

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

Pr **WAKIX**<sup>®</sup>

Pitolisant hydrochloride tablets

5 mg and 20 mg tablets

Histamine H3 receptor antagonist / inverse agonist

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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

WAKIX® (pitolisant hydrochloride tablets) is indicated for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy.

This indication is based on pivotal trials of up to 8 weeks duration, in adults over 18 years of age.

#### 1.1 Pediatrics

**Pediatrics (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

#### 1.2 Geriatrics

**Geriatrics (> 65 years of age):** There is limited information for use of WAKIX in elderly patients. Use WAKIX with caution in elderly, and particularly in very elderly (≥75 years old) patients (see [DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment](#); [WARNINGS AND PRECAUTIONS, Special Populations](#)).

### 2 CONTRAINDICATIONS

- WAKIX® (pitolisant hydrochloride tablets) is contraindicated in patients who are hypersensitive to pitolisant hydrochloride or to any ingredient in the formulation, or component of the container. For a complete listing, see [Dosage Forms, Strengths, Composition and Packaging](#).
- WAKIX is contraindicated in patients with severe hepatic impairment.
- WAKIX is contraindicated in breastfeeding patients.

### 3 DOSAGE AND ADMINISTRATION

#### 3.1 Dosing Considerations

- WAKIX® must be taken in the morning upon waking.
- WAKIX should be taken with food.
- WAKIX tablets should not be chewed, divided or crushed before swallowing.
- WAKIX should be used at the lowest effective dose, depending on individual patient response and tolerance.
- The total daily dose should not exceed 40 mg per day.  
Greater exposures of pitolisant are expected in patients:
  - with hepatic impairment
  - with renal impairment
  - who are CYP2D6 poor metabolizers
  - who are taking a strong CYP2D6 inhibitorFollow recommended dosage adjustments and monitor closely.
- Patients taking a strong CYP3A4 inducer concomitantly with WAKIX are subject to lower exposures of pitolisant. Follow recommended dosage adjustments and monitor closely.

## 3.2 Recommended Dose and Dosage Adjustment

### Recommended Dose

WAKIX should be used at the lowest effective dose, depending on individual patient response and tolerance. All patients should be initiated at 10 mg per day and titrated as necessary according to the following recommended titration scheme:

- Week 1: initiate treatment with a dose of 10 mg (two 5 mg tablets) once daily
- Week 2: the dose may be increased to 20 mg (one 20 mg tablet) once daily, as needed
- Week 3: the dose may be increased to the maximum recommended dose of 40 mg (two 20 mg tablets) once daily, as needed

The total daily dose should not exceed 40 mg per day.

Patients should be monitored for both efficacy and tolerability and dose should be adjusted accordingly. Some patients may achieve benefit at lower doses and/or require a lower dose based on tolerability.

It may take up to 8 weeks for patients to achieve an optimal response.

### Dosage Adjustments

Pediatric (< 18 years of age): Health Canada has not authorized an indication for pediatric use.

Geriatric (> 65 years of age): Use WAKIX with caution in elderly, and particularly in very elderly ( $\geq 75$  years old) patients. Carefully consider hepatic, renal, and cardiac function before increasing dose and monitor closely (see [WARNINGS AND PRECAUTIONS, Special Population](#); [ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics](#)).

Hepatic Impairment: WAKIX is contraindicated in patients with severe hepatic impairment (see [CONTRAINDICATIONS](#)).

The total daily dose of WAKIX should not exceed 20 mg in patients with moderate hepatic impairment. In addition, prolong each titration step to 2 weeks instead of 1 week due to expected longer half-life and monitor patients closely (see [WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic](#); [ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics](#)).

Renal Impairment: The total daily dose of WAKIX should not exceed 20 mg in patients with mild to severe renal impairment (eGFR 89 to 15 mL/min/1.73m<sup>2</sup>). Patients with renal impairment should be monitored closely (see [ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics](#)).

WAKIX should not be used in patients with end-stage renal disease (see [WARNINGS AND PRECAUTIONS, Renal](#)).

Genetic Polymorphism: The total daily dose of WAKIX should not exceed 20 mg for patients who are poor CYP2D6 metabolizers. Monitor these patients closely (see [ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics](#)).

### Concomitant Medications:

Exercise caution when using WAKIX in combination with strong CYP2D6 inhibitors:

- The total daily dose of WAKIX should not exceed 20 mg.
- For patients taking strong CYP2D6 inhibitors, initiate WAKIX under close monitoring.

- For patients on a stable dose of WAKIX, reduce the WAKIX dose by half upon initiating strong CYP2D6 inhibitors.

Exercise caution when using WAKIX in combination with strong CYP3A4 inducers:

- Assess for loss of efficacy after initiation of a strong CYP3A4 inducer.
- In patients previously stable on 20 mg, consider titrating the dose of WAKIX up to a maximum of 40 mg, if needed.
- If concomitant dosing with a strong CYP3A4 inducer is discontinued, decrease WAKIX dosage by half and monitor closely.

(see [DRUG INTERACTIONS, Drug-Drug Interactions](#))

### 3.3 Administration

The total WAKIX daily dose should be administered orally as a single dose in the morning, upon waking, and should be taken with food. WAKIX tablets should not be chewed, divided or crushed before swallowing.

Taking the medication later in the day (e.g., late afternoon or in the evening) should be avoided as it may affect nighttime sleep.

### 3.4 Missed Dose

If a dose is missed, patients should take the next dose the following day in the morning upon awakening.

## 4 OVERDOSAGE

No case of overdose was observed during clinical trials with WAKIX®. No specific treatment has been established in the event of an overdose with WAKIX.

In case of suspected overdose, patients should be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment should be instituted as required. Consider the need for ECG monitoring.

For management of a suspected drug overdose, contact your regional poison control centre.

## 5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 1.** Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 5 mg and 20 mg of pitolisant hydrochloride	Colloidal anhydrous silica, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, polyvinyl alcohol, purified water, talc, titanium dioxide

5 mg tablets: white, round, biconvex film-coated tablet, marked with “5” on one side and plain on the other side.

20 mg tablets: white, round, biconvex film-coated tablet, marked with “20” on one side and plain on the other side.

WAKIX<sup>®</sup> tablets are supplied in 30 counts white HDPE bottle, capped with a child-resistant closure.

## 6 WARNINGS AND PRECAUTIONS

### Cardiovascular

#### *QTc prolongation*

WAKIX<sup>®</sup> causes a concentration-dependent prolongation of the QTc interval (see [ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics](#)). Although it has not been observed in association with the use of WAKIX at recommended doses in clinical studies, QTc prolongation can increase the risk of the polymorphic ventricular tachyarrhythmia and torsade de pointes. Torsade de pointes can be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender, age  $\geq 65$  years, baseline prolongation of the QTc interval, presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes, family history of sudden cardiac death at  $< 50$  years of age, cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease), history of arrhythmias, symptomatic bradycardia, electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders), acute neurological events, diabetes mellitus, and autonomic neuropathy.

The use of WAKIX should be avoided in patients with known QT prolongation, in patients with risk factors for torsade de pointes or in combination with other drugs that are known to prolong the QT interval or strongly inhibit CYP2D6 (see [DRUG INTERACTIONS, Drug-Drug Interactions](#)).

The extent of QTc prolongation with WAKIX is expected to be higher in patients who are poor metabolizers of CYP2D6 substrates and in patients with hepatic or renal impairment due to higher concentrations of pitolisant. Monitor CYP2D6 poor metabolizers and patients with hepatic or renal impairment for increased QTc. Dosage modification is recommended in CYP2D6 poor metabolizers and patients with moderate hepatic impairment or moderate to severe renal impairment (see [DOSAGE AND ADMINISTRATION, Dosing Consideration](#)). WAKIX is contraindicated in patients with severe hepatic impairment and is not recommended in patients with end stage renal disease (ESRD).

