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June 21, 2024

Re: Docket No. FDA-2023-P-1273

Dear Mr. Kahlon:

This letter responds to your citizen petition received by the Food and Drug Administration (FDA or Agency) on April 3, 2023 (Petition), concerning Wakix (pitolisant hydrochloride) oral tablets, equivalent to (EQ) 4.45 milligrams (mg) and 17.8 mg, approved under new drug application (NDA) 211150. The Petition requests that the Agency take the following actions:

(1) Withdraw approval of Wakix for all current and future indications;

(2) Issue Dear Healthcare Provider (DHCP) Letters to alert prescribers to the safety risks set forth in the Petition; and

(3) Transition Wakix to a compassionate use program in conjunction with risk evaluation and mitigation strategy (REMS) monitoring.

(Petition at 5.) You also state that it may be helpful to convene an advisory committee to discuss the report published by the Petitioner on March 28, 2023 (Petition Attachment A) and actions requested in the Petition. (Id.)

FDA has carefully considered the information submitted in the Petition, other data available to the Agency, and relevant published literature. Based on our review of these materials, and for the reasons stated below, the Petition is denied.

I. BACKGROUND

A. Wakix (Pitolisant Hydrochloride)

On August 14, 2019, FDA approved NDA 211150 for Wakix (pitolisant hydrochloride) oral tablets, 4.45 milligrams (mg) and 17.8 mg, for the treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy, and Wakix was approved for the treatment of cataplexy

in adult patients with narcolepsy in October 2020.[1] On June 21, 2024, FDA approved an efficacy supplement, NDA 211150-s005, to expand the indicated population for the treatment of EDS to include patients 6 years of age and older with narcolepsy.

Relevant to the requests in the Petition, Wakix's labeling includes the following:[2]

- Warnings and Precautions regarding "QT Interval Prolongation," which includes a warning that Wakix should be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval (5.1)

- Drug interaction information with drugs known to prolong the QT interval (5.1)(7.1)(12.3)

- Information regarding the risk of QT prolongation in patients with hepatic or renal impairment as it relates to higher concentrations of Wakix (2.2, 2.3)(5.1)(8.6, 8.7)

- Information regarding dosage recommendations for concomitant use with strong CYP2D6 inhibitors and strong CYP3A4 inducers (2.4) and information regarding use in patients who are known CYP2D6 poor metabolizers (2.5)(8.8)

- Information advising healthcare professionals that Wakix is not recommended in patients with end-stage renal disease (ESRD) (2.3)(5.1)(8.7)

- Contraindication to use in patients with severe hepatic impairment (2.2)(4)(5.1)

- Information about adverse events observed in the postmarketing period, including epilepsy (6.2)

- Guidance for use in Specific Populations (5.1)(8.6, 8.7, 8.8)

- Information regarding the clinical studies upon which approval was based (14)

- Patient counseling information regarding QT Interval (17)

[1] Wakix Supplemental Approval letter, October 2020, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/211150Orig2s000ltr.pdf.
[2] Wakix Prescribing Information, revised December 2022 (Wakix 2022 Prescribing Information), available at www.accessdata.fda.gov/drugsatfda_docs/label/2022/211150s003lbl.pdf.

B. Regulatory Framework

1. Approval Standard

FDA's regulation of drugs is governed by the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301, et seq.) and the Agency's implementing regulations (codified in Title 21 of the Code of Federal Regulations (CFR)). The FD&C Act makes it unlawful to market a new drug product without first obtaining approval of an NDA or abbreviated new drug application (ANDA).[3] Before approving an application, FDA must determine that the drug is both safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling.[4]

The statutory standard for determining whether a new drug is effective is "substantial evidence" derived from "adequate and well-controlled investigations" conducted by qualified experts, from which those experts could fairly and responsibly conclude that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling.[5] With respect to safety, applicants must provide evidence from "adequate tests by all methods reasonably applicable to show whether or not such drug is safe" under the proposed conditions of use.[6]

When analyzing whether a drug meets the standard for approval, FDA conducts a benefit-risk assessment.[7] The benefit-risk assessment:

> is a case-specific determination that requires a thorough assessment of the extensive evidence of safety and effectiveness submitted by a sponsor in an NDA or BLA, as well as a thorough understanding of the data gaps. It also requires careful consideration of a complex set of factors, including the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks.[8]

