CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211150Orig2s000

SUMMARY REVIEW

Joint Supervisory Memo

From	Bernard Fischer, MD, Deputy Director (Acting)/Cross-Discipline Team Leader, Division of Psychiatry (DP) Tiffany R. Farchione, MD, Director (Acting), DP
Subject	Joint Supervisory Memo
NDA/BLA # and Supplement#	NDA 211150; Class 1 resubmission
Applicant	Harmony Biosciences
Date of Submission	08/13/2020
PDUFA Goal Date	10/13/2020
Proprietary Name (code name)	Wakix
Established or Proper Name	Pitolisant
Dosage Form(s) and strengths	Film-coated tablets: 4.45 mg, 17.8 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of cataplexy in adult patients with narcolepsy
Applicant Proposed Dosing Regimen(s)	17.8 to 35.6 mg (two 17.8 mg tablets) once daily
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s)	Treatment of cataplexy in adult patients with narcolepsy
Recommended Dosing Regimen(s)	17.8 mg or 35.6 mg once daily

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

The Applicant submitted pitolisant, a histamine-3 inverse agonist, for the treatment of excessive daytime sleepiness (EDS) and cataplexy in patients with narcolepsy in 2019. The EDS indication was approved, but the Applicant received a Complete Response (CR) for the cataplexy indication. The current submission addresses the deficiencies identified in the CR letter.

Cataplexy is an abrupt involuntary loss of muscle tone, typically triggered by strong emotions. It is a prominent symptom of the condition and defines type 1 narcolepsy. Although the severity of cataplexy is variable, it can be frightening and usually causes additional disability. Sodium oxybate, the only drug FDA-approved treatment for cataplexy, has significant limitations. It is a central nervous system depressant, which has been abused to incapacitate victims for assault. Additionally, it can cause respiratory depression and (unusual for a CNS depressant) can lower the seizure threshold. It is only available through a restricted-access Risk Evaluation and Mitigation Strategy (REMS) program.

The Applicant submitted two studies supporting the cataplexy indication: HARMONY CTP and HARMONY I (neither of which included U.S. data). HARMONY CTP (P11-05) was an adequate and well-controlled study demonstrating a statistically significant and clinically meaningful change from baseline in the weekly rate of cataplexy compared to placebo ($p < 0.0001$). In HARMONY I, 80% of enrolled patients had a history of cataplexy and the daily rate of cataplexy was a secondary endpoint. However, the Applicant did not control for type I error for the cataplexy secondary endpoint, the definition of the cataplexy subgroup was made post hoc, and the study's positive cataplexy results depended on how missing data were handled. Given these statistical issues, HARMONY I initially was not considered to be a well-controlled study in support of the cataplexy indication. Thus, with only one adequate and well-controlled study for the cataplexy indication, and no U.S. data, we believed the data fell short of substantial evidence for the cataplexy indication.

After a post-action Type A meeting with the Applicant, the Agency agreed to a cataplexy NDA resubmission including the following HARMONY I supportive data:

- The Applicant tested their results using several type 1 error controls (including the conservative Bonferroni method) and the results were significant regardless of which method was used.

- The Applicant presented all possible clinically-relevant definitions of the cataplexy subgroup (full analysis set, cataplexy experienced at baseline, cataplexy experienced during the whole trial, cataplexy experience reported in the past) and found that the cataplexy results remained statistically significant.

- The Applicant noted that the original statistical analysis plan (November 2010) proposed analysis of cataplexy using a Poisson regression. However, because of human error, the cataplexy data was analyzed using a t-test. The Applicant made the case that, had the originally-planned Poisson regression been used, the results would not have depended on how missing data were handled.

As reviewed for the original submission, pitolisant is generally well-tolerated. There were few serious adverse events in the short-term narcolepsy trials and none occurred in more than one subject. The most common non-serious adverse events in patients with narcolepsy were headache, insomnia, and nausea with risk differences (versus placebo) of 4%, 4%, and 3%, respectively. This resubmission included a narcolepsy safety update—from the U.S. Expanded Access Program, the European Union Compassionate Use Program, an ongoing European post-authorization study (P15-11), and the ongoing U.S. pediatric study (P11-06)—as well as a safety update from non-narcolepsy programs (Prader-Willi syndrome and obstructive sleep apnea). Based on the Agency review of this data, no new, unlabeled safety signals were identified with the exception of hypersensitivity reactions (anaphylaxis).

Based on the information submitted, we have concluded that the benefits of pitolisant outweigh its risks for the treatment of cataplexy in adult patients with narcolepsy. Pitolisant's adverse event profile—particularly the lack of significant cardiovascular effects or abuse potential—offers a potential safety advantage over other available treatments. The label will be modified to add the cataplexy indication (along with the adverse reaction profile for this indication) and hypersensitivity reactions.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	•Narcolepsy is associated with a range of symptoms including excessive daytime sleepiness (EDS), cataplexy, hallucinations, nighttime sleep fragmentation, and sleep paralysis. •Individuals with narcolepsy have higher rates of depression, anxiety, excessive weight gain, other sleep disorders, and accidents •Symptoms of narcolepsy are frequently disabling	Cataplexy associated with narcolepsy can negatively impact an individual's physical health, psychological well-being, and quality of life.
Current Treatment Options	•Sodium oxybate is approved for the treatment of cataplexy. Risks associated with sodium oxybate include respiratory depression, central nervous system depression, seizure, and abuse. Sodium oxybate is only available with restricted access through a Risk Evaluation and Mitigation Strategy (REMS) program.	Patients with cataplexy due to narcolepsy would benefit from additional treatment options, particularly treatments with low abuse liability and limited effects on the cardiovascular system. The only available pharmacologic treatment for patients with cataplexy is highly restricted because of the risks of life-threatening adverse events and diversion/abuse.
Benefit	Based on the re-submitted analyses, the Applicant conducted two adequate and well-controlled clinical trials to evaluate pitolisant's effect on cataplexy: •HARMONY CTP (P11-05) demonstrated a statistically significant and clinically meaningful reduction in the weekly rate of cataplexy in the pitolisant group as compared to placebo ($p < 0.0001$). •A subgroup analysis of HARMONY I, which included	Considering the Applicant's supportive analyses, two adequate and well-controlled clinical trials demonstrated pitolisant's efficacy on cataplexy in patients with narcolepsy. In both studies, the response to pitolisant was clinically meaningful Therefore, there is substantial evidence of effectiveness to approve pitolisant for the indication of treatment of cataplexy in adult patients with narcolepsy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients with cataplexy reported in the past, demonstrated a statistically significant and clinically meaningful reduction in the daily rate of cataplexy in the pitolisant group as compared to placebo ($p < 0.003$).	
Risk and Risk Management	• Serious adverse events were uncommon in the development program and did not appear to be drug-related. Pitolisant has been available for 4.5 years in the European market and for 1 year in the United States. A safety update submitted with this package appeared consistent with the safety information from the clinical trials (evaluated with the initial NDA). Newly-observed hypersensitivity reactions were described. • There is still limited data available about pitolisant effects on pregnancy and lactation. Two additional cases of pregnancy with pitolisant exposure occurred since approval. In both cases, the patient discontinued pitolisant upon discovering the pregnancy. In one, the pregnancy was uncomplicated; in the other, there was spontaneous fetal demise at 19 weeks.	Although limited data about the long-term safety and efficacy are available, the open-label, long-term safety study and reports of adverse reactions in the postmarketing period have not identified unexpected, concerning safety signals. Additional studies to evaluate the effects on pregnancy and lactation have been required. Identified risks can be mitigated through labeling. Labeling will include the treatment-emergent adverse events that occurred most frequently in placebo-controlled trials for cataplexy and hypersensitivity reactions will be added.

2. Product Quality

No changes to product quality with this submission.

3. Nonclinical; Pharmacology/Toxicology

No new nonclinical data with this submission.

4. Clinical Pharmacology

No new pharmacology data with this submission.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical Efficacy

The primary clinical reviewer was Martine Solages; the secondary reviewer was team leader (and CDTL) Bernard Fischer. The primary biometrics reviewer was Semhar Ogbagaber and the secondary reviewer was team leader Peiling Yang.

The Applicant submitted two studies for the cataplexy indication: HARMONY I and HARMONY CTP (Table 1). Both of the studies submitted to support the cataplexy indication had a 3-week dose-adjustment phase during which pitolisant (and modafinil in HARMONY I) could be titrated based on efficacy and tolerability. Both studies also included a 1-week withdrawal phase during which all patients received placebo.

Table 1. Submitted Phase 3 Pitolisant Narcolepsy Studies for Cataplexy

Study Name	Subjects	Description	Dose	Endpoints
HARMONY I P07-03	≥ 18 years old with narcolepsy ± cataplexy N=94 History of cataplexy: 25 pitolisant 27 modafinil 24 placebo	Randomized, double-blind, placebo- and modafinil-controlled 2-week washout 1-week baseline 3-week titration phase 5-week stable dose 1-week withdrawal	Starting: placebo modafinil 100 mg pitolisant 8.9 mg Range: pitolisant 8.9 mg to 35.6 mg modafinil 100 mg to 400 mg	Primary: ESS at Week 8 Secondary: Daily cataplexy rate MWT SART CGI-C

Study Name	Subjects	Description	Dose	Endpoints
HARMONY CTP P11-05	≥ 18 years old with narcolepsy ≥ 3 cataplexy attacks/week N = 106	Randomized, double-blind, placebo-controlled 1-week washout 2-week baseline 3-week titration phase 4-week stable dose 1-week withdrawal	Starting: placebo pitolisant 4.45mg Range: pitolisant 4.45 mg to 35.6 mg	Primary: Weekly rate of cataplexy attacks during 4-week stable dose period Secondary: ESS MWT

Source: Reviewer-generated
CGI-C=Clinical Global Impression of Change; ESS=Epworth Sleepiness Scale; MWT=Maintenance of Wakefulness Test; SART=Sustained Attention to Response Task

Patients who had been taking stable doses of purportedly anti-cataplectic medications (including sodium oxybate, selective serotonin reuptake inhibitors, norepinephrine reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors) for at least 1 month prior to the trial and nonetheless met the inclusion and exclusion criteria could enroll and continue on the concomitant medication.

