TASIMELTEON: A NOVEL DRUG IN NON-24 HOURS SLEEP WAKE DISORDER

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ABSTRACT
Free-running type or non 24 hour sleep wake disorder is a rare but chronic circadian rhythm sleep disorder (CRSD) that disrupts the sleep-wake cycle and affects the majority of totally blind individuals leading to insomnia. Tasimelteon, a melatonin receptor agonist has proved its potential as a circadian regulator that resets the biological clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, thus synchronizing the body’s melatonin and cortisol circadian rhythm with the day-night cycle in patients with non 24 hour sleep wake disorder. Its potential for use in jet-lag, mood disorders and depression due to circadian rhythm disorder is under evaluation. Tasimelteon (Hetlioz) by Vanda Pharmaceuticals Inc. was approved by U.S. Food and Drug Administration (FDA) on 31st January, 2014 for treatment of non 24 sleep wake disorder.

KEY WORDS: Tasimelteon, circadian rhythm sleep disorder, melatonin, free-running.

INTRODUCTION
Melatonin, the major hormone secreted by the pineal gland, was first identified by Aaron Lerner in 1958. Melatonin (5-methoxy-N-acetyltryptamine) is formed by sequential N-acetylation and O-methylation of indolamines. Its synthesis is controlled by external factors such as environmental light and corresponds to typical sleep-wake cycle. It is considered as...
the chemical signal indicating the length of darkness, as its secretion is greatest during the
dark hours of the night. As it is secreted in its highest levels during the night time in diurnally
active vertebrates, it has been suggested that it has a crucial role in sleep promotion. Owing to
its involvement in the regulation of circadian rhythms, any disruption in melatonin secretion
may play an important part in the etiology of circadian rhythm sleep disorders (CRSD). This
has advocated the use for exogenous melatonin in the treatment of CRSD. It is also being
widely used as a natural supplement or, in its analogue variants, as a drug for various sleep
disorders. Apart from regulation of circadian rhythms, this hormone has a number of
important physiological functions including initiation and maintenance of sleep, anti-
oxidative defense, immune regulation and aging, control of reproductive activity and tumor
growth supression.\textsuperscript{[1-4]}

In 1994, three melatonin receptors MT\textsubscript{1}, MT\textsubscript{2} and MT\textsubscript{3} were characterized and cloned in
humans. MT\textsubscript{1} and MT\textsubscript{2} are involved in sleep physiology. Both the MT\textsubscript{1} and MT\textsubscript{2} type of
receptors belong to the family of G\textsubscript{i}/G\textsubscript{0} protein-coupled receptors linked to the inhibition of
adenylyl-cyclase and subsequent decrease of cyclic AMP.\textsuperscript{[5]} Both the MT\textsubscript{1} and MT\textsubscript{2} type of
receptors are demonstrated in almost all structures of CNS; although the hypothalamic
suprachiasmatic nucleus (SCN) and the pars tuberalis of the pituitary have the highest density
of these two receptors. MT\textsubscript{1} mediated inhibition of neurons in the suprachiasmatic nucleus
helps to promote sleep by decreasing the wake promoting action of suprachiasmatic nucleus.
MT\textsubscript{2} mediated signals in suprachiasmatic nucleus helps in phase shifting effects by
activations of protein kinase C. This explains the action of melatonin as a chronobiotic.\textsuperscript{[1,2,6]}

