HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HETLIOZ safely and effectively. See full prescribing information for HETLIOZ.

HETLIOZ® (tasimelteon) capsules, for oral use
HETLIOZLQ™ (tasimelteon) oral suspension
Initial U.S. Approval: 2014

RECENT MAJOR CHANGES

Indications and Usage (1.2)	12/2020
Dosage and Administration (2.1, 2.3, 2.4)	12/2020

INDICATIONS AND USAGE

HETLIOZ is a melatonin receptor agonist.

HETLIOZ capsules are indicated for the treatment of:
- Non-24-Hour Sleep-Wake Disorder (Non-24) in adults (1)
- Nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in patients 16 years of age and older (1)

HETLIOZ LQ oral suspension is indicated for the treatment of:
- Nighttime sleep disturbances in SMS in pediatric patients 3 years to 15 years of age (1)

DOSAGE AND ADMINISTRATION

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

- HETLIOZ capsules and HETLIOZ LQ oral suspension are not substitutable (2.1)
- Administer at the same time every night (2.2, 2.3)
- Take without food (2.4)

DOSAGE FORMS AND STRENGTHS

- Capsules: 20 mg (3)
- Oral suspension: 4 mg/mL (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

May cause somnolence: After taking HETLIOZ, patients should limit their activity to preparing for going to bed, because HETLIOZ can impair the performance of activities requiring complete mental alertness (5.1)

ADVERSE REACTIONS

The most common adverse reactions (incidence >5% and at least twice as high on HETLIOZ than on placebo) were headache, increased alanine aminotransferase, nightmares or unusual dreams, and upper respiratory or urinary tract infection (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Vanda Pharmaceuticals Inc. at 1-844-438-5469 or www.hetlioz.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Strong CYP1A2 inhibitors (e.g., fluvoxamine): Avoid use of HETLIOZ in combination with strong CYP1A2 inhibitors because of increased exposure (7.1, 12.3)
- Strong CYP3A4 inducers (e.g., rifampin): Avoid use of HETLIOZ in combination with rifampin or other CYP3A4 inducers, because of decreased exposure (7.2, 12.3)

USE IN SPECIFIC POPULATIONS

Hepatic impairment: HETLIOZ has not been studied in patients with severe hepatic impairment and is not recommended in these patients (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 12/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-24-Hour Sleep-Wake Disorder (Non-24)

- HETLIOZ capsules are indicated for the treatment of Non-24 in adults.

1.2 Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)

- HETLIOZ capsules are indicated for the treatment of nighttime sleep disturbances in SMS in patients 16 years of age and older.

- HETLIOZ LQ oral suspension is indicated for the treatment of nighttime sleep disturbances in SMS in pediatric patients 3 to 15 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Non-Interchangeability between HETLIOZ Capsules and HETLIOZ LQ Oral Suspension

HETLIOZ capsules and HETLIOZ LQ oral suspension are not substitutable *[see Clinical Pharmacology (12.3)]*.

2.2 Recommended Dosage for HETLIOZ Capsules for Non-24

Adults

The recommended dosage of HETLIOZ capsules in adults is 20 mg one hour before bedtime, at the same time every night.

Because of individual differences in circadian rhythms, drug effect may not occur for weeks or months.

2.3 Recommended Dosage for HETLIOZ Capsules and HETLIOZ LQ Oral Suspension for Nighttime Sleep Disturbances in SMS

Patients 16 years of Age and Older

The recommended dosage of HETLIOZ capsules in patients 16 years and older is 20 mg one hour before bedtime, at the same time every night.

Pediatric Patients 3 Years to 15 Years of Age

The recommended dosage of HETLIOZ LQ oral suspension in pediatric patients 3 years to 15 years of age is based on body weight (Table 1). Administer HETLIOZ one hour before bedtime, at the same time every night.

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Table 1: Recommended Dosage of HETLIOZ LQ Oral Suspension for the Treatment of Nighttime Sleep Disturbances in SMS in Pediatric Patients 3 Years to 15 Years of Age

Body Weight	Daily Dose (oral suspension)
≤28 kg	0.7 mg/kg one hour before bedtime
>28 kg	20 mg one hour before bedtime

2.4 Important Administration Information

Administer HETLIOZ capsules and HETLIOZ LQ oral suspension without food *[see Clinical Pharmacology (12.3)]*.

If a patient is unable to take HETLIOZ at approximately the same time on a given night, they should skip that dose and take the next dose as scheduled.

HETLIOZ LQ Oral Suspension

See "Instructions for Use" for complete administration instructions.

Shake HETLIOZ LQ oral suspension well for at least 30 seconds before every administration. Remove seal and insert press-in bottle adapter (included in the package) into the neck of the bottle until a tight seal is made. Turn the bottle upside down and withdraw the prescribed amount of HETLIOZ LQ oral suspension from the bottle. Leave the press-in bottle adapter in place on bottle neck and replace cap on bottle. Store refrigerated. After opening, discard after 5 weeks (for the 48 mL bottle) and after 8 weeks (for the 158 mL bottle).

3 DOSAGE FORMS AND STRENGTHS

Capsules: 20 mg size 1 dark blue opaque, hard gelatin capsules printed with “VANDA 20 mg” in white.

Oral suspension: 4 mg/mL white to slightly yellow opaque suspension in 48 mL or 158 mL bottles.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Somnolence

After taking HETLIOZ, patients should limit their activity to preparing for going to bed. HETLIOZ can potentially impair the performance of activities requiring complete mental alertness.

6 ADVERSE REACTIONS

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6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

More than 2080 subjects have been treated with at least one dose of HETLIOZ, of which more than 380 have been treated for > 26 weeks and more than 170 have been treated for > 1 year.

Non-24-Hour Sleep-Wake Disorder (Non-24)

A 26-week, parallel-arm placebo-controlled study (Study 1) evaluated HETLIOZ (n=42) compared to placebo (n=42) in patients with Non-24. A randomized-withdrawal, placebo-controlled study of 8 weeks duration (Study 2) also evaluated HETLIOZ (n=10), compared to placebo (n=10), in patients with Non-24.

In placebo-controlled studies, 6% of patients exposed to HETLIOZ discontinued treatment due to an adverse event, compared with 4% of patients who received placebo.

Table 2 shows the incidence of adverse reactions from Study 1.