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug. Patients should be advised to contact their healthcare provider immediately to report any new chest pain or discomfort, changes in heart beat, palpitations, dizziness, lightheadedness, fainting, or changes in or new use of other medications.

### **Dependence/Tolerance**

Because WAKIX affects the central nervous system, there is a potential risk for drug abuse and misuse, drug dependence and rebound effect. Based on the clinical evidence<sup>1</sup>, WAKIX presents a low abuse liability potential at recommended doses. No withdrawal or rebound effect was observed during clinical trials, at the recommended doses.

### **Driving and Operating Machinery**

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that WAKIX therapy will not adversely affect their ability to engage in such activities.

### **Hepatic/Biliary/Pancreatic**

WAKIX is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see [CONTRAINDICATIONS](#)).

Consider the need to determine liver function prior to initiating WAKIX.

WAKIX is extensively metabolized by the liver and there is a significant increase in pitolisant exposure and longer half-life in patients with moderate hepatic impairment compared to patient with normal hepatic function. Follow recommended dosage adjustments and monitor closely (see [DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment](#)).

### **Neurologic**

Caution is recommended when treating patients with a history of epilepsy. In clinical studies and post-marketing experience there have been reports of seizures or worsening of seizures in patients with a history of epilepsy. In animal studies, pitolisant's metabolites induced convulsions at high doses (see [NON-CLINICAL TOXICOLOGY, General Toxicology](#)).

### **Psychiatric**

WAKIX should be administered with caution in patients with history of psychiatric disorders including anxiety and depression. There have been post-market reports of suicidal ideation and hospitalizations for psychiatric illness in patients receiving pitolisant.

### **Renal**

Determine renal function prior to initiating WAKIX. Higher exposure is expected in patients with mild to severe renal impairment (eGFR 89 to 15 mL/minute/1.73 m<sup>2</sup>). Follow recommended dosage adjustments and monitor closely (see [DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment](#)).

The pharmacokinetics of WAKIX in patients with end stage renal disease (ESRD) (eGFR of <15 mL/minute/1.73 m<sup>2</sup>) is unknown. Pitolisant is unlikely to be dialyzable. Therefore, WAKIX should not be used in patients with ESRD.

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<sup>1</sup> Setnik *et al.* Sleep. 2019

## **Sexual Health**

### **Reproduction**

There are very limited data involving the use of WAKIX in pregnant women (see [Special Populations – Pregnant Women](#)).

Studies in animals have shown reproductive toxicity, including teratogenicity. In rats, pitolisant/metabolites were shown to cross the placenta (fetal blood and tissue levels of pitolisant and its metabolites were comparable to maternal blood concentrations) (see [NON-CLINICAL TOXICOLOGY – Reproductive and Developmental Toxicology](#)).

WAKIX should not be used during pregnancy.

WAKIX may reduce the effectiveness of hormonal contraceptives. Women relying on hormonal therapy for contraception should employ at least one other reliable non-hormonal contraceptive method during treatment with WAKIX and for at least 21 days after discontinuing treatment.

### **Fertility**

Studies in animals have shown effects on semen parameters, without significant impact on reproductive performance in males, and a reduction in the percentage of live fetuses in treated females (see [NON-CLINICAL TOXICOLOGY – Reproductive and Developmental Toxicology](#)).

## **6.1 Special Populations**

### **6.1.1 Pregnant Women**

There is very limited data on WAKIX in pregnant women in clinical trials. WAKIX should not be used during pregnancy unless the clinical condition of the women requires treatment with WAKIX. Based on findings from animal studies, there may be a risk to the fetus from exposure to WAKIX during pregnancy. Oral administration of pitolisant to female rats during pregnancy and lactation adversely affected maternal and fetal health and produced developmental delay (see [NON-CLINICAL TOXICOLOGY – Reproductive and Developmental Toxicology](#)).

Women of childbearing potential should be advised to avoid becoming pregnant while receiving WAKIX. This includes the use of reliable methods of birth control. As WAKIX may reduce the effectiveness of hormonal contraceptives, women relying on hormonal therapy for contraception should employ at least one other reliable non-hormonal method of contraception during treatment with WAKIX and for at least 21 days after discontinuing treatment.

### **6.1.2 Breastfeeding**

It is unknown if WAKIX is excreted in human milk. There is no data on the effects on the breastfed infant, or the effect of this drug on milk production. Pitolisant is present in the milk of lactating rats, with a milk to plasma ratio of up to 3 times, within 6 hours of administration. In rats, milk production was also reduced at higher doses of pitolisant (see [NON-CLINICAL TOXICOLOGY – Reproductive and Developmental Toxicology](#)).

A risk to the breastfeeding child cannot be excluded and therefore breastfeeding is contraindicated (see [CONTRAINDICATIONS](#)).

### **6.1.3 Pediatrics**

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

#### 6.1.4 Geriatrics

Limited pharmacokinetic data are available in healthy elderly subjects.

Of the total number of patients with narcolepsy in clinical studies of WAKIX, 14 patients (~5%) were ≥ 65 years old. No clinically relevant differences in safety or effectiveness were observed between these patients and younger patients in these clinical trials, but greater sensitivity of some older individuals cannot be ruled out. Use WAKIX with caution in elderly, and particularly in very elderly (≥75 years old) patients. Carefully consider hepatic, renal, and cardiac function before increasing dose and monitor closely (see [DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment](#); [ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics](#)).

### 7 ADVERSE REACTIONS

#### 7.1 Adverse Reaction Overview

A total of 172 individual patients were exposed to pitolisant during the double-blind, placebo-controlled narcolepsy clinical trials of up to 8 weeks duration. The most common adverse events reported with pitolisant were: headache (18.0%), nausea (5.2%), insomnia (4.1%) and viral upper respiratory track infection (4.1%). Adverse events are mostly mild to moderate in intensity.

In the double-blind, placebo-controlled narcolepsy studies, the incidence of serious adverse events (SAE) was low and similar between the pitolisant (1.2%) and placebo (0.8%) treatment groups and none was considered related to treatment by the investigator. The incidence of adverse events leading to discontinuation was similar between the pitolisant (3.5%) and placebo (3.8%) treatment groups and included adverse events in the Gastrointestinal Disorders, Nervous System Disorders, and Psychiatric Disorders SOCs.

During the single-blind and open-label studies (n=137), depression (2.2%) was reported as serious adverse events, sometimes leading to discontinuation (1.5%).

#### 7.2 Clinical Trial Adverse Reactions

*Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The safety of WAKIX in adults patients in narcolepsy presented herein was evaluated in three pivotal Phase 3 efficacy studies – HARMONY I, HARMONY Ibis and HARMONY CTP (see [CLINICAL TRIALS](#)).

The most common adverse events reported in WAKIX pivotal double-blind placebo-controlled trials were headache (17.5%), nausea (6.0%) and insomnia (4.7%).

Adverse events leading to discontinuation included adverse events of gastrointestinal, nervous system and psychiatric disorders.

Table 2 and 3 present the adverse reactions that occurred in more than one patient treated with WAKIX in the pivotal double-blind placebo-controlled trials.

