ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

HETLIOZ 20 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 20 mg tasimelteon.

Excipient(s) with known effect: Each hard capsule contains 183.25 mg of lactose (as anhydrous) and 0.03 mg of Orange Yellow S (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Dark blue opaque, hard capsule marked with "VANDA 20 mg" in white ink. The size of the capsule is 'size 1' (dimensions 19.4 x 6.9 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HETLIOZ is indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) in totally blind adults.

4.2 Posology and method of administration

Posology

Dose and timing
The recommended dosage of HETLIOZ is 20 mg (1 capsule) per day taken one hour before bedtime, at the same time every night.

HETLIOZ should be taken without food; if patients eat a high-fat meal, it is recommended to wait at least 2 hours before taking HETLIOZ (see section 5.2).

Patients should be instructed to initiate HETLIOZ treatment without regard to circadian phase. Physicians should evaluate patient response to tasimelteon 3 months after treatment initiation utilising a clinician interview to assess their overall functioning with an emphasis on sleep-wake complaints.

HETLIOZ is intended for chronic use.

Elderly
No dose adjustment is recommended for individuals older than 65 years of age (see section 5.2).

Renal impairment
No dose adjustment is recommended for patients with renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild or moderate hepatic impairment (see section 5.2). HETLIOZ has not been studied in patients with severe hepatic impairment (Child-Pugh Class C); therefore caution is recommended when prescribing HETLIOZ to patients with severe hepatic impairment.

Paediatric population
The safety and efficacy of tasimelteon in children and adolescents aged 0 to 18 years have not been established.
No data are available.

Method of administration
Oral use. Hard capsules should be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

After taking HETLIOZ, patients should limit their activity to preparing for going to bed.

Caution should be used when administering HETLIOZ in combination with fluvoxamine or other strong CYP1A2 inhibitors because of a potentially large increase in tasimelteon exposure and greater risk of adverse reactions (see section 4.5).

Caution should be used when administering HETLIOZ in combination with rifampin or other CYP3A4 inducers because of a potentially large decrease in tasimelteon exposure with reduced efficacy (see section 4.5).

Caution should be used when administering HETLIOZ in combination with omeprazole or other strong CYP2C19 inhibitors because their potential to increase tasimelteon exposure has not been studied (see section 4.5).

Excipients
HETLIOZ hard capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
HETLIOZ hard capsules contain the azo colouring agent Orange Yellow S (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect tasimelteon
CYP1A2 and CYP3A4 are enzymes identified to play a role in the metabolism of tasimelteon. Medicinal products that inhibit CYP1A2 and CYP3A4 have been shown to alter the metabolism of tasimelteon *in vivo*. The involvement of other enzymes (e.g. CYP2C19) in the metabolism of tasimelteon is unknown.

Strong CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin and enoxacin)
Caution should be used when administering tasimelteon in combination with fluvoxamine or other strong CYP1A2 inhibitors such as ciprofloxacin and enoxacin because of a potentially large increase in tasimelteon exposure and greater risk of adverse reactions: the $AUC_{0\text{-}inf}$ and C_{max} of tasimelteon increased by 7-fold and 2-fold, respectively, when co-administered with fluvoxamine 50 mg (after 6 days of fluvoxamine 50 mg per day).

Strong CYP2C19 inhibitors (e.g. omeprazole, fluvoxamine and moclobemide)
Caution should be used when administering tasimelteon in combination with strong CYP2C19 inhibitors such as omeprazole because there is uncertainty regarding the involvement of CYP2C19 and the effect of co-administration of strong CYP2C19 inhibitors has not been studied.

Strong CYP3A4 inhibitors (e.g. ketoconazole)
Tasimelteon exposure was increased by approximately 50% when co-administered with ketoconazole 400 mg (after 5 days of ketoconazole 400 mg per day).

Strong CYP3A4 inducers (e.g. rifampin)
Use of tasimelteon should be avoided in combination with rifampin or other CYP3A4 inducers because of a potentially large decrease in tasimelteon exposure with reduced efficacy: the exposure of tasimelteon decreased by approximately 90% when co-administered with rifampin 600 mg (after 11 days of rifampin 600 mg per day).