FDA will only approve an application if the Agency concludes that the drug product's benefit-risk profile is shown to be favorable under the conditions of use proposed in the application.[9] FDA must deny marketing approval if, among other reasons, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have, the results of safety testing fail to show that the drug is safe, or, on the basis of any other information before

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[3] See section 505(a) of the FD&C Act (21 U.S.C. 355(a)); see also section 301(d) of the FD&C Act (21 U.S.C. 331(d)) (prohibiting the marketing of any article in violation of section 505).
[4] See section 505(c)(1) and (d) of the FD&C Act.
[5] Section 505(d) of the FD&C Act. The characteristics of adequate and well-controlled studies are set forth in FDA regulations at 21 CFR 314.126.
[6] Section 505(d)(1) of the FD&C Act; 21 CFR 314.125(b)(2).
[7] *Benefit-Risk Assessment for New Drug and Biological Products, Guidance for Industry* (Oct. 2023), available at https://www.fda.gov/media/152544/download.
[8] *Benefit-Risk Assessment for New Drug and Biological Products, Guidance for Industry* (Oct. 2023) at 4, available at https://www.fda.gov/media/152544/download.
[9] Section 505(d) of the FD&C Act.

the Agency, there is insufficient evidence to determine whether the drug is safe for use under the conditions prescribed, recommended, or suggested in the labeling.[10]

2. Postmarketing Safety or Effectiveness Information

After an approved drug enters the marketplace, FDA may become aware of new or updated information regarding the drug product's safety or effectiveness, which could affect FDA's assessment of the drug product's risk-benefit profile. The goal of postmarket safety surveillance is to identify and prevent or mitigate emerging safety concerns before they can cause significant harm to patients. FDA considers a broad range of new information relevant to safety relating to a drug's potential serious risks or signals of serious risks (safety signals), including data from adverse event reports, clinical trials, postapproval studies, peer reviewed biomedical literature, and any other scientific data deemed appropriate by FDA. Based on this information, FDA may take action, including regulatory action, as appropriate.

FDA has the authority to require that the applicant take certain actions to address postmarketing safety concerns. Under section 505-1 of the FD&C Act, FDA can require a drug to have a Risk Evaluation and Mitigation Strategy REMS, which consists of certain elements beyond the approved labeling to ensure that the product's benefits outweigh its risks. If certain conditions are met, FDA can require an applicant to implement a REMS based on new safety information that FDA becomes aware of postmarket.[11] Certain REMS include requirements that an applicant notify healthcare providers and other entities of safety information about the product.[12]

In other circumstances, FDA, or the applicant, manufacturer, or distributor of the drug, may elect to send letters, often known as "Dear Healthcare Provider" (DHCP) or "Dear Doctor" letters, to alert physicians and other health care providers about important new or updated information about a drug. FDA has issued guidance providing recommendations on the content and format of DHCP letters.[13]

If, based on the available information, FDA determines that the drug is no longer shown to be safe, or no longer shown to be effective, under its approved conditions of use, FDA may determine it is appropriate to initiate procedures to withdraw approval of the application. Section 505(e)(1)-(2) of the FD&C Act provides for FDA to withdraw approval of an application if FDA finds, after notice and opportunity for a hearing, "that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved," or that:

> new evidence of clinical experience, not contained in such application or not available to [FDA] until after the application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved,

[10] Sections 505(d)(2), (d)(4), and (d)(5) of the FD&C Act.
[11] See sections 505-1(a)(2) and (b)(3) of the FD&C Act.
[12] See, e.g., section 505-1(e)(3) of the FD&C Act.
[13] See the Agency's guidance for industry and FDA staff *Dear Health Care Provider Letters: Improving Communication of Important Safety Information* (January 2014). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

> evaluated together with the evidence available to [FDA] when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved[.]

II. DISCUSSION

The Petition argues that the requested actions are warranted because pitolisant "poses a grave danger to patients" and was approved based "entirely on low-quality foreign clinical trials with numerous methodological red flags" (Petition at 1).[14] With respect to safety, the Petition asserts, among other things, that pitolisant causes cardiotoxicity, arrhythmia, and sudden death due to the pitolisant's effects of QT prolongation (Petition at 1-4). Additionally, the Petition asserts that notations in CDER's pitolisant review regarding sudden deaths, cardiovascular and respiratory adverse reactions, seizures, and convulsions indicate that pitolisant is not safe (Id. at 3-4).

