1. NAME OF THE MEDICINAL PRODUCT

Wakix 4.5 mg
Wakix 18 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Wakix 4.5 mg film-coated tablet
Each tablet contains pitolisant hydrochloride equivalent to 4.45 mg of pitolisant.

Wakix 18 mg film-coated tablet
Each tablet contains pitolisant hydrochloride equivalent to 17.8 mg of pitolisant.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Wakix 4.5 mg film-coated tablet
White, round, biconvex film-coated tablet, 3.7 mm diameter, marked with "5" on one side.

Wakix 18 mg film-coated tablet
White, round, biconvex film-coated tablet, 7.5 mm diameter marked with "20" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Wakix is indicated in adults for the treatment of narcolepsy with or without cataplexy (see also section 5.1).

4.2 Posology and method of administration

Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

Posology

Wakix should be used at the lowest effective dose, depending on individual patient response and tolerance, according to an up-titration scheme, without exceeding the dose of 36 mg/day:
- Week 1: initial dose of 9 mg (two 4.5 mg tablets) per day.
- Week 2: the dose may be increased to 18 mg (one 18 mg tablet) per day or decreased to 4.5 mg (one 4.5 mg tablet) per day.
- Week 3: the dose may be increased to 36 mg (two 18 mg tablets) per day.

At any time the dose can be decreased (down to 4.5 mg per day) or increased (up to 36 mg per day) according to the physician assessment and the patient's response.

The total daily dose should be administered as a single dose in the morning during breakfast.

Maintenance of efficacy
As long-term efficacy data are limited (see section 5.1), the continued efficacy of treatment should be regularly evaluated by the physician.

Special populations

Elderly
Limited data are available in elderly. Therefore, dosing should be adjusted according to their renal and hepatic status.

Renal impairment
In patients with renal impairment, the maximum daily dose should be 18 mg.

Hepatic impairment
In patients with moderate hepatic impairment (Child-Pugh B) two weeks after initiation of treatment, the daily dose can be increased without exceeding a maximal dose of 18 mg (see section 5.2).
Pitolisant is contra-indicated in patients with severe hepatic impairment (Child-Pugh C) (see section 4.3).
No dosage adjustment is required in patients with mild hepatic impairment.

Paediatric population
The safety and efficacy of pitolisant in children aged from 0 to 18 years old have not yet been established. Wakix is not indicated for paediatric population

Poor metabolizers
By comparison to CYP2D6 extensive metabolisers, higher systemic exposure (up to 3 fold) is observed in CYP2D6 poor metabolisers. In the up-titration scheme, dose increment should take into account this higher exposure.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe hepatic impairment (Child-Pugh C).
- Breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Psychiatric disorders

Pitolisant should be administered with caution in patients with history of psychiatric disorders such as severe anxiety or severe depression with suicidal ideation risk.
Suicidal ideation has been reported in patients with psychiatric history treated with pitolisant.

Hepatic or renal impairment

Pitolisant should be administered with caution in patients with either renal impairment or moderate hepatic impairment (Child-Pugh B) and dosing regimen should be adapted according to section 4.2.

Gastrointestinal disorders

Gastric disorders reactions have been reported with pitolisant, therefore it should be administered with caution in patients with acid related gastric disorders (see section 4.8) or when co-administered with gastric irritants such as corticosteroids or NSAID.

Nutrition disorders

Pitolisant should be administered with caution in patients with severe obesity or severe anorexia (see section 4.8). 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-times the therapeutic dose, that is 108 mg to 216 mg) 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 C_{max} and AUC ratio (see section 4.5) or patients with severe renal or moderate hepatic impairment (see section 4.4) should be carefully monitored (see section 4.5).

Epilepsy

Convulsions were reported at high doses in animal models (see section 5.3). In clinical trials, one 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 treatment discontinuation (based on pitolisant/metabolites half-life). Pitolisant may reduce the effectiveness of hormonal contraceptives. Therefore, an alternative method of effective contraception should be used if the woman patient is using hormonal contraceptives (see sections 4.5 and 4.6).

Drug-drug interactions

The combination of pitolisant with substrates of CYP3A4 and having a narrow therapeutic margin should be avoided (see section 4.5).

Rebound effect

No rebound effect was reported during clinical trials. However, treatment discontinuation should be monitored.

Drug abuse

Pitolisant showed absence or low abuse potential according to clinical data (specific human abuse potential study at doses from 36 up to 216 mg, and observed abuse-related adverse effects in phase 3 studies).

4.5 Interaction with other medicinal products and other forms of interaction

Antidepressants

Tri or tetracyclic antidepressants (e.g. imipramine, clomipramine, mirtazapine) may impair the efficacy of pitolisant because they display histamine H1-receptor antagonist activity and possibly cancel the effect of endogenous histamine released in brain by the treatment.

Anti-histamines

Anti-histamines (H1-receptor antagonists) crossing the haemato-encephalic barrier (e.g. pheniramine maleate, chlorpheniramine, diphenydramine, promethazine, mepyramine, doxylamine) may impair the efficacy of pitolisant.

QT-prolonging substances or known to increase the risk of repolarization disorders

Combination with pitolisant should be made with a careful monitoring (see section 4.4).

