CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 211654

Name: Tasimelteon (Capsule), 20 MG

Sponsor: MSN Pharmaceuticals Inc.

Approval Date: January 12, 2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA211654

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211654

APPROVAL LETTER

ANDA 211654

ANDA APPROVAL

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854-3714
Attention: Kondal Reddy Bairy
Associate Director

Dear Kondal Reddy Bairy:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on January 31, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Tasimelteon Capsules, 20 mg.

Reference is also made to the tentative approval letter issued by this office on May 28, 2020, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Tasimelteon Capsules, 20 mg, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Hetlioz Capsules, 20 mg, of Vanda Pharmaceuticals, Inc. (Vanda).

The RLD upon which you have based your ANDA, Vanda's Hetlioz Capsules, 20 mg, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
10,149,829 (the '829 patent)	January 25, 2033
9,060,995 (the '995 patent)	January 25, 2033
RE46,604 (the '604 patent)	January 25, 2033
10,179,119 (the '119 patent)	August 29, 2035
10,449,176 (the '176 patent)	January 25, 2033

10,829,465 (the '465 patent)	February 12, 2035
11,141,400 (the '400 patent)	October 10, 2034
10,071,977 (the '977 patent)	February 12, 2035
10,376,487 (the '487 patent)	July 27, 2035
9,730,910 (the '910 patent)	May 17, 2034
11,266,622 (the '622 patent)	August 29, 2035
10,610,510 (the '510 patent)	January 25, 2033
10,610,511 (the '511 patent)	October 10, 2034
11,285,129 (the '129 patent)	January 25, 2033
10,980,770 (the '770 patent)	January 25, 2033
10,945,988 (the '988 patent)	January 25, 2033
9,549,913 (the '913 patent)	January 25, 2033
9,855,241 (the '241 patent)	January 25, 2033
9,539,234 (the '234 patent)	January 25, 2033

With respect to: 1) the '119 and '622 patents; 2) the portion(s) of the '234 patent pertaining to the use code U-3004: treatment of nighttime sleep disturbances in Smith-Magenis Syndrome by avoiding the use of Tasimelteon in combination with a strong CYP1A2 inhibitor; 3) the portion(s) of the '910 patent pertaining to the use code U-3005: treatment of nighttime sleep disturbances in Smith-Magenis Syndrome by avoiding the use of Tasimelteon with rifampin; 4) the portion(s) of the '829 patent pertaining to the use code U-3006: treatment of nighttime sleep disturbances in Smith-Magenis Syndrome non-24 hour sleep-wake disorder by avoiding the use of Tasimelteon in combination with CYP1A2 strong inhibitors; 5) the portions of the '487, '511, and '400 patents pertaining to the use code U-3007: treatment of nighttime sleep disturbances in Smith-Magenis Syndrome by avoiding the administration of Tasimelteon with food; 6) the portion(s) of the '510 patent pertaining to the use code U-3009: treatment of nighttime sleep disturbances in Smith-Magenis Syndrome by administering Tasimelteon to patients with a smoking history; 7) the portion(s) of the '770 patent pertaining to the use code U-3106:treatment of nighttime sleep disturbances in Smith-Magenis Syndrome by avoiding the administration of Tasimelteon to smokers or to

patients being treated with a CYP1A2 inhibitor); and 8) the portion(s) of the '129 patent pertaining to use code U-3342: treatment of nighttime sleep disturbances in Smith-Magenis Syndrome by avoiding the administration of Tasimelteon beta-adrenergic receptor antagonists, your ANDA contains statements under section 505(j)(2)(A)(viii) of the FD&C Act that these are method-of-use patents that do not claim any indication or other conditions of use for which you are seeking approval under your ANDA.

With respect to the: 1) the '995, '913, '241, '977, '176, '465, '988, and '604 patents; 2) the '234 patent (excluding those portions pertaining to the use code U-3004); 3) the '910 patent (excluding those portions pertaining to the use code U-3005; 4) the '829 patent (excluding those portions pertaining to the use code U-3006); 5) the '487, '511, and '400 patents (excluding those portions pertaining to the use code U-3007); 6) the '510 patent (excluding those portions pertaining to the use code U-3009); 7) the '770 patent (excluding those portions pertaining to the use code U-3106); and 8) the '129 patent (excluding those portions pertaining to use code U-3342)[1], your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Tasimelteon Capsules, 20 mg, under this ANDA. You have notified the Agency that MSN Laboratories Private Limited (MSN) complied with the requirements of section 505(j)(2)(B) of the FD&C Act. Litigation was initiated within the statutory 45-day period against MSN for infringement of the '995, '234, '913, '910, '241, and '604 patents in the United States District Court for the District of Delaware [Vanda Pharmaceuticals Inc. v. MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited., Civil Action No. 18-00690]. You have also notified the Agency that this case was dismissed.

With respect to 180-day generic drug exclusivity, we note that MSN was one of the first ANDA applicants to submit a substantially complete ANDA with a paragraph IV certification for Tasimelteon Capsules, 20 mg. Therefore, with this approval, MSN is eligible for 180 days of shared generic drug exclusivity for Tasimelteon Capsules, 20 mg. FDA notes that after issuance of this approval letter, eligibility for 180-day exclusivity is subject to future events that may result in forfeiture of exclusivity under section 505(j)(5)(D) of the FD&C Act. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the FD&C Act, begins to run from the date of the commercial marketing by any first applicant, as identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA notifying the Agency within 30 days of the date of the first commercial marketing of this drug product or the RLD. If you do not notify the Agency within 30 days, the date of first commercial marketing will be deemed to be the date of the drug product's approval. See 21 CFR 314.107(c)(2).

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: https://www.fda.gov/media/128163/download).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at https://www.fda.gov/media/73013/download. Information and Instructions for completing the form can be found at https://www.fda.gov/media/132152/download. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-ectd.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[2] with respect to self-identification of facilities and payment of annual facility fees. ANDAs that identify at least one facility that is referenced in an approved ANDA are subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval.
FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at https://www.fda.gov/media/71211/download. The SPL will be accessible via publicly available labeling repositories.

We remind you that you must continually monitor available labeling resources such as DRUGS@FDA for changes to your reference listed drug's labels and labeling and make any necessary revisions to your labels and labeling. More information on post-approval labeling changes may be found in the guidance for industry titled "Changes to an Approved NDA or ANDA" at https://www.fda.gov/media/71846/download.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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[1] The Agency notes that the '977, '829, '119, '487, '176, '465, '988, '770, '510, '511, '400, '622, and '129 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.

[2] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

John Ibrahim

Digitally signed by John Ibrahim
Date: 1/12/2023 02:37:00PM
GUID: 542af06d0124375c12e8c1d9fc86e87c

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211654

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TASIMELTEON CAPSULES safely and effectively. See full prescribing information for TASIMELTEON CAPSULES.

TASIMELTEON capsules, for oral use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1, 2.4) 12/2020

---------- INDICATIONS AND USAGE----------

Tasimelteon capsule is a melatonin receptor agonist.

Tasimelteon capsules are indicated for the treatment of

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

- Tasimelteon capsules and tasimelteon oral suspension are not substitutable (2.1)
- Administer at the same time every night (2.2)
- Take without food (2.2)

----------DOSAGE FORMS AND STRENTHS----------

Capsules: 20 mg (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

May cause somnolence: After taking tasimelteon, patients should limit their activity to preparing for going to bed, because tasimelteon 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 tasimelteon 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 MSN Pharmaceuticals Inc. at 1-855-668-2369 or www.msnlabs.com or FDA at 1800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

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

----------USE IN SPECIFIC POPULATIONS----------

- *Hepatic impairment:* Tasimelteon 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

Revised: 01/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Non-Interchangeability between Tasimelteon Capsules and Tasimelteon Oral Suspension

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

2.2 Recommended Dosage for Tasimelteon Capsules for Non-24

Adults

The recommended dosage of tasimelteon 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.

2.4 Important Administration Information

Administer tasimelteon capsules without food [*see Clinical Pharmacology (12.3)]*.

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

3 DOSAGE FORMS AND STRENGTHS

Capsules with blue opaque body imprinted with "20 mg" and circular band in white ink, blue opaque cap imprinted with "MTI" in white ink filled with white to off white powder.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTION

5.1 Somnolence

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

6 ADVERSE REACTIONS

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 tasimelteon, 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 tasimelteon (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 tasimelteon (n=10), compared to placebo (n=10), in patients with Non-24.

In placebo-controlled studies, 6% of patients exposed to tasimelteon 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

	Tasimelteon 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 tasimelteon than on placebo are displayed.

7 DRUG INTERACTIONS

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

Avoid use of tasimelteon 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 tasimelteon 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 betaadrenergic receptor antagonists may reduce the efficacy of tasimelteon.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available postmarketing case reports with tasimelteon 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 physical development, and neurobehavioral impairment in offspring at the highest dose tested which is approximately 220 times the MRHD based on mg/m^2 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 tasimelteon and any potential adverse effects on the breastfed infant from tasimelteon or from the underlying maternal condition.

8.4 Pediatric Use

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

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. Tasimelteon has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Therefore, tasimelteon 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 tasimelteon 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 tasimelteon.

9.3 Dependence

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

10 OVERDOSAGE

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

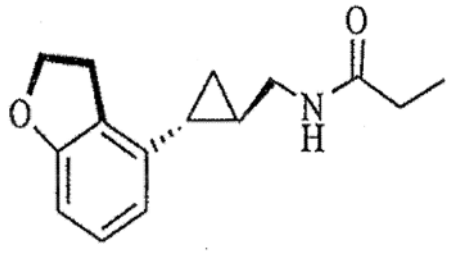
While hemodialysis was effective at clearing tasimelteon and the majority of its major metabolites in patients with renal impairment, it is not known if hemodialysis will effectively reduce exposure in the case of overdose.

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

Tasimelteon capsules 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:



Tasimelteon is a white to off-white crystalline powder. freely soluble in methanol and in 95% ethanol.

Tasimelteon capsules are intended for oral administration. Each capsule contains 20 mg of tasimelteon and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate and magnesium stearate. Each hard gelatin capsule consists of gelatin, titanium dioxide, FD&C Blue #1 and FD&C Red #40.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism by which tasimelteon exerts its therapeutic effect in patients with Non- 24 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.

Absorption

The absolute oral bioavailability is 38.3%. The peak concentration (T_{max}) of tasimelteon occurred approximately 0.5 to 3 hours 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 C_{max} of tasimelteon was 44% lower than when given in a fasted state, and the median T_{max} was delayed by approximately 1.75 hours. Therefore, tasimelteon should be taken without food.

Distribution

The apparent oral volume of distribution of tasimelteon at steady state in young healthy subjects is approximately 59 to 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 tasimelteon 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.

Pediatric Patients

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 C_{max} 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 to 30% greater in female than in male subjects.

Race

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

Hepatic Impairment

The pharmacokinetic profile of a 20 mg dose of tasimelteon 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. Tasimelteon 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 tasimelteon 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 Tasimelteon

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

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 tasimelteon is used in combination with strong CYP3A4 inducers, such as rifampin *[see Drug Interactions (7.2)]*.

Effect of Tasimelteon on Other Drugs

Midazolam (CYP3A4 substrate): Administration of tasimelteon 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 tasimelteon 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 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. There was a trend for an additive effect of tasimelteon 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, 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.

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 tasimelteon 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 tasimelteon 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 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 randomized to receive placebo or continue treatment with tasimelteon 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 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. Treatment with tasimelteon resulted in a significant improvement, compared with placebo, for both of these endpoints in Study 1 and Study 2 (see Table 3).

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

	Study 1		**Study 2**	
Change from Baseline	**Tasimelteon 20 MG N=42**	**Placebo N=42**	**Tasimelteon 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 tasimelteon, compared with 12% (n=5) of patients treated with placebo met the responder criteria.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tasimelteon Capsules

20 mg capsules are available as size 1, blue opaque, hard gelatin capsules, body imprinted with "20 mg" and circular band in white and cap imprinted with "MTl" in white, containing 20 mg of tasimelteon per capsule.

- NDC 69539-081-30 Bottles of 30

Storage and Handling

Tasimelteon Capsules

Store tasimelteon 20 mg 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.