**Table 2.** TEAEs occurring > 2% (n>1) in WAKIX-treated patients – HARMONY I and HARMONY Ibis

<b>SOCs</b>	<b>WAKIX</b>	<b>Modafinil</b>	<b>Placebo</b>
<b>Preferred term</b>	<b>(n=95)</b>	<b>(n=95)</b>	<b>(n=62)</b>
	<b>% (n)</b>	<b>% (n)</b>	<b>% (n)</b>
<b>Any Adverse Event</b>	55.8 (53)	58.9 (56)	48.4 (30)
<b>Gastrointestinal disorders</b>			
Nausea	6.3 (6)	2.1 (2)	4.8 (3)
Diarrhoea	3.2 (3)	6.3 (6)	3.2 (2)
Dry mouth	3.2 (3)	0	1.6 (1)
Vomiting	3.2 (3)	0	0
Abdominal pain	2.1 (2)	4.2 (4)	1.6 (1)
Odynophagia	2.1 (2)	0	0
<b>General disorder and administration site conditions</b>			
Fatigue	3.2 (3)	3.2 (3)	3.2 (2)
Pyrexia	2.1 (2)	1.1 (1)	0
<b>Infections and Infestations</b>			
Viral upper respiratory tract infection	6.3 (6)	6.3 (6)	1.6 (1)
<b>Investigations</b>			
Heart rate increased	2.1 (2)	1.1 (1)	0
<b>Metabolism and Nutrition Disorders</b>			
Decreased appetite	4.2 (4)	1.1 (1)	0
<b>Musculoskeletal and Connective Tissue Disorders</b>			
Back pain	4.2 (4)	0	1.6 (1)
Arthralgia	3.2 (3)	0	0
<b>Nervous system disorders</b>			
Headache	22.1 (21)	12.6 (12)	17.7 (11)
Dizziness	5.3 (5)	5.3 (5)	1.6 (1)
Cataplexy	3.2 (3)	2.1 (2)	1.6 (1)
Somnolence	2.1 (2)	2.1 (2)	1.6 (1)
Hypersomnia	2.1 (2)	1.1 (1)	0
Tremor	2.1 (2)	1.1 (1)	0
<b>Psychiatric disorders</b>			
Insomnia	6.3 (6)	0	3.2 (2)
Anxiety	2.1 (2)	3.2 (3)	0
Irritability	2.1 (2)	3.2 (3)	0
Hallucination	2.1 (2)	1.1 (1)	0

**Table 3.** TEAEs occurring > 3% (n>1) in WAKIX-treated patients – HARMONY CTP

<b>SOCs</b>	<b>WAKIX</b>	<b>Placebo</b>
<b>Preferred term</b>	<b>(n=54)</b>	<b>(n=51)</b>
	<b>% (n)</b>	<b>% (n)</b>
<b>Any Adverse Event</b>	<b>35.2 (19)</b>	<b>31.4 (16)</b>
<b>Gastrointestinal disorders</b>		
Nausea	5.6 (3)	0
<b>General disorder and administration site conditions</b>		
Asthenia	3.7 (2)	3.9 (2)
<b>Infections and Infestations</b>		
Upper respiratory tract infection	3.7 (2)	0
<b>Investigations</b>		
Heart rate increased	3.7 (2)	0
<b>Nervous system disorders</b>		
Headache	9.3 (5)	9.8 (5)
<b>Psychiatric disorders</b>		
Anxiety	5.6 (3)	0
Irritability	5.6 (3)	2.0 (1)
Dyssomnia	3.7 (2)	2.0 (1)

### 7.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions were also reported in the pivotal clinical studies at an incidence of n=1 in adult patients with narcolepsy who were treated with WAKIX.

**Cardiac disorders:** angina pectoris, bundle branch block right, palpitations, sinus tachycardia

**Eye disorders:** dry eye

**Gastrointestinal disorders:** abdominal discomfort, abdominal pain upper, aphthous ulcer, dyspepsia, gastrointestinal pain, hemorrhoids, oral mucosal blistering, stomatitis, toothache

**Hepatobiliary disorders:** cholecystitis chronic

**Immune system disorders:** allergy to metal

**Infections and infestations:** cystitis, erythema migrans, hordeolum, meningitis, pyelonephritis, sinusitis

**Injury, poisoning and procedural complications:** skin abrasion, thermal burn

**Investigations:** alanine aminotransferase increased, aspartate aminotransferase increased, blood creatine phosphokinase increased, electrocardiogram t wave inversion, gamma-glutamyltransferase increased, heart rate irregular, weight increased

**Metabolism and nutrition disorders:** appetite disorder, fluid retention

**Musculoskeletal and connective tissue disorders:** myalgia

**Nervous system disorders:** cluster headache, dyskinesia, migraine, tension headache

**Psychiatric disorders:** abnormal dreams, agitation, apathy, depression and depressive symptoms, dysphoria, hallucination visual, hypnagogic hallucination, initial insomnia, middle insomnia, nervousness, nightmare, restlessness, sleep disorder, sleep talking, stress

**Renal and urinary disorders:** dysuria, pollakiuria, urine odour abnormal

**Reproductive system and breast disorders:** dysmenorrhoea, premenstrual headache

**Respiratory, thoracic and mediastinal disorders:** oropharyngeal pain, respiratory distress

**Skin and subcutaneous tissue disorders:** eczema, hyperhidrosis, rash

**Vascular disorders:** hypertension

#### 7.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

**Table 4.** Incidence of CTCAE Grade 4 post-baseline change in laboratory tests in adult patients during the narcolepsy studies

Parameter and Criterion	WAKIX n=303	Placebo n=131
	n (%)	n (%)
Platelets – low	3 (1.1)	0
Glucose – high	1 (0.4)	0
Potassium – high	2 (0.8)	3 (2.6)
Potassium – low	1 (0.4)	1 (0.9)
Sodium – low	2 (0.8)	0

CTCAE: Common Terminology Criteria for Adverse Events

#### 7.5 Clinical Trial Adverse Reactions (Pediatrics)

The safety profile of WAKIX has not been established in the pediatric population.

#### 7.6 Post-Market Adverse Reactions

The following adverse reactions have been reported from marketing experience with WAKIX outside of Canada. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Ear and labyrinth disorders:** tinnitus

**General disorders and administration site condition:** malaise

**Immune system disorders:** hypersensitivity (anaphylaxis)

**Nervous system disorders:** epilepsy

**Psychiatric disorders:** abnormal behavior, aggression, mania, suicide attempt, suicidal ideation

**Skin and subcutaneous tissue disorders:** pruritus, urticaria

**Vascular disorders:** hot flush

## 8 DRUG INTERACTIONS

### 8.1 Overview

Concomitant administration of WAKIX with strong CYP2D6 inhibitors meaningfully increases pitolisant exposure.

Concomitant use of WAKIX with strong CYP3A4 inducers decreases exposure of pitolisant.

For concomitant use of WAKIX with strong CYP2D6 inhibitors and strong CYP3A4 inducers, follow recommended dosage adjustments and monitor closely (see [DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment](#)).

Avoid use of centrally acting H1 receptor antagonists with WAKIX as these can reduce the effectiveness of WAKIX.

Avoid the use of WAKIX in combination with other drugs known to prolong the QT interval as this can increase the risk of cardiac arrhythmia.

The effectiveness of hormonal contraception may be reduced when used with WAKIX. Women using hormonal contraception should add at least one other reliable non-hormonal method of contraception during treatment with WAKIX and for at least 21 days after discontinuation of treatment.

Exercise caution when pitolisant is administered with a substrate of OCT1.