With respect to effectiveness, in addition to citing "methodological red flags," including use of the Epworth Sleepiness Scale (ESS) in the clinical trials upon which approval was based, the Petition contends, among other things, that the mechanism of action of pitolisant has been "discredit[ed]" (Petition at 4). According to the Petition, reliance on the clinical trials upon which pitolisant's approval was based was flawed for a variety of reasons, including because sites in foreign jurisdictions were used (Petition at 4).

Below, we respond to the Petition's assertions that Wakix is not safe and effective for the conditions of use described in the original NDA, the treatment of EDS and cataplexy in adults with narcolepsy, and we explain why the information in the Petition does not change FDA's conclusion that this NDA met the approval standard. As noted above, on June 21, 2024, FDA approved the efficacy supplemental NDA 211150-s005 to expand the indicated population for the treatment of EDS to include patients 6 years of age and older with narcolepsy. Although the Petition addresses the conditions of use described in the original NDA, we also considered whether any of the information provided in the Petition affects FDA's conclusions about safety and effectiveness of Wakix under the conditions of use described in the sNDA. We have concluded that none of the information in the Petition changes FDA's determination that the

[14] The Petition also includes arguments about the cost of the drug; the fact that the drug is not indicated as a "cure" for narcolepsy, but rather to treat EDS and cataplexy; that pitolisant is "inferior" to another drug that the Petition says is standard of care; and pitolisant "is merely prescribed as a third- or fourth-line add-on to other drugs," and seems to suggest that these factors should have led FDA to conclude that Wakix does not have a favorable benefit-risk profile (Petition at 1). We disagree. FDA's guidance, *Benefit-Risk Assessment for New Drug and Biological Products* (October 2023), describes certain considerations for FDA's assessments of whether the benefits of a drug outweigh its risks under the conditions of use proposed in an application. As described in FDA's clinical review underlying the original NDA for Wakix, FDA considerations that were relevant to FDA's benefit-risk assessment of Wakix for the conditions of use in the original NDA include positive results on endpoints assessing EDS and cataplexy in two adequate and well-controlled studies in subjects with narcolepsy, occurrence of few serious adverse events in the narcolepsy development program, negligible abuse liability potential, lack of association with cardiovascular adverse events in the narcolepsy population, and ability to mitigate identified risks through labeling. Based on these and other factors, FDA determined that the benefits of Wakix outweigh its risks.

sNDA meets the approval standard.[15]

A. The Petitioner's Arguments Do Not Change FDA's Conclusion that Pitolisant is Safe Under Its Approved Conditions of Use

The Petition asserts that "pitolisant's flagrant cardiotoxicity and QT profile" present serious safety risks to its patient population, which the Petition characterizes as "vulnerable and prone to numerous co-morbidities such as obesity, diabetes, hypertension, and other markers of cardiovascular risk" (Petition at 1-2). We interpret the Petition's contentions about cardiotoxicity to refer to risk of QT prolongation and related arrhythmias. We reviewed the premarketing safety database containing data from clinical trials with pitolisant using a customized adverse event (AE) query for QT prolongation/torsades de pointes (TdP) and available electrocardiograms (ECGs).[16] We also undertook a comprehensive review of the arguments and support provided in and with the Petition, including review of postmarket safety data in the FDA Adverse Event Reporting System, the applicant's periodic safety reports, and the scientific literature. Based on this review, we have concluded that pitolisant's labeling adequately addresses risks associated with QT prolongation and arrhythmias.

It is well-recognized that pitolisant prolongs the QTc interval in a concentration-dependent manner via predominant human ether-a-go-go-related gene (hERG) channel blockade. Pitolisant concentrations may be further increased by taking concomitant medications that inhibit CYP2D6 or if the patient is a poor CYP2D6 metabolizer. However, our review of available data does not indicate that increases in pitolisant concentrations under these conditions substantially increase the risk for cardiac arrhythmias.[17]

Because induction of QTc interval prolongation by non-cardiac drugs was well-known prior to Wakix's approval, Wakix's sponsor conducted appropriate assessments for QTc risk in its nonclinical and clinical development program.[18] Following such assessments, pitolisant's effect on QTc prolongation has been appropriately characterized, and the labeling of Wakix adequately addresses the risk of QTc prolongation. Specifically, in addition to the warnings and precautions

[15] For example, your arguments about the active moiety that are not indication-specific, such as those related to pitolisant's effects of QTc interval prolongation (Petition at 1-4), do not change FDA's determination about the safety and effectiveness of Wakix for any of its approved indications for the reasons explained in this response.