Smoking (moderate CYP1A2 inducer)
Tasimelteon exposure decreased by approximately 40% in smokers compared to non-smokers (see section 5.2). This reduction in exposure is not considered clinically relevant and therefore no dose adjustment is necessary.

Beta blockers
The efficacy of tasimelteon may be reduced in patients with concomitant administration of beta adrenergic receptor antagonists.

Potential effect of alcohol on tasimelteon
In a study of 28 healthy volunteers, a single dose of ethanol (0.6 g/kg for women and 0.7 g/kg for men) was co-administered with a 20 mg dose of tasimelteon. On some psychomotor test measures (intoxication, drunk, alertness/drowsiness, balance platform test), there was a trend towards greater effects of tasimelteon plus ethanol versus ethanol alone, but the effects were not deemed significant.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of tasimelteon in pregnant women. In animal studies, administration of tasimelteon during pregnancy resulted in developmental toxicity (embryofoetal mortality, neurobehavioural impairment, and decreased growth and development in offspring) at doses greater than those used clinically. As a precautionary measure, it is preferable to avoid the use of tasimelteon during pregnancy.

Breast-feeding
It is unknown whether tasimelteon/metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from tasimelteon therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on the effects of tasimelteon on human fertility. Reproductive and developmental toxicity studies showed that oestrous cycles were prolonged in rats treated with high doses of tasimelteon, with no effect on mating performance or male fertility, and only a marginal effect on female fertility.

4.7 Effects on ability to drive and use machines

Tasimelteon may cause somnolence. After taking tasimelteon, patients should limit their activity to preparing to go to bed and not use machines because tasimelteon can impair performance of activities requiring complete mental alertness.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions (>3%) during clinical trials were headache (10.4%), somnolence (8.6%), nausea (4.0%), and dizziness (3.1%). The most frequently reported adverse reactions were mostly mild to moderate in severity and transient in nature.

Adverse reactions leading to discontinuation occurred in 2.3% of tasimelteon-treated patients. The most frequent adverse reactions leading to discontinuation were: somnolence (0.23%), nightmare (0.23%), and headache (0.17%).

Tabulated list of adverse reactions

The following are adverse reactions that were reported in tasimelteon-treated adult patients, derived from patient trials in 1772 patients treated with tasimelteon. The following terms and frequencies are applied and presented by MedDRA System Organ Class: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Summary of Adverse Drug Reactions

System Organ Class	Very common	Common	Uncommon
Psychiatric disorders		Sleep disorder, insomnia, abnormal dreams	Nightmare
Nervous system disorders	Headache	Somnolence, dizziness	Dysguesia
Ear and labyrinth disorders			Tinnitus
Gastrointestinal disorders		Dyspepsia, nausea, dry mouth	
Renal and urinary disorders			Pollakiuria
General disorders and administrative site conditions		Fatigue	Foggy feeling in head
Investigations		Alanine aminotransferase increased	Aspartate aminotransferase increased, gamma-glutamyl transferase increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is limited clinical experience with the effects of an overdose of tasimelteon.

As with the management of any overdose, general symptomatic and supportive measures should be used, along with immediate gastric lavage, where appropriate. Intravenous fluids should be administered as needed. Respiration, pulse, blood pressure, and other appropriate vital signs should be monitored, and general supportive measures employed.

While haemodialysis was effective at clearing tasimelteon and the majority of its major metabolites in patients with renal impairment, it is not known if hemodialysis will effectively reduce exposure in the case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, melatonin receptor agonists, ATC code: N05CH03

Mechanism of action
Tasimelteon is a circadian regulator that resets the master body clock in the suprachiasmatic nucleus (SCN). Tasimelteon acts as a Dual Melatonin Receptor Agonist (DMRA) with selective agonist activity at the MT_1 and MT_2 receptors. These receptors are thought to be involved in the control of circadian rhythms.