Table 2: Adverse Reactions in Study 1

	HETLIOZ N=42	**Placebo N=42**
Headache	17 %	7 %
Alanine aminotransferase increased	10 %	5 %
Nightmare/abnormal dreams	10 %	0 %
Upper respiratory tract infection	7 %	0 %
Urinary tract infection	7 %	2 %

*Adverse reactions with an incidence > 5% and at least twice as high on HETLIOZ than on placebo are displayed.

Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)

A 9-week, double-blind, randomized, placebo-controlled, two-period crossover study evaluated HETLIOZ (capsules and oral suspension; n=25) compared to placebo (n=26) in the treatment of nighttime sleep disturbances in patients with Smith-Magenis Syndrome. Pediatric patients (n=11, age 3 to 15 years) received HETLIOZ LQ oral suspension, and patients ≥16 years of age (n=14) received HETLIOZ capsules.

Adverse reactions were similar in patients treated for Non-24 and patients with Smith-Magenis syndrome treated for nighttime sleep disturbances. Adverse reactions were also similar in pediatric patients (3 years to 15 years) who received HETLIOZ LQ oral suspension, and patients ≥16 years of age who received HETLIOZ capsules.

7 DRUG INTERACTIONS

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7.1 Strong CYP1A2 Inhibitors (e.g., fluvoxamine)

Avoid use of 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 Clinical Pharmacology (12.3)]*.

7.2 Strong CYP3A4 Inducers (e.g., rifampin)

Avoid use of HETLIOZ in combination with rifampin or other CYP3A4 inducers because of a potentially large decrease in tasimelteon exposure with reduced efficacy *[see Clinical Pharmacology (12.3)]*.

7.3 Beta-adrenergic Receptor Antagonists (e.g., acebutolol, metoprolol)

Beta-adrenergic receptor antagonists have been shown to reduce the production of melatonin via specific inhibition of beta-1 adrenergic receptors. Nighttime administration of beta-adrenergic receptor antagonists may reduce the efficacy of HETLIOZ.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available postmarketing case reports with HETLIOZ use in pregnant women are not sufficient to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In pregnant rats, no embryofetal developmental toxicity was observed at exposures of 50 mg/kg/day, or up to 24 times higher than the human exposure at the maximum recommended human dose (MRHD) (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In pregnant rats administered tasimelteon at oral doses of 5, 50, or 500 mg/kg/day during the period of organogenesis, there were no effects on embryofetal development. The highest dose tested is approximately 240 times the MRHD of 20 mg/day, based on mg/m^2 body surface area.

In pregnant rabbits administered tasimelteon at oral doses of 5, 30, or 200 mg/kg/day during the period of organogenesis, embryolethality and embryofetal toxicity (reduced fetal body weight and delayed ossification) were observed at the highest dose tested. The highest dose is approximately 200 times the MRHD.

Oral administration of tasimelteon at 50, 150, or 450 mg/kg/day to rats throughout organogenesis resulted in persistent reductions in body weight, delayed sexual maturation, and

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physical development, and neurobehavioral impairment in offspring at the highest dose tested which is approximately 220 times the MRHD based on mg/m2 body surface area. Reduced body weight in offspring was also observed at the mid-dose. The no effect dose (NOEL), (50 mg/kg/day) is approximately 25 times the MRHD based on mg/m^2 body surface area.

8.2 Lactation

Risk Summary

There are no data on the presence of tasimelteon or its metabolites in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HETLIOZ and any potential adverse effects on the breastfed infant from HETLIOZ or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of HETLIOZ for the treatment of Non-24 in pediatric patients have not been established.

Safety and effectiveness of HETLIOZ LQ oral suspension for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) have been established in pediatric patients 3 years and older. Use is based on a placebo-controlled crossover study of pediatric and adult patients *[see Clinical Studies (14.2)]*.

Safety and effectiveness of HETLIOZ for the treatment of nighttime sleep disturbances in SMS have not been established in patients younger than 3 years old.

Juvenile Animal Toxicity Data

Juvenile rats received oral doses of tasimelteon at 50, 150, or 450 mg/kg from weaning (day 21) through adulthood (day 90). These doses are approximately 12 to 108 times the maximum recommended human dose (MRHD) of 20 mg based on a mg/m^2 body surface area. Toxicity was observed mainly at the highest dose and included mortality (females only), tremors, unsteady gait, decrease in growth and development compared to controls. The former reflected as decreases in bone growth, bone mineral content, bone ossification, and a delay in attainment of sexual maturation. Tasimelteon had no effect on fertility, reproduction, or learning and memory. The No Observed Adverse Effect Level (NOAEL) is 150 mg/kg/day, which is approximately 178 times the MRHD based on AUC.

8.5 Geriatric Use

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.

8.6 Hepatic Impairment

Dose adjustment is not necessary in patients with mild or moderate hepatic impairment. HETLIOZ has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

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Therefore, HETLIOZ is not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Smokers

Smoking causes induction of CYP1A2 levels. The exposure of tasimelteon in smokers was lower than in non-smokers and therefore the efficacy of HETLIOZ may be reduced in smokers *[see Clinical pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Tasimelteon is not a controlled substance under the Controlled Substances Act.

9.2 Abuse

Tasimelteon did not produce any abuse-related signals in animal behavioral studies. Rats did not self-administer tasimelteon, suggesting that the drug does not have rewarding properties. There were also no signs or symptoms indicative of abuse potential in clinical studies with HETLIOZ.

9.3 Dependence

Discontinuation of HETLIOZ in humans following chronic administration did not produce withdrawal signs. HETLIOZ does not appear to produce physical dependence.

10 OVERDOSAGE

There is limited premarketing clinical experience with the effects of an overdosage of HETLIOZ.

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 hemodialysis was effective at clearing HETLIOZ 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.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. Contact a poison control center for current information on the management of overdose.

11 DESCRIPTION

HETLIOZ contains tasimelteon, a melatonin receptor agonist, chemically designated as (1*R*, 2*R*)-N-[2- (2,3-dihydrobenzofuran-4-yl)cyclopropylmethyl]propanamide, containing two chiral centers.
The molecular formula is $C_{15}H_{19}NO_2$, and the molecular weight is 245.32. The structural formula is:

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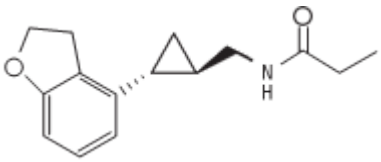

Tasimelteon is a white to off-white crystalline powder. It is very slightly soluble in cyclohexane, slightly soluble in water and 0.1 N hydrochloric acid, and freely soluble or very soluble in methanol, 95% ethanol, acetonitrile, isopropanol, polyethylene glycol 300, propylene glycol and ethyl acetate.

