

Brand name: Hetlioz

Generic Name: Tasimelteon

Manufacturer^{1, 2}: Vanda Pharmaceuticals

Drug Class^{1, 2, 3, 4, 5}: Melatonin receptor agonist; psychotropic agents, anxiolytics, sedatives, and hypnotics; central nervous system agent;

Uses:

- **Labeled^{1,2,3, 4, 5}:** Treatment of Non-24-hour sleep-wake disorder; Non-24-Hour Sleep Wake Disorder (Non-24) is a disorder that affects the normal 24-hour synchronization of circadian rhythms⁹
- **Unlabeled:** None listed

MOA^{1, 2, 3, 4, 5}: Tasimelteon is a melatonin receptor agonist with greater affinity for M₂ vs. M₁ receptor. M₁ induces sleep while M₂ regulates circadian rhythm.

Pharmacokinetics:

Absorption/Distribution:

T_{max}^{1, 2, 3,4, 5}	0.5 -3 hr. (fasting) Delayed w/ high-fat meal by 1.75 hr
Vd^{1, 2, 3, 4, 5}	56-126 L
t_{1/2}^{1,2, 3, 4, 5}	1-2 hrs.
Clearance	Not reported
Protein binding^{1, 2, 3, 4,}	90%
Bioavailability^{1, 2, 3, 4, 5}	Delayed w/ high-fat meal by ~ 1.75; C _{max} reduced by 44% with a high-fat meal*

*Tasimelteon should be administered without food³

Metabolism^{1, 2, 3, 4, 5}:

The hepatic route is the major route of metabolism for tasimelteon with specific Cytochrome P450 involvement of CYP 1A2 and 3A4. Primary metabolites half-life is from 1.3-3.7 hours with a 13 fold or less activity than the parent drug

Elimination^{1, 2,3,4,5}:

The major route of elimination is renal with 80% excreted in urine and approximately 4% in feces. Less than 1% of the dose was excreted in urine as the parent compound.

Efficacy:

Rajaratnam SM, Polymeropoulos MH, Fisher DM, Roth T, Scott C, Birznieks G, et al. Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomized controlled multicentre trials. *Lancet* [serial online]. 2009, 373:482-91

- **Study design:** A phase II and phase III randomized, double-blind, placebo-controlled study.
- **Description:** *Methods:* In the phase II study 39 individuals were randomized; participants were men and women aged between 18 and 50. In the phase III study 411 participants were between 21 and 50. Participants were in good health and didn't report any major sleep disorders. Participants maintained a regular 8 hr sleep schedule for 2 weeks before the inpatient study. After a seven night protocol, individuals were randomly assigned to double-blind study medication or matched placebo 30 minutes before bed. The study was done between July 14, 2004, and April 1, 2005. The study was done at two US sites, each with a single-bed suite that was free of time cues and had controlled light intensity and induced transient insomnia by a 5 hour advance of the sleep-wake cycle. Analysis was by intent to treat. *Outcomes:* Primary outcomes were: phase II polysomnographic sleep efficacy and circadian phase shifting; phase III persistent sleep. Secondary outcomes: Phase II wake after sleep onset and latency to sleep onset; phase III wake after sleep onset. *Results:* In the phase II study, tasimelteon reduced sleep latency and increased sleep efficacy compared with placebo. In the phase III study, tasimelteon improved sleep latency, sleep efficacy, and wake after sleep onset. Adverse effects had similar frequency between the two groups. Tasimelteon improves sleep initiation and maintenance concurrently with a shift in endogenous circadian rhythms after an abrupt advance in sleep time.
- **Limitations:** Several authors were employed by the manufacturer and the study support was provided by the manufacturer which could introduce bias. There was a small sample size in the phase II study. This study used a short term induction of sleep-wake disorder. Efficacy in patients with chronic circadian rhythm sleep disorders wasn't tested and daytime performance and alertness needs to be assessed to detect carryover sedative effect using the appropriate model for patients with chronic circadian rhythm sleep disorders.
- **Conclusion:** Further research is needed to determine therapeutic effect for transient insomnia, carryover sedative effect and adverse effects in chronic circadian rhythm sleep disorders.