## 8.2 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

**Table 5.** Established or Potential Drug-Drug Interactions

Drug Class and/or Name	Source of Evidence	Effect	Clinical comment
Strong CYP2D6 Inhibitors (e.g., bupropion, cinacalcet, fluoxetine, paroxetine, quinine, terbinafine, venlafaxine)	CT	Strong CYP2D6 inhibitors increased pitolisant $C_{max}$ and AUC by 2.2-fold.	<ul style="list-style-type: none"> <li>For patients taking strong CYP2D6 inhibitors, initiate WAKIX under close monitoring.</li> <li>For patients on a stable dose of WAKIX, reduce the WAKIX dose by half upon initiating strong CYP2D6 inhibitors.</li> <li>Maximum recommended dose is 20 mg.</li> </ul>
Strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin)	CT	Strong CYP3A4 inducers decreased pitolisant $C_{max}$ and AUC by 50%.	<ul style="list-style-type: none"> <li>Assess for loss of efficacy after initiation of a strong CYP3A4 inducer.</li> <li>In patients previously stable on 20 mg, consider titrating the dose of WAKIX to a maximum of 40 mg if needed.</li> <li>If concomitant dosing with a strong CYP3A4 inducer is discontinued, decrease WAKIX dosage by half and monitor closely.</li> </ul>
Histamine-1 (H1) Receptor Antagonists (e.g., pheniramine maleate,	T	WAKIX increases the levels of histamine in the brain; therefore, H1 receptor	Avoid concomitant use of centrally acting H1 receptor antagonists.

Drug Class and/or Name	Source of Evidence	Effect	Clinical comment
diphenhydramine, promethazine (anti-histamines), imipramine, clomipramine, mirtazapine (tri or tetracyclic antidepressant))		antagonists that cross the blood-brain barrier may reduce the effectiveness of WAKIX.	
QTc Prolonging Drugs (e.g., Class 1A antiarrhythmics (procainamide, disopyramide), Class 3 antiarrhythmics (amiodarone, sotalol), antipsychotics (ziprasidone, chlorpromazine) and antibiotics (moxifloxacin))*	T	Concomitant use of drugs that prolong the QT interval may add to the QTc-prolonging effects of WAKIX and increase the risk of cardiac arrhythmia.	Avoid the use of WAKIX in combination with other drugs known to prolong the QT interval.
Drugs that Can Reduce Serum Electrolytes (e.g., loop, thiazide, and related diuretics, laxatives and enemas, amphotericin B, high dose corticosteroids)*	T	Hypokalemia, hypocalcemia, and/or hypomagnesemia may increase the QTc prolongation effect of WAKIX.	Caution should be observed if WAKIX is administered with drugs that can decrease serum levels of potassium, magnesium, and/or calcium because of potential augmentation of the QTc prolongation effect (see <a href="#">WARNINGS AND PRECAUTIONS, Cardiovascular</a> ; <a href="#">ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology</a> ). Monitoring of electrolytes is recommended.
Sensitive CYP3A4 Substrates (e.g., midazolam, hormonal contraceptives, cyclosporine)	CT	WAKIX is a weak inducer of CYP3A4. Therefore, reduced effectiveness of sensitive CYP3A4 substrates may occur when used concomitantly with WAKIX.  The effectiveness of hormonal contraceptives (e.g., ethinyl estradiol) may	Women relying on hormonal therapy for contraception should employ at least one other reliable non-hormonal concomitant method of contraception during treatment with WAKIX and for at least 21 days after discontinuation of treatment.

Drug Class and/or Name	Source of Evidence	Effect	Clinical comment
		be reduced when used with WAKIX up to 21 days after discontinuation of therapy.	
Strong inhibitors of uridine glucuronyl transferases (UGT) (e.g. antineoplastic kinase inhibitors)	CT	Probenecid at steady state modestly decreased pitolisant AUC but increased AUC of its inactive metabolites, some greater than 6-fold. The clinical relevance of this effect has not been established.	Exercise caution when WAKIX is administered with a strong inhibitor of UGT.
Substrates of organic cation transporters 1 (OCT1) (e.g., metformin or biguanides)	T	<i>In vitro</i> , pitolisant showed greater than 50% inhibition towards OCT1 at 1.33 $\mu$ M, the extrapolated IC <sub>50</sub> of pitolisant is 0.795 $\mu$ M. The clinical relevance of this effect has not been established.	Exercise caution when WAKIX is administered with a substrate of OCT1.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

\*This list is not comprehensive. Current information sources should be consulted for lists of QTc-prolonging drugs and/or drugs that can reduce serum electrolytes.

A clinical study was conducted to evaluate the concomitant use of WAKIX with sodium oxybate or modafinil. WAKIX did not meaningfully alter the pharmacokinetics of sodium oxybate or modafinil. Pitolisant exposure was modestly reduced (15 to 20%) when given concomitantly with these medications. No dosage adjustment is necessary.

A clinical study showed that a strong CYP3A4 inhibitor did not meaningfully affect the pharmacokinetics of WAKIX.

A clinical study showed that WAKIX did not meaningfully affect the pharmacokinetics of a CYP2B6 substrate.

### 8.3 Drug-Food Interactions

Food (high-fat, high calorie breakfast) delays  $T_{max}$  and reduces the rate and extent of absorption of pitolisant. In Phase III clinical studies, WAKIX was administered in the morning, without regards to food.

Consumption of grapefruit and grapefruit juice may impact exposure to WAKIX.

## 8.4 Drug-Herb Interactions

Interactions with herbs have not been established; however, precautions consistent with those outlined above, including dose adjustment and close monitoring, should be exercised when WAKIX is taken with herbs that are:

- potent CYP2D6 inhibitors (e.g., goldenseal)
- potent CYP3A4 inducers (e.g. St. John's Wort)

## 8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 8.6 Drug-Lifestyle Interactions

Interactions with lifestyle have not been established.

# 9 ACTION AND CLINICAL PHARMACOLOGY

## 9.1 Mechanism of Action

Pitolisant is a potent, highly selective, orally active antagonist/inverse agonist of the human histamine 3 (H<sub>3</sub>) receptor. By binding to presynaptic histaminergic H<sub>3</sub> autoreceptors, it increases the synthesis and release of histamine, a wakefulness promoting neurotransmitter, as well as other neurotransmitters that promote wakefulness (e.g., acetylcholine, dopamine, norepinephrine). Histamine is important for stabilizing sleep/wake states via direct activation of wake-promoting brain regions and by directly and indirectly inhibiting REM and non-REM sleep-promoting brain regions.

Whereas WAKIX<sup>®</sup> increases neurotransmitter (norepinephrine, dopamine, serotonin, acetylcholine) release in the brain, it does not cause an increase in dopamine release in the striatal complex, including the nucleus accumbens.

## 9.2 Pharmacodynamics

Pitolisant binds to H<sub>3</sub> receptors with a high affinity (K<sub>i</sub> = 1nM) and has no appreciable binding to other histamine receptors (H<sub>1</sub>, H<sub>2</sub>, or H<sub>4</sub> receptors; K<sub>i</sub> >10 μM).

**Cardiac Electrophysiology:** In a randomized, double-blind, placebo- and positive-controlled, 4-period crossover ECG assessment study in healthy subjects (N=56), single 40 mg (therapeutic dose) and 120 mg (3X multiple of therapeutic dose) doses of pitolisant resulted in QTcF (QTcF=QT/RR<sup>0.33</sup>) prolongation. At the 40 mg dose, the 90% CI for the difference from placebo in mean change to baseline QTcF excluded zero only at the 2 h post-dose time point: 3.7 ms (90% CI 1.4, 5.9). In the 120 mg treatment arm, the 90% CI excluded zero from 1 h to 12 h post-dose, inclusive, and at 24 h, with a maximum difference from placebo of 9.9 ms (90% CI 7.6, 12.2) at 2 h post-dose. The geometric mean C<sub>max</sub> values of pitolisant after the single 40 mg and 120 mg doses were 50.2 ng/mL and 175.4 ng/mL, respectively.