The master body clock regulates the circadian rhythms of hormones including melatonin and cortisol and aligns/synchronises the physiological processes of the sleep-wake cycle and metabolic and cardiovascular homeostasis.

Pharmacodynamic effects
Tasimelteon functions as a DMRA at the MT_1 and MT_2 receptors. Tasimelteon exhibits a greater affinity for the MT_2 as compared to the MT_1 receptor. The most abundant metabolites of tasimelteon have less than one-tenth of the binding affinity of the parent molecule for both the MT_1 and MT_2 receptors.

Tasimelteon and its most abundant metabolites have no appreciable affinity for more than 160 other pharmacologically relevant receptors. This includes the GABA receptor complex, the binding site for sedative hypnotics, and receptors that bind neuropeptides, cytokines, serotonin, noradrenaline, acetylcholine, and opiates.

Clinical efficacy and safety
The effectiveness of tasimelteon in the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) was established in two randomised, double-masked, placebo-controlled, multicentre, parallel-group studies (SET and RESET) in totally blind patients with Non-24.

In SET, 84 patients with Non-24 (median age 54 years) were randomised to receive tasimelteon 20 mg or placebo, one hour prior to bedtime, at the same time every night for up to 6 months.

RESET was a randomised withdrawal trial in 20 patients with Non-24 (median age 55 years) that was designed to evaluate the maintenance of efficacy of tasimelteon after 12-weeks. Patients were treated for approximately 12 weeks with tasimelteon 20 mg one hour prior to bedtime, at the same time every night. Patients 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 randomised to receive placebo or continue daily treatment with tasimelteon 20 mg for 8 weeks.

SET and RESET assessed entrainment of the master body clock as measured by aMT6s and cortisol. Both studies demonstrated the ability of tasimelteon to entrain the master body clock in patients with Non-24 and RESET demonstrated that continued daily dosing of tasimelteon is necessary to maintain entrainment.

Entrainment in Non-24-Hour Sleep-Wake Disorder

In SET, tasimelteon entrained circadian rhythms at month 1 at a significantly higher rate than placebo as measured by aMT6s and cortisol (20% vs. 2.6 % and 17.5% vs 2.6% respectively). Analyses of entrainment at month 7 in a subset of patients demonstrated that 59% of tasimelteon-treated patients entrained by month 7 indicating that response to treatment may take weeks or months for some patients to respond. RESET demonstrated the maintenance of entrainment with tasimelteon treatment compared to placebo withdrawal (aMT6s: 90% vs. 20% and cortisol: 80% vs. 20%).

Clinical Response in Non-24-Hour Sleep-Wake Disorder

The effectiveness of tasimelteon in the treatment of clinical symptoms, including the circadian sleep-wake cycle and clinical global functioning in patients with Non-24 was established in SET and RESET (Table 3). A composite scale of 4 measures of duration and timing of nighttime and daytime sleep and global functioning was used to evaluate clinical response in SET. Entrainment plus a score ≥3 on this scale, called Non-24 Clinical Response Scale (N24CRS) was required to be classified as a clinical responder. The components of the scale can be found in Table 2.

Table 2: Non-24 Scale of Clinical Response

Assessment	**Threshold of Response**
Nighttime sleep on 25% most symptomatic nights	≥45 minutes increase in average nighttime sleep duration
Daytime sleep on 25% most symptomatic days	≥45 minutes increase in average nighttime sleep duration
Timing of sleep	≥30 minutes increase and a standard deviation ≤2 hours during double-masked phase
CGI-C	≤2.0 from the average of Day 112 and Day 183 compared to baseline

Clinical response in sleep-wake amount and timing measures

SET and RESET evaluated the duration and timing of nighttime sleep and daytime naps via patient-recorded diaries. During SET, patient diaries were recorded for an average of 88 days during screening and 133 days during randomisation. During RESET, patient diaries were recorded for an average of 57 days during the run-in phase and 59 days during the randomised-withdrawal phase.