[16] The overall percentages of AEs reported in more than one subject treated with pitolisant were all very low, i.e., <1% each: electrocardiogram QT prolonged and presyncope (n=7 each), syncope (n=4), mild, nonserious arrhythmia (n=3), and electrocardiogram repolarization abnormality (n=2). Three AEs were serious AEs (SAEs): electrocardiogram QT prolonged, sudden death, and death. Both subjects who died did not have QTc prolongation reported prior to their deaths and died in an open-label study or period. Two additional sudden deaths not included in the main dataset occurred during an open-label extension. For one of these subjects, ECG results were normal except for an ST depression that was not clinically significant. For the other subject, the narrative did not include any ECG findings. Of the 9 pitolisant-treated subjects with ECG findings reported as AEs, none had an elevated ECG parameter measurement that was >60 msec from baseline or >500 msec which would represent values consistent with a potential significant risk of AEs.

[17] In addition to the AE query described above, FDA reviewed QT-prolongation data from 22 studies, including 4 placebo-controlled phase 3 narcolepsy studies.

[18] See, e.g., the guidances for industry *S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals* (October 2005) and *E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential--Questions and Answers* (August 2022).

for QTc interval prolongation, the labeling also contains, among other things, dose adjustments related to situations such as CYP2D6 metabolizer status and hepatic or renal impairment, drug-drug interactions, and a contraindication related to hepatic impairment causing an increase in WAKIX exposure.[19]

The Petitioner asserts that "Wakix is a regrettable repeat of the Seldane (terfenadine) saga, another histamine receptor antagonist," approved in 1985, "which the FDA forced off the market in 1997 and which is the poster child for drug-induced cardiotoxicity via QT prolongation and fatal arrhythmias" (Petition at 2). Unlike Wakix, approval of Seldane predated existing scientific knowledge that non-cardiac drugs can induce QTc interval prolongation and cause TdP.[20] As a result, there was no premarket evaluation of terfenadine's risk for QTc prolongation and TdP. In vitro studies conducted after the approval of Seldane found that it is a potent blocker of the cardiac ion channel encoded by the human ether-a-go-go-related gene (hERG) that is responsible for the rapidly activating delayed rectifier potassium current (IKr) and therefore associated with increased risk of QTc prolongation and TdP. In addition, in patients who took both terfenadine and ketoconazole (a CCYP2D6 inhibitor), terfenadine concentrations, which are typically undetectable in blood, substantially increased to levels that are proarrhythmic.[21] By contrast, studies show that when pitolisant concentrations are increased (e.g., in patients who take concomitant medications that inhibit CYP2D6, such as ketoconazole, or who are poor CYP2D6 metabolizers), the risk for cardiac arrhythmias does not rise substantially.[22] Thus, the Petition's comparison of pitolisant to terfenadine is misguided.

We also note that, while the cardiovascular risk factors identified in the Petition including "obesity, diabetes, [and] hypertension" (Petition at 2) are associated with increased risk for atherosclerotic cardiovascular disease,[23] they are not known to increase the risk for QTc prolongation/TdP. Outlier analysis of heart rate and blood pressure measurements do not show a significant difference between pitolisant-treated and placebo-treated subjects in the double-blind phase 3 narcolepsy trials. Analysis of vital signs over time do not show a pattern of increased blood pressure or heart rate in pitolisant-treated subjects in the double-blind studies or the open-label phase 3 narcolepsy study. The premarketing safety database does not contain sufficient information from which conclusions can be drawn regarding the risk of pitolisant among those