Tasimelteon. Advisory Committee Briefing materials. Vanda Pharmaceuticals, Inc. SET STUDY. Nov. 14, 2013. Available at

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM374388.pdf>. Assessed on June 13, 2014

Study design: Multicenter, randomized, double masked, placebo-control, parallel study

Description: *Methods:* this study evaluated the efficacy and safety of tasimelteon 20 mg vs. placebo in patients suffering from Non-24hour sleep wake disorder. This study consisted of 84 totally blind patients with no reported light perception. The screening phase lasted 3 months on average and the double masked phase was 6 months in duration. Patient inclusion criteria included totally blind patients with no reported light perception, asleep-wake complaint as assessed by the Sleep-Wake-Questionnaire and a sleep-wake time shift ≥ 24.25 hours (95% CI 24.1 – 24.9). Exclusion criteria were BMI < 18 or > 33 kg/m², other sleep or psychiatric disorder, medication that could interfere with the evaluation of circadian rhythm and age < 18 or >75. *Outcomes:* Primary endpoints for efficacy included entrainment of

circadian rhythms as measured by aMT6's and clinical response defined as demonstration of entrainment of aMT6 and a score of ≥ 3 on the Non-24 Clinical Response Scale (N24CRS). Secondary endpoints consisted of clinical response defined as a patient with both entrained melatonin rhythm and a score of at least 3 on the N24CRN scale. *Results:* Compared to placebo higher rates were shown with both primary endpoints: patients achieving entrainment ($p=0.0171$) and a clinical response ($p=0.0028$). For secondary endpoints, entrainment rate was not statistically significant ($p = 0.0291$) however, entrainment and N24CRS together was significant ($p=0.0025$)

Limitations: Information came directly from the manufacturer's data and was not peer reviewed. Twenty percent of the treated patients were entrained as early as week 2 compared to just 2.6% in the placebo group, this total is expected to significantly underestimate the true rate of entrainment given the early evaluation. Another limitation was, even though efforts were made to initiate tasimelteon during an aligned portion of the circadian phase, for some patients this didn't happen.

Conclusion: Tasimelteon is an orphan drug and being a melatonin receptor agonist works to regulate the sleep-wake cycle in the treatment of Non-24-hour sleep-wake disorder. In this study, tasimelteon showed clinically significant improvement in decreasing the amount of daytime and increasing the amount of nighttime sleep, optimizing the timing of sleep to a desired time and other sleep/wake parameters controlled by the circadian rhythm. Tasimelteon showed significant improvements over placebo in global functioning. In addition, no clinically relevant events were identified in clinical or laboratory endocrine parameters.

Tasimelteon. Advisory Committee Briefing materials. Vanda Pharmaceuticals, Inc. RESET STUDY. Nov. 14, 2013. Available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM374388.pdf>. Assessed on June 13, 2014

Study design: A multicenter, randomized withdrawal, double masked, placebo-controlled parallel group study designed to evaluate the long-term maintenance effect and safety of tasimelteon