Demographics and baseline characteristics from HARMONY I and HARMONY CTP are presented in Table 2 and Table 3, respectively.

Table 2. HARMONY I Demographics and Baseline Characteristics

	Pitolisant (n= 31)	Placebo (n = 30)	Modafinil (n = 33)
Sex			
Male, n (%)	20 (65%)	13 (43%)	18 (55%)
Female, n (%)	11 (36%)	17 (57%)	15 (46%)
Age			
Mean, years (SD)	35.7 (14.6)	41.3 (14.8)	39.2 (14.6)
Minimum, maximum; years	19, 65	19, 75	18, 65
Race			
White, n (%)	29 (94%)	28 (93%)	32 (97%)
Black, n (%)	2 (7%)	2 (7%)	1 (3%)
Asian, n (%)	0	0	0
Baseline Characteristics			
Duration of narcolepsy, median years	11.1	15.2	12.2
Daily cataplexy rate, geometric mean	0.5	0.4	0.4
Sleep paralysis, n (%)	15 (48%)	15 (50%)	22 (67%)
Hallucinations, n (%)	18 (58%)	19 (63%)	21 (64%)
Baseline ESS, mean (SD)	17.8 (2.5)	18.9 (2.5)	18.5 (2.7)
Taking concomitant anticataplexy medication,[a] n (%)	13 (42%)	10 (33%)	11 (33%)

[a]Including antidepressants taken for anticataplexy activity and sodium oxybate
Source: Reviewer-generated

Table 3. HARMONY CTP Demographics and Baseline Characteristics.

	Pitolisant (n= 54)	Placebo (n = 51)
Sex		
Male, n (%)	26 (48%)	27 (53%)
Female, n (%)	28 (52%)	24 (47%)
Age		
Mean years (SD)	35.8 (12.1)	38.5 (12.9)
Minimum, maximum years	18, 64	18, 66
Race	Not Reported	Not Reported
Baseline Characteristics		
Number of weekly cataplexy episodes, mean (SD)	11.0 (8.9)	9.2 (8.8)
Sleep Paralysis, n (%)	32 (59%)	32 (63%)
Hallucinations, n (%)	36 (67%)	32 (63%)
Baseline ESS, mean (SD)	17.3 (3.3)	17.1 (3.4)
Taking concomitant anticataplexy medication,[a] n (%)	1 (2%)	5 (10%)

[a]Including antidepressants taken for anticataplexy activity and sodium oxybate
Source: Reviewer-generated

Based on the statistical analysis plan for HARMONY I (which used the Poisson regression and did not depend on how missing data were handled), the secondary endpoint of change in daily cataplexy rate was significantly different from placebo regardless of which cataplexy subgroup was chosen. The Division recommended the subgroup with *any* past history of cataplexy as this would present a higher bar for demonstrating an effect. At baseline, 9 patients in the placebo group and 13 patients in the pitolisant group had cataplexy so severe that they were allowed to stay on their anti-cataplectic medication during the study. The CGI-Severity of Cataplexy baseline means for the patients who reported a history of cataplexy were 3.7 ± 1.5 for the placebo group and 4.2 ± 1.3 for the pitolisant group. These data appear to suggest that the pitolisant group had more severe cataplexy at baseline. Despite this potential imbalance in severity between the two groups, the pitolisant group demonstrated a placebo-corrected improvement in the rate ratio (RR) for daily rates of cataplexy of 0.068 (95% CI: 0.013, 0.36; p=0.003). This result survived multiple procedures to control for type I error. Therefore, although a procedure to control for type I error was not prespecified, the Agency confirmed and accepts the statistical significance of the result.

The primary efficacy for HARMONY CTP's anticataplectic activity was assessed by the change in the average number of cataplexy attacks per week (weekly rate of cataplexy) between the 2 weeks of baseline (Day -14 to Day 0) and 4 weeks of the stable treatment period (Day 21 to Day 49). The Applicant's analysis showed that the pitolisant group had a significantly reduced risk of cataplectic events compared to the placebo group (RR = 0.51; 95% CI: 0.4, 0.6; $p < 0.0001$). The Agency confirmed this analysis. This result translated to a decrease in weekly cataplexy rates of 75% for the pitolisant group compared to a decrease of 38% in the placebo group. There was no difference in results by sex.

7. Safety

The primary clinical reviewer was Martine Solages; the secondary reviewer was Team Leader (and CDTL) Bernard Fischer.
The adverse event data from the cataplexy indication was reviewed with the original submission. This resubmission included a safety update from the U.S. Expanded Access Program, the European Union Compassionate Use Program, an ongoing European post-authorization study (P15-11), the ongoing U.S. pediatric study (P11-06), and a safety update from non-narcolepsy programs (Prader-Willi syndrome and obstructive sleep apnea). There were no new, unlabeled safety signals revealed in the updated safety data with the exception of hypersensitivity reactions. Hypersensitivity reactions will be added to the label.

8. Advisory Committee Meeting

This section is not applicable to this application.

9. Pediatrics

The Applicant is conducting a randomized, double-blind, placebo-controlled study to evaluate the effect of pitolisant on EDS and cataplexy in patients aged 6 to 18 years (Study P11-06).

10. Other Relevant Regulatory Issues

There were three pregnancies reported in the updated safety information. In one, the patient discovered she was pregnant prior to taking pitolisant and did not have exposure. In both of the remaining cases, the patient discontinued pitolisant upon discovering the pregnancy. In one, the pregnancy was uncomplicated; in the other, there was spontaneous fetal demise at 19 weeks. Pregnancy and lactation studies were required with the initial Wakix approval and are ongoing.

11. Labeling

The Agency added the efficacy and safety information related to the cataplexy indication as well as information on hypersensitivity.

12. Postmarketing Recommendations

No new commitments or requirements are suggested.

13. Recommended Comments to the Applicant

None.

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/s/

BERNARD A FISCHER
10/13/2020 04:49:33 PM
CDTL

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10/13/2020 04:51:18 PM

Joint Supervisory Memo

Date	8/14/2019
From	Bernard Fischer, MD, Cross-Discipline Team Leader, Division of Psychiatry Products (DPP) Tiffany R. Farchione, MD, Director (Acting), DPP Ellis Unger, MD, Director, Office of Drug Evaluation I
Subject	Joint Supervisory Memo
NDA/BLA # and Supplement#	NDA 211150
Applicant	Bioprojet Pharma
Date of Submission	12/14/2018
PDUFA Goal Date	08/14/2019
Proprietary Name (code name)	Wakix (BF2.649)
Established or Proper Name	Pitolisant
Dosage Form(s) and strengths	Film-coated tablets: 4.44 mg, 17.8 mg
Applicant Proposed Indication(s)/Population(s)	O-1: Treatment of excessive daytime sleepiness in adult patients with narcolepsy O-2: Treatment of cataplexy in adult patients with narcolepsy
Applicant Proposed Dosing Regimen(s)	35.6 mg (two 17.8 mg tablets) once daily
Recommendation on Regulatory Action	O-1: Approve O-2: Complete Response
Recommended Indication(s)/Population(s)	Treatment of excessive daytime sleepiness associated with narcolepsy
Recommended Dosing Regimen(s)	17.8 mg or 35.6 mg once daily

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Pitolisant is a new molecular entity intended for the treatment of excessive daytime sleepiness (EDS) and cataplexy in patients with narcolepsy, an orphan indication. It is a histamine-3 receptor inverse agonist available as a tablet in strengths of 4.45 and 17.8 mg. The European Medicines Agency authorized pitolisant for the treatment of narcolepsy with or without cataplexy in 2016, but it has never been approved for use in the United States.

EDS is a defining feature of narcolepsy. Although sleepiness secondary to insufficient sleep occurs in healthy individuals, the EDS occurring in narcolepsy is more severe and poses significant burdens on patients: Patients with narcolepsy report that EDS is the symptom with the most significant impact on their daily function. Potential consequences of EDS include reduced attention, cognitive impairment, compromised performance on psychomotor tasks, accidents, decreased productivity, interference with social and occupational activities, and an overall decreased quality of life. Existing treatments for EDS are largely stimulant-based and are limited because of abuse potential, short duration of action, development of tolerance to their wakefulness-promoting effects, and possible adverse cardiovascular effects. Given the significant impact of EDS on the lives of patients with narcolepsy—and the limitations of available medications—there is a need for additional treatment options.

Cataplexy is an abrupt involuntary loss of muscle tone, typically triggered by strong emotions. It is a prominent symptom of the condition and defines type 1 narcolepsy. Although the severity of cataplexy is variable, it can be frightening and usually causes additional disability. Sodium oxybate, the only drug FDA-approved treatment for cataplexy, has significant limitations. It is a central nervous system depressant, which has been abused to incapacitate victims for assault. Additionally, it can cause respiratory depression and (unusual for a CNS depressant) can lower the seizure threshold. It is only available through a restricted-access Risk Evaluation and Mitigation Strategy (REMS) program.

The Applicant conducted their development program in Europe/South America and no U.S. patients were enrolled in their studies. Two randomized, double-blind, 8-week, placebo-controlled trials (HARMONY I and HARMONY I-bis) demonstrated pitolisant's effect on EDS in adult patients with narcolepsy. The primary endpoint in both studies was the Epworth Sleepiness Scale (ESS). The ESS assesses self-reported propensity to fall asleep in eight, hypothetical situations. For each situation, scores range from 0 (no chance of dozing) to 3 (high chance of dozing; total maximum score of 24). Severity cut-offs from published literature are:

0 to 5, Lower Normal Daytime Sleepiness
6 to 10, Higher Normal Daytime Sleepiness
11 to 12, Mild Excessive Daytime Sleepiness
13 to 15, Moderate Excessive Daytime Sleepiness
16 to 24, Severe Excessive Daytime Sleepiness

Currently, this scale has fallen out of favor with the Agency because it requires patients to assess a hypothetical situation with which they may or may not have had experience. However, the endpoint was accepted for this application based on a discussion with the Division of Psychiatry Products (DPP).

