New Drug Overview
Tasimelteon (Hetlioz)

- **Overview/Summary:** Non-24 hour sleep-wake disorder (i.e., non-24), also known as free-running disorder, is a neurological sleep disorder that is characterized by the extension of the natural sleep-wake cycle beyond 24 hours. As a result, the affected individual is unable to synchronize their sleep-wake cycle to the length of the day and sleep onset shifts around the clock.[1] Non-24 may occur in sighted or blind individuals; although, it is much more common in blind individuals. There are several possible mechanisms by which non-24 may occur in sighted individuals, including a deficiency in the intrinsically photosensitive retinal ganglion cells (ipRGC) of the retina, under- or oversensitivity to light, differences in the circadian feedback loop and abnormalities in melatonin production and/or secretion. Conversely, non-24 in blind patients is due to the inability of the circadian pacemaker to synchronize to the 24 hour cycle by light given the lack of a functioning retina-retinohypothalamic tract-suprachiasmatic nuclei pathway.[2]

  There are very limited treatment options for blind patients with non-24 who fail to achieve entrainment of their circadian rhythm. Despite the use of strict 24-hour sleep-wake schedules based on melatonin onset determinations, many blind patients still fail to entrain. Hetlioz® (tasimelteon) is the first agent to receive Food and Drug Administration (FDA)-approval for the treatment of non-24 in blind patients.[3] The mechanism of action of Hetlioz® (tasimelteon) is unknown; however, it is an agonist at the melatonin MT_1 and MT_2 receptors, which are thought to be involved in the control of circadian rhythms. In clinical trials, treatment with Hetlioz® (tasimelteon) resulted in an increase in nighttime sleep time and a decrease in daytime nap duration.[4]

Table 1. Dosing and Administration[4]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Tasimelteon	Non-24 hour sleep-wake disorder	Capsule: 20 mg	-

FDA=Food and Drug Administration

Evidence-based Medicine

- The FDA-approval of Hetlioz® (tasimelteon) was based on two double-blind, multi-center, randomized controlled trials, SET and RESET which included totally blind patients with non-24 hour sleep-wake disorder.[6]
- In SET, Patients treated with tasimelteon increased nighttime total sleep time by 50 minutes and decreased daytime sleep by 49 minutes, while patients in the placebo group experienced an increase in nighttime sleep of 22 minutes and a decrease in daytime sleep of 22 minutes. A responder analysis was conducted to determine the proportion of patients who achieved a ≥45-minute increase in nighttime total sleep time and a ≥45-minute decrease in daytime nap time. Of patients treated with tasimelteon, 29% (N=12) met the responder criteria compared to 12% (N=5) in the placebo group.[4,6]
- RESET, a withdrawal trial, patients treated with tasimelteon experienced a decrease in nighttime total sleep of seven minutes and an additional decrease in daytime nap time of nine minutes, compared to a decrease of 74 minutes and an increase of 50 minutes, respectively, for patients who received placebo.[4,6]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The American Academy of Sleep identify appropriately-timed melatonin as a treatment option to help blind patients achieve entrainment. Guidelines also note that there is no data to support the use of hypnotic or stimulant medications in these patients.[5]

- Other Key Facts:
  - The maximum concentration of Hetlioz® (tasimelteon) is approximately 44% lower when administered with a high-fat meal compared to a fasted state. As such, Hetlioz® (tasimelteon) should be taken without food.[4]
  - Hetlioz® (tasimelteon) is currently being evaluated for the treatment of major depressive disorder.[7]

References

1. Circadian Sleep Disorders Network. Non-24 hour sleep-wake disorder [webpage on the internet]. Bethesda (MD): Circadian Sleep Disorders Network; Dec 2013 [cited 2014 Mar 27]. Available from: http://www.circadiansleepdisorders.org/docs/N24-QandA.php.
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New Drug Review

Hetlioz® (tasimelteon)

