

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211150
PDUFA Goal Date	August 14, 2019
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Reviewer Name(s)	Leah Hart, PharmD
Team Leader	Selena Ready, PharmD
Associate Division Director	Doris Auth, PharmD
Review Completion Date	August 13, 2019
Subject	Evaluation of Need for a REMS
Established Name	Pitolisant
Trade Name	Wakix
Name of Applicant	Bioprojet Pharma
Therapeutic Class	Histamine 3 receptor antagonist/inverse agonist
Formulation(s)	4.45mg and 17.8mg tablets for oral administration
Dosing Regimen	35.6 mg orally once daily in the morning upon waking; Dose titrated up from 8.9mg to the target dose over three weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Wakix (pitolisant) is necessary to ensure the benefits outweigh its risks. Bioprojet Pharma (Applicant) submitted a New Drug Application (NDA 211150) for pitolisant with the proposed indication for the treatment of excessive daytime sleepiness in patients with narcolepsy and for the treatment of cataplexy in patients with narcolepsy. The Applicant did not submit a proposed REMS. The Applicant proposed routine pharmacovigilance and has a long-term safety study ongoing with an estimated completion date of 2023.

The identified safety concern with pitolisant is the potential for QT interval prolongation. QT studies demonstrated that pitolisant has the potential to prolong the QT interval at exposures greater than the recommended doses (142.4 mg to 213.6 mg). However, clinically significant QT prolongation was not observed in the clinical trials. Although QT prolongation was not seen in the clinical studies, the proposed PI has been maximized to inform providers about the potential for QT prolongation in certain patients. This is a similar approach as the approved product in the European Union (EU). Wakix has been approved with the same formulation in the EU since March 2016 with the same tradename, and QT interval prolongation is described in the special warnings and precautions for use in EU labeling. During the review of the NDA, the Division of Pharmacovigilance (DPV) completed an analysis of EU postmarketing adverse event (AE) reports, as well as data from the Applicant's most recent Periodic Benefit Risk Evaluation Report and did not have specific regulatory recommendations for further safety analysis, enhanced pharmacovigilance, or postmarketing requirements or commitments.

DRISK determined that a REMS is not needed to ensure the benefits of Wakix outweigh its risks. This decision is supported by the clinical review of the safety data in the development program as well as the analysis of EU postmarketing adverse event (AE) reports provided by DPV¹. The QT prolongation associated with Wakix in certain patients can be addressed in the Warnings and Precautions and other sections of the PI, which will inform healthcare providers about this potential safety concern.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME),^a Wakix (pitolisant), is necessary to ensure the benefits outweigh its risks. Bioprojet Pharma (Applicant) submitted a New Drug Application (NDA) 211150 for Wakix with the proposed indication of treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy and for the treatment of cataplexy in adult patients with narcolepsy. This application is under review in the Division of Psychiatric Products (DPP). The Applicant did not submit a REMS with this application.

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

2 Background

2.1 PRODUCT INFORMATION

Wakix (pitolisant) is a histamine-3 receptor antagonist/inverse agonist proposed for the treatment of excessive daytime sleepiness in adult patients with narcolepsy and for the treatment of cataplexy in adult patients with narcolepsy. The mechanism of action of pitolisant in EDS in adult patients with narcolepsy and cataplexy is unclear, but it is postulated to enhance the histaminergic transmissions in the brain and thereby exhibit strong waking effects as well as inhibition of cataplexy through both direct and indirect effects.

The proposed dosing regimen includes titration; starting Wakix at 8.9 mg (two 4.45 mg tablets) orally once daily during week one, 17.8 mg (one 17.8 mg tablet) orally once daily during week 2, and 35.6 mg (two 17.8 mg tablets) orally once daily during week 3 and thereafter for chronic^b oral administration intended for outpatient use. The once-daily dose of Wakix is to be taken in the morning upon awakening.

Wakix was granted fast track and breakthrough therapy designation for the treatment of cataplexy in adult patients with narcolepsy and fast track designation for the treatment of excessive daytime sleepiness in adult patients with narcolepsy.