In another randomized, double-blind, placebo- and positive-controlled ECG assessment study, pitolisant was administered as single ascending doses of 160 mg, 200 mg, and 240 mg to healthy subjects (N=6/treatment) according to a parallel group design to generate a pharmacokinetic-pharmacodynamic model of the relationship between pitolisant concentration and the placebo- and baseline-adjusted QTcF interval. On the basis of the pharmacokinetic-

pharmacodynamic model, the placebo-adjusted mean change from baseline QTcF is predicted to be 3.6 ms (90% CI 2.4, 4.8) at a concentration of 73 ng/mL (the mean steady-state  $C_{max}$  of pitolisant administered as 40 mg once-daily for 14 days in healthy subjects) and 7.2 ms (90% CI 5.6, 8.8) at 153 ng/mL (expected steady-state  $C_{max}$  for the 40 mg once-daily dose in poor metabolizers of CYP2D6 substrates). At a concentration of 333.5 ng/mL (e.g., expected steady-state  $C_{max}$  for the 40 mg once-daily dose in CYP2D6 poor metabolizers with mild renal impairment), the model-predicted difference from placebo in mean change from baseline QTcF prolongation is mean 15.3 ms (90% CI 12.1, 18.4).

### 9.3 Pharmacokinetics

**Table 6.** Summary of WAKIX Pharmacokinetic Parameters in Healthy Volunteers (geometric mean (%CV))

		$C_{max}$ (ng/mL)	$T_{max}$ <sup>1</sup> (h)	AUC <sup>2</sup> (ng*h/mL)	CL (L/h)
<b>Single dose</b>	20 mg (N=5)	12.6 (53.3)	3.0 (2.0-4.0)	150 (112)	134 (112)
	40 mg (N=5)	51.5 (14.0)	4.0 (2.0-4.0)	468 (13.7)	85.5 (13.7)
<b>Repeat dose (Day 7)</b>	20 mg (EM <sup>3</sup> ) (N=5)	36.4 (37.8)	4.0 (2.0-4.0)	406 (44.1)	43.9 (44.1)
	20 mg (PM <sup>3</sup> ) (N=3)	76.7 (1.9)	3.0 (2.0-4.0)	960 (4.0)	18.5 (4.0)
	40 mg (N=6)	71.1 (17.2)	2.5 (1.0-3.0)	724 (18.6)	41.9 (29.7)

<sup>1</sup> Median (min-max)

<sup>2</sup> AUC<sub>∞</sub> for the single dose and AUC<sub>τ</sub> for the repeat dose

<sup>3</sup> EM = CYP2D6 extensive metabolizer; PM = CYP2D6 poor metabolizer

**Absorption:** WAKIX is a highly permeable drug with complete absorption (90%), but systemic bioavailability is limited by high first pass metabolism.

WAKIX 40 mg at steady-state (as determined at Day 14) produced a mean maximum concentration ( $C_{max}$ ) for pitolisant of 73.1 ng/ml at around a median time ( $T_{max}$ ) of 3.5 hours (range 2 to 4 hours) and an AUC<sub>tau</sub> of 797 ng\*h/ml in patients with undetermined metabolizer status. CYP2D6 metabolizer status affects pharmacokinetic parameters meaningfully (see [Pharmacokinetics, Special Populations and Conditions - Genetic Polymorphism](#)).

Administration of WAKIX with food delays  $T_{max}$  and decreases the rate and extent of absorption of pitolisant.

**Distribution:** WAKIX 40 mg at steady-state (as determined at Day 7) produced a mean volume of distribution of 554L, is highly bound to plasma proteins (91-96%), and likely distributes to the brain (and other organs) through passive mechanisms. The blood to plasma ratio of pitolisant is 0.55 to 0.89.

**Metabolism:** WAKIX is extensively metabolized to many inactive metabolites, which are at least partly subsequently conjugated with glycine or through glucuronidation and excreted in the urine. Metabolism of WAKIX by CYP2D6 is an important pathway while metabolism by CYP3A4 is not.

**Elimination:** After a single dose of 40 mg, the mean half-life of WAKIX is approximately 20 hours (12.3-40.8 hours). The apparent oral clearance (CL/F) of WAKIX is 43.9 L/hr. In a mass balance study, the major path of elimination of radiolabelled WAKIX 20 mg was via the urine, where 89% of radioactivity was recovered, while 2.5% was recovered in the feces. Renal clearance accounted for < 2% of the total clearance of unchanged pitolisant. Pitolisant exposure increases proportionally with increasing single doses and accumulates with daily dosing with a mean accumulation ratio of 2.87 by Day 14. WAKIX steady state is reached by day 7.

## Special Populations and Conditions

**Pediatrics:** WAKIX is not indicated for use in children.

**Geriatrics:** Limited pharmacokinetic data are available. A pharmacokinetic study compared 12 healthy elderly subjects (age 68 to 82 years) to 12 healthy adults (age 18 to 45 years) treated with WAKIX 20 mg for 7 days. There was no evidence of a significant difference in exposure between elderly and non-elderly subjects. However, the data were suggestive of possible elevated exposure in very elderly subjects ( $\geq 80$  years) due to compromised clearance (see [DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment](#)).

**Sex:** No sex-related differences were noted in the clinical studies. As such, no dosage adjustments are needed based on sex.

**Genetic Polymorphism:** Up to 10% of the population may be CYP2D6 poor metabolizers.

In a study comparing CYP2D6 poor metabolizers (n = 3) to CYP2D6 normal metabolizers (n = 5),  $C_{max}$  and  $AUC_{0-24}$  of pitolisant after a single dose of WAKIX were 2.7-fold greater and 3.2-fold greater, respectively, in poor metabolizers than normal metabolizers. Following seven days of administration,  $C_{max}$  and  $AUC_{0-24}$  were 2.1-fold greater and 2.4-fold greater, respectively, in poor metabolizers than normal metabolizers (see [DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment](#)).

**Ethnic origin:** Ethnicity was not collected in the majority of the efficacy studies, so the effect of ethnicity on efficacy or safety could not be evaluated. Based on the PK studies, there were no differences in the dose-normalized  $C_{max}$  or  $AUC_{inf}$  between Caucasians and Blacks subjects. Groups of other ethnicities were too small to make any interpretation.

No dosage adjustment is required based on race.

**Hepatic Insufficiency:** A single dose of WAKIX 20 mg was administered to subjects with mild hepatic impairment (Child-Pugh A, n=6), moderate hepatic impairment (Child-Pugh B, n=6), and healthy subjects (n=12) to assess pharmacokinetics. Moderate hepatic impairment resulted in pitolisant exposure 2.4-fold greater than that observed in subjects with normal hepatic function (see [DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment](#); [WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic](#)).

No studies have been conducted in patients with severe hepatic impairment, for whom WAKIX is contraindicated (see [CONTRAINDICATIONS](#)).

**Renal Insufficiency:** A single dose of WAKIX 20 mg was administered to subjects with mild renal impairment (eGFR of 60 to 89 mL/min/1.73m<sup>2</sup>, n=4), moderate renal impairment (eGFR of 30 to 59 mL/min/1.73m<sup>2</sup>, n = 4), severe renal impairment (eGFR of 15 to 29 mL/min/1.73m<sup>2</sup>, n = 4), and subjects with normal renal function (eGFR of ≥90 mL/min/1.73m<sup>2</sup>, n = 12) to assess. Renal impairment of any degree resulted in C<sub>max</sub> and AUC<sub>inf</sub> of pitolisant that was approximately 2-fold that observed in subjects with normal renal function (see [DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment](#); [WARNINGS AND PRECAUTIONS, Renal](#)).

WAKIX was not studied in subjects with ESRD (see [WARNINGS AND PRECAUTIONS, Renal](#)).

**Obesity:** No BMI-related differences were noted during the clinical studies. As such, no dosage adjustment is needed based on BMI.