Because symptoms of nighttime sleep disruption and daytime sleepiness are cyclical in patients with Non-24, with severity varying according to the state of alignment of the individual patient's circadian rhythm with the 24-hour day (least severe when fully aligned, most severe when 12 hours out of alignment), 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 SET, patients in the tasimelteon group had, at baseline, an average 195 minutes of nighttime sleep and 137 minutes of daytime nap time on the 25% of most symptomatic nights and days, respectively. The average timing of sleep

relative to an individual's desired period for consolidated sleep over at least one circadian period was assessed. Treatment with tasimelteon resulted in a significant improvement, compared with placebo, for all of these endpoints in SET and RESET (see Table 3).

Table 3: Effects of Tasimelteon 20 mg Treatment on Clinical Response in Non-24

	Tasimelteon 20 mg	**Placebo**	**% Difference**	**p-value**
SET Study				
Clinical response (Entrainment + N24CRS ≥3)[(1)]	9/38 (23.7)	0/34 (0.0)	23.7	0.0028
N24CRS ≥ 3[(2)]	11/38 (28.9)	1/34 (2.9)	26.0	0.0031
N24CRS ≥ 2[(2)]	22/38 (57.9)	7/34 (20.6)	37.3	0.0014
Nighttime sleep on 25% most symptomatic nights (minutes)[(3)]	56.80	17.08	39.71	0.0055
Daytime sleep time on 25% most symptomatic days (minutes)[(3),(4)]	-46.48	-17.87	-28.61	0.0050
≥ 45 min improvement in both nighttime and daytime sleep (%)[(5)]	31.6	8.8	22.8	0.0177
Timing of sleep (minutes)[(1),(3)]	35.00	14.48	20.52	0.0123
RESET Study				
Nighttime sleep on 25% most symptomatic nights (minutes)[(3)]	-6.74	-73.74	67.00	0.0233
Daytime sleep time on 25% most symptomatic days (minutes)[(3),(4)]	-9.31	49.95	-59.25	0.0266
Timing of sleep (minutes)[(1),(3)]	19.99	-16.05	36.04	0.0108

(1) Higher numbers indicates improvement
(2) Sensitivity Analysis
(3) P-value was based on analysis of covariance model, units are LS mean minutes
(4) Lower numbers indicates improvement
(5) Post-hoc analysis

Response in Clinical Global Functioning Measures

Patients treated with tasimelteon experienced an overall improvement in clinical global functioning (CGI-C = 2.6) as compared to patients treated with placebo who showed no improvement status (CGI-C = 3.4) compared to the severity of Non-24 at baseline (LS mean difference = -0.8; p=0.0093) (Table 4). The effectiveness of tasimelteon to improve clinical global functioning was evaluated in SET. The Clinical Global Impression of Change (CGI-C) is a reflection of the general social, occupational, and health functioning of the patient and is evaluated on a 7-point scale, centered at *No Change (4),* that investigators used to rate the patients' improvement from baseline in symptoms of global functioning. It was rated as: *1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; or 7 = very much worse.*

Table 4: Clinical Global Functioning in Non-24 Patients

	Tasimelteon 20 mg	Placebo	p-value
CGI-C (LS mean)	2.6	3.4	0.0093

See section 4.8 for safety information.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with HETLIOZ in one or more subsets of the paediatric population who are totally blind with Non-24. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

The pharmacokinetics of tasimelteon is linear over doses ranging from 3 to 300 mg (0.15 to 15 times the recommended daily dosage). The pharmacokinetics of tasimelteon and its metabolites did not change with repeated daily dosing.

Absorption
The peak concentration (T_{max}) of tasimelteon occurred approximately 0.5 hours after fasted oral administration. The mean absolute oral bioavailability of tasimelteon is 38%.

When administered with a high-fat meal, the C_{max} of tasimelteon was 44% lower than when administered in a fasted state, and the median T_{max} was delayed by approximately 1.75 hours. Therefore, tasimelteon should be taken without food; if patients eat a high-fat meal, it is recommended to wait at least 2 hours before taking tasimelteon.