17 PATIENT COUNSELING INFORMATION

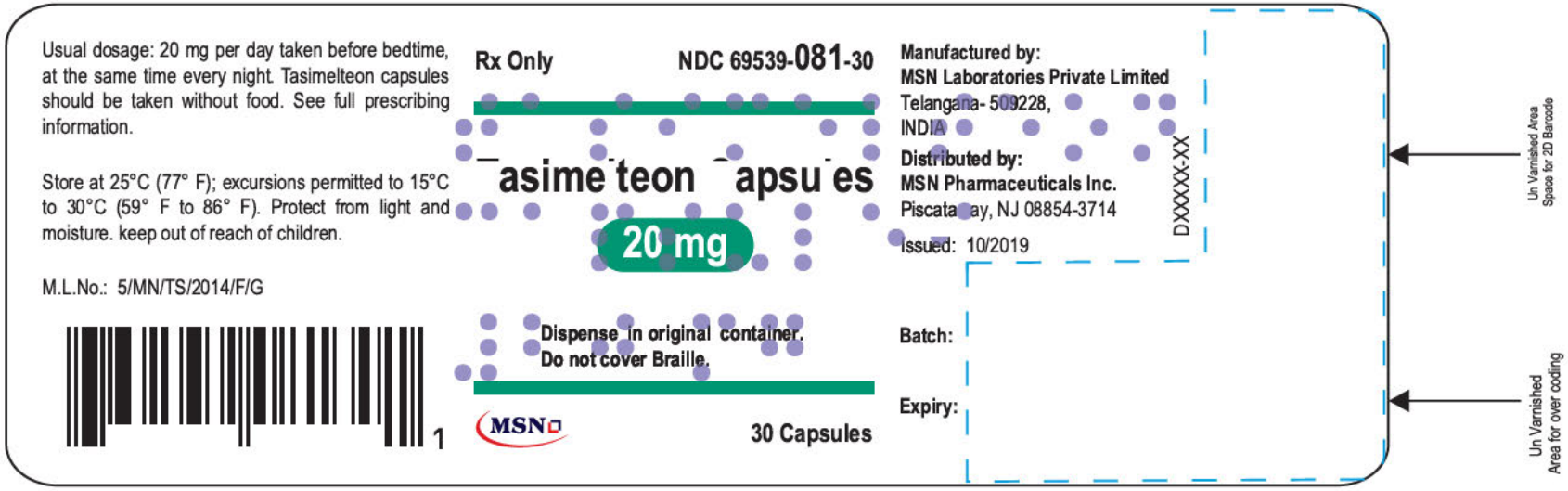
- Advise patients to limit their activities to preparing for going to bed after taking tasimelteon capsules because tasimelteon can potentially impair the performance of activities requiring complete mental alertness *[see Warnings and Precautions (5.1)]*.
- Administration Information for tasimelteon capsules *[see Dosage and Administration (2.1, 2.2,2.4)]*.
  - Advise patients to take tasimelteon without food.
  - Advise patients to take tasimelteon before bedtime at the same time every night.
  - Advise patients to skip the dose that night if they cannot take tasimelteon at approximately the same time on a given night.
  - Advise patients to swallow tasimelteon capsules whole.
- Non-24 (tasimelteon capsules)

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

Manufactured by:
MSN Laboratories Private Limited
Telangana – 509 228,
INDIA

Distributed by:
MSN Pharmaceuticals Inc.
Piscataway, NJ 08854-3714

Issued on:
January 2021



(b) (4)

Tasimelteon
Capsules
#20 mg

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211654

LABELING REVIEW(s)

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	11/15/2022
ANDA Number(s)	211654
Review Number	4
Applicant Name	MSN Laboratories Private Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Tasimelteon Capsules, 20 mg
Proposed Proprietary Name	N/A
Submission Received Date	October 20, 2022 (Patent amendment) January 21, 2021
Primary Labeling Reviewer	Michael Evans
Secondary Labeling Reviewer	Marshall Florence

Review Conclusion

☐ Acceptable - No Comments
☒ Acceptable - Include Post Approval Comments
☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Policy Alert List	☐ Yes	☒ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS (C4)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C4)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C4)

The Division of Labeling has no further questions/comments at this time based on your labeling submissions received January 21, 2021, October 20, 2022.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST-APPROVAL REVISIONS (C4)

These comments will be addressed post approval (in the first labeling supplement review).

1. CONTAINER LABEL
    a. Revise the linear bar code to a vertical orientation to ensure accurate scanning to minimize medication error. Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

2. PRESCRIBING INFORMATION
    a. Revise all instances of [redacted] (b) (4)
    b. Add the following statement at the end of section 17 to read as [redacted] (b) (4)

2 INSTRUCTIONS FOR ASSESSMENT (C4)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

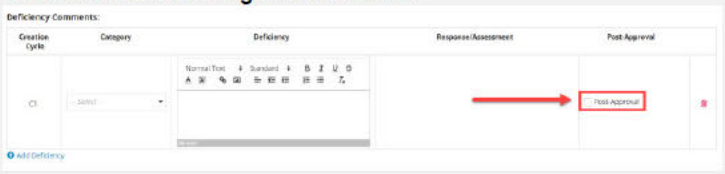
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C4)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	Bottle of 30's	10/16/2019	Satisfactory
Blister	N/A	N/A		
Carton	N/A	N/A		Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: 01/2021	01/21/2021	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C4)

4.1 REGULATORY INFORMATION (C4)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ?

Yes	No	
		(b) (5) [redacted]

For the Record, following is taken from previous review cycle #1:

- RLD Hetlioz has the proprietary name and the strength statement in braille. Inclusion of the braille was proposed by the NDA applicant upon submission of the original NDA to accommodate the needs of the population using the product. Hetlioz is indicated for treatment of Non-24 Hour Sleep – Wake Disorder (Non-24).
- Braille is not required for the generics of Hetlioz.

DLR inquired OND, DMEPA/OSE and OGD Policy group to find out if braille would be required for the generics of Hetlioz. Based on the response gathered by each Offices (see attached below) we find that inclusion of braille language is not a requirement for the generic products on the basis that inclusion of braille language was not condition of approval for the RLD product. We note that braille was proposed by the RLD applicant as "nice to have" information. Subsequently DMEPA had asked

Yes	No	
		the RLD applicant to perform a braille label comprehension study of braille labeling on the container label and found the study and the proposed braille on the label acceptable. In addition, we note from discussion with DMEPA and with OGDP that if ANDA applicant voluntarily proposes braille on their label, Certificate of Translation should be required to support the proposed braille.
☐	☒	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint?

4.2 MODEL PRESCRIBING INFORMATION (C4)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original)**: NDA205677 / S-007 **Supplement Approval Date**: 12/01/2020 **Proprietary Name**: HETLIOZ **Established Name**: Tasimelteon Capsules **Description of Supplement**: This Prior Approval supplemental new drug application provides for the addition of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in patients 16 years of age and older. **Link**: https://analytics.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4709967_4298733_090140af805b5546_NDA205677_3044593
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**
☐ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.
Reviewer Comments: **Deficiency Comments**:		

4.3 PATENTS AND EXCLUSIVITIES (C4)

The Orange Book was searched on 11/15/2022

Table 4 provides Orange Book patents for the Model Labeling (NDA205677) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
20 mg	10071977	02/12/2035			IV	10/20/2022	None
20 mg	10149829	01/25/2033	U-2477	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH CYP1A2 STRONG INHIBITORS	IV	10/20/2022	None
20 mg	10149829	01/25/2033	U-3006	TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENIS SYNDROME NON-24 HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH CYP1A2 STRONG INHIBITORS	viii	10/20/2022	Carve-out
20 mg	10179119	08/29/2035	U-3003	TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENIS SYNDROME BY ADMINISTERING TASIMELTEON	viii	10/20/2022	Carve-out
20 mg	10376487	07/27/2035	U-2615	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY AVOIDING THE ADMINISTRATION OF TASIMELTEON WITH FOOD	IV	10/20/2022	None
20 mg	10376487	07/27/2035	U-3007	TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENIS SYNDROME BY AVOIDING THE ADMINISTRATION OF TASIMELTEON WITH FOOD	viii	10/20/2022	Carve-out
20 mg	10449176	01/25/2033	U-2149	TREATMENT OF NON-24 HOUR SLEEP-WAKE	IV	10/20/2022	None

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
				DISORDER BY ADMINISTERING TASIMELTEON			
20 mg	10610510	01/25/2033	U-2805	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ADMINISTERING TASIMELTEON TO PATIENTS WITH A SMOKING HISTORY	IV	10/20/2022	None
20 mg	10610510	01/25/2033	U-3009	TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENIS SYNDROME BY ADMINISTERING TASIMELTEON TO PATIENTS WITH A SMOKING HISTORY	viii	10/20/2022	Carve-out
20 mg	10610511	10/10/2034	U-2615	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY AVOIDING THE ADMINISTRATION OF TASIMELTEON WITH FOOD	IV	10/20/2022	None
20 mg	10610511	10/10/2034	U-3007	TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENIS SYNDROME BY AVOIDING THE ADMINISTRATION OF TASIMELTEON WITH FOOD	viii	10/20/2022	Carve-out
20 mg	10829465	02/12/2035			IV	10/20/2022	None
20 mg	10945988	01/25/2033	U-2149	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ADMINISTERING TASIMELTEON	IV	10/20/2022	None
20 mg	10980770	01/25/2033	U-3106	TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENISSYNDROME	viii	10/20/2022	Carve-out

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
				BY AVOIDING THE ADMINISTRATION OF TASIMELTEON TO SMOKERS OR TO PATIENTS BEING TREATED WITH A CYP1A2 INHIBITOR			
20 mg	10980770	01/25/2033	U-3107	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY AVOIDING THE ADMINISTRATION OF TASIMELTEON TO SMOKERS OR TO PATIENTS BEING TREATED WITH A CYP1A2 INHIBITOR	IV	10/20/2022	None
20 mg	11141400	10/10/2034	U-2615	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY AVOIDING THE ADMINISTRATION OF TASIMELTEON WITH FOOD	IV	10/20/2022	None
20 mg	11141400	10/10/2034	U-3007	TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENIS SYNDROME BY AVOIDING THE ADMINISTRATION OF TASIMELTEON WITH FOOD	viii	10/20/2022	Carve-out
20 mg	11266622	08/29/2035	U-3003	TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENIS SYNDROME BY ADMINISTERING TASIMELTEON	viii	10/20/2022	Carve-out
20 mg	11285129	01/25/2033	U-3342	TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENIS SYNDROME BY AVOIDING THE ADMINISTRATION OF	viii	10/20/2022	Carve-out

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
				TASIMELTEON WITH BETA-ADRENERGIC RECEPTOR ANTAGONISTS			
20 mg	11285129	01/25/2033	U-3343	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER BY AVOIDING THE ADMINISTRATION OF TASIMELTEON WITH BETA-ADRENERGIC RECEPTOR ANTAGONISTS	IV	10/20/2022	None
20 mg	5856529	12/09/2022	U-2149	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ADMINISTERING TASIMELTEON	III	10/20/2022	None
20 mg	5856529	12/09/2022	U-3003	TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENIS SYNDROME BY ADMINISTERING TASIMELTEON	III	10/20/2022	None
20 mg	9060995	01/25/2033	U-1710	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH FLUVOXAMINE	IV	10/20/2022	None
20 mg	9539234	01/25/2033	U-1934	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH A STRONG CYP1A2 INHIBITOR	IV	10/20/2022	None
20 mg	9539234	01/25/2033	U-3004	TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENIS SYNDROME BY	viii	10/20/2022	Carve-out

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
				AVOIDING THE AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH A STRONG CYP1A2 INHIBITOR			
20 mg	9549913	01/25/2033	U-1486	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER	IV	10/20/2022	None
20 mg	9730910	05/17/2034	U-2085	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH RIFAMPIN	IV	10/20/2022	None
20 mg	9730910	05/17/2034	U-3005	TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENIS SYNDROME BY AVOIDING THE USE OF TASIMELTEON WITH RIFAMPIN	viii	10/20/2022	Carve-out
20 mg	9855241	01/25/2033	U-2149	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ADMINISTERING TASIMELTEON	IV	10/20/2022	None
20 mg	RE46604	01/25/2033	U-2147	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ORALLY ADMINISTERING 20MG OF TASIMELTEON ONCE DAILY BEFORE BEDTIME	IV	10/20/2022	None

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
20 mg	I-850	12/01/2023	TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENIS SYNDROME (SMS) IN PATIENTS 16 YEARS OF AGE AND OLDER	With respect to the exclusivity code "I-850" and "ODE-330" related to "Treatment of nighttime sleep disturbances in smith-magenis syndrome (SMS) in Patients 16 Years of age and older" expiring on December 01, 2023 and December 01, 2027. MSN is not requesting approval of its ANDA to include the indication covered by the above exclusivity. The proposed labeling submitted in this application excludes information pertaining to the treatment of nighttime sleep disturbances in smith-magenis syndrome (SMS) in Patients 16 Years of age and older.	10/20/2022	Carve-out
20 mg	ODE-330	12/01/2027	THE TREATMENT OF NIGHTTIME SLEEP DISTURBANCES IN SMITH-MAGENIS SYNDROME (SMS)	With respect to the exclusivity code "I-850" and "ODE-330" related to "Treatment of	10/20/2022	Carve-out

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
			IN PATIENTS 16 YEARS OF AGE AND OLDER	nighttime sleep disturbances in smith-magenis syndrome (SMS) in Patients 16 Years of age and older" expiring on December 01, 2023 and December 01, 2027. MSN is not requesting approval of its ANDA to include the indication covered by the above exclusivity. The proposed labeling submitted in this application excludes information pertaining to the treatment of nighttime sleep disturbances in smith-magenis syndrome (SMS) in Patients 16 Years of age and older.		