In Study 1 (HARMONY I; P07-03), the mean difference in change-from-baseline between the pitolisant and placebo groups was -3.1 points (95% CI: -5.73, -0.46; p = 0.02). In Study 2 (HARMONY I-bis; P09-15), the mean difference in change-from-baseline between the pitolisant and placebo groups was -2.2 points (95% CI: -4.17, -0.22; p = 0.03). The Applicant also conducted a responder analysis, defining a response as a score of ≤ 10 at the end of the study or improvement by 3 or more units. Based on this definition, the treatment responses in the two studies (respectively) were 45 and 65% in the pitolisant groups and 13 to 35% in the placebo groups. Given the mean baseline ESS score of approximately 18 in both studies, these results are equivalent to decreasing EDS from severe to moderate. A decrease of 3 points would also decrease EDS from moderate to mild.

The Applicant submitted HARMONY CTP (P11-05) for the indication of cataplexy in narcolepsy, with support from HARMONY I. HARMONY I was an adequate and well-controlled study for the indication of EDS in narcolepsy and, because 80% of its patients had a history of cataplexy and because the daily rate of cataplexy was assessed as a secondary endpoint, HARMONY I was submitted as a substantiating study for cataplexy. Importantly, however, the Type-I error rate was not controlled for the cataplexy secondary endpoint and the study's positive results depended on how missing data were handled. Given these statistical issues, HARMONY I was not considered to be a well-controlled study in support of the cataplexy indication. At least two adequate and well-controlled studies are generally required to support approval of an indication. In some cases, as noted in FDA guidance (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products), a single study may support approval; this is not such a case. Although HARMONY CTP (P11-05) was an adequate and well-controlled study, it lacked the characteristics that, per Agency Guidance, might support reliance on a single study. This was a small study, conducted solely in Eastern Europe, where ethnicity and race were not reported. The generalizability of these data to a more diverse U.S. population is unknown. Thus, with only one adequate and well-controlled study for the cataplexy indication, and no U.S. data, we believe the data fall short of substantial evidence for cataplexy.

Based on a small-to-moderately-sized safety database of patients with narcolepsy, pitolisant does not appear to cause serious or irreversible harm. There were few serious adverse events in the short-term narcolepsy trials and none occurred in more than one subject. The most

common non-serious adverse events in patients with narcolepsy were headache, insomnia, and nausea with risk differences (versus placebo) of 4%, 4%, and 3%, respectively. Although some animals exposed to pitolisant developed convulsions, there was no clinical correlate. Patients who received pitolisant did not appear to be at higher risk for adverse cardiovascular outcomes or changes in vital signs. At the recommended doses, pitolisant does not prolong the QT interval. However, patients with moderate liver impairment, patients with moderate-to-severe kidney impairment, and patients taking medications that affect the metabolism of pitolisant may achieve higher blood pitolisant concentrations and a greater risk of QT prolongation. Dosage adjustments for these patients will be described in labeling. Because of the risk of QT prolongation with higher exposures, pitolisant should be contraindicated in patients with severe liver impairment. Laboratory assessments and body weight measurements were comparable in patients receiving pitolisant and patients receiving placebo. Although patients treated with pitolisant did not have higher rates of depression (based on adverse event reports and depression screening questionnaires), pitolisant was associated with a higher rate of psychiatric adverse events (e.g., anxiety, hallucinations, irritability) overall.

An open-label, long-term safety study followed patients on pitolisant for up to 5 years (HARMONY III). A postmarketing observation study in Europe is ongoing and will follow patients for up to 5 years. The adverse event profiles in these long-term studies, and in the European postmarketing databases, are similar to the adverse event profile observed during the short-term clinical trials. Of note, fewer than 100 patients with narcolepsy have received the proposed highest recommended dose of pitolisant (35.6 mg). However, narcolepsy is an orphan indication and there was no clear association between dose and adverse events is evident from the narcolepsy clinical trials.

In contrast to currently approved narcolepsy treatments, pitolisant has shown no potential for abuse and the Agency's Controlled Substances Staff (CSS) does not recommended that the Drug Enforcement Administration (DEA) schedule the drug. Limited data on the impact of pitolisant on pregnancy and lactation are available; the review team suggests postmarketing requirements to study these areas.

Overall, pitolisant's benefit-risk profile is positive. On average, for every three patients treated, one patient can be expected to improve by 3 units on the ESS; e.g., from severe to moderate daytime sleepiness or from moderate to mild daytime sleepiness. This is clinically meaningful. Based on a safety database of 62 patients treated at the to-be-marketed dose for 12 months, no serious adverse events appeared to be causally related to the drug. Using the rule-of-three, with no drug-related serious adverse events reported in a sample size of 62 patients treated with 35.6 mg pitolisant daily through 12 months, the upper limit of the 95% CI for the risk of a serious adverse event is 1/[62/3) or 5%. Pitolisant's adverse event profile—particularly the lack of significant cardiovascular effects or abuse potential—offers a potential safety advantage over other available treatments. Although long-term safety and efficacy data for the highest recommended dose are limited, European long-term safety studies and postmarketing data from the last 3 years have not uncovered unexpected safety signals. Pitolisant will be approved to treat EDS in adult patients with narcolepsy, but for the aforementioned reasons, the drug will not receive the cataplexy claim.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	•Narcolepsy is associated with a range of symptoms including excessive daytime sleepiness (EDS), cataplexy, hallucinations, nighttime sleep fragmentation, and sleep paralysis. •Individuals with narcolepsy have higher rates of depression, anxiety, excessive weight gain, other sleep disorders, and accidents •Symptoms of narcolepsy are frequently disabling	EDS and cataplexy associated with narcolepsy can negatively impact an individual's physical health, psychological well-being, and quality of life.
Current Treatment Options	•FDA-approved treatments for EDS include amphetamines, methylphenidates, modafinil, and armodafinil. These treatments carry risks of abuse and cardiovascular adverse events. Stevens-Johnson Syndrome, a life-threatening dermatologic condition, has been associated with modafinil and armodafinil. •Sodium oxybate is approved for the treatment of both EDS and cataplexy. Risks associated with sodium oxybate include respiratory depression, central nervous system depression, seizure, and abuse. Sodium oxybate is only available with restricted access through a Risk Evaluation and Mitigation Strategy (REMS) program.	Patients with EDS due to narcolepsy would benefit from additional treatment options, particularly treatments with low abuse liability and limited effects on the cardiovascular system. The only available pharmacologic treatment for patients with cataplexy is highly restricted because of the risks of life-threatening adverse events and diversion/abuse.
Benefit	The Applicant conducted two adequate and well-controlled clinical trials to evaluate pitolisant's effect on excessive daytime sleepiness: •HARMONY I (P07-03) demonstrated a statistically significant effect for pitolisant on the primary endpoint of the Epworth Sleepiness Scale (ESS). The least square	Two adequate and well-controlled clinical trials demonstrated pitolisant's efficacy on EDS related to narcolepsy. In both studies, the response to pitolisant was clinically meaningful and could be associated with a decrease in ESS-determined severity categories (e.g., severe to moderate or moderate to mild). Therefore, there is substantial

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mean at Week 8 on the ESS was 12.4 for pitolisant and 15.5 for placebo, with a statistically significant treatment difference of -3.1 (95% CI -5.73, -0.46; p = 0.02). More patients in the pitolisant group (45%) met criteria for treatment response (ESS score ≤ 10) than in the placebo group (13%). Pitolisant also appeared to have a positive effect on the Maintenance of Wakefulness Test (MWT), an objective measure of sleepiness, although the analysis of this endpoint was not prospectively controlled to account for a false positive result. • In HARMONY I-bis (P09-15), the treatment difference between pitolisant and placebo was -2.2 (95% CI -4.17, -0.22; p = 0.03). Pitolisant-treated patients were more likely to be responders (65%) compared to placebo-treated patients (35%). Only one adequate and well-controlled study evaluated pitolisant's effect on the weekly rate of cataplexy (WRC). • HARMONY CTP (P11-05) demonstrated a statistically significant reduction in WRC in the pitolisant group as compared to placebo. • A subgroup analysis of patients with cataplexy in HARMONY I was also suggestive of a positive effect. However, this subgroup analysis was not prospectively controlled for a false positive result and did not have an adequate sample size to detect an effect in patients with	evidence of effectiveness to approve pitolisant for the indication of treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy. One adequate and well-controlled study found that pitolisant reduced the frequency of cataplexy events in patients with narcolepsy. However, this finding was not substantiated by a second adequate and well-controlled trial. The review team found the totality of the data insufficient to support approval for the cataplexy indication, considering: The absence of confirmatory evidence; the fact that this single positive trial did not enroll any U.S. patients; the patient population was unlikely demographically comparable to the U.S. population (information about race and ethnicity was not collected); and concerns regarding a potential false-positive result (i.e., the consequences of approving an ineffective drug). We believe a second, substantiating trial that enrolls U.S. patients will be required for this indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cataplexy. Additionally, positive findings depended on which method was used for handling missing data. •Pitolisant-treated patients had improved scores on the ESS and MWT in HARMONY CTP. However, analyses of these secondary endpoints were not prospectively controlled to account for a false positive result.	
Risk and Risk Management	•Limited data are available regarding long-term safety and efficacy, particularly at the highest recommended dose. Thus far, 62 patients (including 55 patients with narcolepsy) have been exposed to the 35.6 mg dose for at least 12 months in clinical trials. Serious adverse events were uncommon in the development program and did not appear to be drug-related. No irreversible or untreatable non-serious adverse events were identified. Based on exposure in the clinical trials database and the lack of serious adverse events attributable to pitolisant, the upper limit of the 95% CI for the risk of a serious adverse event is 5%. Pitolisant has been available for 3.5 years in the European market. Vigibase (the World Health Organization global database of individual case safety reports) has received 121 adverse event reports in the postmarketing period. The database has not received any reports of abuse, misuse, withdrawal, dependence or QT interval prolongation. Seizures were not reported as an adverse event in narcolepsy clinical trials but have been reported to the postmarketing databases (two reports). Although there were reports of	Although limited data about the long-term safety and efficacy are available, the open-label, long-term safety study and reports of adverse reactions in the postmarketing period have not identified unexpected, concerning safety signals. Additional studies to evaluate the effects on pregnancy and lactation will be required. Identified risks can be mitigated through labeling. Product labeling should include recommended dosage adjustments for patients with hepatic and renal impairment and patients taking relevant concomitant medications. Labeling should also describe the treatment-emergent adverse events that occurred most frequently in placebo-controlled trials.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	seizures in the non-clinical development program, the clinical data are insufficient to conclude that the seizures were drug-related. The most commonly reported adverse events in the postmarketing databases – insomnia (16 reports), headache (15 reports), and nausea (8 reports) – matched the most common adverse events reported in clinical trials. Reports of psychiatric and cardiovascular adverse events appeared consistent with the safety information from clinical trials. • Limited data are available about the effects on pregnancy and lactation. Pitolisant is likely to be used by women of child-bearing potential, and labeling with reflect this. • Patients with hepatic and renal impairment and patients taking medications that affect pitolisant metabolism are at increased risk of QT interval prolongation. • Adverse events most frequently associated with pitolisant (compared with placebo) include: Headache (18.4% vs. 14.7%), insomnia (5.9% vs. 1.8%), nausea (5.9% vs. 2.6%), upper respiratory tract infection (5.3% vs. 2.6%), musculoskeletal pain (4.6% vs. 2.6%), anxiety (4.6% vs. 1%), increased heart rate/tachycardia (3.3% vs. 0%), hallucinations (3.3% vs. 0%), irritability (3.3% vs. 1.8%), dizziness/light-headedness (3.3% vs. 2.6%), abdominal pain (3.3% vs. 1%), decreased appetite (2.6% vs. 0%), and sleep disturbance (2.6% vs. 1.8%).	