## 10 STORAGE, STABILITY AND DISPOSAL

Store between 15-30°C.

## PART II: SCIENTIFIC INFORMATION

### 11 PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name: pitolisant hydrochloride

Chemical name: 1-[3-[3-(4-chlorophenyl)propoxy]propyl]piperidine, hydrochloride

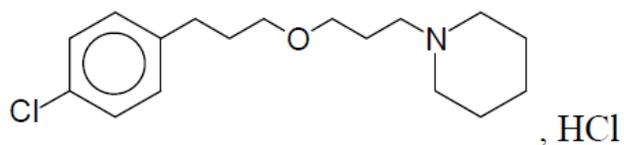
Molecular formula and molecular mass:

#### **Pitolisant Hydrochloride**

$C_{17}H_{26}ClNO$ , HCl

332.3 g/mol

Structural formula:



Physicochemical properties: white or almost white crystalline powder, very soluble in water ethanol and methylene chloride, freely soluble in acetone. Insoluble in cyclohexane.

## 12 CLINICAL TRIALS

### 12.1 Trial Design and Study Demographics

The efficacy of WAKIX® for the treatment of excessive daytime sleepiness in adult patients with narcolepsy was demonstrated in two multicenter, randomized, double-blind, placebo-controlled studies over 8 weeks (HARMONY I and HARMONY Ibis). Patients ≥18 years of age who met the International Classification of Sleep Disorders (ICSD-2) criteria for narcolepsy and who had an Epworth Sleepiness Scale (ESS) score ≥14 were eligible to enroll in the studies. These studies included patients with or without cataplexy (Narcolepsy type 1 or Narcolepsy type 2) and compared WAKIX to both a placebo and an active control (modafinil). The primary endpoint was reduction of Excessive Daytime Sleepiness (EDS). EDS was assessed using Epworth Sleepiness Scale (ESS, a validated scoring tool designed to assess the degree of sleepiness in everyday situations). Secondary endpoints included the Maintenance of Wakefulness Test (MWT), the change in the patient's overall disease status, as measured by the Clinical Global Impression of Change (CGI-C) and the reduction in daily cataplexy attacks.

The efficacy of WAKIX for the reduction of cataplexy attacks in adult patients with narcolepsy was evaluated in one multicenter, randomized, double-blind, placebo-controlled study over 7 weeks (HARMONY CTP). This study included exclusively patients with cataplexy (Narcolepsy type 1) and compared WAKIX to a placebo. The primary endpoint was the reduction in number of cataplexy attacks. Reduction of EDS was also assessed via the ESS and the MWT.

**Table 7.** Summary of patient demographics for WAKIX clinical trials in narcolepsy

Study #	Trial design	Dosage Route of administration Duration	Study subjects (n)	Median age (Range)	Sex (Males)
HARMONY I <sup>2</sup>	Randomized, double-blind, placebo controlled, patients with narcolepsy ± cataplexy	20 mg tablets Up to 40 mg daily Oral 8-week	N=94 WAKIX n=31 Placebo n=30 Modafinil n=33	WAKIX 33.0 (21-49) Placebo 39.5 (30-52) Modafinil 40.0 (25-48)	WAKIX n=20 (64.5%) Placebo n=13 (43.3%) Modafinil n=18 (54.5%)
HARMONY Ibis	Randomized, double-blind, placebo controlled, patients with narcolepsy ± cataplexy	20 mg tablets Up to 20 mg daily Oral 8-week	N=164 WAKIX n=67 Placebo n=32 Modafinil n=65	WAKIX 37.0 (29-52) Placebo 42.5 (29-55) Modafinil 43.0 (32-58)	WAKIX n=32 (47.8%) Placebo n=15 (46.9%) Modafinil n=30 (46.2%)

<sup>2</sup> Dauvillier *et al.* Lancet Neurol. 2013

HARMONY CTP <sup>3</sup>	Randomized, double-blind, placebo-controlled, patients with narcolepsy with cataplexy	20 mg tablets Up to 40 mg daily Oral 7-week	N= 105 WAKIX n=54 Placebo n=51	WAKIX 34.0 (18-64) Placebo 39.0 (18-66)	WAKIX n=26 (48.1%) Placebo n=27 (52.9%)
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In HARMONY I and HARMONY Ibis, 81% and 77% of the patients presented symptoms of cataplexy, respectively, while all patients in HARMONY CTP had cataplexy. About 80% of patients presented with one or more other narcolepsy symptoms (hallucination, dyssomnia, sleep paralysis, automatic behavior).

Thirty-five percent and 27% of patients in HARMONY I and HARMONY Ibis, respectively, were allowed to maintain their anticataplectic medication(s) during the studies while only 11% on the patients in HARMONY CTP were allowed anticataplectic use.

In HARMONY I and HARMONY CTP, approximately 61-64% of patients had a maintenance dose of 40 mg. In HARMONY Ibis, the maximum maintenance dose of 20 mg was administered in more than 60% of patients.

## 12.2 Study Results

### Excessive Daytime Sleepiness

**Table 8.** Results of WAKIX clinical trials for EDS in narcolepsy

Study	Treatment Group (n)	Baseline ESS Score Mean (SD)	Final ESS Score <sup>a</sup> Mean (SD)	Difference vs. WAKIX <sup>b</sup> [95% CI] p-value
HARMONY I**	WAKIX (31)	17.8 (2.5)	12.0 (6.2)	
	Placebo (30)	18.9 (2.5)	15.6 (4.7)	-3.1* [-5.73; -0.46] p=0.022
	Modafinil (33)	18.5 (2.7)	11.6 (6.0)	0.07 [-2.17; 2.32] p=0.932
HARMONY Ibis**	WAKIX (66)	18.2 (2.4)	13.7 (5.4)	
	Placebo (32)	18.2 (2.3)	14.6 (5.8)	-2.19* [-4.17; -0.22] p=0.030
	Modafinil (65)	18.1 (2.8)	10.3 (6.1)	2.75 [1.02; 4.48] p=0.002
HARMONY CTP	WAKIX (54)	17.4 (3.3)	12.0 (5.4)	
	Placebo (51)	17.3 (3.2)	15.4 (5.0)	-3.42* [-4.96; -1.87] p < 0.0001

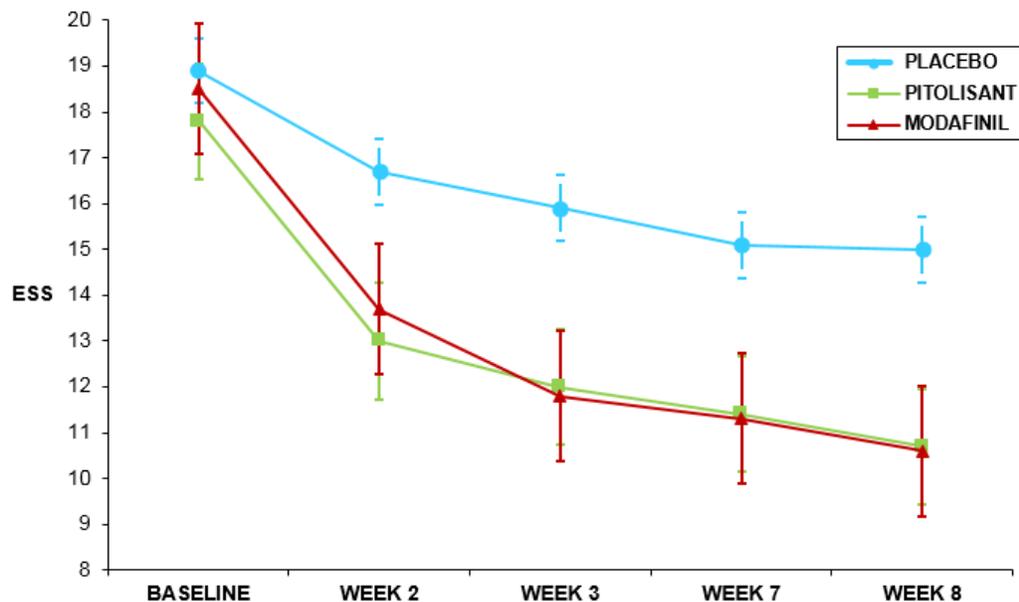
<sup>a</sup> a lower score on the ESS represents improvement; scores range from 0 (no symptoms) to 24 (worst symptoms)