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:

This Review

Since C3 labeling review, the applicant has revised and updated the patent and exclusivity certifications.

Patents

The applicant has revised several patents with **viii certification** that carves out any USE codes that refer to **"Smith-Magenis Syndrome (SMS)" in the refers to the indication of SMS in the use code.** These carve-outs coincides with the two exclusivities that also refer to SMS.

USE CODES REGARDING SMS INDICATIONS.
U-3006
U-3003 - with the exception of patent 5856529, U-3003 and U-2149 since this expires on 12/09/2022, certified as III
U-3004
U-3005
U-3007
U-3009
U-3106
U-3342

Exclusivities I-850- and ODE-350
The applicant has successfully carved out I-850 and ODE-350 (Treatment of nighttime sleep disturbances in **smith-magenis syndrome (SMS)** in patients 16 years of age and older".

Deficiency Comments:

4.4 UNITED STATES PHARMACOPEIA (USP) (C4)

The USP was searched on 11/15/2022

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

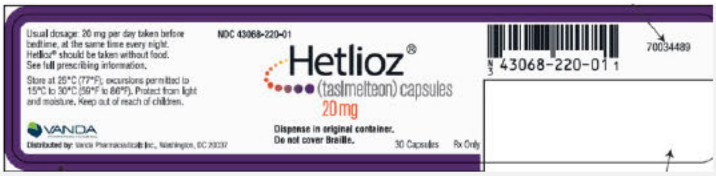
Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
		USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

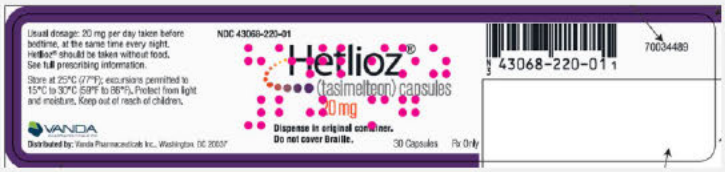
Reviewer Comments:

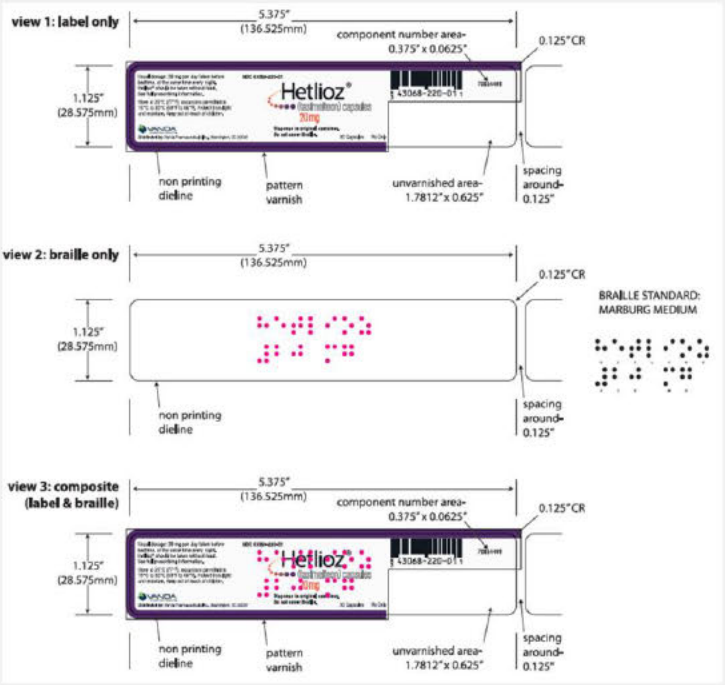
Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C4)

Model container/carton/blister labels (Source: AR-5, 03/29/2019 **)**







5 ASSESSMENT OF ANDA LABELING AND LABELS (C4)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C4)

5.1.1 DRUG PRODUCT REVIEW (C4)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

04/14/2020

LABELING

IQA Review Guide Reference

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description, (e.g., USP test pending. (b) (4)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A

If "No," explain.

For OTC Drugs and Controlled Substances: NA

QUALITY ASSESSMENT

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code
20 mg	Size 1 capsule	Size 1, blue opaque, hard gelatir capsules, body imprinted with "" mg" and circular band in white and cap imprinted with "MTI" i white.

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

NA

List of Deficiencies: NA

Primary Drug Product Reviewer: Bahar Zarabi, 05-03-2018 (v1)

Secondary Reviewer: Yuping Niu, 5-31-2018(v2)

5.1.2 DESCRIPTION (C4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	N/A
Previous ANDA Labeling	(b) (4) [redacted]
Current ANDA Labeling	Tasimelteon capsules are intended for oral administration. Each capsule contains 20 mg of tasimelteon and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate and magnesium stearate. Each hard gelatin capsule consists of gelatin, titanium dioxide, FD&C Blue #1 and FD&C Red #40. **Assessment:** Acceptable - No change

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C4)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	N/A
Previous ANDA Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** Tasimelteon 20 mg capsules are available as size 1 , blue opaque, hard gelatin capsules, body imprinted with "20 mg" and circular band in white and cap imprinted with "MTl" in white, containing 20 mg of tasimelteon per capsule. • NDC 69539-081-30 Bottles of 30 **Storage** Store tasimelteon 20 mg capsules at controlled room temperature, 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Protect tasimelteon 20 mg capsules from exposure to light and moisture.
Current ANDA Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** Tasimelteon Capsules 20 mg capsules are available as size 1, blue opaque, hard gelatin capsules, body imprinted with "20 mg" and circular band in white and cap imprinted with "MTl" in white, containing 20 mg of tasimelteon per capsule. • NDC 69539-081-30 Bottles of 30 **Storage and Handling** Tasimelteon Capsules Store tasimelteon 20 mg 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. **Assessment:** Acceptable - No change

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C4)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	(b) (4) [redacted]
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	**Manufactured by:** **MSN Laboratories Private Limited** Telangana – 509 228, INDIA **Distributed by:** **MSN Pharmaceuticals Inc.** Piscataway, NJ 08854-3714 **Issued on:** January 2021 **Assessment:** Acceptable - No change

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☒	☐	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
		STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		OVERALL ASSESSMENT:
☒	☐	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

This review

Container label was found acceptable in submission dated 10/16/2019.

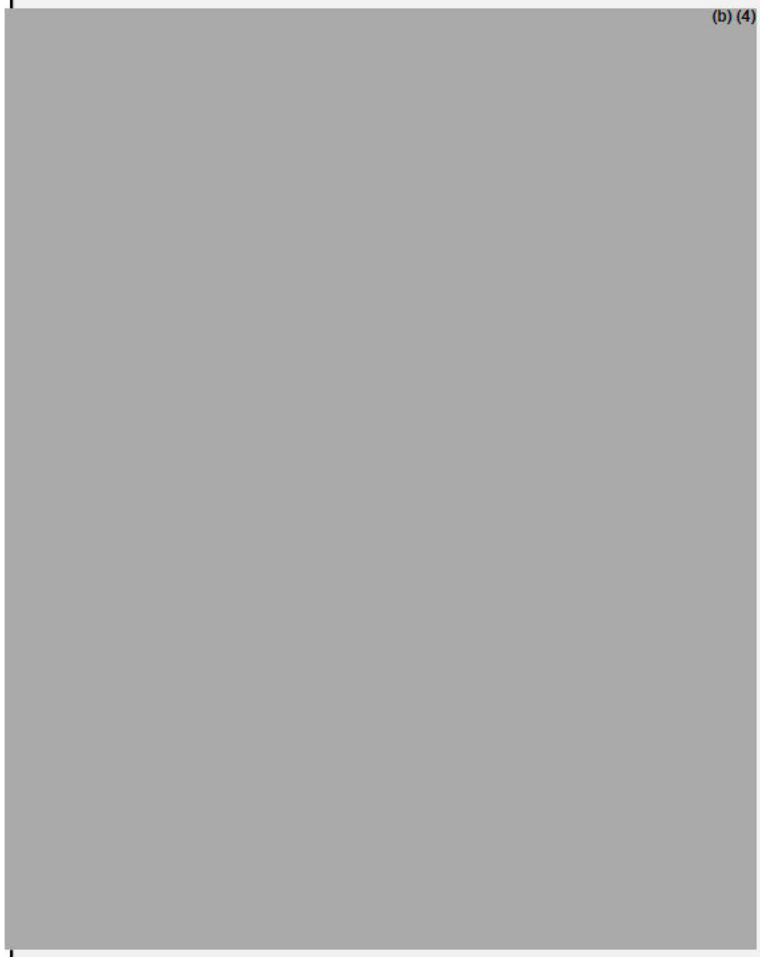
- DLR will issue same post approval comment from cycle 3 regarding barcode orientation.

C3 review

The applicant submitted unsolicited container labels in order to update the manufacturer's pin code, distributor address, and revision dated. The container labels are acceptable with Braille overlay with post the following approval comment.

- DLR will request revision of the barcode in a vertical orientation post approval

Proof of Braille translation from submission dated 07/26/2018



Deficiency Comments:

Deficiency # 1

Created in C4

Container Label

Response / Assessment:

Revise the linear bar code to a vertical orientation to ensure accurate scanning to minimize medication error. Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

5.3 PRESCRIBING INFORMATION (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	

Deficiency	No Deficiency	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
		HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
		HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

This Review

Only the prescribing information for the oral suspension has an IFU. The capsule labeling does not have an IFU.

There are now two indications for the drug product:

1. Non-24-Hour Sleep-Wake Disorder (Non-24) in adults
2. Nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in patients 16 years of age and older

The applicant has carved out references to the "Smith-Magenis Syndrome" indication.

The applicant has successfully carved-out all references to the oral suspension. (b) (4)

(b) (4)

Since C3 labeling review, the applicant has revised and updated the patent and exclusivity certifications and statements and have carved out all information related to the "Smith-Magenis Syndrome (SMS). indication and certified as **viii** to all use codes related to "Smith-Magenis Syndrome (SMS).

Deficiency Comments:

Deficiency # 1 (b) (4) .

Created in C4

Prescribing Information
Response / Assessment:

Deficiency # 2 (b) (4)

Created in C4

Prescribing Information
Response / Assessment:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C4)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Deficiency Comments:

Michael Evans

Digitally signed by Michael Evans
Date: 12/16/2022 01:14:08PM
GUID: 5473743d0009393d289decf0b8b5e69e

Marshall Florence

Digitally signed by Marshall Florence
Date: 12/16/2022 01:21:57PM
GUID: 55eefa420051b501ac3ced124279f785

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	April 1, 2020
ANDA Number(s)	211654
Review Number	3
Applicant Name	MSN Laboratories Private Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Tasimelteon Capsules, 20 mg
Proposed Proprietary Name	None
Submission Received Date	October 16, 2019
Primary Labeling Reviewer	Michael Evans
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments
☒ ACCEPTABLE – Include Post Approval Comments
☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☐ Yes	☒ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on (add date) based on your submission(s) received (add date):

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission received October 16, 2019.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

1. PRESCRIBING INFORMATION

   Revise the bar code to a vertical orientation to ensure accurate scanning to minimize medication error. Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

ANDA labeling history: (GDUFA date – (05/31/2020)

01/31/2018 – Original submission

07/10/2018 – Cycle #1 labeling review

07/26/2018 – Response to labeling DRL

09/21/2018 – Cycle #2 labeling review

10/16/2019 – Unsolicited labeling amendment due to RLD update and revision of container labels, prescribing information and SPL ***(Subject of this review)***

Reviewer Comments:

Summary	
Container	The applicant submitted unsolicited container labels in order to update the manufacturer's pin code, distributor address, and revision date. The container labels are acceptable with Braille overlay with post approval comment. ***(see section 2.1 and Table 6 for more information)***
Prescribing Information	***(see section 3.2 and Table 6 for more information)***
Other Disciplines	Biopharmaceutics – Adequate Bioequivalence – Adequate OPQ – Inadequate (labeling adequate)

Reviewer Comments:

1.4 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
YES

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

The applicant submitted unsolicited container labels in order to update the manufacturer's pin code, distributor address, and revision dated. The container labels are acceptable with Braille overlay **with post the following approval comment**.