Distribution
The apparent oral volume of distribution at steady state of tasimelteon in young healthy subjects is approximately 59 - 126 L. At therapeutic concentrations, tasimelteon is about 88.6 – 90.1% bound to proteins.

Biotransformation
Tasimelteon is extensively metabolised. Metabolism of tasimelteon consists primarily of oxidation at multiple sites and oxidative dealkylation resulting in opening of the dihydrofuran ring followed by further oxidation to give a carboxylic acid. CYP1A2 and CYP3A4 are enzymes identified to play a role in the metabolism of tasimelteon. The involvement of other enzymes (e.g. CYP2C19) in the metabolism of tasimelteon is unknown.

Phenolic glucuronidation is the major phase II metabolic route.

Major metabolites had 13-fold or less activity at melatonin receptors compared to tasimelteon.

Elimination
Following oral administration of radiolabeled tasimelteon, 80% of total radioactivity was excreted in urine and approximately 4% in feces, resulting in a mean recovery of 84%. Less than 1% of the dose was excreted in urine as the parent compound.

The observed mean elimination half-life for tasimelteon is 1.3 ± 0.4 hours. The mean terminal elimination half-life ± standard deviation of the main metabolites ranges from 1.3 ± 0.5 to 3.7 ± 2.2.

Repeated once daily dosing with tasimelteon does not result in changes in pharmacokinetic parameters or significant accumulation of tasimelteon.

Special populations

Elderly
In elderly subjects, tasimelteon exposure increased by approximately two-fold compared to non-elderly adults. Due to the overall inter-subject variability of tasimelteon, this increase is not clinically meaningful and dose adjustment is not recommended.

Gender
The mean overall exposure of tasimelteon was approximately 1.6-fold greater in female than in male subjects. Due to the overall inter-subject variability of tasimelteon, this increase is not clinically meaningful and dose adjustment is not recommended.

Race
Race does not affect apparent clearance of tasimelteon.

Hepatic impairment
The pharmacokinetic profile of a 20 mg dose of tasimelteon was compared among 8 subjects with mild hepatic impairment (Child-Pugh Score ≥5 and ≤6 points), 8 subjects with moderate hepatic impairment (Child-Pugh Score ≥7 and ≤9 points), and 13 healthy matched controls. Tasimelteon exposure was increased less than two-fold in subjects with moderate hepatic impairment. Therefore, no dose adjustment is needed in patients with mild or moderate hepatic impairment. Tasimelteon has not been studied in patients with severe hepatic impairment (Child-Pugh Class C); therefore caution is recommended when prescribing HETLIOZ to patients with severe hepatic impairment.

Renal impairment
The pharmacokinetic profile of a 20 mg dose of tasimelteon was compared among 8 subjects with severe renal impairment (estimated glomerular filtration rate [eGFR] ≤ 29 mL/min/1.73m^2), 8 subjects with end-stage renal disease (ESRD) (GFR < 15 mL/min/1.73m^2) requiring hemodialysis, and 16 healthy matched controls. There was no apparent relationship between tasimelteon CL/F and renal function, as measured by either estimated creatinine clearance or eGFR. Subjects with severe renal impairment had a 30% lower CL/F clearance than match controls; however, when variability is taken into account, the different was not significant. No dose adjustment is necessary for patients with renal impairment.

Smokers (smoking is a moderate CYP1A2 inducer)
Tasimelteon exposure decreased by approximately 40% in smokers, compared to non-smokers (see section 4.5).

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Reproductive toxicology
In pregnant rats administered tasimelteon during the period of organogenesis, there were no effects on embryofoetal development. In pregnant rabbits administered tasimelteon during the period of organogenesis, embryolethality and embryofoetal toxicity (reduced foetal body weight and delayed ossification) were observed at the highest dose tested (200 mg/kg/day).

Oral administration of tasimelteon to rats throughout organogenesis and lactation resulted in persistent reductions in body weight, delayed sexual maturation and physical development, neurobehavioural

impairment in offspring at the highest dose tested, andreduced body weight in offspring at the mid-dose tested. The no effect dose (50 mg/kg/day) is approximately 25 times the RHD on a mg/m^2 basis.