HETLIOZ capsules are intended for oral administration. Each capsule contains 20 mg of tasimelteon and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose anhydrous, magnesium stearate, and microcrystalline cellulose. Each hard gelatin capsule consists of FD&C Blue #1, FD&C Red #3, and FD&C Yellow #6, gelatin, and titanium dioxide.

HETLIOZ LQ oral suspension contains 4 mg of tasimelteon per mL of suspension and the following inactive ingredients: ascorbic acid, cherry flavor, mannitol, microcrystalline cellulose/carboxymethylcellulose sodium, polysorbate 80, sodium benzoate, sodium chloride, sucrose, sucralose, and water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism by which tasimelteon exerts its therapeutic effect in patients with Non-24 or nighttime sleep disturbances in SMS is unclear. However, tasimelteon is an agonist at melatonin MT_1 and MT_2 receptors which are thought to be involved in the control of circadian rhythms.

12.2 Pharmacodynamics

Tasimelteon is an agonist at MT_1 and MT_2 receptors with greater affinity for the MT_2 as compared to the MT_1 receptor (Ki = 0.304 nM and 0.07 nM, respectively). The major 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.

12.3 Pharmacokinetics

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.

<u>Absorption</u>

The absolute oral bioavailability is 38.3%. The peak concentration (T_{max}) of tasimelteon capsule occurred approximately 0.5 to 3 hours after fasted oral administration. The Tmax of

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tasimelteon suspension occurred approximately 15 to 30 minutes after fasted oral administration.

The pharmacokinetic profile of oral suspension has not been directly compared to capsules; therefore, capsules are the only dosage form recommended for use in adults.

Effect of food

When administered with a high-fat meal, the Cmax of tasimelteon was 44% lower than when given in a fasted state, and the median Tmax was delayed by approximately 1.75 hours. Therefore, HETLIOZ should be taken without food.

Distribution

The apparent oral volume of distribution of tasimelteon at steady state in young healthy subjects is approximately 59 - 126 L. At therapeutic concentrations, tasimelteon is about 90% bound to proteins.

Metabolism

Tasimelteon is extensively metabolized. 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 the major isozymes involved in the metabolism of tasimelteon.

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 HETLIOZ does not result in changes in pharmacokinetic parameters or significant accumulation of tasimelteon.

Studies in Specific Populations

Elderly

In elderly subjects, tasimelteon exposure increased by approximately two-fold compared with non-elderly adults.

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Pediatric Patients

Pharmacokinetic information in pediatric patients are available only for the oral suspension formulation. Body weight was found to have significant effect on the pharmacokinetics. The increase in body weight was associated with increase in tasimelteon clearance up to 28 kg. The average dose normalized Cmax and AUC_{inf} at the recommended dose was 231 ng/mL and 310 ng.h/mL. No data are available in patients less than 3 years old.

Gender

The mean overall exposure of tasimelteon was approximately 20-30% greater in female than in male subjects.

Race

The effect of race on exposure of HETLIOZ was not evaluated.

Hepatic Impairment

The pharmacokinetic profile of a 20 mg dose of HETLIOZ was compared among eight subjects with mild hepatic impairment (Child-Pugh Score ≥5 and ≤6 points), eight 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. HETLIOZ has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and is not recommended in these patients.

Renal Impairment

The pharmacokinetic profile of a 20 mg dose of HETLIOZ was compared among eight subjects with severe renal impairment (estimated glomerular filtration rate [eGFR] ≤ 29 $mL/min/1.73m^2$), eight subjects with end-stage renal disease (ESRD) (GFR < 15 $mL/min/1.73m^2$) requiring hemodialysis, and sixteen 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 clearance, and clearance in subjects with ESRD was comparable to that of healthy subjects. 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 Use in Specific Populations (8.7)]*.

Drug Interaction Studies

No potential drug interactions were identified in *in vitro* studies with CYP inducers or inhibitors of CYP1A1, CYP1A2, CYP2B6, CYP2C9/2C19, CYP2E1, CYP2D6, and transporters including P-glycoprotein, OATP1B1, OATP1B3, OCT2, OAT1, and OAT3.

Effect of Other Drugs on HETLIOZ

Drugs that inhibit CYP1A2 and CYP3A4 are expected to alter the metabolism of tasimelteon.

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Fluvoxamine (strong CYP1A2 inhibitor): 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) *[see Drug Interactions (7.1)]*.

Ketoconazole (strong CYP3A4 inhibitor): tasimelteon exposure increased by approximately 50% when co-administered with ketoconazole 400 mg (after 5 days of ketoconazole 400 mg per day) *[see Drug Interactions (7.2)]*.

Rifampin (strong CYP3A4 and moderate CYP2C19 inducer): the exposure of tasimelteon decreased by approximately 90% when co-administered with rifampin 600 mg (after 11 days of rifampin 600 mg per day). Efficacy may be reduced when HETLIOZ is used in combination with strong CYP3A4 inducers, such as rifampin *[see Drug Interactions (7.2)]*.

Effect of HETLIOZ on Other Drugs

Midazolam (CYP3A4 substrate): Administration of HETLIOZ 20 mg once a day for 14 days did not produce any significant changes in the T_{max}, C_{max}, or AUC of midazolam or 1-OH midazolam. This indicates there is no induction of CYP3A4 by tasimelteon at this dose.

Rosiglitazone (CYP2C8 substrate): Administration of HETLIOZ 20 mg once a day for 16 days did not produce any clinically significant changes in the T_{max}, C_{max}, or AUC of rosiglitazone after oral administration of 4 mg. This indicates that there is no induction of CYP2C8 by tasimelteon at this dose.