- **DLR will request revision of the barcode orientation post approval**

Revisions noted -Acceptable

1. Pincode updated specific to MSN
2. Distributed address updated specific to MSN
3. The date of Issue /Revision is specific to MSN

Unsolicited response to update container labels due to change in distributor address, PIN code and Issue/Revision date

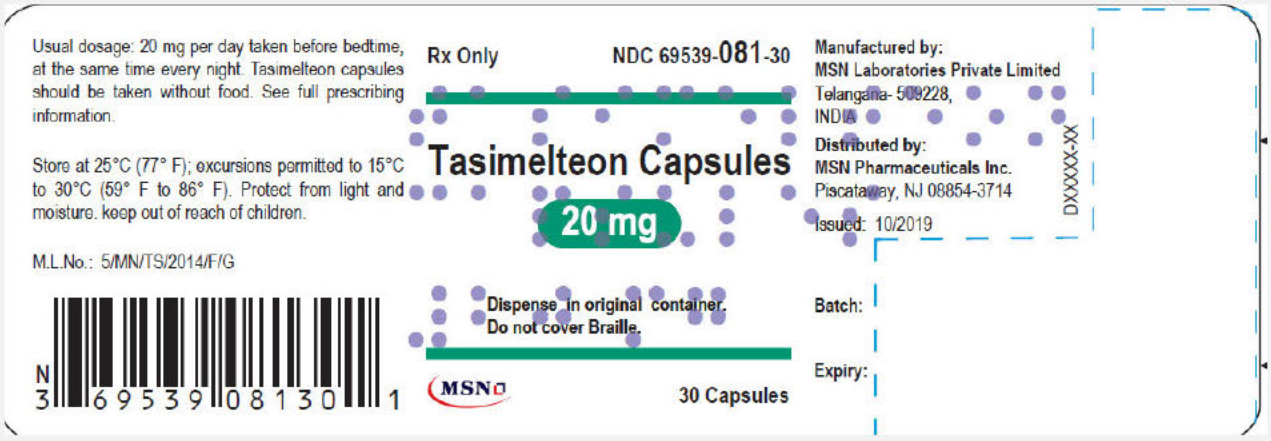
Dear Sir or Madam:

MSN Laboratories Private Limited is submitting the Labeling Amendment for Tasimelteon Capsules, 20 mg pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) for your review and approval.

We have observed RLD Labeling update approved on October 07, 2019 for RLD-Hetlioz NDA 205677. We have updated the labeling sections as per RLD Labeling and the revised package insert label word, PDF, final printable format PI, and SPL have been provided in Module 1.14.1.3 and draft carton container labels and annotated comparison of container labels has been provided in Module 1.14.1.1 and 1.14.1.2. The annotated comparison of revised package insert label with RLD label and RLD Label has been provided in Module 1.14.3.1 and 1.14.3.3 respectively.

Acceptable

Proposed 20 mg (30-count label)



(b) (4)

1.5 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

For the Record, following is taken from previous review cycle #1:

- RLD Hetlioz has the proprietary name and the strength statement in braille. Inclusion of the braille was proposed by the NDA applicant upon submission of the original NDA to accommodate the needs of the population using the product. Hetlioz is indicated for treatment of Non-24 Hour Sleep – Wake Disorder (Non-24).
- **Braille is not required for the generics of Hetlioz.**

DLR inquired OND, DMEPA/OSE and OGD Policy group to find out if braille would be required for the generics of Hetlioz. Based on the response gathered by each Offices (see attached below) we find that inclusion of braille language is not a requirement for the generic products on the basis that inclusion of braille language was not condition of approval for the RLD product. We note that braille was proposed by the RLD applicant as "nice to have" information. Subsequently DMEPA had asked the RLD applicant to perform a braille label comprehension study of braille labeling on the container label and found the study and the proposed braille on the label acceptable. In addition, we note from discussion with DMEPA and with OGDP that if ANDA applicant voluntarily proposes braille on their label, Certificate of Translation should be required to support the proposed braille.

Discussion with OND and consults with OLDP and DMEPA via email may be found in Drug Facts

2009_01_12_readabilit y_guideline_final_en.pc

Guidelines_on_braille_ labelling_of_medicinal

2. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

2.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES
If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Title	Hetlioz (tasimelteon capsules) uses Braille in its labeling
Date:	1/19/2016
Is this a Review?	☐
What Type of File?	E-mails
Attachments	Hetlioz -- Approval of a container label with Braille.msg
Hyperlink to Review	No hyperlink inserted
Active Ingredient	Tasimelteon
Dosage Forms:	Capsules
Manufacturer:	
Brief Description	Hetlioz, tasimelteon capsules (NDA 205677) , is a drug used to treat Non-24 Hour Sleep-Wake Disorder, a condition seen in the blind. Many pieces of the labeling are in Braille.

Above entry in SharePoint is background reference information on the braille language included on the PDP of the RLD labeling for Hetlioz. Refer to section 2.2 Additional Background Information for considerations that are specific to the generic Hetlioz products related to the use of braille.

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO

If Yes, please explain.

Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO

2.2 MODEL LABELING

Table 1: Review Model Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)* **NDA# /Supplement# (S-000 if original): 205677/S-006** **Supplement Approval Date: 10/07/2019** **Proprietary Name: Hetlioz®** **Established Name: Tasimelteon Capsules** **Description of Supplement:** This Prior Approval supplemental new drug application provides for revisions to the US Prescribing Information (USPI) as required according to Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling, referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR, or final rule). ***PENDING LABELNG SUPPLEMENTS*** **S-007, (EFFICACY) REFUSE TO FILE, 03/31/2020** This supplemental application proposes the following change for Hetlioz: adding a new indication for the treatment of the sleep disorder in Smith-Magenis Syndrome.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **YES**

Reviewer Comments:

This review:

The applicant has updated the prescribing information due to an RLD update. The PI is acceptable in FPL

Unsolicited labeling amendment due to RLD update.

RE: ANDA # 211654, Tasimelteon Capsules, 20 mg
Submitted via Electronic Submission Gateway

Dear Sir or Madam:

MSN Laboratories Private Limited is submitting the Labeling Amendment for Tasimelteon Capsules, 20 mg pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) for your review and approval.

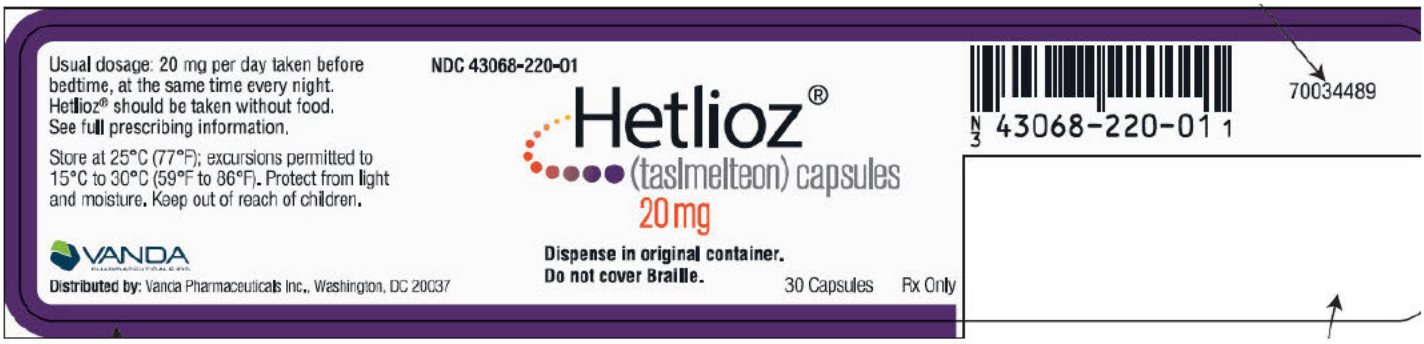
We have observed RLD Labeling update approved on October 07, 2019 for RLD-Hetlioz NDA 205677. We have updated the labeling sections as per RLD Labeling and the revised package insert label word, PDF, final printable format PI, and SPL have been provided in Module 1.14.1.3 and draft carton container labels and annotated comparison of container labels has been provided in Module 1.14.1.1 and 1.14.1.2. The annotated comparison of revised package insert label with RLD label and RLD Label has been provided in Module 1.14.3.1 and 1.14.3.3 respectively.

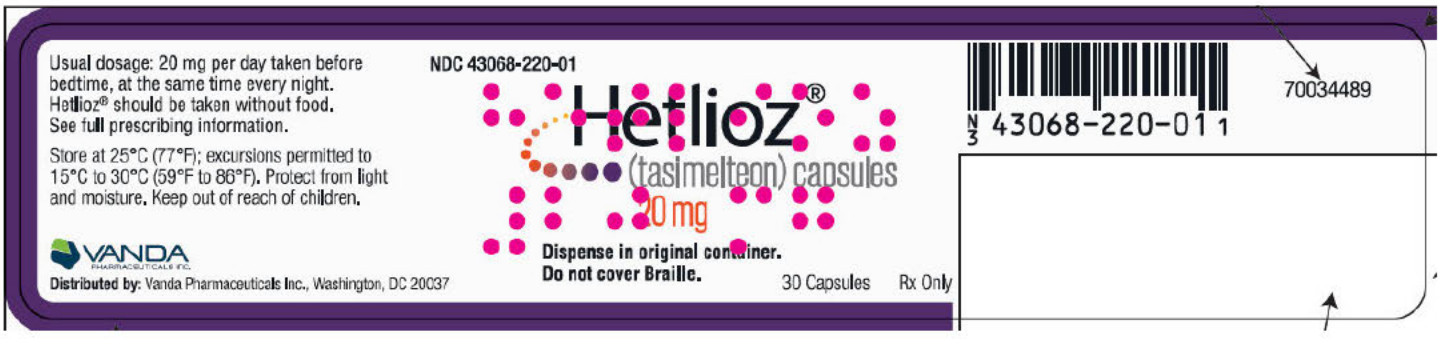
Acceptable

2.3 MODEL CONTAINER LABELS

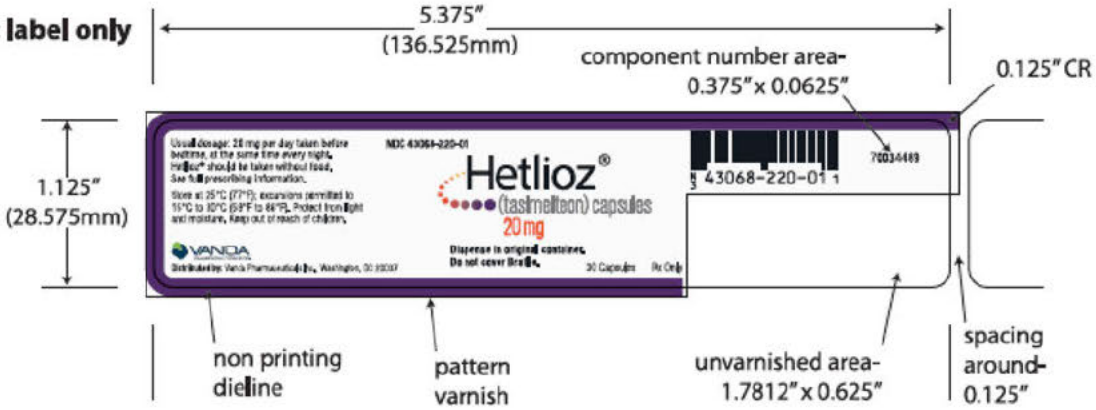
Model RLD NDA container labels

[Source: AR-5, 03/29/2019]