Carcinogenesis
No evidence of carcinogenic potential was observed in mice; the highest dose tested is approximately 75 times the RHD of 20 mg/day, on a mg/m^2 basis. In rats, the incidence of liver tumours was increased in males (adenoma and carcinoma) and females (adenoma) at 100 and 250 mg/kg/day; the incidence of tumours of the uterus (endometrial adenocarcinoma) and uterus and cervix (squamous cell carcinoma) were increased at 250 mg/kg/day. There was no increase in tumours at the lowest dose tested in rats, which is approximately 10 times the recommended human doseon a mg/m^2 basis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard capsule core
Lactose anhydrous
Microcrystalline cellulose
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium sterate

Hard capsule shell
Gelatin
Titanium dioxide
Brilliant Blue FCF
Erythrosine
Orange Yellow S (E110)

White printing ink
Shellac
Propylene glycol
Sodium hydroxide
Povidone K17
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

After first opening of the bottle: 30 days

6.4 Special precautions for storage

Store in the original container and keep the bottle tightly closed in order to protect from moisture and light.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle containing 30 hard capsules with polypropylene child-resistant closures containing polypropylene resin induction seals. Each bottle also contains a 1.5-g silica gel desiccant canister and polyester dunnage. One HDPE bottle per paperboard carton.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Vanda Pharmaceuticals Limited
222 Regent Street, London, W1B 5TR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1008/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSBILE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

FDC International Limited
Unit 6, Fulcrum 1, Solent Way, Solent Business Park, Whiteley, Fareham,
Hampshire, PO15 7FE United Kingdom

B. CONDITIONS OR RESTRICTIONS

Medicinal product subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARETING AUTHORISATION

- Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 30-COUNT BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

HETLIOZ 20 mg hard capsules
tasimelteon

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 20 mg of tasimelteon.

3. LIST OF EXCIPIENTS

Contains lactose and Orange Yellow S (E110).
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 30 days after first opening.

9. SPECIAL STORAGE CONDITIONS

Store in the original container and keep the bottle tightly closed in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vanda Pharmaceuticals Limited
222 Regent Street, London, W1B 5TR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1008/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

HETLIOZ
20 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL FOR 30-COUNT BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

HETLIOZ 20 mg hard capsules
tasimelteon

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 20 mg of tasimelteon.

3. LIST OF EXCIPIENTS

Contains lactose and Orange Yellow S (E110).
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original container and keep the bottle tightly closed in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1008/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

HETLIOZ
20 mg

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

HETLIOZ 20 mg hard capsules
Tasimelteon

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What HETLIOZ is and what it is used for

HETLIOZ contains the active substance tasimelteon. This type of medicine is called a "melatonin agonist" that acts as a regulator of daily body rhythms.

It is used to treat Non-24-Hour Sleep-Wake Disorder (Non-24) in adults who are totally blind.

How HETLIOZ works
In sighted people, the change in light levels between day and night helps to synchronise internal body rhythms, including feeling sleepy at night and being active during the day. The body controls these rhythms through many pathways including increases and decreases in the production of the hormone melatonin.

Patients with Non-24 who are totally blind cannot see light, so their body rhythms shift out of alignment with the 24-hour world, resulting in periods of feeling sleepy during the day and the inability to sleep at night. The active substance in HETLIOZ, tasimelteon, is able to act as a time-keeper for the body rhythms and resets them each day. It aligns body rhythms with the usual 24-hour day and night cycle and so improve sleep patterns. Because of individual differences in each person's body rhythms, it could take weeks or up to 3 months for an improvement in symptoms to be noticed.

2. What you need to know before you take HETLIOZ

Do not take HETLIOZ if
You are allergic to tasimelteon or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
After taking HETLIOZ, you should get ready to go to bed and only carry out activities that you would normally do before going to bed.

Children and adolescents
Do not give HETLIOZ to children under the age of 18 years. This is because HETLIOZ has not been tested in people under 18 years of age and the effects are unknown.