Overview/Summary

Non-24 hour sleep-wake disorder (i.e., non-24), also known as free-running disorder, is a neurological sleep disorder that is characterized by the extension of the natural sleep-wake cycle beyond 24 hours. As a result, the affected individual is unable to synchronize their sleep-wake cycle to the length of the day and sleep onset shifts around the clock.[1] Non-24 may occur in sighted or blind individuals; although, it is much more common in blind individuals. There are several possible mechanisms by which non-24 may occur in sighted individuals, including a deficiency in the intrinsically photosensitive retinal ganglion cells (ipRGC) of the retina, under- or oversensitivity to light, differences in the circadian feedback loop and abnormalities in melatonin production and/or secretion. Conversely, non-24 in blind patients is due to the inability of the circadian pacemaker to synchronize to the 24 hour cycle by light given the lack of a functioning retina-retinohypothalamic tract-suprachiasmatic nuclei pathway.[2]

There are very limited treatment options for blind patients with non-24 who fail to achieve entrainment of their circadian rhythm. Despite the use of strict 24-hour sleep-wake schedules based on melatonin onset determinations, many blind patients still fail to entrain. Hetlioz® (tasimelteon) is the first agent to receive Food and Drug Administration (FDA)-approval for the treatment of non-24 in blind patients.[3] The mechanism of action of Hetlioz® (tasimelteon) is unknown; however, it is an agonist at the melatonin MT_1 and MT_2 receptors, which are thought to be involved in the control of circadian rhythms. In clinical trials, treatment with Hetlioz® (tasimelteon) resulted in an increase in nighttime sleep time and a decrease in daytime nap duration.[4]

Current consensus guidelines from the American Academy of Sleep identify appropriately-timed melatonin as a treatment option to help blind patients achieve entrainment. Guidelines also note that there is no data to support the use of hypnotic or stimulant medications in these patients.[5]

Pharmacokinetics

Table 1. Pharmacokinetics[4]

Generic Name	Tmax (hours)	Protein Binding (%)	Metabolism	Renal Excretion (%)	Serum Half-Life (hours)
Tasimelteon	0.5 to 3	90	CYP1A2, 3A4	80	1.3 ± 0.5

Abbreviations: CYP=cytochrome P, Tmax=time to maximum concentration

Clinical Trials

The FDA-approval of Hetlioz® (tasimelteon) was based on two double-blind, multi-center, randomized controlled trials, SET and RESET which included totally blind patients with non-24 hour sleep-wake disorder. The primary endpoint in SET was path proportion of entrained patients (i.e., patients that responded), and was defined as circadian period (τ) < 24.1 hours with a 95% CI that included 24 hours> Nighttime total sleep time was evaluated on the 25% most symptomatic nights and daytime nap duration on the 25% most symptomatic days. [6]

In SET, patients were randomized to treatment with tasimelteon 20 mg or placebo one hour prior to bedtime for six months. At baseline, patients in the tasimelteon group had an average of 195 minutes of nighttime total sleep time and 137 minutes of daytime sleep on 25% of the most symptomatic nights and days, respectively. Patients treated with tasimelteon increased nighttime total sleep time by 50 minutes and decreased daytime sleep by 49 minutes, while patients in the placebo group experienced an increase in nighttime sleep of 22 minutes and a decrease in daytime sleep of 22 minutes. A responder analysis

was conducted to determine the proportion of patients who achieved a ≥45-minute increase in nighttime total sleep time and a ≥45-minute decrease in daytime nap time. Of patients treated with tasimelteon, 29% (N=12) met the responder criteria compared to 12% (N=5) in the placebo group.[4,6]

RESET was a randomized withdrawal trial during which patients completed a three-month run-in phase consisting of tasimelteon 20 mg per day. Following the three-month run-in phase, patients in whom the calculated time of peak melatonin level occurred at approximately the same time of day during the run-in phase were randomized to tasimelteon or placebo for eight additional weeks.[4,6]

In the withdrawal trial, patients treated with tasimelteon experienced a decrease in nighttime total sleep of seven minutes and an additional decrease in daytime nap time of nine minutes, compared to a decrease of 74 minutes and an increase of 50 minutes, respectively, for patients who received placebo.[4,6]