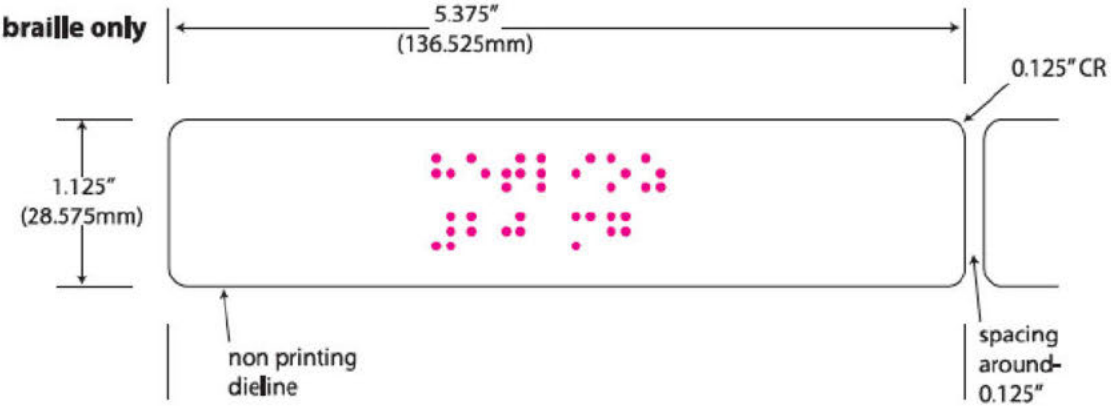




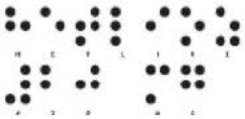
view 1: label only



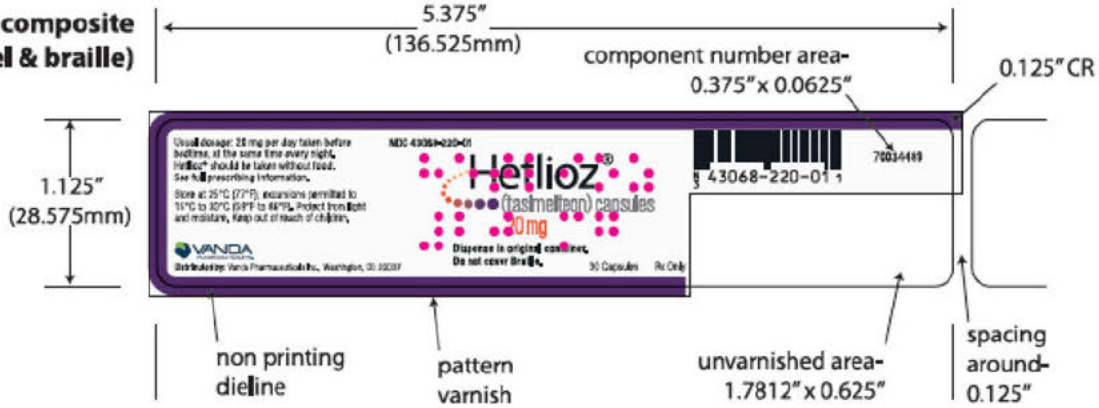
view 2: braille only



BRAILLE STANDARD:
MARBURG MEDIUM



view 3: composite (label & braille)



2.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 4/1/2020.

Table 2: United States Pharmacopeia (USP)				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

Click here to enter text.

2.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 4/1/2020.

Table 3 provides Orange Book patents for the Model Labeling 205677 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
5856529	12/09/2022	U-2149	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ADMINISTERING TASIMELTEON	III	02/10/2020	None
9060995	01/25/2033	U-1710	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH FLUVOXAMINE	IV	02/10/2020	None
9539234	01/25/2033	U-1934	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH A STRONG CYP1A2 INHIBITOR	IV	02/10/2020	None
9730910	05/17/2034	U-2085	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH RIFAMPIN	IV	02/10/2020	None
9855241	01/25/2033	U-2149	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ADMINISTERING TASIMELTEON	IV	02/10/2020	None
10071977	02/12/2035			IV	02/10/2020	None
10149829	01/25/2033	U-2477	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH CYP1A2 STRONG INHIBITORS	IV	02/10/2020	None
10376487	07/27/2035	U-2615	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY AVOIDING THE ADMINISTRATION OF TASIMELTEON WITH FOOD	IV	02/10/2020	None

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
10449176	01/25/2033	U-2149	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ADMINISTERING TASIMELTEON	IV	02/10/2020	None
RE46604	01/25/2033	U-2147	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ORALLY ADMINISTERING 20MG OF TASIMELTEON ONCE DAILY BEFORE BEDTIME	IV	02/10/2020	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

Patent certifications updated on 02/10/2020 but remain unchanged

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter Carve-out or None)**
ODE-59	01/31/2021	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER	MSN Laboratories Private Ltd commits not to market this product until the expiration of the above exclusivities	02/10/2020	None

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

Exclusivities updated on 02/10/2020 but remains unchanged to original statement

3. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **YES**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)	asimelteon capsule is available in 20 mg trength capsules for oral administration. Inactive ngredients are: colloidal silicon dioxide, roscarmellose sodium, lactose monohydrate nd magnesium stearate. Each hard gelatin apsule consists of gelatin, titanium dioxide, D&C Blue #1 and FD&C Red #40.	**NO CHANGE**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)	**16 HOW SUPPLIED/STORAGE AND HANDLING** Tasimelteon 20 mg capsules are available as size 1 , blue opaque, hard gelatin capsules, body imprinted with "20 mg" and circular band in white and cap imprinted with "MTI" in white, containing 20 mg of tasimelteon per capsule. • NDC 69539-081-30 Bottles of 30 **Storage** Store tasimelteon 20 mg capsules at controlled room temperature, 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Protect tasimelteon 20 mg capsules from exposure to light and moisture.	**NO CHANGE**

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)	**Manufactured by:** **MSN Laboratories Private Limited** Telangana – 509 228, INDIA **Distributed by:** **MSN Pharmaceuticals Inc.** Piscataway, NJ 08854-3714	**ACCEPTABLE** (Change in Manufactured by information and. Change in distributed by information)

4. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the Consult Screening flow chart to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-

Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

IQA_DS DP LBL 211654 R02.docx (Final) 07/24/2019

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description, (e.g., USP test pending. (b) (4)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A

If "No," explain.

For OTC Drugs and Controlled Substances: NA

QUALITY ASSESSMENT

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code
20 mg	Size 1 capsule	Size 1, blue opaque, hard gelatin capsules, body imprinted with "20 mg" and circular band in white and cap imprinted with "MTI" in white.

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

NA

5. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column,

you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Draft	20 mg (30s)	10/16/2019	Satisfactory
Blister	NA	NA	NA	NA
Carton	NA	NA	NA	NA
(Other – specify)	NA	NA	NA	NA
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Final	Revised: 10/2019	10/16/2019	Satisfactory
Medication Guide	NA	NA	NA	NA
Patient Information	NA	NA	NA	NA
SPL Data Elements		Revised: 10/2019	10/16/2019	Satisfactory

Marshall Florence

Digitally signed by Marshall Florence
Date: 4/14/2020 09:39:26AM
GUID: 55eefa420051b501ac3ced124279f785

Michael Evans

Digitally signed by Michael Evans
Date: 4/14/2020 06:24:16AM
GUID: 5473743d0009393d289decf0b8b5e69e

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	9/11/2018
ANDA Number(s)	211654
Review Number	2
Applicant Name	MSN Laboratories Private Limited
Established Name & Strength(s)	Tasimelteon Capsules, 20 mg
Proposed Proprietary Name	NA
Submission Received Date	7/26/2018
Primary Labeling Reviewer	Eunjung Esther Chuh
Secondary Labeling Reviewer	Marshall Florence

Review Conclusion

☒ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☐ Yes ☒ No

Combined Insert/Outsert ☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on (add date) based on your submission(s) received (add date):

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission dated July 26, 2018.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

REVIEW HISTORY

1/31/2018 Original ANDA submitted to FDA
7/5/2018 Labeling Review #1 completed – Inadequate
7/26/2018 Response to Discipline Review Letter submitted by the applicant – *subject of this review*

PREVIOUS DEFICIENCY AND APPLICANT'S RESPONSE

Response to Discipline Review Letter Labeling

Comment 1:
GENERAL COMMENTS/ CONTAINER LABEL

Please comment on your inclusion of braille on the container label. We inform you that Certificate of Translation is required to support your proposed braille.

Response:
We acknowledge the agency's comment. We would like to inform the reviewer that the proposed braille is imported on the container label with the Licensed versions of Adobe Illustrator software's or Corel draw. The drugs product manufacturer's (i.e., MSN Laboratories Private Limited) herby certifies that the braille is imported on the container label with authentic licensed software. The proof of Braille translation is enclosed on the container label to support the proposed braille for ready reference.

Reviewer Comments:

Applicant's response is acceptable. Below is the documentation provided by the applicant as the proof of braille translation.

(b) (4)

(b) (4)

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

For the Record, following is taken from previous review cycle #1:

- **RLD Hetlioz has the proprietary name and the strength statement in braille.** Inclusion of the braille was proposed by the NDA applicant upon submission of the original NDA to accommodate the needs of the population using the product. Hetlioz is indicated for treatment of Non-24 Hour Sleep – Wake Disorder (Non-24).

- **Braille is <u>not</u> required for the generics of Hetlioz.**

  DLR inquired OND, DMEPA/OSE and OGD Policy group to find out if braille would be required for the generics of Hetlioz. Based on the response gathered by each Offices (see attached below) we find that inclusion of braille language is not a requirement for the generic products on the basis that inclusion of braille language was not condition of approval for the RLD product. We note that braille was proposed by the RLD applicant as "nice to have" information. Subsequently DMEPA had asked the RLD applicant to perform a braille label comprehension study of braille labeling on the container label and found the study and the proposed braille on the label acceptable. In addition, we note from discussion with DMEPA and with OGDP that if ANDA applicant voluntarily proposes braille on their label, Certificate of Translation should be required to support the proposed braille.

- **Discussion with OND via email**

<u>Communication with OND:</u>
The following question was posed to OND via email:

> OGD is currently reviewing the labeling for the generic version of Hetlioz (tasimelteon), NDA 205677. Some of the applicants have submitted braille on the container label and others have not. We would like to know if OND believes:
>
> a. It is less safe for generic applicants to <u>NOT</u> provide braille on the container labels.
> b. If generic applicants must provide braille, should the generic applicants follow the RLD container label and limit braille to the established name and strength?
> c. If generic applicants must provide braille, should the generic applicants limit the container sizes to unit-of use containers such as 30s, 60s, 90s to ensure that the braille is on the container label?

OND Medical Officer's responses via email were as follows:

> Here is my take:
>
> It is a nice idea (and probably helps with public relations) that the original Sponsor included Braille labeling. However, the Agency did not require it. Although tasimelteon's currently approved indication (non-24) means that the target patient population is blind, it's not the only medication blind people take. Blind people are on cholesterol medications, blood

pressure medications, etc. And we don't worry about making sure all these other medications are dispensed with Braille when given to blind patients.

So, I don't feel that we need to require generic manufacturers to include Braille. If a generic manufacturer wants to include Braille, my opinion is that they should mirror the RLD (as with any other labeling).

I also don't feel like an official consult is needed (from my end).

OND Deputy Director's response:

The product is indicated for a disorder that exclusively affects blind people. We may not have thought to require braille, but I'm not sure that folks for whom the product is intended could use the product safely if they can't read the label. Without braille, they either need someone else to read the label for them or they use it without instruction. So, even if they didn't *need* to add braille, now that they have it, it seems like it might be less safe to not have braille on the generics.

- **Discussion with DMEPA via email**

Communication with DMEPA:
DMEPA was asked a separate question as follows:

OGD is reviewing ANDA-211654 (Tasimelteon). DMEPA had the RLD applicant (Vanda) do a Braille labeling comprehension study, and requested a certificate of translation. However, OGD isn't able to require a labeling comprehension study for the ANDA (wouldn't be allowed to submit as an ANDA). Will a certificate of translation suffice to confirm that the ANDA container label conveys the correct product name and strength in Braille?

DMEPA's response:

If the RLD has braille, and the generic simply wants an identical label with identical braille, then I would not anticipate the need for a translation certificate nor a labeling comprehension study.

If the RLD does not have braille, and the generic wants to have braille, and if this is legally allowable under generic regulation, then I would imagine OGD labeling would want to certify what is stated in braille. Depending on what pieces of labeling will be in braille (e.g., an IFU), if direct translation cannot be done (e.g., for example graphics may not translate), this may raise comprehension questions where additional testing may be warranted, but it's difficult to speak in the hypothetical. Keep in mind also that under generic regulation a sponsor cannot submit new data that supports safety and efficacy, and a labeling comprehension study would likely qualify as new data that supports S&E as labeling comprehension is a type of human factors study. There may be other policy issues raised by these questions. If there's a real example, perhaps it would be best to examine the specific situation, and I would suggest you also loop in OGDP.

Thanks and have a great day.

- **DLR Consult to OGD Policy group and response.**

DLR Consult to OGDP on 5/9/2018

1. **Please describe your request, and recommendation if you have one.**
   DLR has pending ANDAs which reference an RLD that has braille on the container label. One ANDA (211654) has proposed braille on the label; 2 ANDAs (211601, 211607) have not proposed braille on the label. Please provide clarification from a regulatory standpoint on whether generic applicants may propose or omit braille in the label when the RLD has braille on the label. Also, what are the submission requirements for ANDAs that propose braille in the label? Is the certificate of translation sufficient?

OGDP Response via email on 6/25/2018:

For this one, we recommend sending a consult to the OND review division with the following questions:

1. Did OND require the RLD to provide the drug name and strength in braille, or did the applicant voluntarily submit it? (Our understanding from the record is that the applicant voluntarily submitted the braille information, but we wanted to confirm.)
2. Would OND have approved the RLD if no braille information (drug name and strength) on the container had been provided?
3. Is OND aware of any other approved drug products for conditions that affect the blind or visually impaired.
   a. If so, is any of the labeling or container information for those drug products presented in braille?
   b. And if so, did FDA require this information to be presented in braille?

