FDA U.S. FOOD & DRUG ADMINISTRATION

JAN 2 7 2020

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Public Citizen
1600 20th Street NW
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Re: Docket No. FDA-2015-P-2142

Dear Drs. Bardehenn, Almashat, and Wolfe:

This letter responds to your citizen petition received on June 11, 2015 (Petition). The Petition requests that the Food and Drug Administration (FDA or Agency) revise the "Indications and Usage," "Carcinogenesis," "Mutagenesis," and "Pregnancy" sections of the labeling for Hetlioz (tasimelteon) capsules (new drug application (NDA) 205677). The Petition also requests that FDA require the distribution of a medication guide to patients receiving this drug and that FDA ask the drug's applicant to send a "Dear Doctor" letter to physicians and health care providers concerning the narrower indication requested in the Petition. Finally, the Petition requests that FDA require the applicant to conduct an adequately powered long-term postmarketing clinical trial with a large population of totally blind subjects for at least 2 years to obtain safety data on Hetlioz. More specifically, you ask FDA to take the following actions:

(1) Require revision of the indication in the "Indications and Usage" section of the product labeling so it is limited to the indication proposed in new drug application (NDA) 205677 and supported by the clinical trial data which were analyzed and reviewed in the NDA submission (see Appendix A). Specifically, we are requesting the re-insertion of the phrase "in blind patients without light perception" to the "Indications and Usage" section (the indication in the current FDA-approved labeling inexplicably has been expanded beyond that stated in the original NDA submission).

(2) Require revision of the "Carcinogenesis," "Mutagenesis," and "Pregnancy" sections of the product labeling to include additional risk information contained in the FDA's pharmacology review but missing from the current label, as detailed in Appendix B.

(3) Require distribution of a medication guide with each prescription of tasimelteon, informing patients of the newly narrowed indication and the drug's risks.

(4) Ask the sponsor to send a "Dear Doctor" letter notifying physicians and other health care providers of the corrected, narrower indication.

(5) Mandate that the sponsor conduct a large, adequately powered postmarketing clinical trial in totally blind subjects to obtain more robust safety data in this patient population, for which the drug was originally approved. In the preapproval safety database, just 139 subjects received tasimelteon for more than 26 weeks, and only 183 totally blind subjects with non-24-hour sleep-wake disorder received the drug at

> all for any duration. Non-24-hour sleep-wake disorder is a chronic condition for which tasimelteon is intended to be taken for years. The trial should therefore place subjects on tasimelteon for at least two years in order to gain more insight on the long-term risks of therapy. Although non-24 is an orphan indication, tasimelteon's manufacturer estimates that there are 100,000 totally blind patients living with this condition in the U.S., with even more in western Europe and other developed countries, from which subjects could be readily enrolled, thus making such a larger trial feasible.

(Petition at 1-2).

We have carefully considered your Petition, the appendices to the Petition, and other information available, and for the reasons stated below, the Petition is denied.

I. BACKGROUND

A. Non-24 Hour Sleep-Wake Disorder

Sleep is a complex biological process that arises from multiple brain regions and neurotransmitters and is regulated by numerous physiological and environmental factors. The suprachiasmatic nucleus (SCN) of the hypothalamus is the body's primary biological clock.[1] The SCN is composed of approximately 20,000 neurons and is responsible for controlling the circadian rhythm of the body, which for most people is greater than 24 hours.[2] However, the SCN is reset daily back to a 24-hour period through the perception of light.[3] "Entrainment" is the process of resetting the internal rhythm back to 24-hours. Those who cannot perceive light are unable to reset the SCN neurons, or unable to entrain the SCN to a 24-hour day, and as a result, they may experience non-24-hour sleep-wake disorder (Non-24).[4]

Because the internal circadian rhythm is greater than 24 hours, patients with Non-24 go to sleep later each night. Blind patients, on average, have an internal circadian rhythm that is 24.5 hours.[5] For these patients, by Day 24, a complete inversion of the sleep-wake pattern can result, whereby the patient's sleep onset has been delayed into morning hours. In such cases, alignment with the 24-hour clock occurs once every 48 days.

Non-24 can be debilitating for many patients. Some experience severe impairment of the sleep-wake cycle and can suffer from disruption of consolidated nighttime sleep. As a result, these patients often sleep during daytime hours to compensate for lack of nighttime sleep. This pattern

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[1] Garbazza, C, V Bromundt, A Eckert, DP Brunner, F Meier, S Hackethal, and C Cajochen, 2016, Non-24-Hour Sleep-Wake Disorder Revisited–A Case Study, Front Neurol, 7:17, at 1.

[2] Id. at 3-4.

[3] Id. at 4.

[4] Id.