**The sleep-wake cycle**
The sleep-wake cycle is the most evident of the many 24-hour rhythms in humans. It is now
recognized that many peripheral tissues in mammals have circadian clocks that regulate
diverse physiologic processes. These independent tissue-specific oscillations are coordinated
by a central neural pacemaker located in the suprachiasmatic nuclei (SCN) of the
hypothalamus. The genetically determined period of this central neural pacemaker, averages
\(~24.2\) hours in humans, is normally synchronized or entrained to the 24-hours period of the
environmental light-dark cycle. Entrainment or *phase shifts* involves regular adjustments of
the circadian pacemaker, which depends on exposure to environmental time cues, particularly
the daily light–dark cycle. It is mediated via the retinohypothalamic tract, a monosynaptic
pathway that links specialized, photoreceptive retinal ganglion cells directly to the SCN.
Humans are exquisitely sensitive to the resetting effects of light, particularly the shorter wavelengths (~460–500 nm) of the visible spectrum. Paradoxically the endogenous circadian rhythms of sleep tendency, sleepiness, and REM sleep propensity all peak near the habitual wake time, whereas the circadian wake propensity rhythm peaks 1–3 hours before the habitual bedtime. These rhythms are thus timed to oppose the homeostatic decline of sleep tendency during the habitual sleep episode and the rise of sleep tendency throughout the usual waking day, respectively. The timing and internal architecture of sleep are directly coupled to the output of the endogenous circadian pacemaker. Misalignment of the output of the endogenous circadian pacemaker with the desired sleep-wake cycle can, therefore, induce insomnia, decreased alertness, and impaired performance, evident in night-shift workers and airline travellers. As light cues are unavailable in totally blind people, disturbances of circadian rhythms are common.\(^7\)

**Non 24 hours sleep wake disorder**

Among the various types of sleep disorders, Circadian rhythm sleep disorders (CRSDs) constitute a major part. According to the International Classification of Sleep disorders, the essential feature of CRSDs is a persistent or recurrent pattern of sleep disturbance due primarily to alterations in the circadian timekeeping system or a misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep. There are six distinct CRSDs currently recognized in the International Classification of Sleep Disorders (ICSD-2), namely: 1) *delayed sleep phase type* 2) *advanced sleep phase type* 3) *irregular sleep-wake phase type* 4) *free-running type* 5) *jet lag type* and 6) *shift work type*.\(^8,9\) Free-running type, also known as ‘non 24 hours sleep wake disorder’ or non-entrained type or hypernychthemeral sleep wake syndrome, is a rare, orphan, serious, chronic debilitating circadian rhythm sleep disorder (CRSD) that disrupts the sleep-wake cycle, for which there is no available treatment.\(^10,11\) Though it is commonly seen in a blind person, it can occur in sighted patients due to genetic predispositions or significant decrease circadian photoreception due to pupillary miosis and reduced power of the crystalline lens.\(^7\) In sighted people, usually the onset of free-running disorder occurs in their teens or twenties.\(^10\) In the totally blind, the onset is probably coincident with the loss of sight. It affects the majority of totally blind individuals and it is approximately 80,000 Americans have this disorder.\(^12\) In totally blind individuals, without input from the eyes, information about environmental light levels fails to reach the suprachiasmatic nuclei in the hypothalamus to synchronize the internal clock, thus reflecting a failure of entrainment. Therefore, this type of sleep disorder
occurs as a result of the misalignment of the endogenous master body clock to the 24-hour day, disrupting the sleep-wake cycle, resulting in insomnia with excessive daytime sleepiness.\[4,7,8,13\] Although the chief complaint is usually related to the sleep-wake pattern, it has been observed that it is also responsible for the desynchrony of circadian rhythms, which include those of cortisol, core temperature, blood pressure, glucose control, have profound impacts in the cardiovascular and metabolic homeostasis of the body. Since the first description of this disorder in 1948, no definite drug therapy is available till today and the disorder is often under diagnosed or misdiagnosed.\[12\] In most cases, patients have been left either untreated or treated inappropriately. Therapeutic interventions for non 24 hours sleep wake disorder’ is targeted at entraining the patient’s circadian pacemaker at an appropriate phase relative to the environmental light/dark cycle. Use of low dose melatonin have been reported to improve sleep in such cases, and is also used to synchronized the circadian pacemaker with the 24 hours geophysical day.\[10,14,15,16\] In view of these findings, Tasimelteon (Hetlioz), a melatonin receptor agonist was approved by FDA on 31st January, 2014 for treatment of non 24 hours sleep wake disorder.\[12\] We present here a brief overview on the pharmacology of Tasimelteon based on the published data by Vanda Pharmaceuticals Inc.