Because it's not 100% clear from a regulatory perspective what bucket the braille information would fall into (e.g., labeling, packaging, container closure system/quality, or some combination of these), we think it makes sense to start with nailing down the facts of the approval from OND. Assuming they confirm that the braille information was not required, and that they would have approved the RLD without it, we think that should be sufficient information to support approving ANDAs without this "nice-to-have" information, and we would not have to decide exactly which regulatory bucket the braille information falls into (because if OND would have approved the RLD without it, the lack of braille should be acceptable from either a labeling or quality perspective).

For the ANDA that did voluntarily provide the braille information, we agree that the certificate of translation should be sufficient, based in part on DMEPA's email feedback.

Thanks!

- **Further back ground information on the braille used on the container label can be located in DMEPA review in DARRTS with following dates.**

01/29/2014	REV-SURVEPI-06 (Labeling Review)
12/31/2013	REV-SURVEPI-06 (Labeling Review)
09/27/2013	REV-SURVEPI-06 (Labeling Review)

- **"Dispense in original container" statement on the container label:**
  - Following is taken from entry in SharePoint for the RLD Hetlioz:

considered. As far as adding the statement about dispensing in original container and not covering the Braille - this was brought up since we were spending this time/effort to have the Braille on the original container, we wanted to ensure that the patients actually receive the container with the Braille, since it may be beneficial to the patient. The part about not covering the Braille hopefully conveys why to dispense in the original container (vs. a stability type issue).

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Title	Hetlioz (tasimelteon capsules) uses Braille in its labeling
Date:	1/19/2016
Is this a Review?	☐
What Type of File?	E-mails
Attachments	Hetlioz -- Approval of a container label with Braille.msg

Above entry in SharePoint is background reference information on the braille language included on the PDP of the RLD labeling for Hetlioz. Refer to section 2.2 Additional Background Information for considerations that are specific to the generic Hetlioz products related to the use of braille.

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES

If Yes, please explain.

Policy Alert Basis	Docket #	Brand Name (or Drug Class)	Generic Name / Dosage Form / Strengths	Action Requested or Issue Description
CP	FDA-2015-P-2142	Hetlioz	tasimelteon capsules	Requests the FDA require the prescription drug tasimelteon to require the drug labeling to contain specific revisions and language in the Indications and Usage section.

(b) (5)

Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA205677/S-001

Supplement Approval Date: 12/12/2014

Proprietary Name: Hetlioz

Established Name: tasimelteon

Description of Supplement:

This "Prior Approval" supplemental new drug application proposes the addition of the sentence "*The absolute oral bioavailability of tasimelteon is 38.3%.*" in section 12.3 of the full prescribing information. Other minor changes included in this supplement are as follows:

1. Replaced ™ symbol with ® symbol globally for HETLIOZ®.
2. Correction of typo in Prescribing Information from "6.1 Clinical Trial Experience" to "6.1 Clinical Trials Experience".
3. Correction of typo in Section 12.3 related to oral volume of distribution of tasimelteon at steady state from "56 – 126 L" to "59 – 126 L".
4. Correction of number of subjects enrolled in Study 2, Table 2, from "20" to "10" for each treatment group.

Note: S-002 and S-003, approved 4/7/2016 and 11/21/2017, respectively, are CMC only supplements

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.

☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

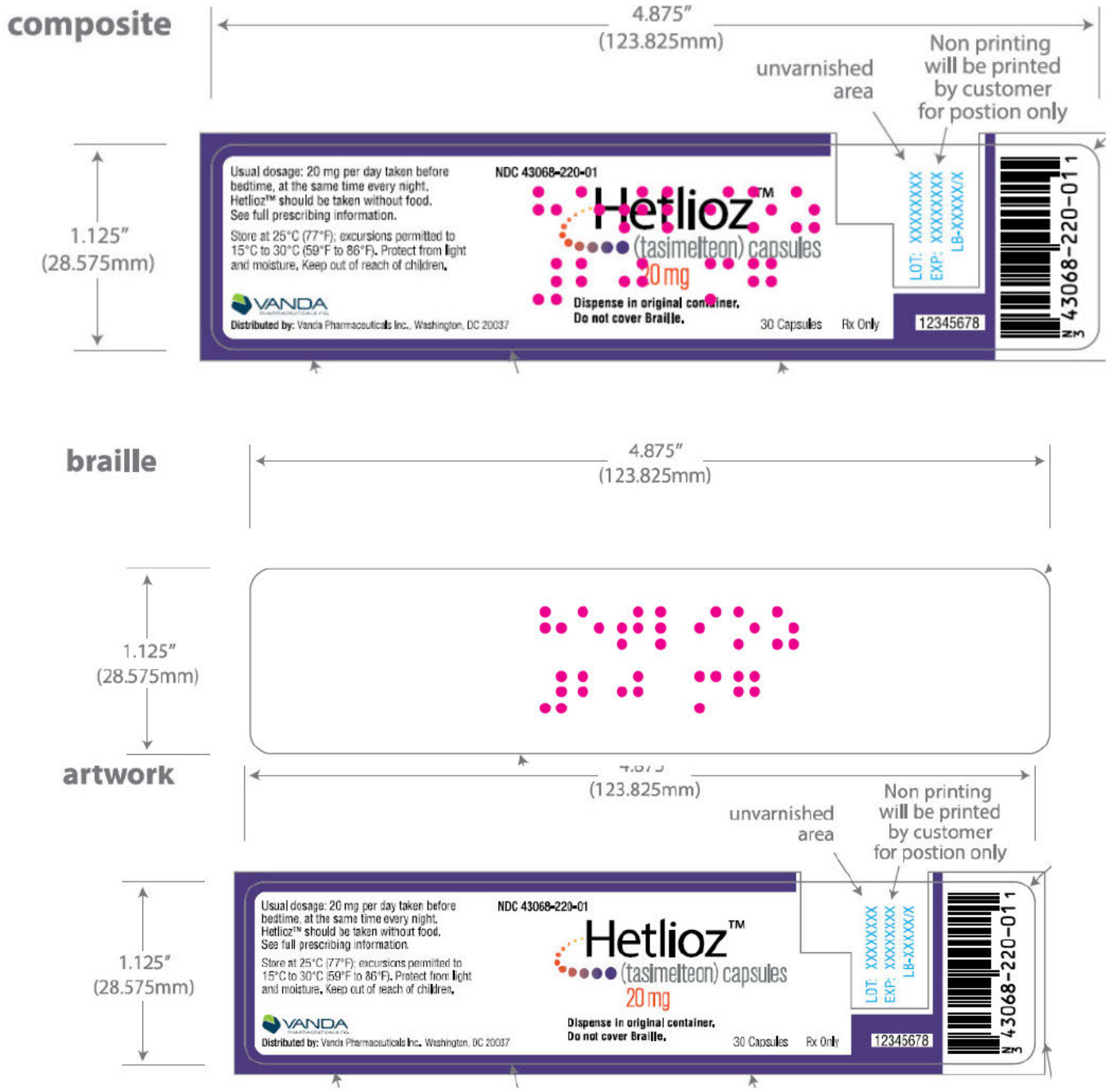
Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

PI remains adequate since previous review cycle. There is no further update in this review cycle.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA205677, original amendment submitted 1/22/2014 (SD#36))]



3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 9/18/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 9/18/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 205677 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
5856529	12/09/2018	U-2149	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ADMINISTERING TASIMELTEON	III	1/31/2018	None
9060995	01/25/2033	U-1710	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH FLUVOXAMINE	IV	1/31/2018	None
9539234	01/25/2033	U-1934	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH A STRONG CYP1A2 INHIBITOR	IV	1/31/2018	None
9549913	01/25/2033	U-1486	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER	IV	1/31/2018	None
9730910	05/17/2034	U-2085	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH RIFAMPIN	IV	1/31/2018	None
9855241	01/25/2033	U-2149	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ADMINISTERING TASIMELTEON	IV	1/31/2018	None
RE46604	01/25/2033	U-2147	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ORALLY ADMINISTERING 20MG OF TASIMELTEON ONCE DAILY BEFORE BEDTIME	IV	1/31/2018	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NCE	1/31/2019	NEW CHEMICAL ENTITY	MSN Laboratories Private Ltd commits not to market this product until the expiration of the above exclusivities.	1/31/2018	None
ODE-59	1/31/2021	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER	Same as above	1/31/2018	None

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment
(b) (4)	no update for this cycle	PI remains adequate since previous labeling review

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
(b) (4)	no update for this cycle	**PI remains adequate since previous labeling review**

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)	no update for this cycle	**PI remains adequate since previous labeling review**

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline (e.g., OPQ, OB, DCR) reviewer(s):

Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

This review follows CMC/Labeling MOU. There is no comment for the labeling reviewer. Following is taken from CMC review dated 7/16/2018 in GDRP.

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. (b) (4)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A

If "No," explain.

For OTC Drugs and Controlled Substances: NA

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code
20 mg	Size 1 capsule	Size 1, blue opaque, hard gelatin capsules, body imprinted with "20 mg" and circular band in white and cap imprinted with "MTI" in white.

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

NA

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**

Container	Final	30's	1/31/2018	Satisfactory (with certificate of translation submitted on 7/26/2018
Blister	NA			
Carton	NA			
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: 1/2018	1/31/2018	Satisfactory per review #1
Medication Guide	NA			
Patient Information	NA			
SPL Data Elements		Revised: 1/2018	1/31/2018	Satisfactory per review #1

Esther Chuh

Digitally signed by Esther Chuh
Date: 9/18/2018 12:57:56PM
GUID: 508da70700028b78f2f9ebd95bfb4a18

Marshall Florence

Digitally signed by Marshall Florence
Date: 9/21/2018 12:55:09PM
GUID: 55eefa420051b501ac3ced124279f785

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	4/5/2017, revised 7/5/2018
ANDA Number(s)	211654
Review Number	1
Applicant Name	MSN Laboratories Private Limited
Established Name & Strength(s)	Tasimelteon Capsules, 20 mg
Proposed Proprietary Name	None
Submission Received Date	1/31/2018
Primary Labeling Reviewer	Eunjung Esther Chuh
Secondary Labeling Reviewer	Marshall Florence

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☒ Yes ☐ No

Acceptable for Filing ☒ Yes ☐ No

TABLE OF CONTENTS

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on July 5, 2018, based on your submission dated January 31, 2018:

GENERAL COMMENTS/ CONTAINER LABEL

Please comment on your inclusion of braille on the container label. We inform you that Certificate of Translation is required to support your proposed braille.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission(s) dated (add date).

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES

If Yes, please explain.

Are there any pending issues in DLR's SharePoint Drug Facts? YES

If Yes, please explain.

Title	Hetlioz (tasimelteon capsules) uses Braille in its labeling
Date:	1/19/2016
Is this a Review?	☐
What Type of File?	E-mails
Attachments	Hetlioz -- Approval of a container label with Braille.msg

Above entry in SharePoint is background reference information on the braille language included on the PDP of the RLD labeling for Hetlioz. Refer to section 5 Special Considerations for considerations that are specific to the generic Hetlioz products related to the use of braille.

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES

If Yes, please explain.

Policy Alert Basis	Docket #	Brand Name (or Drug Class)	Generic Name / Dosage Form / Strengths	Action Requested or Issue Description
CP	FDA-2015-P-2142	Hetlioz	tasimelteon capsules	Requests the FDA require the prescription drug tasimelteon to require the drug labeling to contain specific revisions and language in the Indications and Usage section.

Action Requested or Issue Description	RLD# (or reference standard)	Actions (AP/TA/CR)	Communications (IR/ECD/CC)	Notes	Date Filed (~)	OGD Policy Lead

(b) (4)

Is the drug product listed in the Susceptibility Test Interpretive Criteria web page? NO

Is there a mid-review cycle meeting (MRCM) task in Platform? Or, if filing review is not complete, was there a Product Development or Pre-ANDA Submission Project under the ANDA Program? NO

If **YES** is answered, there is a potential for holding MRCM. What is the proposed agenda from DLR for MRCM?