Description: *Methods:* The 20 patients who completed the RESET study had been screened in the SET study. This study (RESET) had two phases; a pre-randomization phase consisting of an open-label tasimelteon run in phase with an estimation phase and a randomized withdrawal phase. The primary objectives for this study were to demonstrate the maintenance of effect of tasimelteon to entrain circadian rhythms in patients with NON-24 sleep wake disorder. *Outcomes:* Primary endpoints of the RESET study was to demonstrate the maintenance of effect of tasimelteon to entrain circadian rhythms in patients with Non-24 sleep wake disorder. Secondary endpoints were to demonstrate the maintenance of effect of tasimelteon to entrain circadian rhythms; to demonstrate the maintenance of effect of tasimelteon on subjective nighttime total sleep time (nTST); to demonstrate the maintenance of effect of tasimelteon on subjective nTST in patients with Non-24; to demonstrate the maintenance of effect of tasimelteon on subjective daytime total sleep duration (dTSD); and to demonstrate the maintenance of effect of tasimelteon on subjective dTSD in patients. *Results:* Only 20% of tasimelteon treated patients became un-entrained versus 80% of placebo treated patients $p = 0.0118$, demonstrating chronic dosing of tasimelteon is required to maintain entrainment of circadian rhythms. No secondary outcomes showed statistical significance. Results of this study showed tasimelteon treatment is necessary for both induction and maintenance of entrainment and for maintenance of clinical benefits in sleep and wake measures. Tasimelteon was significantly associated with the early relapse in total sleep time as compared to placebo and patients had a lower rate of non-entrainment of the cortisol rhythm as compared to placebo during the randomized withdrawal.

Limitation: Information came directly from the manufacturer’s data and was not peer reviewed. There was a small number of patients included due to difficulty in enrolling patients which may limit the generalizability and clinical significance of the results.

Conclusion: Success was shown in the primary endpoints over placebo. In addition tasimelteion demonstrated significant entrainment of cortisol rhythms and improvements across a number of patient outcomes that can be seen clinically including measures of total nighttime sleep, excessive daytime sleep duration and timing of sleep.

Contraindications^{1, 2, 3, 4, 5}: None

Precautions^{1, 2, 3, 4, 5}:

- Drug-Drug interaction
 - Concomitant use with strong CYP1A2 inhibitors should be avoided
 - Concomitant use with strong CYP3A4 inducers should be avoided
- Elderly
 - Elderly patients (ie, aged 65 years and older); increased risk of adverse events due to ~ 2-fold exposure
- Hepatic impairment
 - If severe (i.e., Child-Pugh class C); not recommended
- CNS depression
 - Impaired mental alertness may occur; limit activity after administration
- Smokers
 - reduced efficacy may occur due to induction of CYP1A2

AE^{1, 2, 3, 4, 5}:

	ADVERSE REACTION	INCIDENCE
CNS	Abnormal dreams	10%
	Headache	17%
GENITOURINARY	Urinary tract infection	7%
HEPATIC	Increased serum ALT*	10%
RESPIRATORY	Upper respiratory infection	7%

*ALT: Alanine aminotransferase

Drug/Drug Interactions^{1, 2, 3, 4, 5}:

- ALCOHOL (ETHYL): CNS depressants may enhance the CNS depressant effect of alcohol (Ethyl).
- AZELASTINE (NASAL): CNS depressants may enhance the CNS depressant effect of azelastine (Nasal).
- BRIMONIDINE (TOPICAL): May enhance the CNS depressant effect of CNS depressants.
- BUPRENORPHINE: CNS depressants may enhance the CNS depressant effect of buprenorphine.
Management: Consider reduced doses of CNS depressants used in combination with buprenorphine. Consider avoiding other CNS depressants in patients thought to be at high risk of buprenorphine overuse or self-injection.
- CANNABIS/TETRAHYDROCANNABINOL: May enhance the CNS depressant effect of CNS depressants.
- CNS DEPRESSANTS: May enhance the adverse/toxic effect of other CNS depressants
EXCEPTIONS: levocabastine (Nasal).