[5] Id. at 5.

impacts social activities and work obligations, which contribute to worsening of quality of life.[6]

Non-24 is most prevalent in patients who are totally blind. It is estimated that over half of totally blind individuals suffer from Non-24 and that approximately 100,000 people in the United States have the disorder.[7] Although very rare, sighted individuals can also suffer from Non-24.[8]

B. Approval of Hetlioz

Hetlioz is an agonist at melatonin MT_1 and MT_2 receptors.[9] These receptors are thought to be involved in the control of circadian rhythms, but the precise mechanism by which Hetlioz exerts its therapeutic effect in patients with Non-24 is not known.[10] The indication proposed by the applicant, Vanda Pharmaceuticals Inc. (Vanda), was for the treatment of Non-24 in the totally blind. However, before approval of the product, the indication in the proposed labeling submitted by Vanda was expanded to include individuals who are not totally blind. The occurrence of Non-24 in normally-sighted patients is very rare. The approved labeling states that Hetlioz is "indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24)."[11] FDA concluded that Hetlioz would also be effective in Non-24 patients with severe visual impairment even if not totally blind. In a memorandum prepared after FDA's approval of Hetlioz, dated October 1, 2014 (October 2014 Memorandum), the Cross Disciplinary Team Leader explained that:

> [i]n such patients there is degradation, but not complete absence, of the environmental light signal from the eyes. The amount of damage to the eyes or visual pathways that can result in Non-24 is not well understood. Anatomically different pathways sense and transmit light for conscious vision and for circadian rhythms, such that typical vision testing may not be a reliable indicator of function of the circadian system.[12]

In other words, patients who are not totally blind but nonetheless suffer from some visual impairment affecting the circadian system would be expected to benefit from Hetlioz. Most importantly, "[v]isual impairment is not a component of the diagnosis."[13] The October 2014

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[6] Id.

[7] Id.

[8] See, e.g., Hayakawa, T, M Uchiyama, Y Kamei, K Shibui, H Tagaya, T Asada, M Okawa, J Urata, and K Takahashi, 2005, Clinical Analyses of Sighted Patients with Non-24 Hour Sleep-Wake Syndrome: A Study of 57 Consecutively Diagnosed Cases, Sleep, 28(8):945-952; Uchiyama, M and S Lockley, 2009, Non-24 Hour Sleep-Wake Syndrome in Sighted and Blind Patients, Sleep Med Clin, 4:195-211.

[9] Hetlioz labeling (January 2014) at 12 CLINCIAL PHARMACOLOGY, 12.1 Mechanism of Action, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205677s001lbl.pdf.

[10] Id.

[11] Hetlioz labeling (January 2014) at 1 INDICATIONS AND USAGE.

[12] FDA, October 1, 2014, Reference ID: 3637846, Cross-Discipline Team Leader Review–Addendum (October 2014 Memorandum), at 1-2, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205677Orig1s000CrossRedt.pdf.

[13] Id. at 1.

Memorandum further noted that "[a]n indication that excluded these patients based on vision would thus be problematic even considering that the group is heterogeneous, poorly characterized, and likely includes patients with damage to the circadian system that would not be treatable with melatonin agonists."[14]

The approval letter to Vanda dated January 31, 2014, contained the incorrect indication statement: "This new drug application provides for the use of HETLIOZ, tasimelteon, 20 mg Capsules for Non-24 hour sleep-wake disorder in blind patients without light perception."[15] However, the INDICATIONS AND USAGE section of the labeling that accompanied the initial approval letter, as approved by FDA, stated that "HETLIOZ is a melatonin receptor agonist indicated for the treatment of Non-24 Sleep-Wake Disorder (Non-24)."[16] Shortly thereafter, a corrected approval letter was sent to Vanda noting that the initial approval letter "contained an error in the 'indications' sentence," and that the statement should have read, "This new drug application provides for the use of HETLIOZ, tasimelteon 20 mg Capsules for Non-24 hour sleep-wake disorder."[17] The corrected approval letter also noted that "[t]he effective approval date will remain January 31, 2014, the date of the original approval letter. The labeling is unchanged."[18]

II. DISCUSSION

The following sections discuss the Petition's requested actions and FDA's responses to those requests.

A. The Indication in the Labeling is Correct

Your Petition asserts that there is a mistake in the INDICATIONS AND USAGE section of the labeling for Hetlioz because the Agency "omitted the reference to blind individuals," even though the original approval letter accompanying the labeling stated that the drug is indicated for

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[14] Id. at 2.

[15] The 2014 Hetlioz approval letter is available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205677Orig1s000Approv.pdf.

[16] Hetlioz labeling at 1 INDICATION AND USAGE, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205677s001lbl.pdf.

[17] Corrected Approval Letter at 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/205677Orig1s000ltr.pdf. You suggest that FDA improperly issued the Corrected Approval Letter because "the true date on which this second approval letter was issued is unclear," and that the wording of the Corrected Approval Letter "strongly suggest[s] that it was issued after January 31, 2014, and therefore backdated" (Petition at 4). The Corrected Approval Letter was indeed sent to Vanda after the approval date and was backdated. This is consistent with FDA's Center for Drug Evaluation and Research (CDER) Document Processing Manual (DPI). See CDER DPI, July 12, 2012, ID: GPR-020, Processing Corrections to NDA/ANDA Action Communications Which Have Been Sent to the Applicant, at 1 (For typographical errors in the communication, "a replacement, backdated action communication that includes wording explaining the mistakes in the original communication will be sent to the company . . . .").