2. Background

Regulatory
Pitolisant is a new molecular entity histamine-3 receptor inverse agonist intended for the treatment of excessive daytime sleepiness (EDS) and cataplexy in patients with narcolepsy.

The Applicant conducted the drug development program entirely outside of the United States (largely in Europe, but some South American sites participated in the clinical trials). The Applicant applied for European Medicines Agency (EMA) Marketing Authorization of pitolisant on May 7, 2014 for the treatment of narcolepsy with or without cataplexy. Marketing Authorization was granted on March 31, 2016.

The Agency granted Orphan Drug designation to pitolisant in March 2010. In April 2018, the Agency granted Fast Track and Breakthrough Therapy designations for the cataplexy indication. For the excessive daytime sleepiness (EDS) indication, the Agency granted Fast Track, but denied a Breakthrough Therapy designation. Rolling review status was granted in June 2018 and the NDA submission was fully received by the Agency in December 2018.

In June 2011, the Division of Neurology Products (DNP) provided written responses to the questions submitted by the Applicant regarding the primary endpoints, the study design, and use of modafinil as an active comparator in the phase 3 studies. DNP noted that the efficacy studies for pitolisant were completed or ongoing at that time and that issues related to the study design would be review issues. DNP advised that efficacy for both EDS and cataplexy should be supported by positive findings in two adequate and well-controlled studies. DNP also noted that an active comparator in the clinical trials was not required.

In May 2015, the Agency provided written responses to questions regarding the adequacy of the Applicant's clinical trial and manufacturing data for filing an NDA. The Agency provided guidance regarding nonclinical, biopharmaceutics, clinical pharmacology, abuse liability studies, and the use of foreign data. The Agency noted that the trial data appeared to support the filing of the NDA, but that the relatively short duration of treatment in the pivotal efficacy studies for a drug expected to be administered chronically would be a review issue.

The Agency also described requirements for the use of foreign data for U.S. approval—including providing a rationale that the assessment and medical care of narcolepsy is the same in the regions where the studies were conducted as in the United States. The Agency referred the applicant to the Final Rule on Foreign Clinical Studies Not Conducted Under and Investigational New Drug Application and the guidance on FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND.

DNP and the Applicant held a pre-NDA meeting on September 7, 2016. DNP again noted that the adequacy of the design and the results from the trials to support safe and efficacious use of pitolisant would be review issues. DNP agreed that the clinical and nonclinical trials were appropriate to support filing of the NDA.

As part of an administrative realignment, the application was transferred from DNP to the Division of Psychiatry Products (DPP) in December 2017.

Pediatric Study Plan
This application was exempt from the Pediatric Research Equity Act (PREA) because of its Orphan designation; however, the Applicant is conducting pediatric studies to satisfy EMA requirements (see Section 9: *Pediatrics*).

Inspections
EMA did not conduct inspections when they authorized pitolisant in 2016. FDA's Office of Scientific Investigation inspected three locations:

- Sites 7 (HARMONY I-bis) and 26 (HARMONY I), Kassel, Germany; Andrea Rodenbeck, MD
- Site 31 (HARMONY I-bis), Buenos Aires, Argentina; Claudio Podesta, MD
- Sites 29 (HARMONY I-bis) and 61 (HARMONY I), Budapest, Hungary; Szakács Zoltán, MD

The inspections raised no concerns regarding data quality or integrity; the data generated by these sites appeared acceptable in support of the application.

3. Product Quality

The product quality review was performed by:
- Drug substance: Raymond Frankewich (primary), Suong Tran (secondary)
- Drug product: Rao Kambhampati (primary), Wendy Wilson-Lee (secondary)
- Process/Facility: Nathan Davis (primary), Rapti Madurawe (secondary)
- Biopharmaceutics: Akm Khairuzzaman (primary), Ta-Chen Wu (secondary)
- Technical lead: David Claffey

Pitolisant hydrochloride is a white-to-near-white, crystalline, water-soluble powder. The drug product is a film-coated, round, biconvex, immediate-release tablet available in two strengths: 4.45 and 17.8 mg. Tablets used in the phase 3 studies were scored, but the proposed commercial tablets are not. Commercial tablets are debossed with an "H" or "S" on one side.

Dosage strengths are expressed in terms of pitolisant free base. Each tablet contains 5 or 20 mg of pitolisant hydrochloride, which is equivalent to 4.45 or 17.8 mg of pitolisant free-base, respectively. The excipients are: (b) (4) microcrystalline cellulose (b) (4) crospovidone (b) (4) talc (b) (4) magnesium stearate, and (b) (4) silicon dioxide (b) (4). A (b) (4) coating is used (b) (4) total tablet weights of 33 and 135 mg and diameters of 3.7 and 7.5 mm, respectively. Tablets are packaged in 30-count bottles.

The drug substance manufacturing process involves (b) (4) However, these are adequately controlled (this assessment was made in consultation with the pharmacology/toxicology review team). The drug product is manufactured (b) (4) Each of the proposed manufacturing and testing sites was found acceptable. Data support the proposed 24-month expiry period at room temperature.

The Quality Review Team recommends approval.

4. Nonclinical; Pharmacology/Toxicology

The primary pharmacology/toxicology reviewer was James Miller; the secondary reviewer was pharmacology supervisor Aisar Atrakchi.

Pitolisant binds with relatively high affinity and selectivity to histamine-3 (H3) receptors (Ki = 1 nM) compared to other histamine receptors (H1, H2, or H4; Ki $\geq$ 10 µM). Pitolisant acts as an inverse-agonist and antagonist at the H3 receptor and, upon binding, causes disinhibition of histaminergic neurons. This results in increased synthesis and release of histamine. In animal models, pitolisant administration caused increased duration of wakefulness with an associated decrease in slow-wave and paradoxical (REM) sleep. In addition to enhanced wakefulness, pitolisant decreased the number of narcoleptic attacks and reduced the total duration of narcolepsy when administered in the narcolepsy mouse model (Orexin-/-). Pitolisant's effects on additional neurotransmitter systems was demonstrated by in vivo microdialysis studies in rodents; pitolisant increased acetylcholine, norepinephrine, and dopamine levels in the prefrontal cortex. However, dopamine levels were not affected in the striatum (including the nucleus accumbens—a brain region known to be associated with abuse potential). In safety pharmacology studies, pitolisant was a moderate hERG channel inhibitor with an IC_{50} of 1.32 µM. However, in studies in rat, rabbit and dog, pitolisant had minimal-to-no effect on QTc intervals and no pro-arrhythmic potential. In telemetered dogs, no QTc effects were observed at up to 14 times the maximum recommended human dose (MRHD) of 35.6 mg (based on C_{max}). In the central nervous system, pitolisant produced slight sedation with pronounced core muscle hypotony. Pitolisant was also proconvulsant after pentylenetetrazol challenge—with mice demonstrating increased spasms and tremors at 4 times MRHD and convulsions at 7 times the MRHD (based on mg/m^2).

Pitolisant is rapidly and efficiently absorbed. However, oral bioavailability is low (~2% in rat and 27% in monkey) due to extensive first-pass metabolism. After oral administration, pitolisant and its metabolites are widely distributed to tissues including the brain. The highest concentrations were measured in liver, kidney, adrenal glands, and pancreas in addition to the gastrointestinal tract organs and tissues. The metabolic profile of pitolisant is complex and species-dependent with humans and monkeys being the most similar. Pitolisant is extensively metabolized primarily by CY2D6 with potential auxiliary metabolism by CYP3A4; only 2% is excreted unchanged. The inactive metabolite BP1.3484 is the major circulating metabolite in both monkey and human. Multiple other circulating metabolites are present and prominent metabolites were recovered in urine. In rats, the major metabolite is BP1.2526, which has low

activity at the H3 receptor and has been demonstrated to cause convulsions in rats when administered intravenously. This metabolite is found at relatively low levels in humans and monkeys.

Single- and repeat-dose toxicity studies were conducted in mice, rats, and monkeys for 1, 6, and 9 months, respectively. The primary target organ of toxicity across all species was the central nervous system; clinical signs included hypoactivity, salivation, staggering gait, tremors, and convulsions. In rats and monkeys, repeated oral administration of pitolisant at 13 times and 3 times the MRHD (based on C_{max}), respectively, produced convulsions in both male and female animals. Convulsions were first observed near T_{max} and usually resolved 2 to 3 hours after administration. Convulsions were not observed after discontinuation of dosing and were not associated with microscopic findings in the brain. Additional target organs of toxicity after oral administration of pitolisant included liver and testes in mice and lung, kidney, and adrenal glands in rats. In general, all adverse findings resolved during recovery except for focal alveolar macrophage infiltration in rats. No other adverse effects were observed in monkeys.

