24SWD
- Ramelteon binds to melatonin receptors with higher affinity than melatonin and appears to be more effective in treating sleep onset insomnia compared with sleep maintenance insomnia
 - i. greater affinity & potency than melatonin for the MT1 receptor; improved sleep onset
- contraindicated in patients taking fluvoxamine (fluvoxamine may decrease ramelteon metabolism)
- Ramelteon and tasimelteon reduce the latency to sleep onset and increase sleep duration, although ramelteon's effects on sleep continuity are inconsistent
- Melatonin binds to all three melatonin receptors and is less potent than ramelteon
 - Not FDA approved for any indication; available as a dietary supplement and is promoted as a sleep aid
 - although no direct comparisons, melatonin is considered a better chronobiotic agent compared to ramelteon
 - may be useful in circadian rhythm disorders such as jet lag and delayed sleep-wake phase syndrome
 - Melatonin also appears to reduce latency to sleep onset; however, its effects on sleep maintenance & duration are inconsistent
- The 2015 American Academy of Sleep Medicine guidelines for the treatment of N24SWD recommended use of melatonin for the treatment of N24SWD in blind pts
 - No recommendation for or against the use of tasimelteon
 - No convincing evidence that tasimelteon is better than melatonin
- Comparison of tasimelteon to ramelteon is lacking and it is not known how tasimelteon compares to a melatonin supplement
- Ramelteon, tasimelteon, and melatonin are not controlled substances and are not associated with abuse or dependence

Price Comparison:

Drug Name	Daily Dose	Monthly Cost*	Comment
Tasimelteon (Hetlioz)	20mg	\$16,643	
Ramelteon (Rozerem)	8mg	\$105	Generic available
Melatonin	3-10mg	\$ 3	OTC

*Wholesale Acquisition Price as of 5/5/2020

Formulary Recommendation:

BHRS and HPSM MediCal: Nonformulary
CA/CMC: ADD to formulary with PA criteria:

Covered Uses: FDA approved indications

Age limit: 18 yrs and older

Required medical information:

All of the conditions have to be met for approval:

- Patient is completely blind, AND
- Patient has a diagnosis of non-24-hour sleep-wake disorder by a sleep specialist or in consult with a sleep specialist, AND
- Tried and failed least 1-month trial of melatonin administration that resulted in an inadequate response or an adverse effect, AND
- Tried and failed least 1-month trial of ramelteon administration that resulted in an inadequate response or an adverse effect

Prescriber restriction: Sleep specialist or in consult with sleep specialist

Duration of approval: 6 months

Quantity Limit: #30/30DS MADD

Renewal requirement:

- Documentation of improvement
- Duration of approval: 12 months
- Quantity Limit #30/30DS MADD

References

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