[19] See FDA's draft guidance for industry QTc Information in Human Prescription Drug and Biological Product Labeling (August 2023). When final, this guidance will represent the FDA's current thinking on this topic.
[20] Roden DM, 2016, Predicting Drug-Induced QT Prolongation and Torsades de Pointes, J Physiol, 594(9):2459-2468.
[21] Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, and Cantilena LR Jr, 1990, Torsades de Pointes Occurring in Association With Terfenadine Use, JAMA, 264(21):2788-2790; Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, and Cantilena LR, 1993, Terfenadine-Ketoconazole Interaction. Pharmacokinetic and Electrocardiographic Consequences, JAMA, 269(12):1513-1518.
[22] The increase in pitolisant concentrations with concomitant use of medications that inhibit CYP2D6, and the mitigation of this risk through pitolisant dose reduction, are addressed in the approved labeling.
[23] Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, and Tomaselli GF, 2014, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Circulation, 129(25 Suppl 2):S49-73.

with the cardiovascular risk factors identified by the Petitioner, but the evidence available from this database does not identify risks that change FDA's benefit-risk assessment.

We also disagree with the Petition's assertion that notations in CDER's review for the original NDA regarding sudden deaths, cardiovascular and respiratory adverse reactions, seizures, and convulsions indicate that pitolisant is not safe (Petition at 3).[24] Our review of the fatal cases in the premarketing safety database, including the eight the Petition classified as sudden deaths, does not support the Petition's assertion about cardiotoxicity for pitolisant.[25] Further, review of other cardiovascular adverse events did not reveal a consistent and clear causal association with pitolisant exposure. Similarly, the few reports of respiratory adverse events in the premarketing database were insufficient to support a conclusion that the events were related to pitolisant. Finally, there were no premarketing reports of seizure in subjects with narcolepsy and no signal for new-onset seizures in the Wakix clinical development program. Although increased seizure frequency was reported for several subjects in open-label studies, most of these seizures occurred in a study for the treatment of treatment-refractory epilepsy. Given the high potential for seizures attributable to refractory epilepsy, the study results are highly vulnerable to confounding and provide little insight into the cause of such seizures.

The Petition and the March 28 Report also include assertions related to pitolisant and hepatotoxicity, hypereosinophilia, phospholipidosis, pharmacokinetic (PK) study data, and study conduct or reporting (Petition at 3. 8). After a thorough review of these contentions and examination of the related evidence, we find that the allegations related to hepatotoxicity,[26]

[24] The Petition's contentions that data in the review is vulnerable to criticisms of "cherry-picking less vulnerable patients via exclusion criteria for cardiovascular, hepatic, or renal disorders" (Petition at 3) is not supported by a review of cases, which show a history of risk factors for cardiac adverse events (e.g., hypertension, type II diabetes mellitus, metabolic syndrome, chronic obstructive pulmonary disease, obesity, atrial fibrillation, heart failure, and smoking).

[25] We consider six of the eight deaths that the Petition labels "sudden deaths" (which includes those previously discussed) as potentially cardiotoxicity related; however, given that all six subjects had confounding medical conditions (e.g., hypertension, metabolic syndrome) and none had abnormal QTcF intervals while on pitolisant, there was insufficient information to determine whether the events were associated with pitolisant. Five of the six deaths occurred during open-label treatment periods without placebo comparator. Of the two other deaths, one subject appears to have been on placebo, not pitolisant, and for the other subject the death was considered a suicide (by overdose of multiple medications; given that subject's confounding medical history (i.e., schizophrenia, depression, prior suicide attempts), there was insufficient information to determine whether the event was related to pitolisant.

[26] The studies described in the Petition and the March 28 Report do not reveal an association between pitolisant and hepatotoxicity (Petition at 3; 9; March 28 Report at 40, 41, 105, 106, 107, 161). You state that "Bioprojet decided to prematurely halt the study," but Study 09-10 was not terminated early.

hyperosinophilia,[27] phospholipidosis,[28] PK study data,[29] and study conduct or reporting[30] are not supported by available evidence and do not warrant the requested actions.

B. Nothing in the Petition Changes FDA's Conclusion that There is Substantial Evidence of Effectiveness of Pitolisant for its Approved Conditions of Use