NA

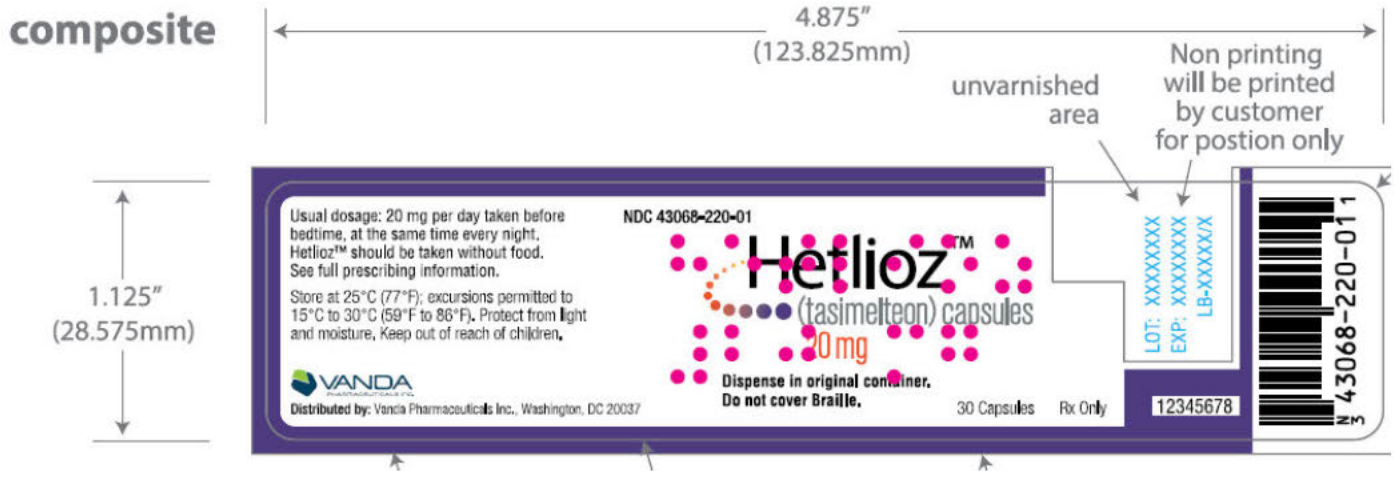
2.2 MODEL LABELING

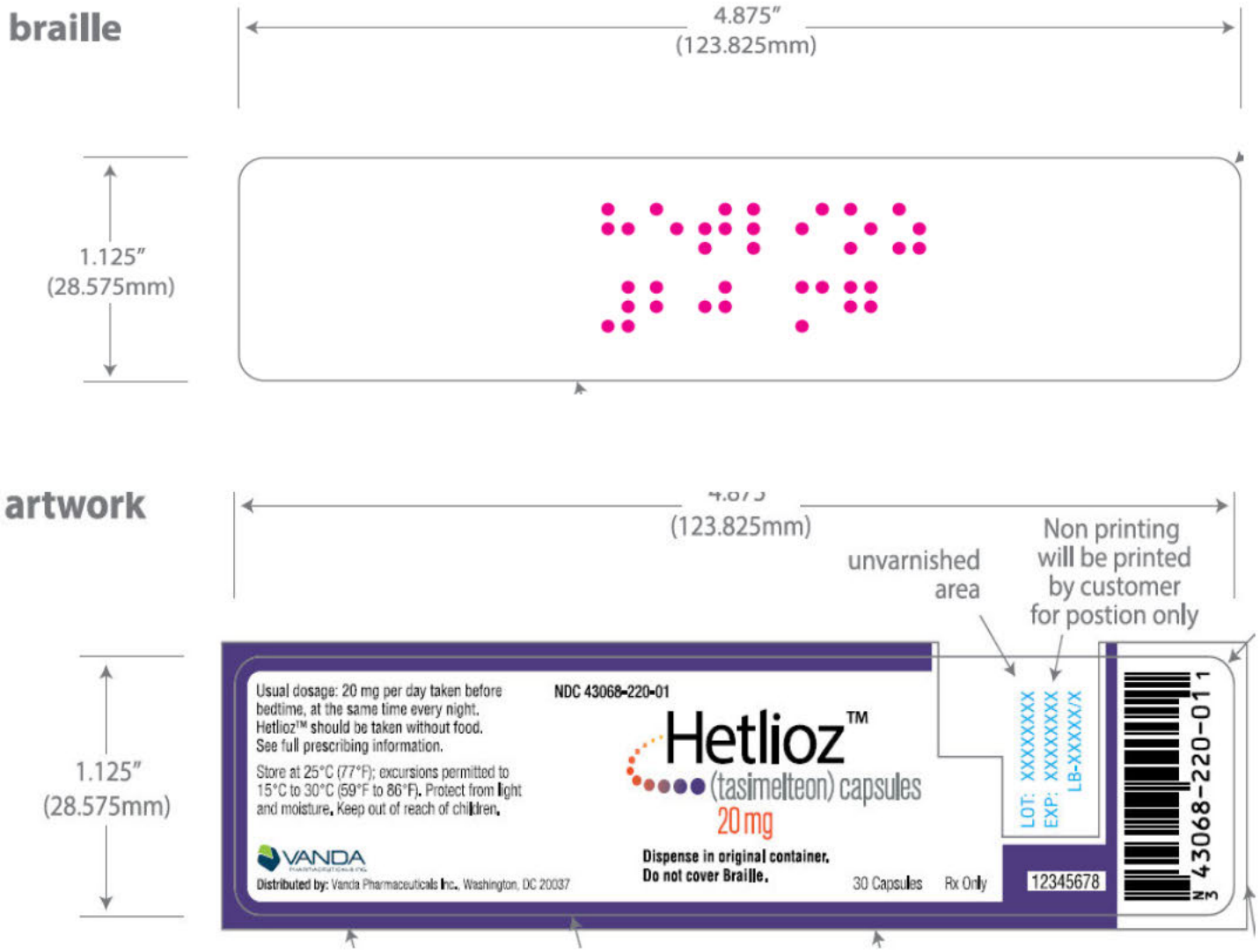
2.2.1 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original):** NDA205677/S-001 **Supplement Approval Date:** 12/12/2014 **Proprietary Name:** Hetlioz **Established Name:** tasimelteon **Description of Supplement:** This "Prior Approval" supplemental new drug application proposes the addition of the sentence "*The absolute oral bioavailability of tasimelteon is 38.3%.*" in section 12.3 of the full prescribing information. Other minor changes included in this supplement are as follows: 1. Replaced ™ symbol with ® symbol globally for HETLIOZ®. 2. Correction of typo in Prescribing Information from "6.1 Clinical Trial Experience" to "6.1 Clinical Trials Experience". 3. Correction of typo in Section 12.3 related to oral volume of distribution of tasimelteon at steady state from "56 – 126 L" to "59 – 126 L". 4. Correction of number of subjects enrolled in Study 2, Table 2, from "20" to "10" for each treatment group.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):**

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: NDA205677, original amendment submitted 1/22/2014 (SD#36))





2.3 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 7/5/2018.

Table 2: USP				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	No		NA	NA
Pending Monograph Proposed	NO	NA	NA	NA

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/5/2018.

Table 3 provides Orange Book patents for the Model Labeling (NDA 205677) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
5856529	12/09/2018	U-2149	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ADMINISTERING TASIMELTEON	III	1/31/2018	None
9060995	01/25/2033	U-1710	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH FLUVOXAMINE	IV	1/31/2018	None
9539234	01/25/2033	U-1934	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH A STRONG CYP1A2 INHIBITOR	IV	1/31/2018	None
9549913	01/25/2033	U-1486	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER	IV	1/31/2018	None
9730910	05/17/2034	U-2085	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER BY AVOIDING THE USE OF TASIMELTEON IN COMBINATION WITH RIFAMPIN	IV	1/31/2018	None
9855241	01/25/2033	U-2149	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ADMINISTERING TASIMELTEON	IV	1/31/2018	None
RE46604	01/25/2033	U-2147	TREATMENT OF NON-24 HOUR SLEEP-WAKE DISORDER BY ORALLY ADMINISTERING 20MG OF TASIMELTEON ONCE DAILY BEFORE BEDTIME	IV	1/31/2018	None

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter Carve-out or None)**
NCE	1/31/2019	NEW CHEMICAL ENTITY	MSN Laboratories Private Ltd commits not to market this product until the expiration of the above exclusivities.	1/31/2018	None
ODE-59	1/31/2021	TREATMENT OF NON-24-HOUR SLEEP-WAKE DISORDER	Same as above	1/31/2018	None

2.5 MANUFACTURING FACILITY

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	**Name and Address on ANDA Container**	**Name and Address on ANDA Prescribing Information**

(b) (4)	Manufactured by: MSN Laboratories Private Limited Telangana – (b) (4) INDIA Distributed by: MSN Pharmaceuticals Inc. Edison, NJ 08837

3. ASSESSMENT OF ANDA LABELING AND LABELS

Is this product Rx or OTC? Please check one.

☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT.)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Is the established name the same as the USP monograph title appearing in section 2.3? **NA**
Is the established name the same as the RLD's nonproprietary name? **YES**
If YES is answered to both questions, then continue with review.
If NO is answered to EITHER questions, then advise firm to revise to the USP name (if applicable) and include justification language under Reviewer Comments.
Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **NO**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the Manufacturer statement acceptable? **YES**

Reviewer Comments:
PI is acceptable.

3.1.1.1 RX: DESCRIPTION

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling Inactive Ingredients	(b) (4)
HETLIOZ is available in 20 mg strength capsules for oral administration. Inactive ingredients are: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. Each hard gelatin capsule consists of gelatin, titanium dioxide, FD&C Blue #1, FD&C Red #3, and FD&C Yellow #6.	

Reviewer Assessment:

Are the inactive ingredients accurate? **YES**
For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**
Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling? **NA**

If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NO** Has the statement been verified by chemistry? **NA**

Reviewer Comments:
This review follows CMC/Labeling MOU. This section is acceptable. Refer to section 4.

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

Table 7: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	**HOW SUPPLIED/STORAGE AND HANDLING** HETLIOZ 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 **Storage** Store HETLIOZ 20 mg capsules at controlled room temperature, 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Protect HETLIOZ 20 mg capsules from exposure to light and moisture.
ANDA Labeling	(b) (4)

Reviewer Assessment:

Are all of the submitted labels and labeling reflected in the How Supplied section? **YES**
Is the description (e.g., scoring, color, imprint) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? **YES**
Does the ANDA require the same color coding as the Model Labeling? **NO**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NO**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**
Is the storage or dispensing statement acceptable as compared to the USP? **NA**

Reviewer Comments:
This review follows CMC/Labeling MOU. HS section is acceptable. Refer to section 4.

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **CLICK HERE**
Is the Medication Guide same as the model labeling, except for allowable differences? **CLICK HERE**
Has the Applicant committed to provide a sufficient number of medication guides? **CLICK HERE**
Is the phonetic spelling of the proprietary or established name present? **CLICK HERE**
Is FDA 1-800-FDA-1088 phone number included? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **CLICK HERE**
Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES**
(For BLISTER labels go to section 3.1.5.)

Reviewer Assessment:

Is the established name acceptable? **YES**
Is title case used in expressing the established name? **YES**
Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**
If the container label is too small to contain all required information, does it meet the "too small" exemption found in 21 CFR 201.10(i)? **NA**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**
Is the following information properly displayed?

- Net quantity statement: **YES**
- Route(s) of administration (other than oral): **NA**
- Warnings (if any) or cautionary statements (if any): **YES**
- Medication Guide Pharmacist instructions per 21 CFR 208.24(d): **NA**
- Controlled substance symbol: **NA**
- Usual Dosage statement: **YES**
- Product strength equivalency statement: **NA**
- NDC: **YES**
- Bar code per 21 CFR 201.25(c)(2): **YES**

Is the Manufacturer/Distributor/Packager statement acceptable? **YES**
For foreign manufacturers, does the labeling have the country of origin? **YES**
Are the USP recommendations and/or differences in test methods (e.g., organic impurities, assay) reflected on the label(s)? **NA**
Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **NA**
Does the ANDA require the same color coding as the Model Labeling? **NA**
Are requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100)? **YES**

Reviewer Comments:

- **Braille on RLD Label**:
  We note that the proposed product includes braille as the RLD product includes the product name and the strength statement in braille. As inclusion of braille is not condition of approval for this drug product, we will ask the applicant to comment on their decision to include the braille on their container

label. Applicant will need to submit Certificate of Translation to support their proposed braille on the label. Refer to *Section 5 Special Considerations* on DLR's communication with OND, DMEPA, and the OGD Policy team.