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lockley et al[6] SET Tasimelteon 20 mg one hour prior to bedtime vs placebo Sedative or stimulant central nervous system-active drugs were not allowed.	DB, MC, PC, PG, RCT Patients 18 to 75 years of age who are totally blind and diagnosed with non-24 hour sleep-wake disorder and had a non-24 hour τ of 24.5 hours or longer were eligible for the randomization phase (patients with a non-24 hour τ > 24.0 and <24.25 hours were eligible for the open label phase)	N=84 6 months	Primary: Proportion of entrained patients at month one assessed by aMT6s Secondary: Clinical response rate at month one or month seven (assessed by aMT6s and N24CRS score), entrainment (assessed by cortisol) at one month, LQ-nTST, UQ-dTSD, MoST, CGI-C score	Primary: Entrained was defined as τ < 24.1 hours with a 95% CI that included 24 hours as assessed by aMT6s rhythms for four weeks starting from day 14 (month one). At one month, eight of 40 patients (20%) were considered entrained in the tasimelteon group compared with one of 38 patients (3%) in the placebo group (P=0.0171). Primary (step-down): Clinical response was defined as being entrained at month one or during the RESET run-in phase (month seven) plus a score of three or more on the N24CRS (range zero to four). Clinical response was observed in nine of 38 patients (24%) in the tasimelteon group and zero of 34 patients (0%) in the placebo group (P=0.0028). Secondary: Entrainment, as assessed by urine cortisol rhythm, at one month was observed in seven of 40 patients (18%) in the tasimelteon group and one of 38 patients (23%) in the placebo group (P=0.0313). Patients who received tasimelteon had more night-time total sleep per day in the worst quartiles of treatment days (LQ-nTST) relative to baseline at 56.80 minutes compared with placebo at 17.08 minutes (P=0.0055). The decrease in the upper quartile of subjective daytime total sleep duration (UQ-dTSD) was significantly reduced in the tasimelteon group (-46.48 minutes) compared with the placebo group (-17.87 minutes; P=0.0050). Increase in the midpoint of sleep timing (MoST) was 35.00 minutes for tasimelteon and 14.48 minutes for placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(P=0.0123). CGI-C score was lower for the tasimelteon group than for the placebo group (2.6 compared with 3.4; P=0.0093).
Lockley et al[6] RESET Tasimelteon 20 mg one hour prior to bedtime vs placebo	DB, MC, PC, PG, RCT, WT Patients 18 to 75 years of age who are totally blind and diagnosed with non-24 hour sleep-wake disorder and had a non-24 hour τ of 24.1 (open-label phase); patients considered entrained were eligible for randomization; or patients who completed SET	N=40 20 weeks	Primary: Proportion on non-entrained patients measured in the four weeks from day 21 Secondary: Proportion of non-entrained patients (assed by urinary cortisol rhythm), difference in proportion of patients with non-entrainment and more than 30 min decrement in nTST; average nTST or dTST, LQ-nTST, UQ-dTST, and MoST	Primary: Entrained was defined as τ < 24.1 hours with a 95% CI that included 24 hours as assessed by aMT6s rhythms for four weeks starting from day 14 (month one). At one month, nine of 10 patients (90%) that continued tasimelteon maintained entrainment compared with two of 10 patients (20%) that withdrew from tasimelteon (P=0.0026). Secondary: Maintenance of entrainment as assessed by cortisol was observed in eight of 10 patients that continued tasimelteon (80%) compared with two of 10 patients (20%) that withdrew tasimelteon (P=0.0118). Patients that continued tasimelteon had improved LQ-nTST, QU-dTST, M0st, and dTSD when compared to patients that withdrew tasimelteon (P<0.05 for all). There was no statistically significant difference in nTST (P=0.13).

Study abbreviations: DB=double-blind, MC=multicenter, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, WT=withdrawal trial
Miscellaneous abbreviations: τ=circadian period, aMT6s= rhythm of urinary 6-sulphatoxymelatonin, CGI-C=Clinical Global Impression of Change scale, dTSD=daytime total sleep duration, LQ-nTST=lower quartile of subjective night0time total sleep, MoST=midpoint of sleep timing, N24CRS=Non-24 Clinical Response Scale, nTST=night-time total sleep time, UQ-dTSD=upper quartile of subjective daytime total sleep duration

Special Populations

Table 3. Special Populations[4]

Population	Precaution
Elderly	Patients ≥65 years old are at increased risk of adverse reactions because tasimelteon exposure is increased approximately two-fold compared to younger patients; caution is advised.
Renal Dysfunction	No dosage adjustment required in renal impairment.
Hepatic Dysfunction	No dosage adjustment required in mild or moderate hepatic impairment. Not studied in severe hepatic impairment.
Pregnancy / Nursing	Category: C Excretion through breast milk: unknown; caution is advised.
Children	Safety and efficacy in children have not been established.
Age Restrictions	FDA approved for use in patients ≥18 years old.