Effect of Alcohol on HETLIOZ

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 HETLIOZ. There was a trend for an additive effect of HETLIOZ and ethanol on some psychomotor tests.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Tasimelteon was administered orally for up to two years to mice (30, 100, and 300 mg/kg/day) and rats (20, 100, and 250 mg/kg/day). No evidence of carcinogenic potential was observed in mice; the highest dose tested is approximately 75 times the maximum recommended human dose (MRHD) of 20 mg/day, based on a mg/m^2 body surface area. In rats, the incidence of liver tumors was increased in males (adenoma and carcinoma) and females (adenoma) at 100 and 250 mg/kg/day; the incidence of tumors of the uterus (endometrial adenocarcinoma) and uterus and cervix (squamous cell carcinoma) were increased at 250 mg/kg/day. There was no increase in tumors at the lowest dose tested in rats, which is approximately 10 times the MRHD based on a mg/m^2 body surface area.

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Mutagenesis

Tasimelteon was negative in an *in vitro* bacterial reverse mutation (Ames) assay, an *in vitro* cytogenetics assay in primary human lymphocytes, and an *in vivo* micronucleus assay in rats.

Impairment of Fertility

When male and female rats were given tasimelteon at oral doses of 5, 50, or 500 mg/kg/day prior to and throughout mating and continuing in females to gestation day 7, estrus cycle disruption and decreased fertility were observed at all but the lowest dose tested. The no-effect dose for effects on female reproduction (5 mg/kg/day) is approximately 2 times the MRHD based on a mg/m^2 body surface area.

14 CLINICAL STUDIES

14.1 Non-24-Hour Sleep-Wake Disorder (Non-24)

The effectiveness of HETLIOZ in the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) was established in two randomized double-masked, placebo-controlled, multicenter, parallel-group studies (Studies 1 and 2) in totally blind patients with Non-24.

In study 1, 84 patients with Non-24 (median age 54 years) were randomized to receive HETLIOZ 20 mg or placebo, one hour prior to bedtime, at the same time every night for up to 6 months.

Study 2 was a randomized withdrawal trial in 20 patients with Non-24 (median age 55 years) that was designed to evaluate the maintenance of efficacy of HETLIOZ after 12-weeks. Patients were treated for approximately 12 weeks with HETLIOZ 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 randomized to receive placebo or continue treatment with HETLIOZ 20 mg for 8 weeks.

Study 1 and Study 2 evaluated the duration and timing of nighttime sleep and daytime naps via patient-recorded diaries. During Study 1, patient diaries were recorded for an average of 88 days during screening, and 133 days during randomization. During Study 2, patient diaries were recorded for an average of 57 days during the run-in phase, and 59 days during the randomized-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 Study 1, patients in the HETLIOZ 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. Treatment with HETLIOZ resulted in a significant improvement, compared with placebo, for both of these endpoints in Study 1 and Study 2 (see Table 3).

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Table 3: Effects of HETLIOZ 20 MG on Nighttime Sleep Time and Daytime Nap Time in Study 1 and Study 2

	Study 1		Study 2	
Change from Baseline	**HETLIOZ 20 MG N=42**	**Placebo N=42**	**HETLIOZ 20 MG N=10**	**Placebo N=10**
Nighttime sleep time on 25% most symptomatic nights (minutes)	50	22	-7	-74
Daytime nap time on 25% most symptomatic days (minutes)	-49	-22	-9	50

A responder analysis of patients with both ≥ 45 minutes increase in nighttime sleep and ≥ 45 minutes decrease in daytime nap time was conducted in Study 1: 29% (n=12) of patients treated with HETLIOZ, compared with 12% (n=5) of patients treated with placebo met the responder criteria.

14.2 Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)

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

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

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

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

Reference ID: 4709967

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

HETLIOZ Capsules
20 mg capsules are available as size 1, dark blue opaque, hard gelatin capsules printed with "VANDA 20 mg" in white, containing 20 mg of tasimelteon per capsule.

- NDC 43068-220-01 Bottles of 30

HETLIOZ LQ Oral Suspension
4 mg/mL white to slightly yellow opaque suspension. Each bottle has a child resistant cap and packaged in a carton. Each carton contains a bottle of HETLIOZ LQ oral suspension, a 5 mL oral dosing syringe and a press-in bottle adapter.

- NDC 43068-304-02 Bottles of 48 mL
- NDC 43068-304-06 Bottles of 158 mL

Storage and Handling

HETLIOZ Capsules
Store HETLIOZ capsules at controlled room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Protect from exposure to light and moisture.

HETLIOZ LQ Oral Suspension

Reference ID: 4709967

Store HETLIOZ LQ oral suspension at refrigerated temperature 5°C (41°F); excursions permitted to 2°C to 8°C (36°F t o 46°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling for HETLIOZ LQ oral suspension, if appropriate (Instructions for Use).

- Advise patients to limit their activities to preparing for going to bed after taking HETLIOZ capsules or HETLIOZ LQ oral suspension because HETLIOZ can potentially impair the performance of activities requiring complete mental alertness *[see Warnings and Precautions (5.1)]*.

- Administration Information for HETLIOZ capsules and HETLIOZ LQ oral suspension *[see Dosage and Administration (2.1, 2.2, 2.3, 2.4)]*.
  - Advise patients to take HETLIOZ without food.
  - Advise patients to take HETLIOZ before bedtime at the same time every night.
  - Advise patients to skip the dose that night if they cannot take HETLIOZ at approximately the same time on a given night.
  - Advise patients to swallow HETLIOZ capsules whole.
  - HETLIOZ LQ oral suspension:
    Advise patients to shake the bottle for at least 30 seconds before each administration; use the press-in bottle adapter included in the package; leave the adapter in place on the bottle neck; replace the cap; and refrigerate after each use. After opening, discard after 5 weeks (for the 48 mL bottle) and after 8 weeks (for the 158 mL bottle).

- Non-24 (HETLIOZ capsules)
  Advise patients that because of individual differences in circadian rhythms, daily use for several weeks or months may be necessary before benefit from HETLIOZ is observed *[see Dosage and Administration (2.2)]*.

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Vanda Pharmaceuticals Inc.
Washington, D.C. 20037 USA
www.hetlioz.com

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Reference ID: 4709967

Pharmaceuticals Inc. in the United States and other countries.

Reference ID: 4709967

INSTRUCTIONS FOR USE
HETLIOZ LQ™ (HeT-lee-ōz eL-Cue)
(tasimelteon) oral suspension

Read this Instructions for Use before you give HETLIOZ LQ to your child and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.