**TASIMELTEON**

**Chemistry**
The IUPAC name is (1R, 2R)-N-[2-(2,3-Dihydrobenzofuran-4-yl) cyclopropylmethyl] propanamide. It has a molecular weight of 245.14 and the molecular formula is $C_{15}H_{19}NO_{2}$. The structural formula is:\[17\]

![Tasimelteon Structural Formula]

**Mechanism of Action:**\[12\]
The therapeutic goal of non 24 hours sleep wake disorder is to keep in phase the endogenous circadian rhythms with the local environment. Thus, the melatonin receptors which are present in high density at the suprachiasmatic nucleus (SCN) are targeted to exert melatonergic actions to phase shift circadian rhythm and promote sleep. Tasimelteon is a
MT₁ and MT₂ receptor agonist, with greater affinity to MT₂ receptor than MT₁, hence it is also known as Dual Melatonin Receptor Agonist (DMRA). Its major metabolites also bind, though at least with 10 times lower affinity to MT₁ and MT₂ receptors. Tasimelteon or its metabolite do not have affinity to other pharmacologically relevant receptors including receptors of neurotransmitter systems associated with abuse potential such as dopamine, norepinephrine, serotonin, gamma-aminobutyric acid (GABA), acetylcholine, opioid, N-methyl-D-aspartate (NMDA) and cannabinoid. Two recent randomized controlled trials (phase II and III) demonstrated that tasimelteon by improving sleep latency and maintenance of sleep with a shift in circadian rhythms, has the potential to treat patients with transient insomnia associated with circadian rhythm sleep disorders.¹⁸,¹⁹ It acts as a circadian regulator that resets the biological clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, thus synchronizing the body’s melatonin and cortisol circadian rhythm with the day-night cycle in patients with non 24 hour sleep wake disorder. It phase advances circadian rhythm and minimizes disruption in sleep efficiency, wake after sleep onset and sleep latency. Preclinical studies showed that it has similar phase-shifting properties to melatonin, but with less vasoconstrictive effects.²⁰

**Pharmacokinetics**²¹

The following Pharmacokinetic information is available.

**Absorption**

Tasimelteon is rapidly absorbed orally under fasting condition with a $T_{\text{max}}$ of approximately 0.5 hours. Co-administration with fatty or high calorie meals delayed its absorption. However, in accordance with phase III efficacy studies (SET and RESET), tasimelteon can be administered without regard to meals.

**Distribution**

The apparent oral volume of distribution at steady state is 59-126 L and it is 89-90% plasma protein bound at therapeutic concentration.

**Metabolism**

Orally administered Tasimelteon undergoes rapid metabolism by CYP1A2 and CYP3A4. Phase I metabolism consists mainly of oxidation and oxidative dealkylation resulting in opening of the dihydrofuran ring followed by further oxidation to give a carboxylic acid. CYP1A1, CYP2D6, CYP2C19 and CYP2C9 also minimally metabolize tasimelteon. Phase II
metabolism is through phenolic glucuronidation. It is metabolized in humans to five metabolites: M9, M11, M12, M13, M14. The mean elimination half-life $t_{1/2}$ of Tasimelteon is $1.32 \pm 0.4$ hours. The mean terminal elimination half-life ± standard deviation of the main metabolites ranges from $1.3 \pm 0.5$ to $3.7 \pm 2.2$ hours.

**Excretion**

The pharmacokinetics of tasimelteon is linear over doses ranging from 1 to 300 mg. More than 80% is excreted through urine and about 4% through the faeces and less than 1% is excreted unchanged in the urine. Repeated once daily dosing with tasimelteon does not result in PK parameter changes or significant accumulation owing to the short half-life of Tasimelteon.

**Contraindications**\(^{21}\)

Patients should avoid engaging in activities requiring coordination and concentration, including driving or operating machinery after taking tasimelteon. It is contraindicated in pregnant and lactating mothers.