[18] Corrected Approval Letter at 1.

"Non-24-hour sleep-wake disorder in blind patients without light perception" (Petition at 5). You further state that references in various review documents to the proposed indication as the treatment of Non-24 "in blind individuals," "in blind patients without light perception," or "in totally blind individuals," is evidence that the omission of the limitation to blind patients is incorrect (Petition at 3). You also characterize the October 2014 Memorandum to be a "post-hoc rationale for change in tasilmelteon's indication" (Petition at 4). There has been no mistake other than the misstatement of the approved indication in the original approval letter; a mistake that was subsequently corrected. The approved indication is "the treatment of Non-24-Hour Sleep-Wake Disorder."

The correct indication is stated in the approved labeling, which was sent to Vanda on January 31, 2014, along with the original approval letter. The approved indication was reemphasized in the corrected approval letter which also noted "[t]he labeling is unchanged."[19] As explained above and in the corrected approval letter, the error was in the original approval letter, not the labeling. Proposed labeling is subject to change during an NDA's review phase up until the time the drug product is approved.[20]

The October 2014 Memorandum was intended to clarify that the labeled indication is correct as well as to clarify the basis for indicating Hetlioz for Non-24 without a qualification based on visual impairment. As explained in the October 2014 Memorandum, visual impairment is *not* a component of the diagnosis.[21] Essential to the diagnosis is the inability to entrain to a 24-hour-sleep-wake pattern due to a variety of factors, which may or may not be the result of lack of sightedness.[22] There are reported cases of sighted patients with severe brain damage and those who have been deprived of circadian light who suffer from Non-24.[23] Based in part on evidence of similar clinical and other biomarker effects of tasimelteon in sighted individuals in other models of circadian rhythm disruption, the Agency concluded that:

> . . . the drug would be effective in the closely related group of Non-24 patients with severe visual impairment who are not totally blind. In such patients there is degradation, but not complete absence, of the environmental light signal from the eyes.[24]

Accordingly, the benefits of Hetlioz therapy are not limited to those Non-24 patients who are totally blind. Given the rare occurrence of Non-24 in sighted individuals, the broadening of the

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[19] Corrected Approval Letter at 1.

[20] See FDA's guidance for industry *Good Review Management Principles and Practices for PDUFA Products* (April 2005), discouraging applicants from printing labels for commercial distribution before drug product's approval "because the label can change until it is approved." We update guidances periodically. For the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[21] October 2014 Memorandum at 1.

[22] Id.

[23] Id.

[24] Id.

indication originally proposed by the applicant to include sighted and totally blind individuals does not significantly expand the indicated population.[25]

Under section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the available evidence may support an indication that is broader or narrower than the precise population studied. FDA's approach regarding Hetlioz is consistent with the statute, implementing regulations, and associated Agency guidance. For example, the regulations governing labeling contemplate situations where evidence to support the safety and effectiveness of a drug product is demonstrated only in a subgroup of the larger population (e.g., patients with mild disease or patients in a special age group), and require corresponding limitations on the indication where scientifically appropriate (21 CFR 201.57(c)(2)(i)(B)).

Similarly, FDA's July 2018 draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription and Biological Products—Content and Format*[26] (Indications and Usage draft guidance), describes when expansion of the indicated population may be appropriate:

> The INDICATIONS AND USAGE section should clearly communicate the scope of the approved indication, including the population to which the determination of safety and effectiveness is applicable. The indicated population may mirror the studied population, for example, in terms of patient demographics or severity of disease or condition, but can sometimes differ. In some cases, FDA's expert reviewers may fairly and responsibly conclude, based on their scientific training and experience, that the available evidence supports approval of an indication that is broader or narrower in scope than the precise population studied. Applicants should discuss the scope of a proposed indication with the applicable review division.
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> [I]f a drug was studied only in patients with a moderate form or stage of a disease and there is reason to believe, based on the generalizability of the data, consistencies in the disease process, and the drug's benefits and risks, that the drug would be both safe and effective in a broader group with the condition, an indication covering the broader population may be appropriate. In some cases, an indication covering the overall disease population can be considered. *Specifics regarding the patient population studied should be described in the CLINICAL STUDIES section of the labeling.*[27]

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[25] You contend that Hetlioz was improperly designated an orphan drug under the Orphan Drug Act of 1983 (Orphan Drug Act) because Vanda obtained orphan drug status based on an indicated population of blind individuals without light perception (Petition at 2). As stated previously, there are estimated to be about 100,000 visually impaired patients in the United States with Non-24, and Non-24 in sighted individuals is considered very rare. A rare disease is defined by the Orphan Drug Act as a disorder or condition that affects less than 200,000 persons in the United States. Public Law 97-414, 96 Stat. 2049 (1983), amended by Public Law 98-551 (1984) to add a numeric prevalence threshold to the definition of rare diseases. Because of the rare occurrence of Non-24 in sighted individuals, the total population of patients suffering from Non-24, both blind and sighted, would not exceed 200,000. The Agency has determined that the approved indication falls within the orphan designation.