Adverse Drug Events

Table 4. Adverse Events[4]

Adverse Event	Reported Frequency	
	Hetlioz® (tasimelteon) n (%), N=42	Placebo n (%), N=42
Alanine aminotransferase increased	10	5
Headache	17	7
Nightmare/abnormal dreams	10	0
Upper respiratory tract infection	7	0
Urinary tract infection	7	2

Contraindications / Precautions

Hetlioz® (tasimelteon) is not associated with any contraindications to therapy.[4]

Patients should limit their activity to preparing for bed following a dose of Hetlioz® (tasimelteon), as it may reduce mental alertness.[4]

Drug Interactions

Table 5. Drug Interactions[4]

Interacting Medication or Disease	Interaction Severity Rating*	Potential Result
Strong CYP1A2 inhibitors	Major	Concurrent use of tasimelteon and CYP1A2 inhibitors may result in a potentially large increase in tasimelteon exposure and greater risk of adverse reactions and should be avoided.
Strong CYP3A4 inducers	Major	Concurrent use of tasimelteon and CYP3A4 inducers may result in a potentially large decrease in tasimelteon exposure with reduced efficacy and should be avoided.

*Severity rating per Clinical Pharmacology

Dosage and Administration

Table 6. Dosing and Administration[4]

Adult Dose	Pediatric Dose	Availability
Non-24 hour sleep-wake disorder: Capsule: 20 mg per day taken before bedtime at the same time every night	Safety and efficacy in children have not been established.	Capsule: 20 mg

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
The American Academy of Sleep Medicine (AASM): **Circadian Rhythm Sleep Disorders: Part II, Advanced Sleep Phase Disorder, Delayed Sleep Phase Disorder, Free-Running Disorder, and Irregular Sleep-Wake Rhythm (2007)**[5]	Timed Melatonin · Appropriately-timed administration of melatonin, in doses of 0.5 to 10 mg, has been shown to entrain totally blind patients who have free-running disorder. · Treatment with melatonin must be sustained or relapse will occur. · Entrainment may not occur for weeks or months after treatment initiation, depending on the phase of the patient's melatonin rhythm at treatment initiation and the period of the patient's free-running rhythm. Hypnotic Medications · The safety and efficacy of hypnotic medications for the promotion of sleep in free-running disorder in the blind have not been established. Stimulant Medications · The safety and efficacy of stimulant medications in the promotion of wakefulness in free-running disorder in the blind have not been established.

Conclusions/Recommendations

Hetlioz® (tasimelteon) is the first FDA-approved treatment for non-24 in blind individuals. Although the exact mechanism of action is unknown, it works as a melatonin agonist at the MT_1 and MT_2 receptors, which are thought to be involved in the control of circadian rhythms. In clinical trials, treatment with Hetlioz® (tasimelteon) resulted in an increase in total nighttime sleep time, as well as a decrease in total daytime nap duration.[3,4,6]

There are currently very limited treatment options for blind patients with non-24. Treatment has historically consisted of the use of strict 24-hour sleep-wake schedules based on melatonin onset determinations. In addition, current consensus guidelines recommend timed melatonin administration as a treatment option; however, many patients still fail to achieve entrainment using these treatment strategies.[1,2,4] Hetlioz® (tasimelteon) may provide a unique and effective treatment option for patients who fail to achieve entrainment.

Given its mechanism of action as a melatonin agonist and that Hetlioz® (tasimelteon) is currently only approved for the treatment of non-24 in blind individuals, there is potential for off-label use for the treatment of non-24 in sighted individuals, as well as in patients with other types of sleep disorders. In addition, current consensus guidelines have not yet been updated to address the place in therapy for Hetlioz® (tasimelteon).

References

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