Pitolisant was non-genotoxic in an adequate battery of genotoxicity assays. Pitolisant was not carcinogenic and did not induce tumors in rats or mice at doses up to 4 and 10 times the MRHD (based on mg/m^2).

Pitolisant did not significantly affect mating or fertility indices at doses up to 22 times the MRHD (based on mg/m^2). Pitolisant caused abnormalities in sperm morphology and decreased motility without any significant effect on fertility at doses $\geq$ 13 times the MRHD (based on mg/m^2).

In pregnant rabbits, intramuscular administration of pitolisant during organogenesis caused maternal toxicity, including significant body weight loss and decreased food consumption, at doses greater than the MRHD (based on AUC) and instances of convulsions at 4 times the MRHD (based on AUC). At maternally toxic doses, increased incidence of pre-implantation loss and abortion occurred with a consequent decrease in both the number of implantations and live fetuses. Pitolisant was not teratogenic in rabbits at doses up to 4 times the MRHD (based on AUC). However, delayed skeletal development (incomplete ossification and supernumerary ribs) was observed. The no-observed adverse-effect level for maternal and embryofetal development are 0.7 and 1.4 times the MRHD (based on AUC). In pregnant rats, oral administration of pitolisant during organogenesis caused maternal toxicity including decreased weight gain and food consumption at 22 times the MRHD (based on mg/m^2). No increase in fetal mortality, resorption, or abortions occurred and no apparent fetal toxicity was observed. The no-observed-adverse-effect level for maternal and embryofetal development are 22 and 27 times the MRHD (based on mg/m^2). In the pre- and postnatal developmental toxicity study in the rat, oral administration of pitolisant caused maternal toxicity including mortality, severe central nervous system clinical signs (including convulsions) and a significant decrease in weight gain at 22 times the MRHD (based on mg/m^2). At the maternally toxic doses, fetal toxicity included stillbirths, postnatal pup mortality (due to lack of milk or failure to nurse), and decreased pup length and weight. Pitolisant was teratogenic at 22 times the MRHD (based on mg/m^2), causing major malformations (including cleft palate and abnormal limb flexure). A

delay in postnatal development (decrease weight and length and a delay in incisor eruption and testes descent) occurred at ≥ 13 times the MRHD (based on mg/m^2). The no-observed-adverse-effect level for maternal and developmental toxicity is approximately 7 times the MRHD (based on mg/m^2). After oral administration of ^{14}C-pitolisant, radioactivity is measurable in fetal tissue with peak levels occurring at 30 minutes post-dose. No retention in fetal tissue was observed. Radioactivity was measurable in the milk of lactating rats at concentrations 1 to 3 times higher than measured in plasma.

Because of low systemic exposure to the major human metabolite BP1.8054 in animals, the Applicant conducted separate rat studies with direct dosing of this metabolite. The nonclinical safety of this metabolite was adequately assessed. Significant systemic exposure was attained with all other human metabolites after oral administration of pitolisant resulting in adequate nonclinical assessment of these metabolites.

The pharmacology/toxicology team recommends approval.

5. Clinical Pharmacology

The primary clinical pharmacology review team was Praveen Balimane, Venkatesh A. Bhattaram, Jeffrey B. Kraft, and Christian Grimstein. The secondary reviewer was team leader Luning (Ada) Zhuang. The final clinical pharmacology signatory was Mehul Mehta.

Clinical Pharmacology is supported by several clinical studies:

- Six Phase I clinical studies (P02-02, P03-04, P09-11, P14-05, P11-01, and P11-03) evaluating the single dose pharmacokinetics (PK) of pitolisant from 5 to 240 mg in healthy subjects

- Four Phase I clinical studies (P03-03, P04-06, P09-12, and P15-02) evaluating the repeat dose PK of pitolisant from 20 to 50 mg QD in healthy subjects

- Six clinical studies with nine study parts (P11-03 Parts II and III, P11-10, P03-08, P03-01 Part I, P14-07 Parts I and II, P15-15 Parts I and II), assessing drug interactions with pitolisant in healthy subjects

- Three clinical studies with PK data from adult (P05-03 and P06-06) and pediatric (P11-11) patients with narcolepsy (ages 6 to <12 years and ages 12 to <18 years)

- Four clinical studies assessing PK in specific populations, including cytochrome P450 CYP2D6 poor metabolizers (P15-02), elderly subjects (P09-12), subjects with hepatic impairment (P09-14), and subjects with renal impairment (P09-13)

Several pharmacodynamic studies were also conducted:

- Two TQTc (thorough QT/QTc) studies (P09-11 and P14-05);
- A positron emission tomography (PET) study (P14-08; REB 103/2014);

- A human abuse potential (HAP) study (P16-02, INC Research 1008541).

The recommended dose of pitolisant is 35.6 mg to be administered orally once daily in the morning upon waking up. The dosage should be titrated to 35.6 mg once daily according to the following schedule:

- Week 1: initiate treatment with a dose of 8.9 mg once daily
- Week 2: increase dose to 17.8 mg once daily
- Week 3: increase to the recommended dose of 35.6 mg once daily

The entire clinical development program, including all the efficacy and safety studies and all the clinical pharmacology studies, were conducted in Europe and South America. Though none of the clinical studies were conducted in the United States, pitolisant's PK characteristics are likely similar in U.S. and European patients (the PK of pitolisant is not impacted by gender, age, or body mass index).

Following oral administration of pitolisant 35.6 mg once daily, the steady state C_{max} and AUC are 73 ng/mL (range 42.9 to 126 ng/mL) and 812 ng*hr/mL (range 518 to 1468 ng*hr/mL), respectively. Pitolisant exposure increases proportionally with dose and steady state is reached by Day 7. The median time to maximum plasma concentration (T_{max}) of pitolisant is 3.5 hours (range 2 to 5 hours). Pitolisant has an oral absorption ~90%. No clinically significant differences in the pharmacokinetics of pitolisant were observed following administration with a high-fat meal.

The apparent volume of distribution of pitolisant is approximately 700 L (range 5 to 10 L/kg). Serum protein binding is approximately 91% to 96%. The blood to plasma ratio of pitolisant is 0.55 to 0.89. After a single dose of 35.6 mg, the median half-life of pitolisant is approximately 20 hours (range 7.5 to 24.2 hours). The apparent oral clearance (CL/F) of pitolisant is 43.9 L/hr and renal clearance accounts for < 2% of the total clearance of pitolisant.

Pitolisant is extensively metabolized; primarily by polymorphic CYP2D6 and, to a lesser extent, by CYP3A4 and Phase 2 glucuronidation. Though there are many circulating metabolites, all the major circulating metabolites were determined to be "inactive." Additionally, the exposure ratio (i.e., AUC of metabolite/AUC of parent) of all major circulating metabolites is 0.5 or lower. After a single, oral, radiolabeled pitolisant dose of 17.8 mg, approximately 90% of the dose was excreted in urine (< 2% as unchanged parent) and 2.3% in feces.

A dedicated hepatic impairment study demonstrated that pitolisant exposures (C_{max} and AUC) were generally similar in patients with mild impairment versus healthy subjects. However, patients with moderate hepatic impairment had 2-fold increases in AUC and $T_{½}$. There were no data for patients with severe hepatic impairment. Though the Applicant recommended some dose-adjustment strategies for moderate and severe hepatic impairment, the clinical pharmacology team provided alternate recommendations. The details of their determination are provided in the primary Clinical Pharmacology review. The alternate recommendations are:

- Mild hepatic impaired = no dose adjustment
- Moderate hepatic impaired = titrate the dose for a longer duration (i.e., 2 weeks (b) (4) with a maximum dose of 17.8 mg/day
- Severe hepatic impaired = contraindicated

A dedicated renal impairment study demonstrated that pitolisant exposures (C_{max} and AUC) were generally 2-fold higher in all categories of renal impairment (i.e., mild, moderate and severe) versus healthy subjects. There were no data for patients with end-stage renal disease (ESRD). The Applicant recommended (b) (4). The clinical pharmacology team disagreed and provided alternate recommendations. The details of their determination are provided in the primary Clinical Pharmacology review. The alternate recommendations are:

- Mild renal impaired = no dose adjustment
- Moderate renal impaired = maximum dose of 17.8 mg/day
- Severe renal impaired = maximum dose of 17.8 mg/day
- ESRD = not recommended

An approximate 2-fold increase in exposure was observed in CYP2D6 poor metabolizers as compared to CYP2D6 "normal" metabolizers. Additionally, a dedicated drug interaction study with paroxetine (a strong CYP2D6 inhibitor) resulted in a similar increase in exposure of pitolisant, which supports the conclusion that exposures can be expected to be 2-fold higher in CYP2D6 poor metabolizers. Therefore, the maximum dose of pitolisant should be 17.8 mg/day in known CYP2D6 poor metabolizers. The dose of pitolisant should also be reduced by half during concomitant dosing with a CYP2D6 inhibitor.

Concomitant use of pitolisant with rifampin (a strong CYP3A4 inducer) decreased pitolisant C_{max} and AUC and by 39% and 48%, respectively. The detailed dose adjustments recommended for pitolisant when co-administered with strong CYP3A4 inducers (e.g., rifampicin, phenytoin etc.) are:

- For patients stable on pitolisant 8.9 mg/day or 17.8 mg/day: Dose to be increased gradually over 1 week to reach double the original dose level. Maintain for the duration of use of CYP3A4 inducers.

- For patients stable on the highest recommended pitolisant dose of 35.6 mg/day: No dose adjustment is recommended

The QTc studies demonstrated no clinically-relevant QT prolongation at the recommended highest dose of 35.6 mg. The QT Interdisciplinary Review Team (IRT) did not recommend a Warning and Precaution statement in labeling (see Section 11: *Other Relevant Regulatory Issues*). However, there was a clear and direct correlation of pitolisant exposure with QTc prolongation. Supratherapeutic single doses of pitolisant (106.8, 142.4, 178, and 213.6 mg) all resulted in increases in QTcF with upper bounds of 90% CI between 12 to 18 msec. Therefore, the primary clinical pharmacology reviewer, Dr. Balimane, disagreed with the QT IRT

recommendation. He believes that, in scenarios where pitolisant is administered with a CYP2D6 inhibitor or to a patient with hepatic or renal insufficiency, clinically relevant QT prolongation could occur. The clinical review team agreed, and a Warning and Precaution for QT prolongation was added to labeling. Of note, the European summary of product characteristics for pitolisant also includes a warning about QT prolongation.