Other medicines and HETLIOZ
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes:

- medicines known to reduce the activity of an enzyme called 'CYP1A2'. An example is fluvoxamine, which is used to treat depression and obsessive compulsive disorder (OCD).
- medicines known to reduce the activity of an enzyme called 'CYP3A4'. An example is ketoconazole, which is used to treat fungal infections.
- medicines known to increase the activity of an enzyme called 'CYP3A4'. An example is rifampicin, which is used to treat tuberculosis (TB).
- medicines known to reduce the activity of an enzyme called 'CYP2C19'. An example is omeprazole, which is used to treat hearburn and gastroesophageal reflux disease (GERD).
- medicines called "beta blockers" used to treat high blood pressure and other heart problems. Some examples include atenolol, metoprolol, and propanolol.

If any of the above applies to you (or you are not sure), talk to your doctor or pharmacist before taking HETLIOZ.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. If you become pregnant while taking HETLIOZ, consult your doctor immediately as it is recommended not to take HETLIOZ while you are pregnant or breast feeding.

HETLIOZ contains lactose
HETLIOZ contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

HETLIOZ contains Orange Yellow S (E110)
Tell your doctor if you have an allergy to Orange Yellow S (E110). HETLIOZ contains Orange Yellow S (E110) which may cause allergic reactions.

3. How to take HETLIOZ

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The recommended dose is one capsule every night, taken one hour before you go to bed. Try to take the medicine at the same time every night. Because of individual differences in each person's body rhythms, it could take weeks or months for you to notice an improvement in your symptoms. Therefore, your doctor may ask you to take HETLIOZ for up to 3 months before checking if it is working for you.

Taking HETLIOZ

- Take the medicine by mouth.
- Swallow the capsule whole.
- It is best to take HETLIOZ on an empty stomach as food can reduce the amount of the medicine that is absorbed into your body. If you eat a high-fat meal close to the time you would normally take the medicine, it is best to wait 2 hours before taking HETLIOZ.
- To open the bottle, push the cap down and turn counter-clockwise.

If you take more HETLIOZ than you should
If you accidentally take more HETLIOZ than your doctor recommended, contact your doctor at once or contact the nearest hospital for advice. Keep the bottle with you so that you can easily describe what you have taken.

If you forget to take HETLIOZ
- Skip the missed dose. Take your next dose at the usual time the next day. Do not take a double dose.

If you stop taking HETLIOZ
Do not stop taking HETLIOZ without talking to your doctor.
- If HETLIOZ is not taken every night, the body rhythms will lose alignment with the usual 24-hour day and night cycle again. This means that symptoms will come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine.

Very common: may affect more than 1 in 10 people
- headache

Common: may affect up to 1 in 10 people
- change in sleeping pattern
- difficulty in sleeping
- dizziness
- dry mouth
- tiredness
- indigestion
- feeling sick in the stomach
- blood tests which show changes in the way the liver is working (alanine aminotransferase)
- unusual dreams
- sleepiness

Uncommon: may affect up to 1 in 100 people
- abnormal or change in taste
- blood tests which show changes in the way the liver is working (aspartate aminotransferase and gamma-glutamyl transferase)
- increase in daytime urination
- nightmares
- ringing in the ears
- feeling foggy in the head

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store HETLIOZ

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the botttle and the carton. The expiry date refers to the last day of that month.
- Store in the original container and keep tightly closed in order to protect from moisture and light.

- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What HETLIOZ contains
- The active substance is tasimelteon. Each hard capsule contains 20 mg of tasimelteon.
- The other ingredients are lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.
- The shell of the capsule consists of gelatin, titanium dioxide, Brilliant Blue FCF, Erythrosine, and Orange Yellow S (E110).
- The white printing ink contains shellac, propylene glycol, sodium hydroxide, povidone K17 and titanium dioxide.

What HETLIOZ looks like and contents of the pack
HETLIOZ hard capsules are opaque dark blue printed with "VANDA 20 mg" in white. Each bottle has a child-resistant cap and contains 30 hard capsules. Push the cap down and turn counter-clockwise to open the bottle.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.