<sup>b</sup> a negative value for the difference represents improvement

\*Statistically significant

\*\* primary endpoint

<sup>3</sup> Szakacs *et al.* Lancet Neurol. 2017



**Figure 1.** Changes in Epworth Sleepiness Scale Score (Mean ± SD) from Baseline to Week 8 in HARMONY I

### Cataplexy

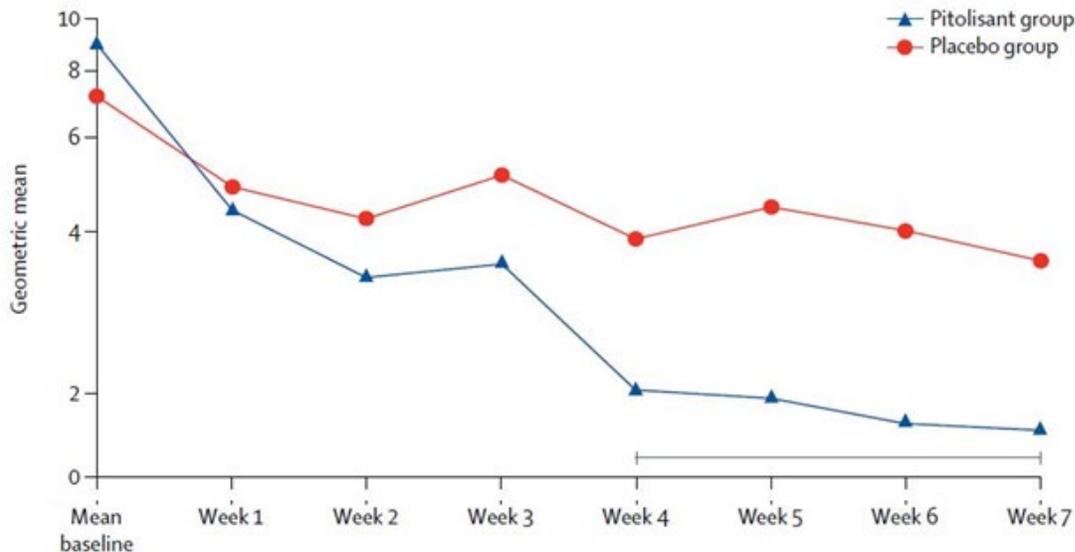
**Table 9.** Results of WAKIX clinical trial for cataplexy rate in narcolepsy

Study	Treatment Group (n)	Baseline GMT [95%IC]	Final GMT [95%IC]	Ratio of GMT vs. WAKIX [95% CI] p-value
<b>Weekly Cataplexy Rate</b>				
HARMONY CTP**	WAKIX (54)	9.15 [7.60; 11.01]	2.27 [0.17; 0.36]	
	Placebo (51)	7.31 [6.02; 8.87]	4.51 [2.90; 7.02]	0.49* [0.36; 0.66] p<0.0001
<b>Daily Cataplexy Rate</b>				
HARMONY I	WAKIX (20)	0.5	0.2	
	Placebo (14)	0.4	0.4	0.38* [0.15; 0.93] p=0.034
	Modafinil (23)	0.4	0.3	0.54 [0.24; 1.23] p=0.138
HARMONY Ibis	WAKIX (37)	0.32	0.10	
	Placebo (18)	0.50	0.16	-0.06 [-0.83; 0.71] p=0.873
	Modafinil (38)	0.35	0.08	N/AV

GMT: Geometric Mean Titre, N/AV: not available

\*Statistically significant

\*\* Primary endpoint



**Figure 2.** Changes in the Weekly Cataplexy Rate during Treatment in HARMONY CTP

### **Long-Term Efficacy**

The effectiveness of pitolisant in long-term use has not been systematically evaluated in placebo-controlled trials beyond 8 weeks of treatment duration.

A long-term (up to 5 years) open-label study (HARMONY III<sup>4</sup>) demonstrated ongoing reduction of the main efficacy endpoint, ESS, for the single arm of this trial.

## **13 MICROBIOLOGY**

Not applicable

## **14 NON-CLINICAL TOXICOLOGY**

### **Safety Pharmacology**

The various safety pharmacology studies indicate that pitolisant displays satisfactory safety margins when comparing plasma levels at the no-observed-adverse-effect-level (NOAEL) doses in these trials with the plasma levels in humans receiving the drug chronically at therapeutic doses.

### **General Toxicology**

After single and repeated oral administration of pitolisant across multiple species, transient adverse CNS-related clinical signs, including tremors and convulsions, occurred around  $T_{max}$  with a  $C_{max}$  approximately 8.7 times and 2.6 times the human  $C_{max}$ , in rats and monkeys respectively. These convulsive episodes were not observed after discontinuation of dosing and were not associated with microscopic findings in the brain. They may be attributable to metabolite BP1.2526, which is abundant in rats and monkeys, but not in humans (intravenous administration to rats confirmed the pro-convulsive effect at brain concentrations of 24393-39790 ng/g). After 6 months (rats) or 9 months (monkeys) of administration, there was limited

<sup>4</sup> Dauvilliers *et al.* SleepJ. 2019

evidence of systemic toxicity, with histopathological findings mostly in rats (liver, lungs, thymus, adrenals, duodenum). The NOAEL in these studies were respectively 30 and 12 mg/kg/day, providing an AUC-based safety margin of exposure of respectively 1.2 and 0.5 times the expected exposure at the recommended dose.

### **Carcinogenicity**

Pitolisant was not carcinogenic in mice or rats.

Oral administration of pitolisant at 15, 30 and 75 mg/kg/day for 6 months to CB6F1 TgrasH2 transgenic mice did not increase tumor incidence. These doses correspond to 1.3, 6.9 and 11.8 times the MRHD, based on the respective AUCs.

Oral administration of pitolisant at 5, 15, and 30 mg/kg/day for 105 weeks to Sprague-Dawley rats did not increase tumor incidence. These doses correspond to 0.02, 0.3 and 1.4 times the MRHD, based on the respective AUCs.

### **Genotoxicity**

Pitolisant and its metabolites were not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames) or clastogenic in the *in vitro* mammalian chromosomal aberration assay. Pitolisant was negative in the *in vivo* mouse micronucleus assay.

### **Reproductive and Developmental Toxicology**

Pitolisant administration to rats (30, 52, or 90 mg/kg/day) was associated with dose-related abnormalities in sperm morphology and motility, with limited effects on fertility indices in males, and with increased post-implantation loss and fewer live conceptuses in females. The NOAEL for fertility was established at 30 mg/kg/day (7.3 times the MRHD based on mg/m<sup>2</sup> body surface area).

Maternal and embryofetal toxicity were associated with pitolisant administration to female rats and rabbits with AUC-based safety margins of exposure between 0.2 and 0.7. When administered during pregnancy and lactation to female rats, prolonged gestation and an increase in stillborn pups and postnatal pup mortality (due to lack of milk/nursing) were observed at the highest dose (90 mg/kg/day). Milk production and nursing were affected at doses  $\geq$  52 mg/kg/day. Malformations (cleft palate, abnormal limb flexure) and developmental delays (physical, motor and behavioral) were noted in pups at maternally toxic doses. The NOAEL is considered 30 mg/kg/day.