The clinical pharmacology team recommends approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical Efficacy

The primary clinical reviewer was Martine Solages; the secondary reviewer was team leader (and CDTL) Bernard Fischer. The primary biometrics reviewer was Semhar Ogbagaber, the secondary reviewer was acting team leader Jinglin Zhong, and the final biometrics signatory was James Hung.

Excessive Daytime Sleepiness

The Applicant submitted two studies for the excessive daytime sleepiness (EDS) indication (HARMONY I and HARMONY I-bis; see Table 1). Both studies had a 3-week dose-adjustment phase during which pitolisant and modafinil could be titrated based on efficacy and tolerability. Both studies also included a 1-week withdrawal phase in which all patients received placebo. Neither of the studies prespecified secondary endpoints or controlled the Type-I error rate

Table 1. Submitted Phase 3 Pitolisant Narcolepsy Studies for EDS

Study Name	Subjects	Description	Dose	Endpoints
HARMONY I P07-03	≥ 18 years old with narcolepsy ± cataplexy, ESS ≥ 14 N=94 Patients with history of cataplexy: 25 pitolisant 27 modafinil 24 placebo	Randomized, double-blind, placebo- and modafinil-controlled 2-week washout 1-week baseline 3-week titration phase 5-week stable dose phase 1-week withdrawal phase	Starting: placebo modafinil 100 mg pitolisant 8.9 mg Range: pitolisant 8.9 mg to 35.6 mg modafinil 100 mg to 400 mg	Primary: ESS at Week 8 Secondary: Daily cataplexy rate MWT SART CGI-C
HARMONY I-bis P09-15	≥ 18 years old with narcolepsy ± cataplexy, ESS ≥ 14 N=166 Patients with history of cataplexy: 50 pitolisant 50 modafinil 26 placebo	Randomized, double-blind, placebo- and modafinil-controlled 2-week washout 1-week baseline 3-week titration phase 5-week stable dose phase 1-week withdrawal	Starting: placebo modafinil 100mg pitolisant 4.45 mg Range: pitolisant 4.45 mg to 17.8 mg modafinil 100 mg to 400 mg	Primary: ESS at Week 8 Secondary: Daily cataplexy rate MWT SART CGI-C Polysomnography

CGI-C=Clinical Global Impression of Change; ESS=Epworth Sleepiness Scale; MWT=Maintenance of Wakefulness Test; SART=Sustained Attention to Response Task.

The primary endpoint in both studies was the Epworth Sleepiness Scale (ESS). The ESS assess self-reported propensity to fall asleep in eight, hypothetical situations. For each situation, scores range from 0 (no chance of dozing) to 3 (high chance of dozing); the total maximum score is 24. Cut-offs from published literature are:

- 0 to 5, lower normal daytime sleepiness
- 6 to 10, higher normal daytime sleepiness
- 11 to 12, mild excessive daytime sleepiness
- 13 to 15, moderate excessive daytime sleepiness
- 16 to 24, severe excessive daytime sleepiness

Currently, this scale has fallen out of favor with the Agency because it requires patients to assess a hypothetical situation with which they may or may not have had experience and is subject to recall bias. However, the Agency accepted the ESS for this application based on precedents from other narcolepsy development programs.

The Maintenance of Wakefulness Test (MWT) assesses a patient's ability to remain awake in a comfortable, controlled environment. The maximum score is 40 minutes (i.e., the patient has

not fallen asleep for 40 minutes); lower scores indicate the patient has fallen asleep more quickly. The Sustained Attention to Response Task (SART) is a computer go/no-go task that asks patients to withhold a response to an infrequent target while responding to frequent nontargets.

Demographics and baseline characteristics from HARMONY I and HARMONY I-bis are presented in Table 2 and Table 3, respectively.

Table 2. HARMONY I Demographics and Baseline Characteristics

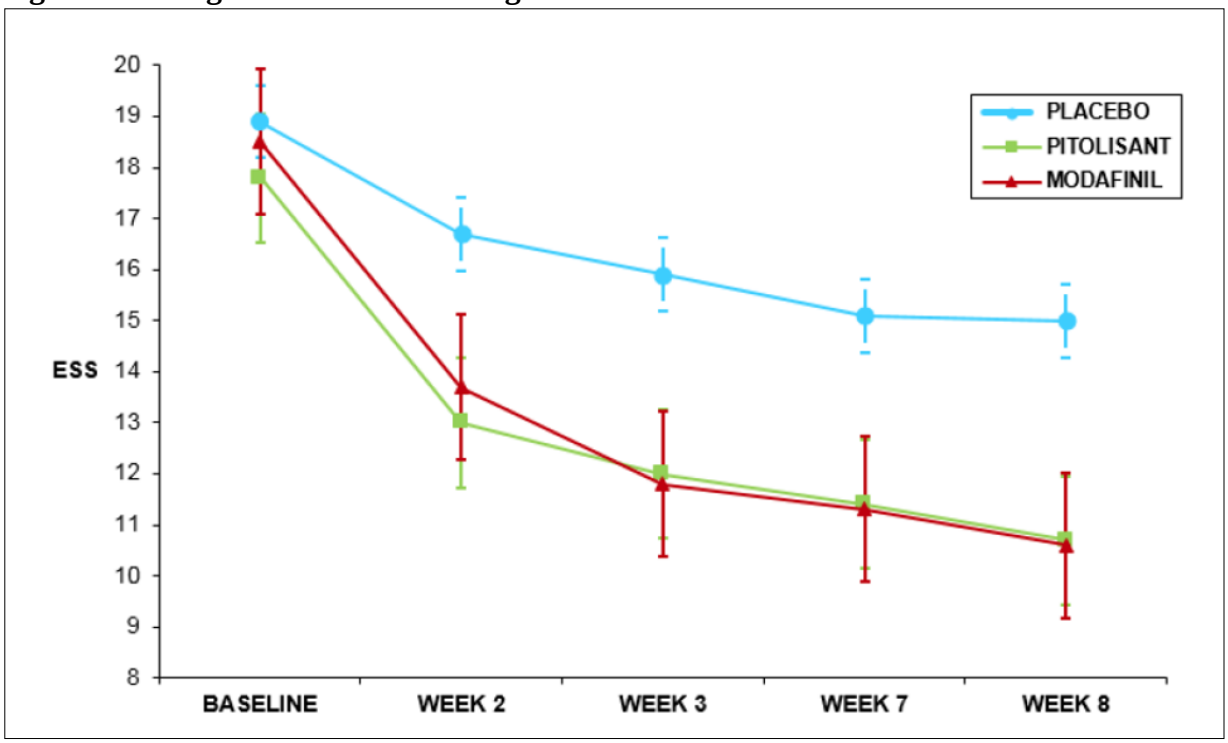
	Pitolisant (n= 31)	**Placebo** (n = 30)	**Modafinil** (n = 33)
Sex			
Male, n (%)	20 (65%)	13 (43%)	18 (55%)
Female, n (%)	11 (36%)	17 (57%)	15 (46%)
Age			
Mean, years (SD)	35.7 (14.6)	41.3 (14.8)	39.2 (14.6)
Minimum, maximum; years	19, 65	19, 75	18, 65
Race			
White, n (%)	29 (94%)	28 (93%)	32 (97%)
Black, n (%)	2 (7%)	2 (7%)	1 (3%)
Asian, n (%)	0	0	0
Baseline Characteristics			
Duration of narcolepsy, median years	11.1	15.2	12.2
Daily cataplexy rate, geometric mean	0.5	0.4	0.4
Sleep paralysis, n (%)	15 (48%)	15 (50%)	22 (67%)
Hallucinations, n (%)	18 (58%)	19 (63%)	21 (64%)
Baseline ESS, mean (SD)	17.8 (2.5)	18.9 (2.5)	18.5 (2.7)
Taking concomitant anticataplexy medication,[a] n (%)	13 (42%)	10 (33%)	11 (33%)

[a]Including antidepressants taken for anticataplexy activity and sodium oxybate.

Patients in the pitolisant group were more likely to be male than patients in the placebo group; however, there is no known pathophysiologic or mechanistic reason for a significant sex effect. The pharmacokinetics of pitolisant are not impacted by sex. Therefore, we do not expect that the difference in sex distribution between the pitolisant and placebo groups affected the study's results.

The Applicant's analysis of the primary efficacy endpoint, confirmed by the Agency, found that the least square mean at Week 8 on the ESS was 12.4 in the pitolisant group and 15.5 in the placebo group, with a statistically significant treatment difference of -3.1 ($p = 0.022$; see Figure 1). This mean effect is equivalent of moving severe EDS (baseline score of 18) to moderate EDS and is clinically meaningful.

Figure 1. Change in ESS Score during HARMONY I.



Source: Applicant's Study Report, p. 60.

The Applicant found that pitolisant-treated patients demonstrated increased sleep latency on the MWT as compared to patients in the placebo group (p = 0.044). Error rates on the SART were comparable in the pitolisant and placebo groups at baseline but significantly lower (p = 0.041) in the pitolisant group versus placebo after treatment. At the request of the biometrics reviewer, the Applicant conducted additional analyses using the Mann-Whitney test (with and without imputation of the last observed value); the results of these analysis were consistent with the original findings. Although these secondary endpoints were not prespecified or controlled for type I error, they supported the Division's efficacy finding based on the ESS.

Table 3. HARMONY I-bis Demographics and Baseline Characteristics

	Pitolisant (n= 67)	**Placebo** (n = 33)	**Modafinil** (n = 65)
Sex			
Male, n (%)	32 (48%)	15 (47%)	30 (46%)
Female, n (%)	35 (52%)	18 (53%)	35 (54%)
Age			
Mean years (SD)	40.7 (15.7)	43.4 (17.9)	44.1 (14.7)
Minimum, maximum; years	29, 52	29, 55	32, 58
Race			
White, n (%)	60 (90%)	28 (88%)	54 (83%)
Black, n (%)	0	0	1 (2%)
Asian, n (%)	0	0	0
Baseline Characteristics			
Duration of narcolepsy, median years	15	11	10
Sleep paralysis, n (%)	30 (45%)	22 (69%)	34 (52%)
Hallucinations, n (%)	35 (52%)	20 (63%)	36 (55%)
Baseline ESS, mean (SD)	18.2 (2.4)	18.2 (2.3)	18.1 (2.8)

Patients in the pitolisant group had a slightly longer duration of illness, but other baseline disease characteristics were comparable between groups. It is possible that a longer duration of illness indicates some degree of treatment resistance; however, if so, this would have biased the results against pitolisant.