Important information you need to know before giving HETLIOZ LQ to your child:

- Give HETLIOZ LQ exactly as your healthcare provider tells you to. Your healthcare provider will prescribe the dose of HETLIOZ that is right for your child based on body weight.
- Give HETLIOZ LQ one hour before bedtime, at the same time every night.
- Give HETLIOZ LQ without food.
- Skip the dose that night if you cannot give HETLIOZ LQ at about the same time on a given night.
- Limit your child's activities to preparing for going to bed after taking HETLIOZ LQ because HETLIOZ LQ can potentially decrease mental alertness.
- People who have problems using their hands may need help to draw up and give the correct dose of HETLIOZ LQ.
- Write the date that you first open the bottle on the bottle label.

Each HETLIOZ LQ carton includes:

- 1 bottle of HETLIOZ LQ oral suspension
- 1 press-in bottle adapter
- A 5 mL oral dosing syringe. Always use the oral dosing syringe that comes with HETLIOZ LQ to measure your child's prescribed dose.

(see Figure A)

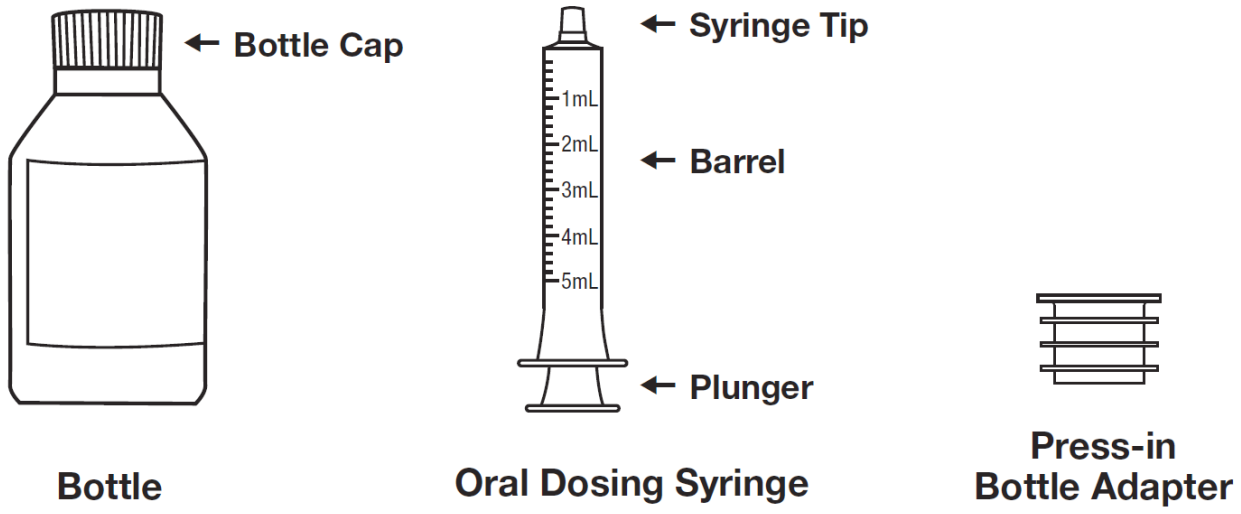

Figure A

Preparing a dose of HETLIOZ LQ:

Step 1. Remove the HETLIOZ LQ bottle, bottle adapter, and oral dosing syringe from the carton. Shake the bottle well for at least 30 seconds before each use **(see Figure B)**.

Figure B

Step 2. Press down on the child-resistant cap and twist the cap counterclockwise to open bottle **(see Figure C)**.
Do not throw away the child-resistant cap.

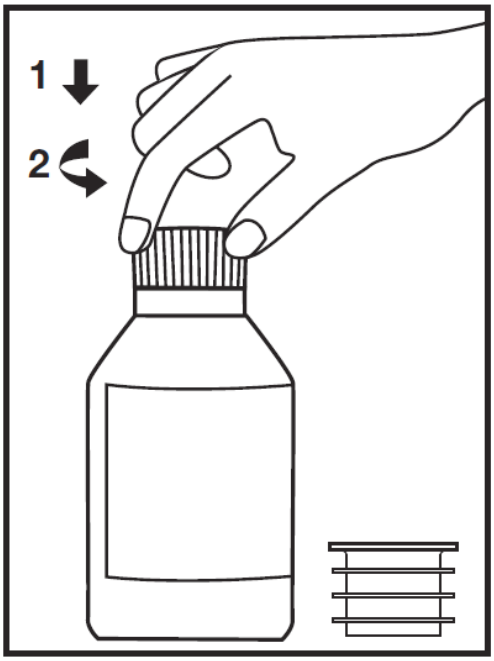

Figure C

Step 3. **First time use only:** Remove seal from bottle and insert press-in bottle adapter into the bottle. Press on the bottle adapter until it is even with the top of the bottle **(see Figure D)**.
After the bottle adapter is in place, it should not be removed.

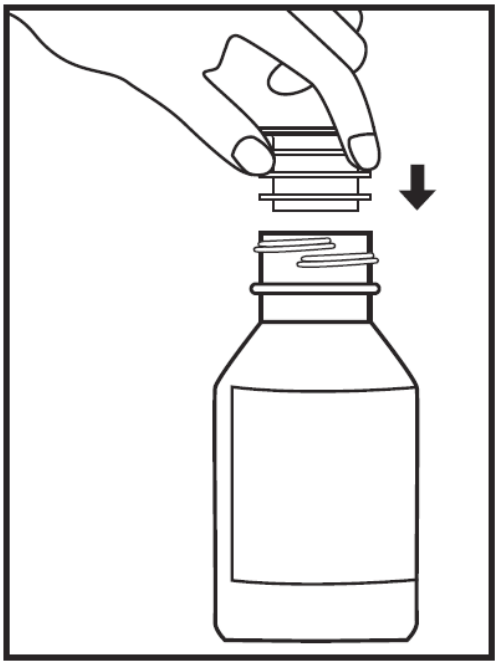

Figure D

Step 4. **First time use of bottle only:** Replace child-resistant cap tightly by turning clockwise and shake well again for at least 30 seconds **(see Figure E)**.