The Petition asserts that pitolisant's mechanism of action has been "discredit[ed]" (Petition at 4). In support of this contention, the Petition notes that pitolisant is a histamine receptor antagonist and points to a 2012 paper by Bioprojet that "unequivocally disproves any association between histamine levels and hypersomnia conditions such as narcolepsy, excessive daytime sleepiness, cataplexy, and others" (Petition at 4). Approval of the original NDA for Wakix relied upon adequate and well-controlled investigations to establish the drug's effectiveness for the treatment of EDS and cataplexy in adults with narcolepsy using clinical endpoints that reflect patient benefit.[31,32] Although narcolepsy type 1 appears to generally involve deficiencies in hypocretin/orexin signaling at a high level, the specific pathophysiologies of EDS and cataplexy in narcolepsy are not well understood, and, like many drugs approved to treat conditions in patients with narcolepsy, the mechanism of action of pitolisant is unclear. However, mechanistic evidence of pitolisant's treatment effect was not necessary to establish effectiveness under the application's proposed conditions of use. Contrary to assertions made in the Petition (Petition at 4), irrespective of uncertainty about pitolisant's mechanism of action, the approved application for Wakix provided substantial evidence of effectiveness based on statistically significant

[27] The March 28 Report does not accurately characterize the European Medicines Agency (EMA) safety review report (March 28 Report at 163). Contrary to the assertion in the March 28 Report, the EMA's safety review does not reveal a "safety signal absent in the FDA review" (Id. at 163).

[28] The Petition and the March 28 Report refer to a risk of phospholipidosis (Petition at 8; March 28 Report at 170-172.) Although, due to the chemical nature of pitolisant as a cationic amphiphilic drug, there is a potential risk for induction of phospholipidosis, the nonclinical studies included in the Wakix NDA did not reveal a definitive finding of phospholipidosis. Furthermore, phospholipidosis is typically not considered an adverse finding in the absence of associated histopathological findings such as degeneration or inflammation and with no apparent toxicological effects on cellular function, as was the case with the Wakix NDA.

[29] With respect to PK data, the March 28 Report states that the "claim of 90% oral bioavailability/absorption in the package insert [for Wakix] is simply false" (March 28 Report at 307). However, oral absorption, which the package insert reports to be 90%, is distinct from bioavailability. We also find no basis for the argument in the March 28 Report that "the 2007 pilot study" "conceal[ed] the danger of elevated and variable plasma levels" of pitolisant (March 28 Report at 39, 122). In Study P05-03, referenced in the March 28 Report, the subjects with elevated plasma levels were not the same five subjects excluded from the sample and appear to have been included in the plasma level average calculation (March 28 Report at 39, 122).

[30] We do not agree with any of the assertions in the March 28 Report regarding study conduct or reporting. For example, you erroneously assert that "the Harmony 1 pivotal trial didn't even conduct ECG's on treatment groups – just a baseline ECG" (March 28 Report at 111); however, Study P07-03 conducted electrocardiograms at baseline, Visit 7, and/or early termination. Additionally, you erroneously assert that certain study data were not submitted to FDA in the Wakix NDA (March 28 Report at 111, 112, 143, 144); in the instances that you identify, the data were submitted, and FDA considered them before approving the NDA.

[31] See FDA guidance for industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) (explaining that, as relevant here, "[t]he Agency accepts clinical endpoints that reflect patient benefits (i.e., how patients feel, function, or survive) . . . as the basis for traditional approval").

[32] Similarly, the efficacy supplement, NDA 211150-s005, relied upon adequate and well-controlled investigations with clinical endpoints to reflect patient benefit to establish the drug's effectiveness for the treatment of EDS in patients 6 years of age and older with narcolepsy.

treatment effect on clinically meaningful endpoints in adequate and well-controlled clinical trials.[33]

We also disagree with the Petition's argument about the integrity of the clinical trials on which approval of the original Wakix NDA was based.[34] Specifically, the Petition asserts that such clinical trials were "flaw[ed]" because they "were primarily conducted in questionable foreign jurisdictions." (Petition at 4). According to the Petition, certain "foreign trials" are susceptible to "fraud and integrity issues" (Petition at 4; March 28 Report at 233, 237). However, the Petition does not support these allegations. The Petition and the March 28, 2023, Report do not include, and we are not aware of, evidence of trial misconduct that would affect the results of the studies. Moreover, the clinical study reports (CSRs) for studies P07-03, P09-15, and P11-05 all state that the studies were conducted in accordance with the Declaration of Helsinki, ICH guidelines for Good Clinical Practice, and following European Medicines Agency or local directives. Per the CSRs, the studies were approved by the independent ethics committees or institutional review boards (IRBs) of the participating centers and relevant competent authority in each country. Studies P09-15 and P11-05 included independent Safety Data Monitoring Committees. Additionally, FDA conducted inspections at three study sites. Those inspections did not raise concerns about the conduct of the studies or about the quality of the data generated by these sites.