[26] Available on the FDA Drugs guidance web page. When final, this guidance will represent the FDA's current thinking on this topic.

[27] Indications and Usage draft guidance at 3 (emphasis added).

Consistent with the regulations and the Indications and Usage draft guidance, the CLINICAL STUDIES section of the labeling for Hetlioz states that:

> The effectiveness of HETLIOZ in the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) was established in two randomized double-masked, placebo-controlled, multicenter, parallel-group studies (Studies 1 and 2) *in totally blind patients with Non-24.*[28]

The CLINICAL STUDIES section of the labeling specifies the patient population studied (i.e., totally blind patients with Non-24) even though the INDICATIONS AND USAGE section of the labeling is indicated for the broader population of sighted and blind patients.

The labeling for Hetlioz is not unique. Indications for other biological and drug products have similarly been broadened to a wider population when the clinical studies that support approval focused on a narrower study population. For instance, Simponi (golimumab) injection is indicated for the treatment of active psoriatic arthritis (PsA) alone, or in combination with methotrexate.[29] As described in the CLINICAL STUDIES section of the labeling, the safety and efficacy of Simponi were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 405 adult patients with moderately to severely active PsA.[30] In other words, the clinical studies were conducted on a much narrower study population with moderately to severely active PsA, but Simponi is indicated for a broader population suffering from active PsA without any qualification regarding the severity of symptoms.

For the reasons stated above, the approved indication for Hetlioz is "the treatment of Non-24-Hour Sleep-Wake Disorder," and should remain so. Accordingly, your request that FDA require revisions to the indication to narrow the indicated population to totally blind individuals without light perception is denied.

B. Changes to the Carcinogenesis, Mutagenesis, Impairment of Fertility, and Pregnancy Sections of the Labeling are Unnecessary

The goals of the nonclinical safety evaluation generally include a characterization of toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential reversibility.[31] This information is used to estimate an initial safe starting dose and dose range for the human trials and to identify parameters for clinical monitoring for potential adverse effects. You state that the nonclinical studies raise concerns regarding genotoxicity, carcinogenicity, and target organ toxicity, and therefore, Section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) and Section 8.1 (Pregnancy) of Hetlioz's labeling should be revised to address these concerns. For the reasons explained below, we decline to require the

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[28] Hetlioz labeling at 14 CLINICAL STUDIES (emphasis added).

[29] Simponi labeling (April 2009) at 1 INDICATIONS AND USAGE, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125289s127lbl.pdf.

[30] Simponi labeling (April 2009) at 14 CLINICAL STUDIES, 14.2 Psoriatic Arthritis.

[31] See the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (M3(R2) Guidance) (January 2010), at 3, available on the FDA Drugs guidance web page.

labeling changes you requested.

1. Genotoxicity

You state that "[a]ccording to the pharmacology reviewer, both tasimelteon and its M11 metabolite were clastogenic (capable of causing disruption or breaking of chromosomes) in genotoxicity studies" (Petition at 7). This overstates the pharmacology reviewer's conclusion and does not take into account that the supervisory pharmacologist reached a different conclusion, finding little potential for genotoxicity.[32]

The pharmacology reviewer found that Hetlioz was negative in an in vitro Ames assay and in an in vivo rat micronucleus assay.[33] An in vitro chromosomal aberration assay demonstrated clastogenic effects, and the reviewer also found that metabolite M11 (a non-major human circulating metabolite that has poor coverage in the animal species) was also negative in an in vitro Ames assay but was clastogenic in an in vitro chromosomal aberration assay in CHO cells.[34] The pharmacology reviewer notes, however, that "[t]aken together, there is limited evidence that tasimelteon has genotoxic properties."[35]

The supervisory pharmacologist states:

> While [the pharmacologist's] conclusions are reasonable regarding the in vitro cytogenetic assay, the increases in % of cells with structural aberrations were ≤2-fold, even in the presence of maximum recommended or clearly excessive cytotoxicity. Overall, the data suggest a lack of genotoxic potential for tasimelteon.[36]

With respect to the M11 metabolite, the supervisory pharmacologist notes that:

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[32] You also claim that the chemistry review team identified two potentially genotoxic impurities in Hetlioz but that information regarding the final outcome was redacted, "leaving the impression that there was something that the team did not want the public to learn" (Petition at 8). Under applicable law and FDA regulations, trade secrets and commercial or financial information that is privileged or confidential is not subject to public disclosure (See, e.g., 21 CFR 20.61). Information concerning impurities in a drug product (e.g., including chemical identities and acceptance criteria) is often trade secret or confidential commercial information because it may provide insight into confidential manufacturing methods. Moreover, the chemistry review identified genotoxic impurities, but the sponsor adequately tightened the acceptance criteria for the drug substance upon comment by the Agency. FDA, November 12, 2013, Reference ID: 3405492, Quality (CMC) Review, at 7, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205677Orig1s000ChemR.pdf. The specific limits set for the two potentially genotoxic impurities were adequate to control the daily dose of each to a level acceptable for a genotoxic impurity. Ultimately, the chemistry reviewer recommended approval and noted that Vanda "satisfactorily addressed all the deficiencies that were communicated during the review" (Quality (CMC) Review at 8).