Wakix has been approved with the same dosing and tradename in the European Union (EU) since March 31, 2016, and potential risks are outlined in a risk management plan (RMP) (see Appendix 1). The product is authorized in all 27 EU countries; however, it is currently marketed in 6 countries: Belgium, France, Germany, Ireland, Italy, and the United Kingdom.

The EU labeling has the following contraindications: hypersensitivity to the active substance or to any excipients, severe hepatic impairment, and breast feeding. Table 1 describes the special warnings and precautions for use in EU labeling².

Special Warning and Precaution for Use	Description
Psychiatric disorders	Administer with caution in patients with history of psychiatric disorders such as severe anxiety or severe depression with suicidal ideation risk.
Hepatic or renal impairment	Administer with caution in patients with either renal impairment or moderate impairment (Child-Pugh B) with adjusted dosing regimen.
Gastrointestinal disorders	Gastric disorders reactions have been reported with pitolisant, therefore it should be administered with cautions in patients with acid relation gastric disorders or when co-administered with gastric irritants such as corticosteroids or NSAID.
Nutrition disorders	Administer with caution in patients with severe obesity or severe

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

	anorexia. In case of significant weight change, treatment should be re-evaluated by the physician.
Cardiac disorders	In two dedicated QT studies, supra-therapeutic doses of pitolisant (3-6-fold the therapeutic dose) produced mild to moderate prolongation of QTc interval (10-13 ms). In clinical trials, no specific cardiac safety signal was identified at therapeutic doses of pitolisant. Nevertheless, patients with cardiac disease, co-medicated with other QT-prolonging medicinal products or known to increase the risk of repolarization disorders, or co-medicated with medicinal products that significantly increase pitolisant Cmax and AUC or patients with severe renal or moderate hepatic impairment should be carefully monitored
Epilepsy	Convulsions were reported at high doses in animal models. In clinical trials, one case of epilepsy aggravation was reported in one epileptic patient. Caution should be taken for patients with severe epilepsy.
Women of childbearing potential	Women of childbearing potential have to use effective contraception during treatment and at least up to 21 days after discontinuation. Pitolisant may reduce the effectiveness of hormonal contraceptives. Therefore, an alternative method of effective contraception should be used if the patient is using hormonal contraceptives
Drug-drug interactions	The combination of pitolisant and substrates of CYP3A4 having a narrow therapeutic margin should be avoided.
Rebound effect	No rebound effect was reported during clinical trials. However, treatment discontinuation should be monitored.

REGULATORY HISTORY

The following is a summary of the regulatory history for Wakix NDA 211150 relevant to this review:

- 05/17/2010: Orphan drug designation granted
- 4/25/2018: Fast track designation granted for the treatment of excessive daytime sleepiness in adult patients with narcolepsy and the treatment of cataplexy in adult patients with narcolepsy.
- 04/27/2018: Breakthrough designation granted for the treatment of cataplexy in adult patients with narcolepsy; fast track designation was granted (b) (4) for the excessive daytime sleepiness indication.
- 12/14/2018: NDA 211150 full submission for the treatment of excessive daytime sleepiness in adult patients with narcolepsy and cataplexy in adult patients with narcolepsy received

3 Therapeutic Context and Treatment Options^{3,4,5,6,7,8}

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Narcolepsy is a chronic sleep disorder characterized by EDS that interferes with functioning and is typically accompanied by at least some associated symptoms such as cataplexy, hypnagogic hallucinations, and/or sleep paralysis. Patients with narcolepsy may experience fragmented nighttime sleep.

Narcolepsy is categorized as type 1 (with cataplexy) and type 2 (without cataplexy). Cataplexy is sudden onset of a REM sleep-like state with loss of voluntary muscle tone and can be triggered by strong positive or negative emotions. Type 1 narcolepsy is thought to be caused by the loss of hypothalamic neurons that produce hypocretin, and post-infectious or autoimmune processes may also play a role. Type 2 narcolepsy presents with similar symptoms but without hypocretin deficiency or cataplexy; the pathophysiology is unclear.

