CLINICAL UPDATE

Brand Name	Hetlioz LQ®
Generic Name	tasimelteon
Drug Manufacturer	Vanda Pharmaceuticals Inc.

Clinical Update

TYPE OF CLINICAL UPDATE

New Dosage Form (Oral Suspension)

FDA APPROVAL DATE

December 01, 2020

LAUNCH DATE

March 03, 2021

REVIEW DESIGNATION

Type 3 - New Dosage Form

TYPE OF REVIEW

Priority; Orphan; New Drug Application (NDA): 214517

DISPENSING RESTRICTIONS

Specialty

Overview

INDICATION(S) FOR USE

Hetlioz®:

- For the treatment of:
  - Non-24-Hour Sleep-Wake Disorder (Non-24) in adults
  - Nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in patients 16 years of age and older.

Hetlioz LQ®:

- For the treatment of night-time sleep disturbances in SMS in pediatric patients 3 years to 15 years of age.

MECHANISMS OF ACTION

The mechanism by which tasimelteon exerts its therapeutic effect in patients with Non-24 or night-time sleep disturbances in SMS is unclear. However, tasimelteon is an agonist at melatonin MT and MT receptors which are thought to be involved in the control of circadian rhythms.

DOSAGE FORM(S) AND STRENGTH(S)

- Capsules: 20 mg
- Oral Suspension: 4 mg/mL

DOSE & ADMINISTRATION

Indicated Population	Dosage Form	Body Weight	Recommended Dosage
Non-24 (2.2)			
Adults	Capsules	Not applicable	20 mg one hour prior to bedtime
Nighttime sleep disturbances in SMS (2.3)			
Patients 16 years of age and older	Capsules	Not applicable	20 mg one hour prior to bedtime
Pediatric Patients 3 to 15 years of age	Oral Suspension	≤ 28 kg	0.7 mg/kg one hour before bedtime
		>28 kg	20 mg one hour before bedtime

- Capsules and oral suspension are not substitutable.
- Administer at the same time every night.
- Take without food.

EFFICACY

Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)

The effectiveness of Hetlioz® in the treatment of nighttime sleep disturbances in SmithMagenis Syndrome (SMS) was established in a 9-week, double-blind, placebo- controlled crossover study in adults and pediatric patients with SMS (Study 3; NCT 02231008). Patients 16 years of age and older received Hetlioz® 20 mg capsules, and pediatric patients 3 years to 15 years of age received a weight-based dose of oral suspension.

Study 3 had two 4-week periods, separated by a 1-week washout interval. Patients were randomized to a treatment sequence of Hetlioz® in the first period and placebo in the second period, or placebo in the first period and Hetlioz® in the second period. Patients were to take the study drug one hour prior to bedtime.

The primary endpoints in Study 3 were nighttime total sleep time and nighttime sleep quality from a parent/guardian-recorded diary. Nighttime total sleep time was reported as a time unit in hours and minutes. Nighttime sleep quality was rated as follows: 5 = excellent; 4 = good; 3 = average; 2 = fair; 1 = poor. The efficacy comparisons for nighttime sleep quality and total sleep time were based on the 50% of nights with the worst sleep quality and the 50% of nights with the least nighttime sleep in each 4-week period. In accordance with the cross-over design, the efficacy comparisons were within patient.

A total of 25 patients were randomized in Study 3. During screening, the mean quality score of the 50% of nights with the worst sleep quality was 2.1, and the total sleep time of 50% of nights with the least nighttime sleep was 6.4 hours.

Compared to placebo, treatment with Hetlioz® resulted in a statistically significant improvement in the 50% worst nights' sleep quality. Although improvement on the 50% worst total nighttime sleep time numerically favored Hetlioz® treatment, the difference was not statistically significant (Table 4).

Table 4: Primary Efficacy Results for Effects of HETLIOZ on Nighttime Sleep Quality and Nighttime Total Sleep Time in Patients with Smith-Magenis Syndrome (Study 3)

Primary Efficacy Measures	Treatment Group	LS Mean[a] (SE)	Placebo-subtracted Difference[b] (95% CI)
Average of 50% Worst Daily Nighttime Sleep Quality*	HETLIOZ (n=25)	2.8 (0.15)	0.4 (0.1, 0.7)
	Placebo (n=25)	2.4 (0.15)	--
Average of 50% Worst Daily Nighttime Total Sleep Time, hours	HETLIOZ (n=25)	7.0 (0.26)	0.3 (-0.0, 0.6)
	Placebo (n=25)	6.7 (0.26)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval unadjusted for multiplicity.
[a] LS Means are the model-based averages based on the 50% worst days per 4-week period.
[b] Difference (drug minus placebo) in least-squares means.
* Endpoint on which HETLIOZ was statistically significant different from placebo after controlling for multiple comparisons.