The Petition also points to perceived flaws in the ESS to question the demonstration of effectiveness in the original NDA (Petition at 4). The Petition and the March 28, 2023, Report reference literature publications raising concerns regarding the psychometric qualities of the ESS (Petition at 4; March 28 Report at 215-219). During FDA's review of the NDA, FDA acknowledged that the ESS has limitations, but noted that it has been used previously in clinical trials for similar indications. Specifically, the ESS has been used to support the effectiveness of drugs for EDS in narcolepsy and idiopathic hypersomnia and other sleep-related conditions. The Wakix NDA provided appropriate justification for use of the ESS to assess the effectiveness of pitolisant for EDS in narcolepsy. Additionally, the treatment benefit demonstrated on the ESS was supported by positive results from objective EDS endpoints (i.e., the Maintenance of Wakefulness Test (MWT)).

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[33] The March 28 Report asserts concerns about the interpretability of cataplexy endpoints regarding whether the size of placebo response or the onset to treatment effect observed in the studies undermined the results (March 28 Report at 238). The March 28 Report also questions the reliability of the definition of cataplexy in the protocol and the statistical analysis of cataplexy data. However, these claims are not scientifically supported. Although a placebo response occurred, pitolisant did statistically separate from placebo. Additionally, there is no reason to infer that the rapidity of the response somehow indicates a questionable or suspect response (particularly as the pathophysiology of disease is not well understood and the mechanism of action of pitolisant is unknown), and the separation from placebo generally appears to be maintained over the treatment duration and is consistent with a durable treatment effect. The protocol included a definition of cataplexy that appears consistent with the ICSD-2 definition as per the CSR. Furthermore, the Agency's statistical review included a comprehensive evaluation of the analyses used to support the cataplexy indication.

[34] In addition to arguments regarding the conduct of trials in foreign jurisdictions and use of the ESS, the March 28 Report makes assertions related to other alleged flaws in the trials used to support the NDA, such as: the use of "ancient" trials (March 28 Report at 210); "cherry-picking" trials (Id. at 213; 215); "unreasonably short" trial durations (Id. at 215; 226); "fuzzy inclusion criteria" (Id. at 215); a "huge placebo effect" (Id. at 215, 221, 241); use of flexible dosing (Id. at 216, 227, 241); concomitant medication allowance (Id. at 216, 225); and "statistical tricks and obfuscations" (Id. at 216, 228, 241). These assertions are not supported by available evidence or do not warrant the requested actions (or both).

Finally, the Petition places a disproportionate amount of weight on pitolisant's status as an unscheduled substance, citing that as one of two reasons it was approved (Petition at 1, 5, 9). In conducting its benefit-risk assessment, FDA's practice is to consider, among other things, whether the drug represents a specific important advantage over available therapies.[35] The fact that pitolisant is an unscheduled substance was relevant to FDA's benefit-risk assessment to the extent that, as noted in the NDA clinical review, in contrast to the approved treatments for EDS and cataplexy in adults with narcolepsy, pitolisant has shown negligible potential for abuse. However, this was not determinative, as the Petition seems to suggest; it was just one of the factors bearing on FDA's benefit-risk assessment.

C. Requested Actions

As set forth above, the Petition requests the following actions: (1) withdraw approval of Wakix for all current and future indications; (2) issue DHCP letters to alert prescribers to the safety risks set forth in the Petition; and (3) transition Wakix to a compassionate use program in conjunction with REMS monitoring. The Petition also states that it may be helpful for FDA to convene an advisory committee to discuss the March 28, 2023 Report and actions requested in the Petition (Petition at 5). For the reasons that follow, FDA denies each of these requests.

1. "Withdraw Approval of Pitolisant for All Current and Future Indications"

We interpret this request to be for FDA to initiate the process of withdrawing the approved applications for Wakix. We deny this request because, as discussed above, the drug has been shown to be safe and effective under its approved conditions of use, including for the approved indications; the arguments in the Petition do not change this conclusion.

Further, FDA declines to commit to withdrawing approval of "future indications," or to determine that it will not approve any future application for pitolisant.