Narcolepsy is a lifelong problem and symptoms often start between the ages 7 to 25 but can occur at any time in life. Nearly half of patients with narcolepsy report that their sleepiness and cataplexy substantially interfere with their daily lives, including school, work, marriage or social life.^c It is estimated that anywhere from 135,000 to 200,000 people in the United States have narcolepsy. However, since this condition often goes undiagnosed, the number may be higher.^d Sleep studies are required to establish a diagnosis of narcolepsy.

Patients with narcolepsy are at risk for motor vehicle accidents, falls and fractures. Narcolepsy is associated with comorbidities such as excessive weight gain, obstructive sleep apnea, depression, nocturnal myoclonus, sleepwalking and other parasomnias.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Therapeutic options are based on symptom presentation: (1) EDS and sleep attacks; (2) disturbed nighttime sleep, and; (3) cataplexy, hypnagogic hallucinations, and sleep paralysis. The goals of therapy are to obtain alertness during waking hours or to maximize alertness at important times of the day.

Currently approved treatments for excessive daytime sleepiness in patients with narcolepsy include armodafinil, modafinil, methylphenidate, dextroamphetamine, sodium oxybate, and solriamfetol. Solriamfetol was recently approved in March 2019, is not commercially available. All approved treatments for EDS or cataplexy in patients with narcolepsy are controlled substances; armodafinil, modafinil, and solriamfetol are schedule 4, methylphenidate and dextroamphetamine are schedule 2, and sodium oxybate is schedule 1.

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

Modafinil and armodafinil are approved to improve wakefulness in adult patients with EDS associated with narcolepsy, obstructive sleep apnea, or shift work. Armodafinil and modafinil have wake-promoting actions similar to sympathomimetic amines, which are central nervous system (CNS) stimulants including amphetamine and methylphenidate, although their pharmacologic profile is not identical to that of the sympathomimetic amines^{9,10}.

Modafinil 200 mg is dosed once daily in the morning with a reduced dose for hepatic impairment. Warnings and Precautions include Stevens-Johnsons Syndrome, angioedema and anaphylaxis, multi-organ hypersensitivity, persistent sleepiness, and psychiatric symptoms. In patients with known cardiovascular disease increased monitoring is recommended due to an increase in cardiovascular events.

Armodafinil is dosed as 150 mg to 250 mg once daily in the morning and hepatic impairment requires a reduced dose. The Warnings and Precautions are identical to modafinil with the addition of drug rash with eosinophilia and systemic symptoms (DRESS) /Multi-organ hypersensitivity reactions.

Methylphenidate is a CNS stimulant approved for the treatment of narcolepsy. Stimulants promote alertness by increasing monoaminergic activity, specifically targeting the neurotransmitters dopamine and norepinephrine. Doses vary widely and depend on the effect on patient symptoms. Stimulants have not been effective in treating most cases of cataplexy and are typically prescribed as ancillary medications when first-line treatments are not fully effective or in patients unable to tolerate them. Stimulants can be addictive, and warnings and precautions include serious cardiovascular events, blood pressure and heart rate increases, psychiatric adverse reactions, and priapism¹¹.

Sodium oxybate is a CNS depressant indicated for the treatment of cataplexy in narcolepsy and EDS in narcolepsy. Given this is a sodium salt of gamma hydroxybutyrate (GHB), a Schedule 1 controlled substance, it has a boxed warning for respiratory depression and a REMS for the risk of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of sodium oxybate.

The REMS for sodium oxybate includes informing prescribers, pharmacists, and patients of the risk of significant CNS and respiratory depression, the contraindications of using sodium oxybate with hypnotics and alcohol, the potential for abuse, misuse, and overdose associated with sodium oxybate, and the safe use, handling and storage. Healthcare providers who prescribe sodium oxybate products must be specially certified, sodium oxybate must be dispensed only by pharmacies that are specially certified and dispensed and shipped only to patients who are enrolled in the REMS program with documentation of safe use conditions.