**Dose regime**

It is available as capsules for oral consumption. The recommended dose is 20 mg per day taken at bed time, to be taken at the same time every night. Because of individual difference in circadian rhythm, it may take weeks to months for its effect. Although exposure to tasimelteon was increased approximately 2-fold in subjects with hepatic impairment after a single 20 mg/day dose, dose adjustment is not necessary in patients with mild or moderate hepatic impairment. However it has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). No dose reduction is required in renal impairment as well as based on age, gender, or body mass index (BMI).\(^{12}\)

**Clinical use**

FDA approved use of Tasimelteon for ‘non 24 hour sleep wake disorder’ in totally blind patients. Its potential for use in jet-lag, mood disorders and depression due to circadian rhythm disorder is under evaluation.\(^{2,22,23}\)

**Potential Drug interactions of Tasimelteon:**\(^{12}\)

1. Fluvoxamine, a strong inhibitor of CYP1A2 increased $C_{\text{max}}$ of tasimelteon by 2 fold on co-administration. So, Tasimelteon should be used with caution in combination with Fluvoxamine and other CYP1A2 inhibitors.
2. Dose adjustment may be needed in people who smoke as smoking is a moderate CYP1A2 inducer.

3. Rifampin, a strong CYP3A4 and moderate CYP1A2 inducer reduced exposure to Tasimelteon, thus needing dose adjustments.

4. Ketoconazole, a strong CYP3A4 inhibitor increases tasimelteon’s exposure by approximately 54%, compared to administration of tasimelteon alone. However, no dose adjustment is recommended as the clinical significance of this change is unclear.

5. Tasimelteon at 20 mg/kg dose does not have any additive effect or psychomotor performance or memory task when combine with other CNS depressant like midazolam or alcohol.

**Adverse effects and Safety Profile**

Tasimelteon is well-tolerated in the indicated population of totally blind individuals with Non-24-Hour Disorder and the safety profile is favorable. Pre clinical studies showed no significant reproductive toxicity, embyotoxicity, genotoxic and carcinogenic findings at clinically relevant exposures for humans. Clinical study 1103, a thorough QT study, a four-period, randomized, double-blind, multiple-dose, crossover study, demonstrated that it has no potential to interfere with cardiac repolarization. In both the SET pivotal efficacy study and the RESET randomized withdrawal study, events reported among tasimelteon-treated patients were comparable to events occurring in placebo-treated patients. Among all tasimelteon-treated patients in placebo-controlled Phase 2 and 3 efficacy studies, no serious adverse events (SAE) or laboratory abnormalities were reported. Throughout the clinical development program, the most common adverse reactions occurring at a level clinically different from placebo are headache and vivid or unusual dreams. Others like raised alanine aminotransferase, upper respiratory tract infection, urinary tract infection, somnolence, conduction disorder, sleep disorder and nasopharyngitis were also reported.

**CONCLUSION**

The benefits of tasimelteon in the treatment of totally blind patients with this serious and orphan Non-24-Hour Disorder have been established in two pivotal clinical studies. Specifically, tasimelteon was shown to entrain (synchronize) the Master clock to a 24-hour period, as measured by both the melatonin and cortisol circadian rhythm measurements. More than fifty percent of patients that received tasimelteon treatment for an adequate duration (approximately one circadian cycle length or 40 to 80 days) and at the same time every night...
were successfully entrained. In addition tasimelteon was shown to restore the 24-hour synchrony of the sleep-wake cycle. As a result, tasimelteon significantly and meaningfully improved the timing and amount of sleep episodes, allowing sleep to be consolidated during the night and minimized sleep during the day. Physician derived global functioning impression showed consistent improvements in the overall function and well-being of tasimelteon-treated study participants. Tasimelteon was also shown to be well tolerated with a mild side effect profile compatible with chronic use, thus making it suitable for the treatment of Non-24 sleep disorder in the totally blind.

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