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP General Chapter <7> Labeling **CLICK HERE**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable (other than Pharmacy Bulk Package)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **CLICK HERE**
Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **CLICK HERE**
Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **CLICK HERE**
Does the container label include graduation marks? **CLICK HERE**
Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **CLICK HERE**
Do proprietary name, established name, strength, bar code, and manufacturer appear accurately on each blister cell? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **CLICK HERE** If no, please explain the differences in the Reviewer Comments section.
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **CLICK HERE**
If country of origin is not on Container, does it appear on outer packaging labeling? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **CLICK HERE**
Does "Questions?" have a toll-free number no less than 6 pt. font size per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" per 21 CFR 201.66 (c)(5)(vii)? **CLICK HERE**
Did firm submit a Labeling Format Information Table to evaluate the font size? **CLICK HERE**
Is the applicant's "patent carve out" acceptable? **CLICK HERE**
Is the applicant's "exclusivity carve out" acceptable? **CLICK HERE**
Is the established name for this ANDA acceptable? **CLICK HERE**
Is title case used in expressing the established name? **CLICK HERE**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **CLICK HERE**
Is the following information properly displayed?

- Pharmacological category: **CLICK HERE**
- Net quantity statement: **CLICK HERE**
- Route(s) of administration (other than oral): **CLICK HERE**
- Warnings (if any) or cautionary statements (if any): **CLICK HERE**
- NDC: **CLICK HERE**
- Bar code per 21 CFR 201.25(c)(2): **CLICK HERE**

Is the Manufacturer/Distributor/Packager statement acceptable? **CLICK HERE**
For foreign manufacturers, does the labeling have the country of origin? **CLICK HERE**
Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling? **CLICK HERE**
Is the storage statement acceptable? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
Are multiple strengths differentiated by use of different color or other acceptable means? **CLICK HERE**
Are the labels of related products differentiated to avoid selection errors? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients	**ANDA Inactive Ingredients**
Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? **CLICK HERE**
Are the inactive ingredients listed in alphabetical order? **CLICK HERE**
For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **CLICK HERE** Has the statement been verified by chemistry? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

Table 9: Comparison of Model Labeling to ANDA finished product	
Model Labeling	**Description of Finished Product** (Source: Click here to enter text.) Click here to enter text. **Package Configurations** (Source: Click here to enter text.) Click here to enter text. **Storage Conditions** (Source: Click here to enter text.) Click here to enter text.
ANDA	**Description of Finished Product** (Source: Click here to enter text.) Click here to enter text. **Package Configurations** (Source: Click here to enter text.) Click here to enter text. **Storage Conditions** (Source: Click here to enter text.) Click here to enter text.

Reviewer Assessment:

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **CLICK HERE**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **CLICK HERE**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **CLICK HERE**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **CLICK HERE**
Is the storage statement acceptable as compared to the Model Labeling? **NA**
Is the storage statement acceptable as compared to USP? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.2.2 OTC: PATIENT LABELING

Is patient labeling required? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was patient labeling submitted? **CLICK HERE**
Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.3 CONTAINER/CLOSURE

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.
Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **YES**
Are the tamper evident requirements met for OTC, Ophthalmic and Controlled Substances **NA**

For ophthalmic products:
Does this ophthalmic product cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**

For parenteral products:
Is there text on the cap/ferrule overseal of this injectable product? **NA**
If YES, does text comply with the recommendations in USP General Chapter <7> Labeling? **NA**
What is the cap color? **Click here to enter text.**
NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:
Proposed product is in 30's CRC.
Below container closure information is taken from Quality Module section

3.2.P.7.1 Summary of Container/Closure System

MSN Laboratories Private Limited proposes to pack the Tasimelteon Capsules, 20 mg in 30's counts bottle pack.

The 30's count bottle packaging configuration are packed in (b) (4) polyethylene bottles, utilizing polypropylene child resistant (CR) caps.

Summary of Packaging Configuration sizes for Tasimelteon Capsules, 20 mg:

Tasimelteon Capsules, 20 mg– 30's count bottle pack

HDPE Bottle	Closure	Desiccant
(b) (4) white opaque HDPE containers with (b) (4) neck	(b) (4) closure with induction sealing wad	(b) (4) silica gel canister

3.4 CALCULATIONS FOR CONTENTS AND VERIFICATION OF ALUMINUM CONTENT

Is calculation of ingredient(s) or verification of aluminum content required? **NO**

Table 10: Ingredients		
Ingredient	**Stated Content**	**Location of the Information**
Click here to enter text.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the stated contents in the table above acceptable? **CLICK HERE**
Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per 21 CFR 201.323.
Did the chemistry reviewer verify the aluminum content? **CLICK HERE**
Are the labeling requirements met per 21 CFR 201.323? **CLICK HERE**

Reviewer Comments:

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

Was SPL submitted? **YES**

Table 11: ANDA Tablet/Capsule Size and Imprint		
Capsule Strength	**ANDA Tablet/Capsule Size (mm) and imprint code from SPL**	**ANDA Tablet/Capsule Size (mm) and imprint code (source: Chemistry Review, Product Specification in 3.2.P.5.1)**
20 mg	**Product Characteristics** Color: BLUE Shape: CAPSULE Score: no score Size: 19mm Imprint Code: 20;mg;MT1	Size"1" empty hard gelatin capsules with Blue opaque body imprinted with "20mg" and circular band in white ink and Blue opaque cap imprinted with "MT1" in white ink.

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **YES**
Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

Reviewer Comments:
SPL is acceptable.

4. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other review discipline (e.g., OPQ, OB) reviewer(s):

Reviewer Comments:
This review follows CMC/Labeling MOU. There is no comment for the labeling reviewer. Following is taken from CMC review dated 6/7/2018 in GDRP.

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description (e.g., USP test pending. (b) (4)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A

If "No," explain.

For OTC Drugs and Controlled Substances: NA

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code
20 mg	Size 1 capsule	Size 1, blue opaque, hard gelatin capsules, body imprinted with "20 mg" and circular band in white and cap imprinted with "MTI" in white.

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

NA

5. SPECIAL CONSIDERATIONS

- **RLD Hetlioz has the proprietary name and the strength statement in braille.** Inclusion of the braille was proposed by the NDA applicant upon submission of the original NDA to accommodate the needs of the population using the product. Hetlioz is indicated for treatment of Non-24 Hour Sleep – Wake Disorder (Non-24).

- **Braill is not required for the generics of Hetlioz.**

  DLR inquired OND, DMEPA/OSE and OGD Policy group to find out if braille would be required for the generics of Hetlioz. Based on the response gathered by each Offices (see attached below) we find that inclusion of braille language is not a requirement for the generic products on the basis that inclusion of braille language was not condition of approval for the RLD product. We note that braille was proposed by the RLD applicant as "nice to have" information. Subsequently DMEPA had asked the RLD applicant to perform a braille label comprehension study of braille labeling on the container label and found the study and the proposed braille on the label acceptable. In addition, we note from discussion with DMEPA and with OGDP that if ANDA applicant voluntarily proposes braille on their label, Certificate of Translation should be required to support the proposed braille.

- **Discussion with OND via email**

Communication with OND:

The following question was posed to OND via email:

> OGD is currently reviewing the labeling for the generic version of Hetlioz (tasimelteon), NDA 205677. Some of the applicants have submitted braille on the container label and others have not. We would like to know if OND believes:
>
> a. It is less safe for generic applicants to NOT provide braille on the container labels.
> b. If generic applicants must provide braille, should the generic applicants follow the RLD container label and limit braille to the established name and strength?
> c. If generic applicants must provide braille, should the generic applicants limit the container sizes to unit-of use containers such as 30s, 60s, 90s to ensure that the braille is on the container label?

OND Medical Officer's responses via email were as follows:

> Here is my take:
>
> It is a nice idea (and probably helps with public relations) that the original Sponsor included Braille labeling. However, the Agency did not require it. Although tasimelteon's currently approved indication (non-24) means that the target patient population is blind, it's not the only medication blind people take. Blind people are on cholesterol medications, blood pressure medications, etc. And we don't worry about making sure all these other medications are dispensed with Braille when given to blind patients.
>
> So, I don't feel that we need to require generic manufacturers to include Braille. If a generic manufacturer wants to include Braille, my opinion is that they should mirror the RLD (as with any other labeling).
>
> I also don't feel like an official consult is needed (from my end).

OND Deputy Director's response:

> The product is indicated for a disorder that exclusively affects blind people. We may not have thought to require braille, but I'm not sure that folks for whom the product is intended could use the product safely if they can't read the label. Without braille, they either need someone else to read the label for them or they use it without instruction. So, even if they didn't *need* to add braille, now that they have it, it seems like it might be less safe to not have braille on the generics.

- **Discussion with DMEPA via email**

Communication with DMEPA:
DMEPA was asked a separate question as follows:

> OGD is reviewing ANDA-211654 (Tasimelteon). DMEPA had the RLD applicant (Vanda) do a Braille labeling comprehension study, and requested a certificate of translation. However, OGD isn't able to require a labeling comprehension study for the ANDA (wouldn't be allowed to submit as an ANDA). Will a certificate of translation suffice to confirm that the ANDA container label conveys the correct product name and strength in Braille?

DMEPA's response:

> If the RLD has braille, and the generic simply wants an identical label with identical braille, then I would not anticipate the need for a translation certificate nor a labeling comprehension study.
>
> If the RLD does not have braille, and the generic wants to have braille, and if this is legally allowable under generic regulation, then I would imagine OGD labeling would want to certify what is stated in braille. Depending on what pieces of labeling will be in braille (e.g., an IFU), if direct translation cannot be done (e.g., for example graphics may not translate), this may raise comprehension questions where additional testing may be warranted, but it's difficult to speak in the hypothetical. Keep in mind also that under generic regulation a sponsor cannot submit new data that supports safety and efficacy, and a labeling comprehension study would likely qualify as new data that supports S&E as labeling comprehension is a type of human factors study. There may be other policy issues raised by these questions. If there's a real example, perhaps it would be best to examine the specific situation, and I would suggest you also loop in OGDP.
>
> Thanks and have a great day.

- **DLR Consult to OGD Policy group and response.**

DLR Consult to OGDP on 5/9/2018

1. **Please describe your request, and recommendation if you have one.**
   DLR has pending ANDAs which reference an RLD that has braille on the container label. One ANDA (211654) has proposed braille on the label; 2 ANDAs (211601, 211607) have not proposed braille on the label. Please provide clarification from a regulatory standpoint on whether generic applicants may propose or omit braille in the label when the RLD has braille on the label. Also, what are the submission requirements for ANDAs that propose braille in the label? Is the certificate of translation sufficient?

OGDP Response via email on 6/25/2018:

For this one, we recommend sending a consult to the OND review division with the following questions:

1. Did OND require the RLD to provide the drug name and strength in braille, or did the applicant voluntarily submit it? (Our understanding from the record is that the applicant voluntarily submitted the braille information, but we wanted to confirm.)
2. Would OND have approved the RLD if no braille information (drug name and strength) on the container had been provided?
3. Is OND aware of any other approved drug products for conditions that affect the blind or visually impaired.
    a. If so, is any of the labeling or container information for those drug products presented in braille?
    b. And if so, did FDA require this information to be presented in braille?

Because it's not 100% clear from a regulatory perspective what bucket the braille information would fall into (e.g., labeling, packaging, container closure system/quality, or some combination of these), we think it makes sense to start with nailing down the facts of the approval from OND. Assuming they confirm that the braille information was not required, and that they would have approved the RLD without it, we think that should be sufficient information to support approving ANDAs without this "nice-to-have" information, and we would not have to decide exactly which regulatory bucket the braille information falls into (because if OND would have approved the RLD without it, the lack of braille should be acceptable from either a labeling or quality perspective).

For the ANDA that did voluntarily provide the braille information, we agree that the certificate of translation should be sufficient, based in part on DMEPA's email feedback.

Thanks!

- **Further back ground information on the braille used on the container label can be located in DMEPA review in DARRTS with following dates.**

01/29/2014	REV-SURVEPI-06 (Labeling Review)
12/31/2013	REV-SURVEPI-06 (Labeling Review)
09/27/2013	REV-SURVEPI-06 (Labeling Review)

- **"Dispense in original container" statement on the container label:**
    - Following is taken from entry in SharePoint for the RLD Hetlioz:

considered. As far as adding the statement about dispensing in original container and not covering the Braille - this was brought up since we were spending this time/effort to have the Braille on the original container, we wanted to ensure that the patients actually receive the container with the Braille, since it may be beneficial to the patient. The part about not covering the Braille hopefully conveys why to dispense in the original container (vs. a stability type issue).

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	30's	1/31/2018	Revise or submit Certificate of Translation
Blister	NA			
Carton	NA			
(Other – specify)	NA			
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: 1/2018	1/31/2018	Satisfactory
Medication Guide	NA			
Patient Information	NA			
SPL Data Elements	NA	Revised: 1/2018	1/31/2018	

Esther Chuh

Digitally signed by Esther Chuh
Date: 7/05/2018 05:50:05PM
GUID: 508da70700028b78f2f9ebd95bfb4a18

Marshall Florence

Digitally signed by Marshall Florence
Date: 7/10/2018 10:47:28AM
GUID: 55eefa420051b501ac3ced124279f785