Sodium oxybate is given as 4.5 grams per night administered orally in two equal divided doses: 2.25 g at bedtime and 2.25 g 4 hours later. It can be titrated to effect in increments of 1.5 g per night at weekly intervals with the recommended dose range of 6 g to 9 g per night¹².

Sodium oxybate is contraindicated in combination with sedative hypnotics or alcohol. Warnings and Precautions include CNS depression, depression and suicidality, confusion/anxiety, and parasomnias. Patients care cautioned against hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after the first initiating treatment until certain that

sodium oxybate does not affect them adversely. Given the high sodium content, patients with heart failure, hypertension, or impaired renal function should be monitored.

Solriamfetol is a dopamine and norepinephrine reuptake inhibitor (DNRI) indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy. The warnings and precautions include blood pressure and heart rate increases as well as psychiatric symptoms. It is administered starting at 75 mg once daily upon awakening and the dose may be increased at intervals of at least 3 days to a maximum dose of 150 mg once daily. Patients are instructed to avoid administration within 9 hours of planned bedtime because of the potential to interfere with sleep¹³.

Non-FDA approved treatments include antidepressants- selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs). These are commonly used to treat cataplexy, sleep paralysis, and hypnagogic hallucinations¹⁴ although data from clinical trials are lacking. Antidepressants that inhibit norepinephrine reuptake have been reported as especially effective in treating cataplexy³.

Non-pharmacological therapies include napping and good sleep hygiene, cognitive behavioral therapy (CBT), and avoidance of certain drugs (benzodiazepines, opiates, antipsychotics, caffeine alpha-1 antagonists, and alcohol).

4 BENEFIT ASSESSMENT^{15,16,17}

The pivotal trials supporting the proposed indication of treatment of EDS in adult patients with narcolepsy and for the treatment of cataplexy in adult patients are studies P07-03 (HARMONY 1) and P11-05 (HARMONY CTP) with an additional supportive study P09-15 (HARMONY 1bis).

HARMONY 1 was an 8-week, randomized, double-blind, placebo and modafinil-controlled trial in patients with narcolepsy with or without cataplexy and an Epworth Sleepiness Scale (ESS) ≥ 14 . The primary outcome was the change in ESS score. Although not pre-specified in the study protocol, the Applicant assessed the frequency and severity of cataplexy attacks as a “second primary endpoint” in patients with cataplexy. This study was a multi-center study conducted at 24 sites in France, Germany, Hungary, the Netherlands, and Switzerland. Of the 94 patients randomized, 79 completed the study (25 in the pitolisant group, 25 in the placebo group, and 28 in the modafinil group). The majority of patients in each treatment group (25 patients in the pitolisant group, 27 in the modafinil group, and 24 in the placebo group) were identified as having narcolepsy associated with cataplexy.

The pitolisant treatment group had a statistically significant improvement in ESS with a treatment effect of -3.1 ($p=0.022$) over the placebo regimen. Assessment of the frequency and severity of cataplexy attacks, based on sleep diary entries, did not demonstrate a statistically significant improvement in daily rates of cataplexy over placebo (when subjects with zero or missing cataplectic events are ignored).

(b) (4)

HARMONY 1bis was an 8-week, randomized, double-blind, trial in patients with narcolepsy with or without cataplexy to determine the efficacy and safety of pitolisant administered by escalating dose (5 mg, 10 mg, or 20 mg once daily) compared to placebo and modafinil. The primary endpoint was the change from baseline to final (mean of weeks 7 and 8) in EES. Secondary endpoints included the MWT, Sustained Attention to Response Task (SART), EES responder rate (final EES score of ≤ 10 or change in baseline ≥ 3), daily cataplexy rate, CGI-C, EQ-5D, patient global opinion, and polysomnography. A total of 153 patients completed the study (31 in the placebo group, 62 in the modafinil group, and 60 in the pitolisant group). The mean reduction in ESS score in the pitolisant group as compared to placebo was statistically significant ($p = 0.030$).