Pitolisant/metabolites were shown to cross the placenta barrier in rats. Radiolabeled [14C]-pitolisant (30 mg/kg, free base; 8 times the MRHD based on mg/m<sup>2</sup>) was administered to female rats during lactation on day 14 post-partum. Radioactivity in milk was first measured at 0.25 hours post-administration and reached a maximum by 6 hours post-administration.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**  
**PATIENT MEDICATION INFORMATION**

**PrWAKIX®**  
**Pitolisant hydrochloride tablets**

Read this carefully before you start taking **WAKIX®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **WAKIX**.

**What is WAKIX used for?**

WAKIX is used in adults with narcolepsy (a type of sleep disorder) to reduce:

- Excessive sleepiness during the day
- Cataplexy (sudden weak or paralyzed muscles)

**How does WAKIX work?**

WAKIX contains pitolisant, which attaches to receptors in the brain that are involved in making you feel more alert. This helps to combat daytime sleepiness and cataplexy and promote wakefulness.

**What are the ingredients in WAKIX?**

Medicinal ingredient: pitolisant hydrochloride

Non-medicinal ingredients: colloidal anhydrous silica, croscopovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, polyvinyl alcohol, purified water, talc, titanium dioxide

**WAKIX comes in the following dosage forms:**

Tablets; 5 mg and 20 mg

**Do not use WAKIX if:**

- you are allergic to pitolisant hydrochloride or to any of the other ingredients in this medication or to any part of the container.
- you have severe liver problems.
- you are breastfeeding or plan to breastfeed.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take WAKIX. Talk about any health conditions or problems you may have, including if you:**

- have or have had heart problems, or problems with the way your heart beats.
- have a severe kidney disease or are on dialysis.
- have or have had anxiety, depression, or depressive symptoms.
- have a history of seizures; WAKIX may make your seizures worse.

**Other warnings you should know about:**

**Heart rhythm disorder:** WAKIX may cause a heart rhythm disorder. This disorder is called Long QT Syndrome. You may have no symptoms or you may:

- feel dizzy
- have chest pain or discomfort
- have a rapid and/or irregular heart beat
- faint

- have seizures

Tell your doctor immediately if you have these symptoms. If you continue to have these symptoms, you could develop a more serious heart rhythm problem that could lead to death.

**Driving and using machines:** Before you do tasks which may require special attention, wait until you know how you respond to WAKIX.

**Pregnancy:** If you are pregnant, think you may be pregnant or are planning to have a baby, do not use this medicine unless your doctor tells you to. It is not known if WAKIX will harm your unborn baby. If you are taking a hormonal birth control, you should use an additional reliable non-hormonal method to avoid getting pregnant during treatment and for at least 21 days after you stop taking WAKIX.

**Dependence and Tolerance:** Because WAKIX works on the brain, there is a small risk of drug abuse, misuse or dependence. If you find you are craving more WAKIX than you are supposed to take, talk to your healthcare professional **right away**.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with WAKIX:**

- medicines used for depression, such as paroxetine, fluoxetine, venlafaxine and bupropion
- medicines used to control seizures/epilepsy, such as phenytoin and carbamazepine
- medicines used to control allergic reactions, such as pheniramine maleate, diphenhydramine and promethazine (H1 receptor antagonist)
- tri- and tetra-cyclic antidepressants, such as imipramine, clomipramine and mirtazapine
- medicines used for irregular heart rhythm, such as procainamide, disopyramide, amiodarone and sotalol
- medicines used to manage psychosis, such as ziprasidone and chlorpromazine
- medicines used to treat fungal infections, such as terbinafine and amphotericin B
- medicines used to increase your production of urine (diuretics or “water pills”)
- medicines known as “inhibitors of uridine glucuronyl transferases”, such as probenecid. If you are unsure, ask your healthcare professional.
- rifampin, used for tuberculosis
- moxifloxacin, used to control infections
- metformin, used to improve your blood sugar
- midazolam, used for sedation
- cyclosporine, used to suppress the immune system (e.g. in transplant rejection)
- cinacalcet, used for increased parathyroid hormone
- quinine, used for malaria
- strong corticosteroids (used to lower inflammation)
- laxatives and enemas
- types of plants called goldenseal and St. John’s Wort
- hormonal birth control

**How to take WAKIX:**

- Take WAKIX once a day when you wake up.
- Take WAKIX with food.

- Swallow tablets whole, do **not** chew, divide or crush the tablets before swallowing.
- Only take WAKIX in the morning. If you take it in the afternoon you may have difficulty sleeping at night.
- It might take a few days before you feel the benefit of the medicine and the maximum benefits are usually felt after a few weeks.

**Usual dose:**

Take WAKIX every day as prescribed by your doctor. Do not decrease, stop or change your dose on your own.

The usual starting dose is 10 mg (two 5 mg tablets) once daily. Your doctor will slowly increase your dose if necessary. The total daily dose should not exceed 40 mg per day.

**Overdose:**

If you think you, or a person you are caring for, have taken too much WAKIX, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If you miss a dose, take the next dose when you wake up the next morning. Do not take an extra dose to make up for a missed dose.

**What are possible side effects from using WAKIX?**

These are not all the possible side effects you may feel when taking WAKIX. If you experience any side effects not listed here, contact your healthcare professional.

- |                      |                               |
|----------------------|-------------------------------|
| • Acid reflux        | • Fatigue                     |
| • Anxiety            | • Headache                    |
| • Back pain          | • Insomnia (trouble sleeping) |
| • Diarrhea           | • Irritability                |
| • Dizziness          | • Joint pain                  |
| • Decreased appetite | • Nausea                      |
| • Dry mouth          | • Stomach pain                |

<b>Serious side effects and what to do about them</b>			
<b>Symptom / effect</b>	<b>Talk to your healthcare professional</b>		<b>Stop taking drug and get immediate medical help</b>
	<b>Only if severe</b>	<b>In all cases</b>	
<b>COMMON</b>			
<b>Hallucinations:</b> seeing or hearing things that are not there		✓	
Increased heart rate	✓		
<b>Upper respiratory tract infection</b> (a cold): runny or stuffy nose, sore throat, cough, sinus congestion, body aches, headache, sneezing, fever	✓		
<b>RARE/UNKNOWN</b>			
Abnormal or aggressive behaviour or		✓	

hostility			
<b>Allergic reaction:</b> difficulty swallowing or breathing, hives or rash, swelling of the face, lips, tongue or throat			✓
<b>Depression</b> (sad mood that won't go away): changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, reduced libido (sex drive), worsening of depression		✓	
<b>Heart problems:</b> abnormal heart rhythms, palpitations			✓
<b>Seizures</b> (fit): uncontrollable shaking		✓	
<b>Suicidal thoughts:</b> thoughts of death or killing yourself			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

<p><b>Reporting Side Effects</b>  You can report any suspected side effects associated with the use of health products to Health Canada by:</p> <ul style="list-style-type: none"> <li>• Visiting the Web page on Adverse Reaction Reporting (<a href="https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html">https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html</a>) for information on how to report online, by mail or by fax; or</li> <li>• Calling toll-free at 1-866-234-2345.</li> </ul> <p><i>NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>
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**Storage:**

Store between 15 and 30°C.

Keep out of reach and sight of children.

**If you want more information about WAKIX:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the distributor's website [www.paladinlabs.com](http://www.paladinlabs.com), or by calling 1-888-867-7426.

This leaflet was prepared by Endo Ventures Ltd.

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