- CYP1A2 INHIBITORS (STRONG): May decrease the metabolism of CYP1A2 substrates, therefore, increase serum concentration of tasimelteon.
- CYP3A4 INDUCERS (STRONG): May decrease the serum concentration of tasimelteon
- DOXYLAMINE: May enhance the CNS depressant effect of CNS depressants. Management: The manufacturer of Diclegis (doxylamine/pyridoxine) intended for use in pregnancy, specifically states that use with other CNS depressants is not recommended.
- DRONABINOL: May enhance the CNS depressant effect of CNS Depressants.
- DROPERIDOL: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use.
- HYDROCODONE: CNS depressants may enhance the CNS depressant effect of hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted.
- HYDROXYZINE: May enhance the CNS depressant effect of CNS depressants.
- KAVA KAVA: May enhance the adverse/toxic effect of CNS depressants.
- MAGNESIUM SULFATE: May enhance the CNS depressant effect of CNS depressants.
- METHOTRIMPAZINE: CNS depressants may enhance the CNS depressant effect of methotrimeprazine. methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established.
- METYROSINE: CNS Depressants may enhance the sedative effect of metyrosine.
- MIRTAZAPINE: CNS depressants may enhance the CNS depressant effect of Mirtazapine.
- NABILONE: May enhance the CNS depressant effect of CNS depressants.
- PARALEHYDE: CNS depressants may enhance the CNS depressant effect of paraldehyde.
- PERAMPANEL: May enhance the CNS depressant effect of CNS depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination.
- PRAMIPEXOLE: CNS depressants may enhance the sedative effect of pramipexole.
- ROPINIROLE: CNS depressants may enhance the sedative effect of ropinirole.
- ROTIGOTINE: CNS depressants may enhance the sedative effect of rotigotine.
- RUFINAMIDE: May enhance the adverse/toxic effect of CNS depressants. Specifically, sleepiness and dizziness may be enhanced.
- SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI's): CNS depressants may enhance the adverse/toxic effect of selective serotonin reuptake inhibitors. Specifically, the risk of psychomotor impairment may be enhanced.
- SODIUM OXYBATE: Non-benzodiazepine hypnotics may enhance the CNS depressant effect of Sodium Oxybate.
- TAPENTADOL: May enhance the CNS depressant effect of CNS depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression.
- THALIDOMIDE: CNS depressants may enhance the CNS depressant effect of thalidomide.
- ZOLPIDEM: CNS depressants may enhance the CNS depressant effect of zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also

receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol.

Dosing/Administration:

- **Usual dose**^{1, 2, 3, 4, 5}: 20mg, without food, at the same time each night prior to bed
- **Geriatric dose**^{1, 2, 3}: 20mg, without food, at the same time each night prior to bed. The risk of adverse reactions may be greater in elderly (>65 years) patients than younger patients because exposure to tasimelteon is increased by approximately 2-fold compared with younger patients.
- **Pediatric dose**: Safety and efficacy has not been established
- **Renal impairment dose**^{1, 2, 3, 4, 5}: No dosage adjustment needed
- **Hepatic impairment dose**^{1, 2, 3, 4, 5}:
 - MILD: No dosage adjustment needed
 - MODERATE: No dosage adjustment needed
 - SEVERE (Child-Pugh class C): Not recommended; has not been studied

Use in special circumstances^{1, 2, 3, 4, 5}:

- **Pregnancy**: Category C (All trimesters)
- **Lactation**: Unknown if secreted in breast milk; use caution

Conclusion:

Hetlioz (tasimelteon) received FDA approval in 2014 as a melatonin receptor agonist indicated for the treatment on Non-24-hour sleep wake disorder. It's designated as an orphan drug for the treatment of Non-24 hour sleep wake-disorder primarily in the blind; it is not used as a general insomnia drug. Tasimelteon is available as a 20mg capsule. Effectiveness may take weeks to months to be seen due to individual variability in circadian rhythm. Tasimelteon is extensively metabolized through the liver via CYP 1A2 and 3A4; therefore several drug-drug interactions exist. Patients taking tasimelteon should take it just prior to bed without food and limit their activity when preparing for bed since impairment in performance and mental alertness are affected. During trials, both animal and human, tasimelteon did not show any signs of abuse potential or dependence; as such tasimelteon is not a controlled substance. Tasimelteon may be an important option in patients who suffer from non-24 hour sleep wake disorder, as the only current options are medications used to treat insomnia which are not effective in this patient population as those medications do not change the underlying problem with the circadian rhythms associated with this disorder.

References:

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