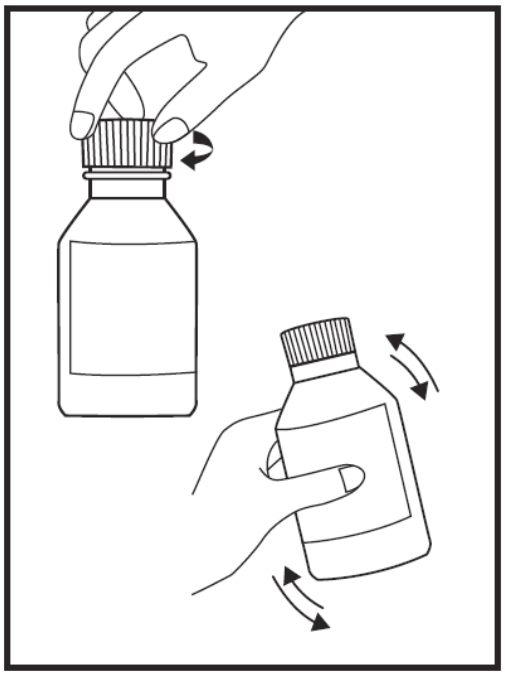

Figure E

Step 5. Press down on the child-resistant cap and twist the cap counterclockwise to open bottle. Push plunger of oral dosing syringe completely down. Insert the oral dosing syringe into the opening of the press-in bottle adapter as far as it will go **(see Figure F)**.

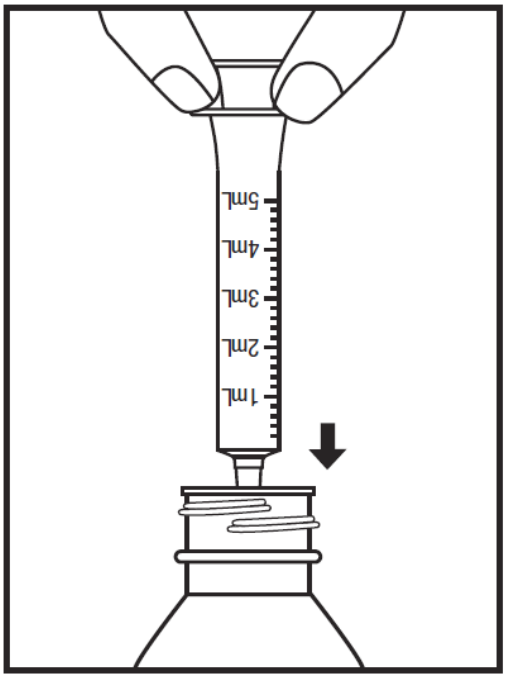

Figure F

Step 6. With the oral dosing syringe in the bottle adapter, carefully turn the bottle upside down. Slowly pull back on the plunger to withdraw the prescribed amount of HETLIOZ LQ from the bottle. **Line up** the end of the plunger with the mL (milliliter) marking for your child's prescribed dose of HETLIOZ LQ **(see Figure G)**.

If you see more than a few air bubbles in the oral dosing syringe, fully push in the plunger so that the liquid flows back into the bottle. Repeat **Step 6** until the air bubbles are mostly gone.

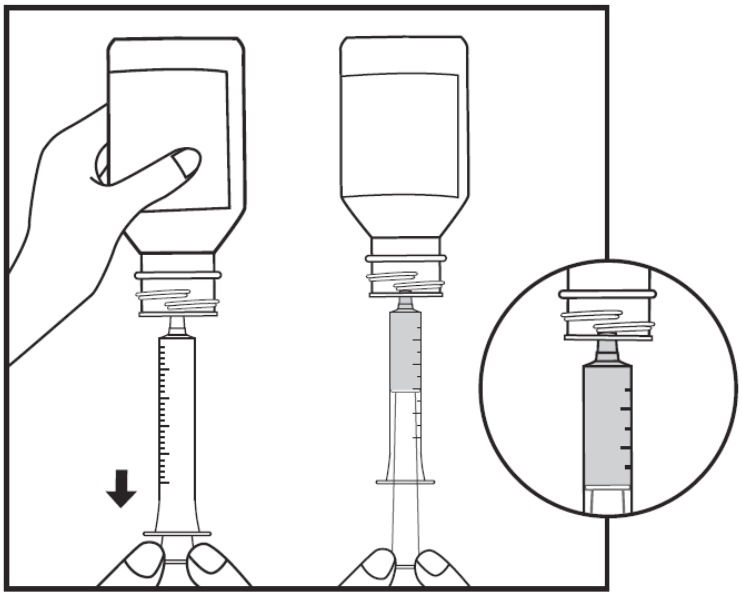

Figure G

Step 7. Leave the oral dosing syringe in the bottle adapter and turn the bottle upright. Carefully remove the

oral dosing syringe from the bottle adapter. Replace the child-resistant cap securely **(see Figure H)**.

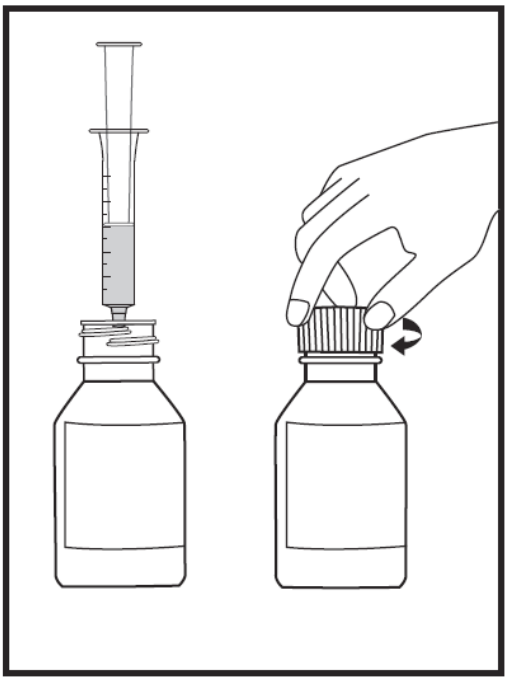

Figure H

Step 8. Place the tip of the oral dosing syringe in the child's mouth and toward the inside of their cheek. Slowly push the plunger all the way in to give the entire dose. Make sure the child has time to swallow the medicine **(see Figure I)**.

Figure I

Step 9. Remove the plunger from the barrel of the oral dosing syringe. Rinse the oral dosing syringe barrel and plunger with water **(see Figure J)**. When the barrel and plunger are dry, put the plunger back

into the oral dosing syringe.
Do not wash the oral dosing syringe in the dishwasher.
Do not throw away the oral dosing syringe. Keep this oral dosing syringe for use with this bottle of HETLIOZ LQ.