[33] FDA, July 15, 2013, Reference ID: 3399188, Pharmacology/Toxicology NDA Review and Evaluation (Pharmacology/Toxicology Review), at 179, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205677Orig1s000PharmR.pdf.

[34] Id. at 179-180.

[35] Id. at 180.

[36] FDA, November 12, 2013, Reference ID: 3405615, Supervisory Pharmacologist Review, at 4, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205677Orig1s000PharmR.pdf.

> While M11 was undetectable in rat plasma, plasma M11 levels estimated to have been achieved in the mouse carcinogenicity study are 1.1-2.2 times that in humans at the recommended daily dose of 20 milligrams (mg). Therefore, the carcinogenic potential of this minor human metabolite has been adequately addressed.[37]

2. Carcinogenicity

You claim that the pharmacology review discussed findings in the rat carcinogenicity study of drug-related neoplasms in the liver, uterus, and uterine cervix, increased neoplasm incidences in ovaries and mammary glands in high-dose females, and increased incidences of neoplasms in the pituitary, testes, and the skin in males (Petition at 8). Further, you state that the pharmacology reviewer found that increases in the incidences of hepatocellular adenomas were statistically significant in male and female rats, the incidences of endometrial adenocarcinoma and uterine squamous cell carcinoma were increased above the historical control range and were identified as drug-related causes of death, and the combination of squamous cell carcinoma in the uterus and uterine cervix was almost statistically significant (Petition at 8). You claim that the labeling "plays down the importance of these findings by omitting any mention of the fact that most of these tumors were both drug-related and statistically significant, and that there were, in addition, non-neoplastic findings in these same tissues" (Petition at 8).[38]

Although the review contains a discussion of potentially drug-related neoplasms, sections of the review are selectively referenced to support the arguments raised in the Petition. The same pharmacology reviewer notes that "[t]he relevance of these tumors to humans is unknown. The pharmacology reviewer concluded that no drug-related neoplasms were reported in mice."[39] The supervisory pharmacologist's review agrees with these statements and concludes that "[t]here were no drug-related increases in neoplasms in the mouse study. In [the] rat, the following neoplasms were identified as drug-related: uterus (endometrial adenocarcinoma at the [high dose] HD), uterus and cervix (squamous cell carcinoma at the [high-dose] HD), and liver (adenoma in [mid-dose female] MDF and [high-dose female] HDF; adenoma and carcinoma combined in [mid-dose male] MDM and [high-dose male] HDM). The positive findings in uterus were statistically significant, whereas those in other organs were identified as drug-related

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[37] Id.

[38] Relying on the U.S. Environmental Protection Agency's Guidelines for Carcinogen Risk Assessment (EPA Guidelines), you also assert that findings from the carcinogenicity studies expressed as human equivalent doses by conversion of animal doses based on body surface area is inappropriate (Petition at 10). However, the EPA Guidelines are inapposite here. Applicable FDA guidance states that this type of animal/human dose conversion based on body surface area is entirely appropriate. See FDA's guidance for industry *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapies in Adult Healthy Volunteers* (July 2005) at 7 (stating that the conversion factors for animal doses to human equivalent doses based on body surface area can also be applied when comparing safety margins for reproductive toxicity and carcinogenicity), available on FDA Drugs guidance web page. We also note that EPA and FDA look at toxicity, including carcinogenicity, of the products they regulate with differing uses and other considerations in mind, and not all testing methodology can be utilized across purposes.

[39] Pharmacology/Toxicology Review at 5.

based on the incidences exceeding historical control ranges."[40] The FDA statistical reviewer's assessment is consistent with the pharmacology reviewer's and supervisory pharmacologist's finding.[41]

With respect to increased neoplasm incidences in ovary and mammary gland in high-dose female rats, the results are not conclusive. The pharmacology reviewer noted that although "the trend test [for ovaries] was close to reaching statistical significance, no pairwise comparison was found significant."[42] The incidence of mammary adenocarcinoma was increased in high dose female rats but was within the historical background range of 9.4 to 38.3 percent and considered "an incidental finding by the sponsor."[43] The statistical reviewer's assessment is generally consistent with this finding, and the reviewer found that the incidence of mammary adenocarcinoma was *potentially* statistically significant in high dose female rats.[44] Regarding the pituitary, testes, and skin of male rats, the pharmacology reviewer found that "a few neoplasias were observed at low incidence and/or with unclear dose-relatedness," and the effects on these organs were "[o]f uncertain toxicological importance."[45]

To the extent the findings raised concerns about the carcinogenic potential of Hetlioz, they are adequately reflected in the labeling as required by regulation. The applicable regulations governing the Nonclinical Toxicology section of the labeling states:

> This subsection must state whether long term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If results from reproduction studies or other data in animals raise concern about mutagenesis or impairment of fertility in either males or females, this must be described. Any precautionary statement on these topics must include practical, relevant advice to the prescriber on the significance of these animal findings. Human data suggesting that the drug may be carcinogenic or mutagenic, or suggesting that it impairs fertility, as described in the "Warnings and Precautions" section, must not be included in this subsection of the labeling.[46]

Section 13.1 of the approved labeling states:

> Tasimelteon was administered orally for up to two years to mice (30, 100, and 300 mg/[kilogram]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

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[40] Supervisory Pharmacologist Review at 4.