The mean reduction in ESS score in the pitolisant group of 2.2 was statistically significant compared to placebo (p = 0.030). Although not as impressive as the results of the HARMONY I study, a decrease of 2 points on the ESS is still considered clinically meaningful based on published literature.[1] Of the pitolisant group, 53% had an ESS decrease from baseline of at least 3 points; only 36% of the placebo group had a similar decrease. We also note that the maximum dose of pitolisant in this study was 17.8 mg (whereas it was 35.6 mg in HARMONY I). The MWT and SART results were not statistically significant.

The Applicant conducted a non-inferiority test of ESS between pitolisant and modafinil in both HARMONY I and HARMONY I-bis. In both cases, pitolisant did not demonstrate non-inferiority (i.e., in neither case was pitolisant statistically equivalent to modafinil).

Cataplexy

The Applicant submitted two studies for the cataplexy indication: HARMONY I and HARMONY CTP, see Table 1 and Table 4, respectively. Study HARMONY I-bis included a subgroup of patients with cataplexy, but the difference between pitolisant and placebo groups on the least-square mean daily cataplexy rate was not statistically significant (p = 0.87).

[1] Patel et al. Minimum clinically important difference of the Epworth Sleepiness Scale. Eur Resp J 2017; 50: DOI: 10.1183/1393003.congress-2017.PA330

Table 4. HARMONY CTP – Second Submitted Phase 3 Pitolisant Narcolepsy Study for Cataplexy

Study Name	Subjects	Description	Dose	Endpoints
HARMONY CTP P11-05	≥ 18 years old with narcolepsy ≥ 3 cataplexy attacks/week, ESS ≥ 12 N = 106	Randomized, double-blind, placebo-controlled 1-week washout 2-week baseline 3-week titration phase 4-week stable dose phase 1-week withdrawal phase	Starting: placebo pitolisant 4.45mg Range: pitolisant 4.45 mg to 35.6 mg	Primary: Weekly rate of cataplexy attacks (WRC) during 4-week stable dose period Secondary: ESS MWT

Both of the studies submitted to support the cataplexy indication had a 3-week dose-adjustment phase during which pitolisant (and modafinil in HARMONY I) could be titrated based on efficacy and tolerability. Both studies also included a 1-week withdrawal phase during which all patients received placebo. Neither study had a prospective plan to control the Type-I error rate for secondary endpoints; for HARMONY I, the rate of cataplexy was a secondary endpoint.

Patients who had been taking stable doses of purportedly anti-cataplectic medications (including sodium oxybate, selective serotonin reuptake inhibitors, norepinephrine reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors) for at least 1 month prior to the trial and nonetheless met the inclusion and exclusion criteria could enroll and continue on the concomitant medication.

The Applicant's HARMONY I analysis found that the relative risk of cataplexy (among those at-risk for cataplexy) in the pitolisant group was significantly reduced compared to the placebo group (RR = 0.38; 95% CI: 0.2, 0.9; p=0.034). In this analysis, missing or zero cataplectic events were assigned a value of 0.5, based on the average of no cataplectic crises (0) and the smallest possible count (1). This value was selected to allow calculations on a logarithmic scale for computing the geometric means. When subjects with zero or missing cataplectic events were ignored, however, the improvement over placebo was not statistically significant (RR = 0.45; 95% CI: 0.1, 1.5; p=0.17).

Given the lack of a prospective plan to control the Type-I error rate, Dr. Ogbagaber, the biometrics reviewer, notes that the HARMONY I cataplexy finding should be considered exploratory. Additionally, the sponsor performed a post hoc analysis based on subgroups defined on the basis of post-randomization events (i.e., defining a population based on cataplexy events), which violates the principle of randomization and leads to invalid statistical comparisons.

Because HARMONY I's cataplexy analysis was not prespecified, was not prospectively controlled for the Type-I error rate, and depended on the values assigned for missing data, we

determined that it does not meet the regulatory standard for an adequate and well-controlled trial (with respect to the cataplexy indication).

Demographics and baseline characteristics from HARMONY CTP are presented in Table 5. The primary efficacy for HARMONY CTP's anticataplectic activity was assessed by the change in the average number of cataplexy attacks per week (weekly rate of cataplexy) between the 2 weeks of baseline (Day -14 to Day 0) and 4 weeks of the stable treatment period (Day 21 to Day 49).

Table 5. HARMONY CTP Demographics and Baseline Characteristics.

	Pitolisant (n= 54)	**Placebo** (n = 51)
Sex		
Male, n (%)	26 (48%)	27 (53%)
Female, n (%)	28 (52%)	24 (47%)
Age		
Mean years (SD)	35.8 (12.1)	38.5 (12.9)
Minimum, maximum years	18, 64	18, 66
Race	Not Reported	Not Reported
Baseline Characteristics		
Number of weekly cataplexy episodes, mean (SD)	11.0 (8.9)	9.2 (8.8)
Sleep Paralysis, n (%)	32 (59%)	32 (63%)
Hallucinations, n (%)	36 (67%)	32 (63%)
Baseline ESS, mean (SD)	17.3 (3.3)	17.1 (3.4)
Taking concomitant anticataplexy medication,[a] n (%)	1 (2%)	5 (10%)

[a]Including antidepressants taken for anticataplexy activity and sodium oxybate.

The Applicant's analysis showed that the pitolisant group had a significantly reduced risk of cataplectic events compared to the placebo group (RR = 0.51; 95% CI: 0.4, 0.6; $p < 0.0001$). The Agency confirmed this analysis. This result translated to a decrease in weekly cataplexy rates of 75% for the pitolisant group compared to a decrease of 38% in the placebo group. There was no difference in results by sex.

Although not prespecified or controlled for Type-I error rate, the ESS score in HARMONY CTP also significantly improved in the pitolisant group compared to the placebo group with a treatment effect of 3.4 (95% CI: -5.0, -1.9; $p < 0.0001$). Sleep latency as measured by the MWT increased significantly in the pitolisant group. The Applicant calculated a mean ratio of MWT scores (pitolisant:placebo) of 1.78 (95% CI: 1.2, 2.6; $p = 0.003$).

Determination of Efficacy

Both HARMONY I and HARMONY I-bis demonstrated statistically significant and clinically meaningful improvements in EDS in pitolisant-treated versus placebo-treated patients. The secondary endpoints of MWT in HARMONY I and the ESS and MWT in HARMONY CTP, although exploratory in nature, offered reinforcing evidence of pitolisant's effectiveness. Therefore, based on substantial evidence of effectiveness, the clinical/biometrics team recommend approval for the treatment of excessive daytime sleepiness in adult patients with narcolepsy.

Because of the limitations in the statistical analysis of cataplexy in HARMONY I, this trial could not be considered adequate and well-controlled. Only HARMONY CTP offered evidence of pitolisant's effectiveness for cataplexy. The FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products states that the Agency may consider approval based on a single study and that such a study should, for example:

- be a large, multisite trial
- demonstrate consistent results across study subpopulations
- have a statistically "very persuasive finding"

HARMONY CTP was a multisite trial with a statistically significant finding and a very small p-value ($p < 0.0001$). However, the study itself was not large ($N = 105$) and the only subgroup analysis that could be performed was by sex (race and ethnicity were not reported, < 10% were elderly). The relevant guidance also states:

> "…whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible (p. 13)."

Throughout their meetings with the Agency (DNP and DPP), the Applicant was advised that two adequate and well-controlled trials should be submitted for each indication. The Agency also has precedent for requiring two positive studies in other narcolepsy development programs (e.g., sodium oxybate, modafinil).

In examining the totality of the evidence for cataplexy, we have one, small, positive study (HARMONY CTP), conducted in Eastern Europe; supportive evidence from HARMONY I; and no support from HARMONY I-bis (although the maximum pitolisant dose was half that of the other two studies). Therefore, we believe a trial substantiating the results of HARMONY CTP is required. We will not include the treatment of cataplexy in adult patients with narcolepsy in the indications statement. In order to obtain the second indication, the Applicant must submit a positive, randomized, double-blind, placebo-controlled, fixed-dose trial of pitolisant for cataplexy and enroll U.S. patients. Estimates place the U.S. narcolepsy prevalence at more than 130,000 people,[2] suggesting that such a trial is quite feasible.

[2] https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Narcolepsy-Fact-Sheet

8. Safety

The primary clinical reviewer was Martine Solages; the secondary reviewer was Team Leader (and CDTL) Bernard Fischer.

Exposures

Table 6 reflects the total exposures to pitolisant across all indications. The long-term safety data for the 35.6 mg dose are limited: a total of 83 patients were exposed to the 35.6 mg dose for 6 months to 1 year; 72 of these patients participated in narcolepsy clinical trials. A total of 62 patients in trials for all indications were exposed to the 35.6 mg for ≥ 1 year; 55 of these patients participated in narcolepsy clinical trials.

Table 6. Pitolisant Maintenance Dose Exposures across All Indications[a]

Pitolisant Dose	Number of Participants
4.45 mg	99 (7%)
8.9 mg	264 (17%)
17.8 mg	828 (55%)
26.7 mg	1 (<1%)
35.6 mg	315 (21%)
53.4 mg	6 (<1%)
TOTAL	**N=1513**

[a]Including narcolepsy, Parkinson's disease, obstructive sleep apnea, epilepsy, schizophrenia, dementia, and attention deficit hyperactivity disorder.

A U.S. Expanded Access Program (under IND 111842) has provided pitolisant to 366 patients. Thus far, 86 patients have completed ≥ 6 months of treatment. The maximum exposure duration in the program has been 10 months (in a single patient). There have been 309 patients who have completed titration to the 35.6 mg dose.