The Applicant found that patients in the pitolisant group (65%) were more likely than patients in the placebo group (34%) to meet criteria for response rate ($p = 0.001$). No significant difference in the daily cataplexy rate was found among patients in the three treatment groups. In the pitolisant group, patients had a greater increase in sleep latency as compared with the placebo group ($p = 0.021$). The Applicant found that patients in the pitolisant group had lower mean SART TOTAL error (0.8) and SART error scores (0.74) compared to patients in the placebo group (1.03; $p = 0.043$ and 0.002 , respectively).

CGI-C scores for EDS improved significantly more in pitolisant-treated patients than in placebo-treated patients ($p < 0.001$). No significant difference between the pitolisant and placebo groups on the CGI-C for cataplexy was observed. No significant difference on EQ-5D scores or patient global opinion on treatment was found between the pitolisant and placebo groups. There were also no significant differences in polysomnography parameters observed among the treatment groups.

The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness for the treatment of EDS in patients with narcolepsy.^e The studies for pitolisant for the treatment of EDS in patients with narcolepsy met their primary endpoints. Secondary endpoints, including the MWT, provided additional evidence in support of a meaningful clinical effect. The trials provide adequate evidence to approve pitolisant for the treatment of EDS in narcolepsy.

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5 Risk Assessment & Safe-Use Conditions^{6,7}

Studies P07-03 (HARMONY 1) and P11-05 (HARMONY CTP) along with three additional supportive studies P09-15 (HARMONY 1bis) were used to compile the safety database. In addition, European Postmarketing data is publicly available in the EudraVigilance database and two thorough QT studies were submitted by the Applicant.

At the time of NDA submission, 1513 unique patients had been exposed to pitolisant in clinical trials. While 774 patients in clinical trials have been exposed to pitolisant for 6 months to 1 year and 334 patients in clinical trials have been exposed for ≥ 1 year.

Nine deaths occurred in the pitolisant development program; all occurred in patients receiving pitolisant. The clinical reviewer concluded that *“although these patients had co-morbid health conditions that could have contributed to their risk of death, the data are insufficient to conclude whether the deaths were related to pitolisant.”*

In the narcolepsy development program, the most common Treatment Emergent Adverse Events (TEAEs) occurring most frequently in pitolisant-treated patients and at a frequency greater than in the placebo group were headache, sleep disorder (including insomnia and poor-quality sleep), and nausea. Nervous System Disorders, Psychiatric Disorders, and Gastrointestinal Disorders were the most frequently reported SOCs for TEAEs. Per the clinical reviewer, Serious Adverse Events (SAEs)^{f,g} were rare in the narcolepsy development program and no consistent pattern linking the SAEs could be discerned.

QT studies (P09-11 and P14-05) demonstrated that pitolisant has the potential to prolong the QT interval at exposures greater than the recommended doses (142.4 mg to 213.6 mg). However, clinically significant QT prolongation was not observed in the clinical trials. In May 2019, DPV completed an analysis of EU postmarketing adverse event (AE) reports, as well as data from the Applicant’s most

^f Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

^g Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

recent (fourth) Periodic Benefit Risk Evaluation Report (PBRE-4) and did not have specific regulatory recommendations for further safety analysis, enhanced pharmacovigilance, or postmarketing requirements or commitments¹.

The proposed Prescribing Information (PI) contains a Warning (Section 5.1) that states Wakix prolongs the QT interval and should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval. A list of these drugs are provided in the drug interaction section (7.1) of the PI. The Warning will also state that Wakix should also 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.

Lastly, the PI Warning states that patients with hepatic or renal impairment may be at greater risk for QT prolongation due to higher concentrations of pitolisant. [REDACTED] (b) (4)

[REDACTED] PI instructs patients with moderate hepatic impairment and moderate or severe renal impairment be monitored for increased QTc and not recommended in patients with end stage renal disease (ESRD). Dosing recommendations are provided for this patient population. Wakix is contraindicated (Section 4) in patients with severe hepatic impairment due to the risk of QT prolongation.