[41] Pharmacology/Toxicology Review at 111, 180 (referring to the FDA biostatistical evaluation and the Executive CAC conclusions that the only statistically significant drug-related neoplasm involved endometrial adenocarcinomas in the uterus).

[42] Id. at 89.

[43] Id. at 90.

[44] Id. (see Table 3).

[45] Id.

[46] 21 CFR 201.57(c)(14).

> times the recommended human dose (RHD) of 20 mg/day, on a mg/m^2 basis. 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 RHD on a mg/m^2 basis.[47]

3. Target Organ Toxicity and Adverse Effects on Reproduction

You list a number of target organs of Hetlioz toxicity and suggest that target organ toxicity is inadequately addressed in Hetlioz's approved labeling (Petition at 8-9). However, you leave out one of the pharmacology reviewer's key conclusions, which is that the effect doses were many times the recommended human dose. As noted by the pharmacology reviewer:

> The no adverse effect levels for the general toxicity studies were within the clinical range; however, effect doses were approximately 20 times the recommended human dose (RHD) of 20 mg on a mg/m^2 basis.[48]

Pivotal toxicology studies are intended to characterize the safety profile of a drug product.[49] The toxicities observed in the pivotal studies of Hetlioz are either not serious or occurred in animals at a dose or plasma exposure that provided an acceptable safety margin. Such toxicities are typically not described in labeling because of their lack of relevance to clinical use of the drug.[50]

You further claim that the pharmacology reviewer found that "the carcinogenic and reproductive effects are considerable," and "should be fully disclosed in the labeling" (Petition at 10). As explained previously in Section II.B.2 of this letter, the carcinogenicity findings are fully disclosed in the labeling. With respect to reproductive effects, the labeling also accurately describes the reproductive and development study findings. Section 13.1 states:

> 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 RHD on a mg/m^2 basis.[51]

Section 8.1 of the labeling states:

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[47] Hetlioz labeling, 13 NONCLINICAL TOXICOLOGY, 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility.

[48] Pharmacology/Toxicology Review at 5.

[49] See M3(R2) Guidance at 3-5.

[50] Only "[s]ignificant animal data necessary for safe and effective use of the drug in humans that is not incorporated in other sections of labeling" must be included in section 13.2 Animal toxicology and/or pharmacology (21 CFR 201.57(c)(14)(ii)). None of the toxicities observed in the general toxicology studies of Hetlioz, other than those included in other sections of labeling, warranted inclusion in section 13.2.

[51] Hetlioz labeling, 13 NONCLINICAL TOXICOLOGY, 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility.

> There are no adequate and well-controlled studies of HETLIOZ in pregnant women. In animal studies, administration of tasimelteon during pregnancy resulted in developmental toxicity (embryofetal mortality, neurobehavioral impairment, and decreased growth and development in offspring) at doses greater than those used clinically. HETLIOZ should be used during pregnancy only if the potential benefit justifies the potential risks.
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> 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 recommended human dose (RHD) of 20 mg/day, on a mg/m^2 basis.
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> 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 not associated with adverse effects (30 mg/kg/day) is approximately 30 times the RHD on a mg/m^2 basis.[52]

You further claim that the labeling for Hetlioz stresses findings of adverse effects on fertility and reproduction only at the high doses despite the pharmacology reviewer's findings, which include drug-related slight delays in development and decreased fetal body weights at mid-dose and high-dose in rats and rabbits, and increase in abortions at high-dose and slightly increased late resorptions at mid-dose and high-dose in rabbits (Petition at 9).

Although the pharmacology reviewer found that drug-related slight delays in development and decreased fetal body weight were observed at mid-dose and high-dose in rats and rabbits, the reviewer also noted that "[t]he no-adverse-effect doses in rats and rabbits were approximately 25 and 30 times the [recommended human dose] on a mg/m^2 basis."[53] Moreover, the supervisory pharmacologist did not reach the same conclusion as the pharmacology reviewer and found that only the rabbit study indicated "embryolethality, reduced fetal body weight, and delayed fetal development."[54]

The supervisory pharmacology review noted that "[t]hese findings are consistent with a Pregnancy Category C, as recommended by the sponsor and [the pharmacology reviewer]. It is of note, however, that these findings were primarily observed at the highest doses tested, with the highest no effect doses generally providing substantial safety margins for humans based on plasma levels of parent compound and metabolites M9, M12, and M13 in rat or body surface area (mg/m2) comparisons for rabbit."[55]

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[52] Hetlioz labeling, 8 USE IN SPECIFIC POPULATIONS, 8.1 Pregnancy.

