Hetlioz (tasimelteon)

STRENGTH	DOSAGE FORM	ROUTE	GPID
20 mg	capsule	oral	36068

MANUFACTURER

Vanda Pharmaceuticals, Inc.

INDICATION(S)

For the treatment of non-24-hour sleep-wake disorder

DRUG CLASS
BEHAVIORAL HEALTH; HYPNOTICS, MELATONIN MT1/MT2 RECEPTOR AGONISTS

PLACE IN THERAPY

Hetlioz is the first FDA approved treatment for non-24 hour sleep-wake disorder (N24HSWD), a chronic circadian rhythm disorder in which a person's day length is not synchronized with the 24-hour day-night cycle. Hetlioz is a melatonin receptor agonist that has high affinity for MT1 and MT2 receptors in the suprachiasmatic nucleus of the brain, which are thought to synchronize the body's melatonin and cortisol circadian rhythms with the day-night cycle. The majority of people with N24HSWD are completely blind due to the lack of light information received from the eyes, which normally regulates the 24-hour day-night cycle. Currently there are 1.3 million legally blind people in the United States (US); 130,000 are completely blind and approximately 70% of those people suffer from N24HSWD.

Treatments for N24HSWD are aimed at resynchronizing the patient's internal body clock to the 24-hour day-night cycle. Phototherapy and dietary melatonin are commonly used to help manage symptoms, as there is no permanent cure for the disorder. In sighted patients, exposure to bright light may counteract the tendency for circadian rhythms to delay. It involves 30-120 minutes of exposure to 3,000 to 10,000 lux light intensity upon awakening daily. Use of melatonin may also be successful in advancing a patient’s circadian rhythm, however the dosage and time of administration need to be adjusted on an individual basis.

Aside from Hetlioz, branded Rozerem (ramelteon) is the only other melatonin receptor agonist approved in the US. However, Rozerem is not indicated for N24HSWD, but rather for the treatment of insomnia characterized by difficulty with sleep onset. Hetlioz offers another option for the treatment of N24HSWD in which there is FDA oversight and regulation, unlike over-the-counter dietary melatonin.

EFFICACY

The efficacy of Hetlioz in the treatment of N24HSWD was established in two randomized double-masked, placebo-controlled, multicenter, parallel-group studies (Studies 1 and 2) in totally blind patients with N24HSWD. In study 1, 84 subjects (median age 54 years) were randomized to receive Hetlioz 20 mg or placebo, one hour prior to bedtime, at the same time every night for up to 6 months. Study 2 was a randomized withdrawal trial in 20 subjects (median age 55 years) that was designed to evaluate the maintenance of efficacy of Hetlioz after 12 weeks. Subjects were treated for approximately 12 weeks with Hetlioz 20 mg one hour prior to bedtime, at the same time every night. Subjects 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 Hetlioz 20 mg for 8 weeks. Both studies evaluated the duration and timing of nighttime sleep and daytime naps via patient-recorded diaries. 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 Hetlioz group had an average baseline of 195 minutes (3 hours, 15 minutes) of nighttime sleep and 137 minutes (2 hours, 17 minutes) of daytime nap time on the 25% of most symptomatic nights and days, respectively. The data shows that patients taking Hetlioz gained an extra 50 minutes of nighttime sleep, an improvement from roughly 3 hours of sleep at baseline to 4 hours; the decrease in duration of daytime naps was 49 minutes, meaning patients who napped roughly 2 hours at baseline were napping about 1 hour with Hetlioz. In both studies, treatment with Hetlioz resulted in significant improvement compared to placebo, both in increasing nighttime sleep and decreasing daytime sleep duration, however this may not be clinically significant.

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

Obtained from the Hetlioz Package Insert

SAFETY

Hetlioz is extensively metabolized via oxidation involving CYP1A2 and CYP3A4 isozymes. Use of Hetlioz in combination with strong CYP1A2 inhibitors (e.g. fluvoxamine) may potentially increase Hetlioz exposure and thus increase the risk of adverse reactions. Co-administration with CYP3A4 inducers may potentially decrease Hetlioz exposure and result in reduced efficacy. Patients who smoke may also experience reduced efficacy since smoking causes induction of CYP1A2 levels.

The most frequently reported adverse reactions in patients receiving Hetlioz include headache (17%), alanine aminotransferase increase (10%), nightmare/abnormal dreams (10%), upper respiratory tract infection (7%), and urinary tract infection (7%). In placebo-controlled studies, 6% of patients exposed to Hetlioz discontinued treatment due to an adverse event, compared with 4% of patients who received placebo.

There were no signs or symptoms indicative of abuse potential or physical dependence in clinical studies with Hetlioz. Discontinuation of Hetlioz following chronic administration did not produce withdrawal signs.

Hetlioz is classified as a pregnancy category C.

DOSAGE

The recommended dosage of Hetlioz is 20 mg per day taken before bedtime, at the same time every night. Because of individual differences in circadian rhythms, drug effect may not occur for weeks or months.

Hetlioz should be taken without food.

COST

Drug	**Cost/unit**	**Maximum Cost per 30 Days***
Hetlioz (tasimelteon) 20mg capsule	AWP $280.77	$8423.10
Rozerem (ramelteon) 8mg tablet[#]	AWP $8.38	$251.40
Melatonin OTC 0.3mg, 1mg, 2.5mg, 3mg, 5mg, 10mg[#]	AWP $0.01-0.39	$0.30-11.70

*Pricing based on the following dosages: Hetlioz 20mg daily, Rozerem 8mg daily, melatonin 0.3mg-10mg daily
[#] Not FDA approved for the treatment of Non-24-Hour Sleep-Wake Disorder

FORMULARY PLACEMENT RECOMMENDATIONS

Based on this initial assessment of available clinical and financial information, consider NOT ADDING Hetlioz to the formulary pending complete review by the appropriate oversight committee for the plan.

REFERENCES

- Hetlioz [Prescribing Information]. Washington, D.C., Vanda Pharmaceuticals, Inc., Jan 2014.
- FDA News Release on Jan 31, 2014: FDA approves Hetlioz: first treatment for non-24 hour sleep-wake disorder in blind individuals.
  Available online at:
  http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm384092.htm
- Circadian Sleep Disorders Network. http://www.circadiansleepdisorders.org/index.php