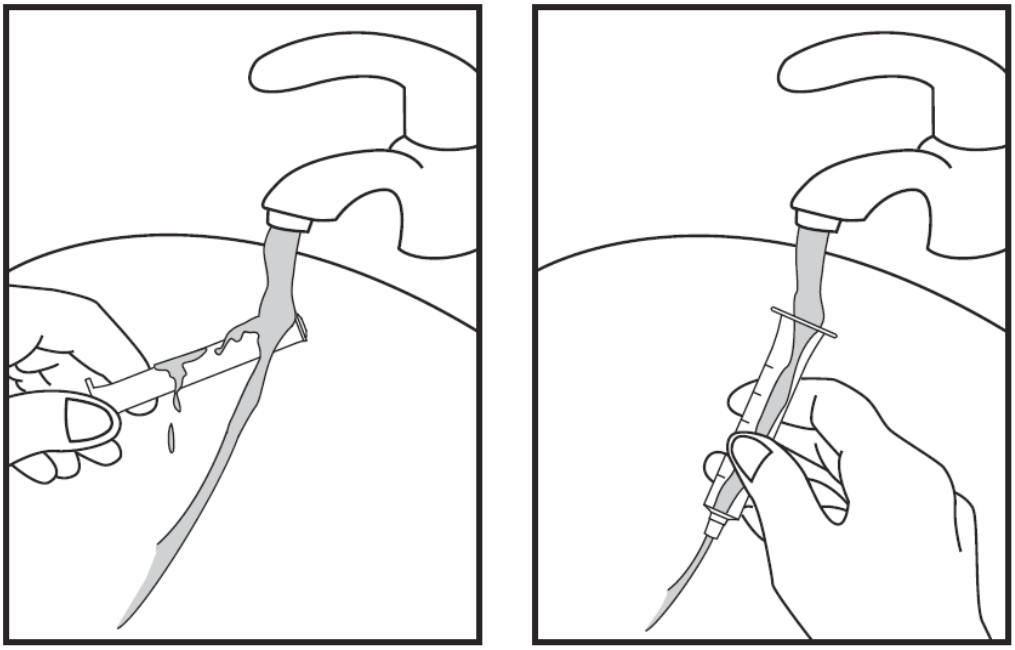

Figure J

Storing HETLIOZ LQ:

- Store HETLIOZ LQ in a refrigerator at 36°F to 46°F (2°C to 8°C).
- **Keep HETLIOZ LQ and all medicines out of the reach of children.**

Disposal of HETLIOZ LQ Suspension:

Once opened, the 48 mL bottle can be stored for 5 weeks and the 158 mL bottle can be stored for 8 weeks, both at refrigerated temperature. Safely throw away any unused HETLIOZ LQ suspension after these time points. Ask your pharmacist how to properly throw away (dispose of) medicines you no longer use.

What are the ingredients in HETLIOZ LQ oral suspension?

Active ingredient: tasimelteon
Inactive ingredients: ascorbic acid, cherry flavor, mannitol, microcrystalline cellulose/carboxymethylcellulose sodium, polysorbate 80, sodium benzoate, sodium chloride, sucrose, sucralose, and water.

Distributed by:
Vanda Pharmaceuticals Inc. Washington,
D.C. 20037 USA www.hetlioz.com

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This Instructions for Use has been approved by the U.S. Food and Drug Administration. Issued: December 2020

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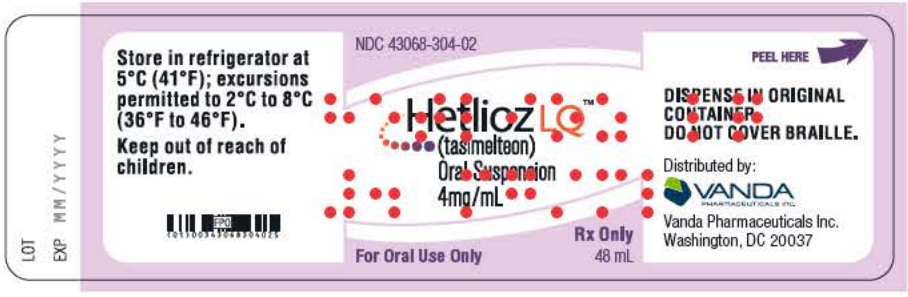

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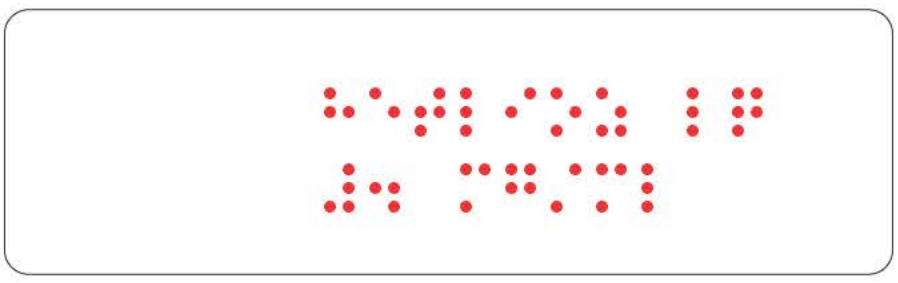

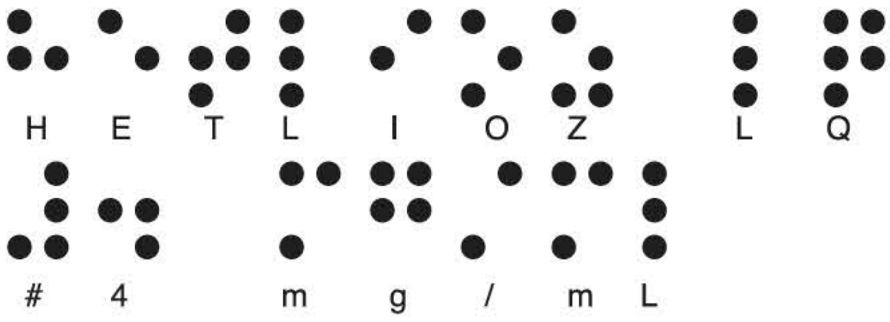

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view 2
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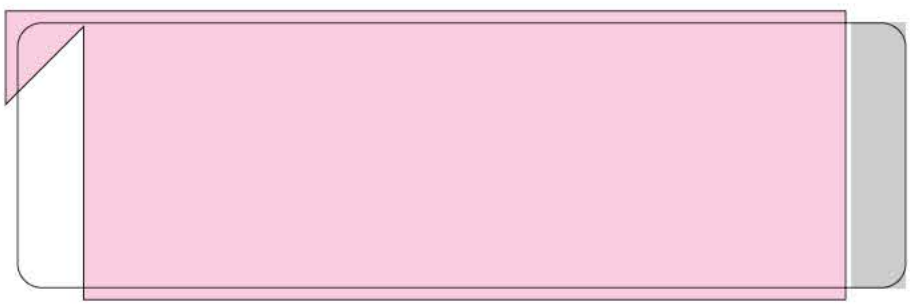