[53] Pharmacology/Toxicology Review at 5.

[54] Supervisory Pharmacologist Review at 3.

[55] Supervisory Pharmacologist Review at 3-4. On December 3, 2014, the Agency published the final rule, "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling" (79 FR 72063). This rule is commonly referred to as the pregnancy and lacation labeling rule (PLLR). The rule (21 CFR 201) requires, in part, the removal of the pregnancy categories A, B, C, D, and X from all drug product labeling. Prescription drugs and biologic products submitted after June 30, 2015, will use the new

4. Conclusion of the Pharmacology Review

Finally, you contend that the labeling does not list many findings of concern to the pharmacology reviewer including tumors in the liver, uterus, and uterine cervix, the altered cyclicity observed in female rats and suggested in female monkeys (and potential effects on fertility in humans), and the persistent effects on growth of offspring exposed during gestation and lactation (Petition at 10). We disagree. These findings are documented in the approved labeling.[56]

For all of the reasons stated above, your request to revise the Carcinogenesis, Mutagenesis, Impairment of Fertility, and the Pregnancy sections of the labeling to include certain risk information contained in the pharmacology review is denied.

C. Medication Guide and "Dear Doctor" Letter Are Unnecessary

Because your request that we revise the INDICATIONS AND USAGE, Carcinogenesis, Mutagenesis, Impairment of Fertility, and Pregnancy sections of the labeling for Hetlioz is denied, your request that FDA require distribution of a medication guide to patients concerning the narrower indication requested in your Petition and the drug's risks is denied. Likewise, your request that FDA ask the applicant to send a "Dear Doctor" letter to physicians and health care providers describing the narrower indication requested in your Petition is denied.

D. The Study Population for the Clinical Studies was Adequate and Additional Postmarketing Studies are Unnecessary

You state that FDA's clinical reviewer listed the following adverse effects that occurred in at least three subjects with Non-24 in the tasimelteon group with at least a twofold increase in frequency over the placebo group: abnormal dreams/nightmares, sleep disorder, headache, increased alanine aminotransferase levels, upper respiratory tract infection, urinary tract infection, cardiac conduction disorder, and somnolence (Petition at 11). You contend that because of the small size of the clinical trials, it cannot be determined whether these adverse events are true safety signals and that long-term postmarketing safety trials with a larger study population are necessary (Petition at 11).

We continue to believe that the safety of Hetlioz was appropriately evaluated and the drug is safe and effective for its labeled indication. Safety data from 22 clinical studies were used to assess

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format as described in the final rule immediately, while labeling for prescription drugs approved on or after June 30, 2001, will be phased in gradually. Because Hetlioz was approved before publication of the PLLR, the review memorandum still references Pregnancy Category C.

[56] Hetlioz labeling, 13 NONCLINICAL TOXICOLOGY, 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility (describing the incidence of liver tumors in male and female rats, tumors of the uterus (endometrial adenocarcinoma), and uterus and cervix (squamous cell carcinoma), and estrus cycle destruction); see also 8 USE IN SPECIFIC POPULATIONS, 8.1 Pregnancy (explaining that in animal studies, administration of tasimelteon during pregnancy resulted in developmental toxicity including decreased growth and development in offspring).

the safety of the drug product.[57] The 22 studies include 14 Phase I studies, 2 Phase II studies and 6 Phase III studies. A total of 1,346 subjects received at least one dose of tasimelteon during the course of all 22 clinical studies.[58] Based on the review of these data the clinical reviewer recommended approval of Hetlioz and found that "[t]here are no major safety issues associated with the use of tasimelteon in the submitted safety database, which includes subjects with Non-24 Disorder" and that "[t]he clinical benefit outweighs the risks in subjects with Non-24 Hour Disorder."[59] Additionally, FDA's Peripheral and Central Nervous System Advisory Committee (Advisory Committee) voted 11 to 0 that the safety data were "compelling."[60] The Advisory Committee also voted 11 to 0 that the safety profile of tasimelteon in Non-24 was adequately addressed.[61] Although Advisory Committee recommendations are not binding on the Agency, the committee's unanimous view "that the safety profile of tasimelton in Non-24 was adequately addressed" further supports the Agency's determination that Hetlioz is safe and effective for its labeled indication.[62] As set forth below, we disagree with your assertion that the population size of the clinical studies was too small and that additional postmarketing studies are necessary.

1. Study Population

You state that the clinical studies supporting approval of Hetlioz, in particular Study 3204 and 3202, are inadequate because the studies would have:

> . . . enrolled a total of only 340 subjects between them, raising considerable doubts over the power of the studies to detect all potential adverse effects from long-term tasimelteon therapy, especially more serious, but perhaps less common, side effects.

(Petition at 6).

A rare disease, such as Non-24, is defined under the FD&C Act to include a disease or condition that affects less than 200,000 persons in the United States.[63] Because of the small population of affected patients, sponsors of orphan drugs face unique challenges in developing their clinical programs. Such challenges, however, do "not create a statutory standard for the approval of orphan drugs that is different from the standard for approval of drugs for common conditions."[64]

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[57] FDA, May 31, 2013, Reference ID 3415078, Medical Review, at 65, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205677Orig1s000MedR.pdf.