6 Expected Postmarket Use

Wakix will likely be used by primary care physicians, sleep specialists, and psychiatrists to manage adult patients with narcolepsy in any treatment setting, inpatient or outpatient. Since narcolepsy is a lifelong condition, Wakix will most likely be used as a chronic outpatient medication, with or without other concomitant treatments for narcolepsy/cataplexy. Since it is the first medicine proposed for narcolepsy that is not a controlled substance, if approved, it may be used broadly in the relatively small patient population diagnosed with narcolepsy (<200,000 in the US).

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Wakix beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

Pitolisant is a histamine-3 receptor antagonist/inverse agonist proposed for the treatment of excessive daytime sleepiness in adult patients with narcolepsy and for the treatment of cataplexy in adult patients with narcolepsy. Its mechanism of action is different from any other class of medication approved in the US for the treatment of EDS in patients with narcolepsy or cataplexy in patients with narcolepsy. Pitolisant has been approved for the treatment of narcolepsy with or without cataplexy since March 2016 in the EU.

Currently, there are 6 FDA-approved treatments for excessive daytime sleepiness in patients with narcolepsy and 1 FDA-approved treatment for the treatment of cataplexy that is approved with a REMS. All the approved treatments are scheduled controlled substances. Sodium Oxybate is a sodium salt of gamma hydroxybutyrate (GHB), a schedule 1 controlled substance. A REMS for sodium oxybate is in place to mitigate the risk of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion. If approved, pitolisant would be the first non-controlled therapy approved for the treatment of EDS in patients with narcolepsy.

Pitolisant efficacy and safety in the treatment of EDS in patients with narcolepsy is supported by 3 clinical studies in adult patients and the Clinical Reviewer recommends approval of Wakix for EDS in patients with narcolepsy based on the efficacy and safety information currently available. The identified safety concern with pitolisant is the potential for QT prolongation, especially in patients at a higher risk of developing QT prolongation. Although QT prolongation was not seen in the clinical studies, the proposed PI has been maximized to inform providers about the potential for QT prolongation in certain patients. We agree with the clinical reviewer that the risk associated with pitolisant use at recommended doses in narcolepsy appear to be manageable in the context of standard clinical care.

This is a similar approach as the approved product in the European Union (EU). Wakix has been approved (b) (4) in the EU since March 2016 with the same tradename, and QT interval prolongation is described in the special warnings and precautions for use in EU labeling. During the review of the NDA, the Division of Pharmacovigilance (DPV) completed an analysis of EU postmarketing adverse event (AE) reports, as well as data from the Applicant's most recent Periodic Benefit Risk Evaluation Report and did not have specific regulatory recommendations for further safety analysis, enhanced pharmacovigilance, or postmarketing requirements or commitments. Given that QT prolongation can be monitored and easily recognized, measures beyond labelling are not necessary for the benefits of Wakix to outweigh the risk of QT prolongation.

9 Conclusion & Recommendations

DRISK determined that a REMS is not necessary to ensure the benefits of Wakix outweigh the risk. This decision is supported by the clinical review of the safety data in the development program as well as the analysis of EU postmarketing adverse event (AE) reports provided by DPV. The QT prolongation associated with Wakix in certain patients can be addressed in the Warnings and Precautions and other sections of the PI, which will inform healthcare providers about this potential safety concern.

Should DPP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 REFERENCES

-
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- ¹⁵ Bioprojet Pharma Wakix (pitolisant), Module 2.5 Clinical Overview
- ¹⁶ Bioprojet Pharma Wakix (pitolisant), Module 2.7.3 Summary of Clinical Efficacy
- ¹⁷ Bioprojet Pharma Wakix (pitolisant), Module 2.7.4 Summary of Clinical Safety

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