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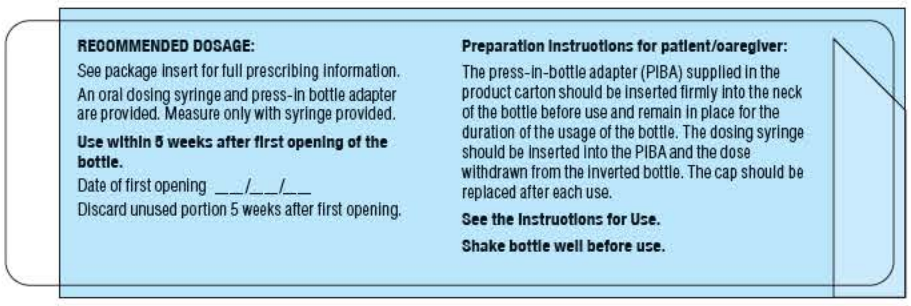

NDC 43068-304-02
HetliozLQ™
(tasimelteon)
Oral Suspension
4mg/mL
48 mL
Contents:
One 48 mL bottle
One oral dosing syringe
One press-in bottle adapter
Measure only with syringe provided.
Store in refrigerator at 5°C (41°F); excursions permitted to 2°C to 8°C (36°F to 46°F).
Keep out of reach of children.
RECOMMENDED DOSAGE:
See package insert for full prescribing information.
Use within 5 weeks after first opening of the bottle.
Date of first opening ___/___/___
Discard unused portion 5 weeks after first opening.
Distributed by:
VANDA PHARMACEUTICALS INC.
Vanda Pharmaceuticals Inc.
Washington, DC 20037
3 43068 30402 5
Preparation instructions for patient/caregiver:
The press-in-bottle adapter (PIBA) supplied in the product carton should be inserted firmly into the neck of the bottle before use and remain in place for the duration of the usage of the bottle. The dosing syringe should be inserted into the PIBA and the dose withdrawn from the inverted bottle. The cap should be replaced after each use.
See the Instructions for Use.
Rx Only
48 mL
For Oral Use Only
DISPENSE IN ORIGINAL CONTAINER.
Shake bottle well before use.
FPO
GTIN: XXXXXXXXXXXXX
S/N: XXXXXXXXXXX
EXP: MM/YYYY
LOT: XXXX

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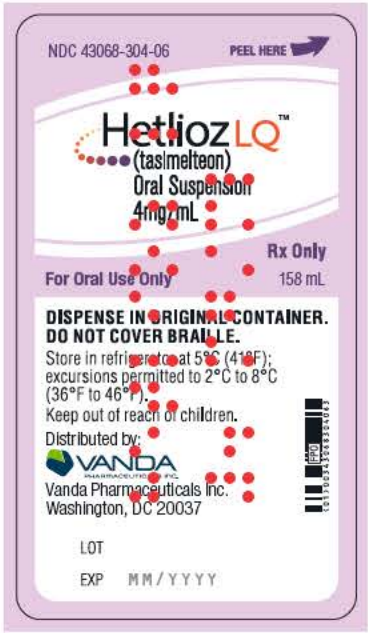

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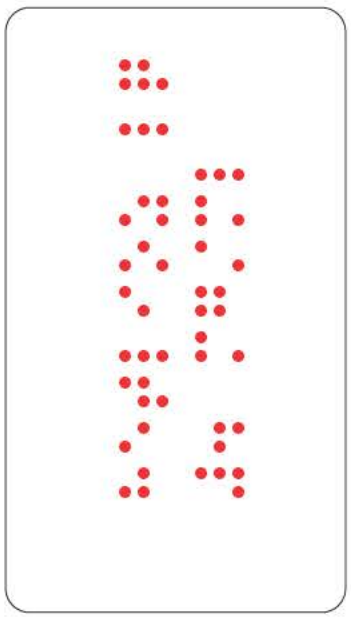

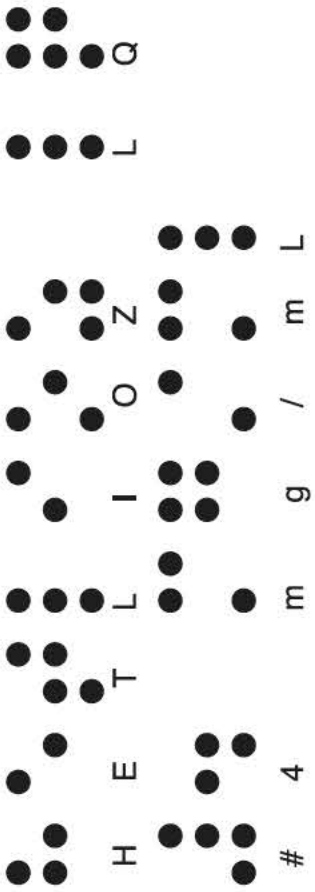

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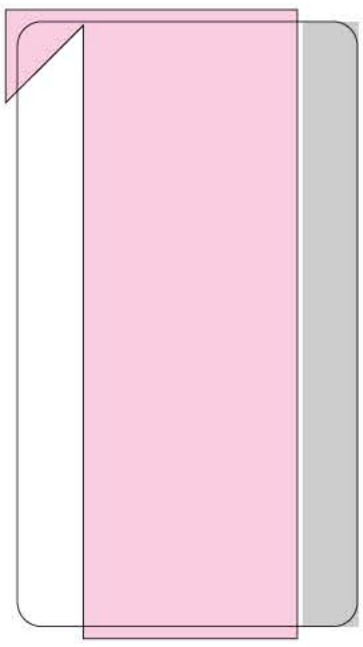

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DRAFT ARTWORK – SIZE MAY CHANGE