[58] Id. at 67.

[59] Id. at 10.

[60] FDA, January 23, 2014, Reference ID: 3440713, Summary Review for Regulatory Action (Summary Review), at 7, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205677Orig1s000SumR.pdf.

[61] Id.

[62] Id.

[63] 21 USC 360bb(a)(2).

[64] See the FDA revised draft guidance for industry *Rare Diseases: Common Issues in Drug Development* (February 2019) (Rare Diseases), at 3, available on the FDA Drugs guidance web page. When final, this guidance will represent the FDA's current thinking on this topic.

"Approval of any drug – for either a rare or a common disease or condition – must be based on substantial evidence of the drug's effectiveness for its intended use and sufficient information to conclude that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling."[65] However, regulations governing drug approval provide some flexibility. As set forth in regulation, "FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards."[66] The Rare Diseases draft guidance also states that "a smaller number of patients may be acceptable when the intended treatment population is small."[67]

FDA, in its scientific judgment, found the study populations to be adequate. As explained by the clinical reviewer:

> The safety exposures at the proposed marketing dose do not meet the minimum ICH E1 guideline of 100 subject exposures for ≥ 1 year and 300 subject exposures for ≥ 6 months for medicines intended for long-term treatment of non-life threatening conditions. The Applicant estimates prevalence of subjects with Non-24 Hour Disorder to be about 100,000 in the United States based on extrapolation from published literature. However, during drug development the Applicant stated that most of [sic] subjects who have this condition were unaware that they have it and that there was low awareness of this condition among healthcare providers, and noted difficulty in recruiting a reasonable number of patients to enroll in clinical studies. The Applicant also began a comprehensive outreach effort to identify and recruit totally blind patients with [Non-24] to a patient registry. For these reasons, the size of the safety database is not unreasonable.[68]

Clinical studies with small population sizes may not be able to detect all possible adverse effects associated with a drug, and there is no statutory requirement to identify all potential adverse effects prior to a drug product's approval. The Agency appropriately exercised its scientific judgment in determining that the size of the study population was sufficient to meet the statutory standard for approval. Moreover, FDA maintains a system of postmarketing surveillance and risk assessment programs to identify adverse events that may not appear during the drug approval process. FDA monitors adverse events and uses this information to take regulatory action, such as requiring drug labeling changes, when such action is warranted.

2. Postmarketing Studies

You state that because of the small study populations for the clinical studies, an additional postmarketing safety trial that uses a larger study population than Studies 3202 and 3204 should

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[65] Id.

[66] 21 CFR 314.105(c).

[67] Rare Diseases at 15. This is consistent with the ICH final guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* (March 1995), available on the FDA Drugs guidance web page.

[68] Medical Review at 70-71.

be conducted (Petition at 11). We disagree with your claim that an additional postmarketing study with a larger number of totally blind study subjects is necessary. You express concern about accurately ascertaining the causal relationship between tasimelteon and adverse events identified by FDA's clinical reviewer, and state that it is "impossible to determine" if the following are "true safety signals or chance findings": abnormal dreams/nightmares, sleep disorder, headache, increased alanine aminotransferase levels, upper respiratory tract infection, urinary tract infection, cardiac conduction disorder, and somnolence (Petition at 11). Almost all of these events are already listed in tasimelteon's labeling and there has been no postmarketing safety signal that would suggest that a postmarketing safety study is necessary for any further assessment.[69] If there are any serious but currently unknown risks associated with tasimelteon, such risks would be expected to be identified through postmarketing surveillance.

III. CONCLUSION

Based upon our review of all of the available evidence, we believe that the approved indication for "the treatment of Non-24-Hour Sleep-Wake Disorder" is appropriate. Accordingly, your request that FDA require revisions to the indication to narrow the indicated population to totally blind individuals is denied. We also continue to believe that Hetlioz's benefits outweigh its risks for its approved indications and that its risks are adequately addressed in the current labeling. Accordingly, we deny your request that FDA require revisions to labeling sections 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) and 8.1 (Pregnancy) of Hetlioz's approved labeling. We also deny your request that FDA require the distribution of a medication guide to patients and require the applicant to send a "Dear Doctor" letter to physicians and health care providers. We further deny your request that FDA require the applicant to conduct additional postmarketing clinical studies to obtain additional safety data on Hetlioz. As with all FDA-approved drug products, FDA will continue to monitor and review available safety information related to Hetlioz throughout the drug product's life cycle.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[69] Hetlioz labeling, 5 WARNINGS AND PRECAUTIONS and 6 ADVERSE REACTIONS. The exception is "cardiac conduction disorder," which was not included in the labeling. Although cardiac-related adverse events or adverse changes in ECG were found in the tasimelteon group compared to the placebo group, the medical reviewer found no clear discernable safety signal. Medical Review at 125-131.