Deaths and Serious Adverse Events (SAEs)

One death occurred in the narcolepsy development program. This patient was a 73-year-old female with no co-morbid medical conditions listed who died suddenly at home while participating in the long-term pitolisant open-label extension study (HARMONY III). The investigator hypothesized that hot weather conditions may have contributed to her death, but no autopsy was performed.

During the placebo-controlled studies, SAEs in the pitolisant-exposed patients only occurred during HARMONY I: One patient reported pyelonephritis and another reported hemorrhoids. One placebo-exposed patient had the SAE of biliary colic. Table 7 shows the SAEs reported during HARMONY III; Table 8 shows the SAEs reported during the U.S. expanded access program.

The most frequent SAEs were psychiatric in nature. In HARMONY III, the three patients with depression all had a previous history of depression and the patient who developed psychosis had a history of psychosis and had stopped his antipsychotic (resulting in relapse). In the expanded access program, the patients with bipolar disorder, suicidal ideation, and suicide

attempt cases all had significant psychiatric histories. Thus, in all reported cases of serious psychiatric adverse events, patients had a history of psychiatric illness preceding exposure to pitolisant and no clear temporal relationship between the introduction of pitolisant and the worsening of their symptoms was noted.

Table 7. SAEs during HARMONY III; N=101.

Patient Identifier	Serious Adverse Event (SAE)
Year 1	
(b) (6)	depression
	transient ischemic attack
	pulmonary carcinoid tumor, thoracic surgery
	depression
	pregnancy and spontaneous abortion
	pregnancy and abortion
	pilonidal cyst
Years 2 to 5	
(b) (6)	ovarian cyst
	gastric bypass
	trapeziectomy
	depression
	psychotic disorder, rebound psychosis, psychiatric decompensation
	increased hepatic enzymes
	bladder surgery

Table 8. SAEs from U.S. Expanded Access Program.

Patient Identifier	Serious Adverse Event (SAE)
(b) (6)	Fall, cellulitis, blood infection
	Worsening of lymphoma
	Alcoholic relapse
	Bipolar disorder, suicidal ideation
	Suicide attempt

Of note, one patient in the obstructive sleep apnea development program had an SAE of prolonged QT interval: 443 msec at the selection visit and 468 msec after starting pitolisant 10 mg. The 468 msec reading was an automated calculation and a thorough evaluation (including Holter monitoring) could not determine whether the automated calculation was correct.

Adverse Events (AEs) Leading to Discontinuation

AEs leading to pitolisant and placebo patient discontinuations are presented in Table 9. There was no pattern evident in these discontinuations (only placebo patients discontinued for an AE in HARMONY I; only pitolisant patients discontinued for an AE in HARMONY I-bis and HARMONY CTP).

Table 9. AEs Leading to Discontinuations.

Treatment Group	Adverse Event Leading to Discontinuation
HARMONY I	
Placebo	Arthrosis
Placebo	Pregnancy
Placebo	Mild fluid retention, renal colic
Placebo	Biliary colic
HARMONY I-bis	
Pitolisant	Anxiety and depression
Pitolisant	Anxiety
Pitolisant	Insomnia, hypnagogic hallucination, cataplexy, myalgia
Pitolisant	Somnolence, cataplexy
Pitolisant	Abdominal pain, headache
HARMONY CTP	
Pitolisant	Nausea

Treatment-emergent AEs

Treatment-emergent AEs from all three pivotal studies are presented in Table 10.

Table 10. Pitolisant Treatment-emergent AEs >2% and > Placebo.

Adverse Reaction	Pitolisant (n=152) %	Placebo (n=114) %
Cluster headache; headache; migraine; premenstrual headache; tension headache	18	15
Initial insomnia; insomnia; middle insomnia; poor quality sleep	6	2
Nausea	6	3
Upper respiratory infection (pharyngitis; rhinitis; sinusitis; upper respiratory tract infection; upper respiratory tract inflammation; viral upper respiratory tract infection)	5	3
Arthralgia; back pain; carpel tunnel syndrome; limb discomfort; musculoskeletal pain; myalgia; neck pain; osteoarthritis; pain in extremity; sciatica	5	3
Anxiety; nervousness; stress; stress at work	5	1
Heart rate increased; sinus tachycardia; tachycardia	3	0
Hallucination; hallucination visual; hypnagogic hallucination	3	0
Irritability	3	2
Abdominal discomfort; abdominal pain; abdominal pain upper	3	1
Dyssomnia; sleep disorder; sleep paralysis; sleep talking	3	2
Decreased appetite	3	0

Laboratory Values and Vital Signs
There were no patients who met criteria for Hy's law. There were no clinically meaningful differences between the placebo-treated and pitolisant-treated patients on electrolytes, liver function tests, or hematology parameters.

Patients in the pitolisant group were more likely to report significant weight gain, which was associated with metabolic changes in some cases. However, the mean change in weight in the pitolisant group was modest. Although patients in the pitolisant group were more likely to report tachycardia as a treatment-emergent AE, the mean post-treatment heart rates, the mean change in heart rate, and the proportion of patients with measured tachycardia or bradycardia were similar in the pitolisant and placebo groups. Overall, pitolisant appears to be relatively neutral in its effects on weight, blood pressure, and heart rate.

Determination of Safety
The clinical review team believes pitolisant's risks are acceptable for the proposed indications. Risks can be mitigated through labeling.

9. Advisory Committee Meeting

This section is not applicable to this application.

10. Pediatrics

The Applicant is conducting a randomized, double-blind, placebo-controlled study to evaluate the effect of pitolisant on EDS and cataplexy in patients aged 6 to 18 years (Study P11-06). No SAEs had been reported by the 120-day safety update submission date. The study is ongoing, and no additional data are available. The Applicant has also conducted Study P11-11, a single-dose trial to evaluate the pharmacokinetics of pitolisant in children aged 6 to 18 years. This study enrolled 24 children with narcolepsy and tested a single dose of 20 mg once daily. TEAEs reported in the study included headache and dizziness. No SAEs were reported. Per the study report, no clinically significant abnormalities in vital signs, laboratory assessments, physical examinations, or ECGs were observed. The Applicant found higher exposures in pediatric patients as compared with young adult patients, independent of body weight and gender.

11. Other Relevant Regulatory Issues

QT Interdisciplinary Review Team (IRT)
The QT IRT was Jose Vicente Ruiz, Ferdouse Begum, Dalong Huang, Mohammad A. Rahman, Girish K Bende, Michael Y. Li, Lars Johannesen, Christine E. Garnett.

A concentration-dependent QTc prolongation over a dose range of 40 to 240 mg was detected in the QT assessment for pitolisant. At steady state concentrations with the 40 mg dose, the expected mean (90% CI) increase in QTc is 4.2 (range 3.2 to 5.2) msec. The highest clinical exposure identified is when patients who are CYP2D6 poor metabolizers take pitolisant 40 mg/day. In this scenario, the expected mean (90% CI) increase in QTc is

8.6 (range 6.7 to 10.5) msec. The highest dose tested (240 mg) provides a 1.8-fold exposure margin over the highest clinical exposure scenario and the expected mean increase is 15.5 (range 12.0 to 18.9) msec. The QT IRT recommended—if there was reasonable assurance that the 240-mg dose represented drug exposures that were unlikely to be seen in the patient population—no Warning and Precaution statement for QTc prolongation. They believed that the Applicant's evaluation of the QTc interval over a large dose/exposure range provided safety reassurance because patients were unlikely to experience a clinically significant QTc effect.

The primary pharmacology reviewer, Dr. Balimane, disagreed with the QT IRT labeling recommendation (see Section 5: *Clinical Pharmacology*).

Controlled Substance Staff (CSS) Review
The CSS review was completed by primary reviewer Katherine Bonson, team leader Silvia Calderon, and CSS statistician Wei Liu.

CSS determined that pitolisant has low abuse liability potential at recommended doses and did not recommend DEA Scheduling.

Division of Pediatrics and Maternal Health (DPMH)
The primary reviewer was Carrie Ceresa.

There were three pregnancies in the pitolisant groups and one in a placebo-treated patient. Of the pitolisant-exposed pregnancies, one was electively terminated, one resulted in miscarriage at 7 weeks, one was delivered prematurely (birthweight 1.9 kg).

DPMH determined that postmarketing studies to obtain data on pregnancy and lactation should be required (see Section 13: *Postmarketing Recommendations*).

12. Labeling

The Office of Clinical Pharmacology made the following labeling recommendations:

- Specific dose adjustments for patients with hepatic impairments
- Specific dose adjustments for patients with renal impairments
- Specific dose adjustments for patients who are known CYP2D6 poor metabolizers (PMs)
- Specific dose adjustments when patients are co-administered CYP2D6 inhibitors
- Specific dose adjustments when patients are co-administered CYP3A4 inducers
- Specific dose adjustments for patients on oral contraceptives
- A warning and precaution for QT prolongation

The clinical review team made the following labeling recommendations:

- (b) (4) The recommended dose will be 17.8 to 35.6 mg daily.

- Because no secondary endpoints were prespecified or controlled for type I error, none were included in labeling.

DPMH made the following labeling recommendations:

- A prospective and observational pregnancy registry.
- Pitolisant may reduce the effectiveness of oral contraceptives.
- Although pitolisant is not indicated for use in pediatric population, include available pediatric PK data in labeling. Pitolisant exposures are 2-fold higher in pediatric patients aged 12 to < 18 years and 3-fold higher in patients aged 7 to 12 years.

13. Postmarketing Recommendations

DPMH determined that the following postmarketing studies should be required:

1) The Applicant should be required to conduct a prospective, registry-based, observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to pitolisant during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

2) The applicant should be required to conduct an additional pregnancy study that uses a different design from the Pregnancy Registry (e.g., a case control study or a retrospective cohort study using claims or electronic medical record data with outcome validation) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to pitolisant during pregnancy compared to an unexposed control population.

3) The applicant should be required to conduct a lactation study in lactating women who have received therapeutic doses of pitolisant using a validated assay to assess concentrations of pitolisant in breast milk.

14. Recommended Comments to the Applicant

As above, we will advise the Applicant that a second positive adequate and well-controlled study will be needed in order to obtain the cataplexy indication. The letter will also describe the various post-marketing requirements/commitments, as applicable.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Lead Medical Officer

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