Each application filed with the Agency is judged on its own merits; FDA reviews each application to determine whether the drug product meets the approval standard under the conditions prescribed, recommended, or suggested in the proposed labeling.[36] Accordingly, even if FDA were to agree with the Petition's arguments about safety and effectiveness of Wakix for its currently approved conditions of use, that would not necessarily have any bearing on whether a different application for pitolisant, relying on different data and information, or proposing different conditions of use, would meet the approval standard.[37]

[35] *See* FDA Guidance for Industry, Benefit-Risk Assessment for New Drug and Biological Products (Oct. 2023) at 4.
[36] See section 505(d) of the FD&C Act.
[37] As noted above, before FDA approved NDA 211150-s005, we considered whether any of the arguments in this Petition affected FDA's analysis about the safety and effectiveness of pitolisant for the conditions of use described in that application and concluded that they do not.

2. Require Applicant to "Distribute An Immediate Alert to all Wakix Prescribers in the Form of a [DHCP]"

Your Petition requests that FDA require the sponsor to issue a DHCP letter, "specifically an Important Drug Warning Letter per section IV(a) of the FDA's DHCL industry guidance, when safety information 'concerns a significant hazard to human health.'" (Petition at 5). As explained in the guidance document referenced in your Petition, a DCHP letter "is used to notify health care providers about new or updated information about a drug," often as the "the information relates to an important safety concern that could affect the decision to use a drug or require some change in behavior by health care providers, patients, or caregivers to reduce the potential for harm from a drug."[38] As discussed above, FDA has determined that the approved labeling for Wakix includes sufficient information about warnings, contraindications, and other conditions of use to ensure that the drug can be used safely and effectively. The Agency is not aware of new or updated information, such as safety concerns that could affect decision making about prescribing or use of the drug, that would be appropriate to communicate to practitioners in a DHCP letter. Accordingly, we deny this request.

3. "Transition Wakix to a Compassionate Use Program in Conjunction with a REMS Protocol for Current Patients Who Stay on Wakix."

We understand your Petition to request that FDA withdraw approval of pitolisant and make it available only through expanded access as described in FDA's regulations at 21 CFR Part 312, Subpart I. Expanded access refers to the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. Because, as discussed above, FDA denies your request to withdraw approval of pitolisant's approved indications, and because the indications are not investigational, we do not address the issue of expanded access to pitolisant.

Because we deny your request to "[t]ransition Wakix to a compassionate use program," we need not address your request to do so "in conjunction with a REMS protocol for current patients who stay on Wakix" (Petition at 5). However, to the extent that you are requesting that FDA require a REMS for Wakix independent of your requests regarding withdrawal of approval and "compassionate use," FDA also denies that request. As discussed above, at the time of approval, FDA determined that Wakix has a favorable benefit-risk profile under its approved conditions of use, and your Petition did not provide information that changes that assessment.[39] Thus, based on information currently available, a REMS is not needed to ensure that the benefits of Wakix outweigh its risks.

4. Advisory Committee

In addition to the three requested actions above, the Petition includes a suggestion that "it may be helpful for the FDA to convene an Ad Comm to discuss the issues raised in the attached report as

[38] See FDA Guidance for Industry, Dear Health Care Provider Letters: Improving Communication of Important Safety Information (Jan. 2014) at 3.
[39] See section 505-1(a)(2) of the FD&C Act.

well as the actions requested in this Citizen Petition" (Petition at 5). Under certain circumstances, FDA may convene an advisory committee composed of experts from outside the Agency to provide the Agency with independent advice and recommendations on scientific and technical matters related to the development and evaluation of regulated drug products. FDA disagrees that convening an advisory committee is warranted here. As noted in the Petition, FDA's NDA approval letter stated that the "application for Wakix was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a drug in the intended population" (Id.). The Petition states that this is concerning because of "the known toxicity risks within the histamine antagonist class, and in particular the well-documented 40-year history of toxicity and lack of efficacy in the H3 receptor antagonist/inverse agonist class specifically" (Id.).

FDA addressed the Petition's arguments about safety and effectiveness of drug products containing pitolisant above. For the reasons summarized above, FDA declines to convene an advisory committee.

III. CONCLUSION

For the reasons described above, the Petition is denied. FDA will continue to monitor and review available safety information related to pitolisant and take any further action as appropriate.

Sincerely,

Douglas C. Throckmorton -S

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Patrizia Cavazzoni, M.D.
Director
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