Pharmacokinetic interactions

Medicinal products affecting pitolisant metabolism

- Enzyme inducers

Co-administration of pitolisant with rifampicin in multiple doses significantly decreases pitolisant mean C_{max} and AUC ratio about 39% and 50%, respectively. Therefore, co-administration of pitolisant with potent CYP3A4 inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) should be done with caution. With St John's Wort (Hypericum Perforatum), due to its strong CYP3A4 inducing effect, caution should be exercised when taken concurrently with pitolisant. A clinical monitoring should be made when both active substances are combined and, eventually a dosage adjustment during the combination and one week after the inducer treatment.
In a clinical multiple dose study, the combination of pitolisant with probenecid decreases the AUC of pitolisant by about 34%.

- CYP2D6 inhibitors

Co-administration of pitolisant with paroxetine significantly increases pitolisant mean C_{max} and $AUC_{0—72h}$ ratio about 47% and 105%, respectively. Given the 2-fold increase of pitolisant exposure, its coadministration with CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, venlafaxine, duloxetine, bupropion, quinidine, terbinafine, cinacalcet) should be done with caution. A dosage adjustment during the combination could eventually be considered.

Medicinal products that pitolisant may affect metabolism

- CYP3A4 and CYP2B6 substrates

Based on *in vitro* data, pitolisant and its main metabolites may induce CYP3A4 and CYP2B6 at therapeutic concentrations and by extrapolation, CYP2C, UGTs and P-gp. No clinical data on the magnitude of this interaction are available. Therefore, the combination of pitolisant with substrates of CYP3A4 and having a narrow therapeutic margin (e.g. immunosuppressants, docetaxel, kinase inhibitors, cisapride, pimozide, halofantrine) should be avoided (see section 4.4). With other CYP3A4, CYP2B6 (e.g. efavirenz, bupropion), CYP2C (e.g. repaglinide, phenytoin, warfarin), P-gp (e.g. dabigatran, digoxin) and UGT (e.g. morphine, paracetamol, irinotecan) susbtrates, caution should be made with a clinical monitoring of their efficacy.

With oral contraceptives, the combination with pitolisant should be avoided and a further reliable contraceptive method used.

- Substrates of OCT1

Pitolisant shows greater than 50% inhibition towards OCT1 (organic cation transporters 1) at 1.33 µM, the extrapolated IC_{50} of pitolisant is 0.795 µM.

Even if the clinical relevance of this effect is not established, caution is advised when pitolisant is administered with a substrate of OCT1 (e.g. metformin (biguanides)) (see section 5.2).

The combination of pitolisant with modafinil or sodium oxybate, usual treatments of narcolepsy was evaluated in healthy volunteers, at therapeutic doses. No clinically relevant pharmacokinetic drug-drug interaction was evidenced either with modafinil or with sodium oxybate.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment and at least up to 21 days after treatment discontinuation (based on pitolisant/metabolites half-life). Pitolisant/metabolites may reduce the effectiveness of hormonal contraceptives. Therefore, an alternative method of effective contraception should be used if the woman is using hormonal contraceptives (see section 4.5).

Pregnancy

There are no or limited amount of data from the use of pitolisant in pregnant women. Studies in animals have shown reproductive toxicity, including teratogenicity. In rats, pitolisant/metabolites were shown to cross the placenta (see section 5.3).

Pitolisant should not be used during pregnancy unless the potential benefit outweighs the potential risk for foetus.

Breast-feeding

Animal study has shown excretion of pitolisant/metabolites in milk. Therefore, breastfeeding is contraindicated during treatment with pitolisant (see section 4.3).

Fertility

Study in animals has shown effects on semen parameters, without a significant impact on reproductive performance in males and reduction on the percentage of live foetuses in treated females (see section 5.3).

4.7 Effects on ability to drive and use machines

Pitolisant has minor influence on the ability to drive and use machines.

Patients with abnormal levels of sleepiness who take pitolisant should be advised that their level of wakefulness may not return to normal. Patients with excessive daytime sleepiness, including those taking pitolisant should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse drug reactions (ADRs) reported with pitolisant were insomnia (8.4%), headache (7.7%), nausea (4.8%), anxiety (2.1%), irritability (1.8%), dizziness (1.4%), depression (1.3%), tremor (1.2%), sleep disorders (1.1%), fatigue (1.1%), vomiting (1.0%), vertigo (1.0%), dyspepsia (1.0%), weight increase (0.9%), abdominal pain upper (0.9%). The most serious ADRs are abnormal weight decrease (0.09%) and abortion spontaneous (0.09%).

Tabulated list of adverse reactions

The following adverse reactions have been reported with pitolisant during clinical studies in narcolepsy and other indications and are listed below as MedDRA preferred term by system organ class and frequency; frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000); within each frequency group, adverse reactions are presented in order of decreasing seriousness:

	Common	**Uncommon**	**Rare**
Metabolism and nutrition disorders		Decreased appetite Increased appetite Fluid retention	Anorexia Hyperphagia Appetite disorder
Psychiatric disorders	Insomnia Anxiety Irritability Depression Sleep disorder	Agitation Hallucination Hallucination visual, auditory Affect lability Abnormal dreams Dyssomnia Middle insomnia Initial insomnia Terminal insomnia Nervousness Tension Apathy Nightmare Restlessness Panic Attack Libido decreased Libido increased Suicidal ideation	Abnormal behaviour Confusional state Depressed mood Excitability Obsessive thoughts Dysphoria Hypnopompic hallucination Depressive symptom Hypnagogic hallucination Mental impairment
Nervous system disorders	Headache Dizziness Tremor	Dyskinesia Balance disorder Cataplexy Disturbance in attention Dystonia On and off phenomenon Hypersomnia Migraine Psychomotor hyperactivity Restless Legs Syndrome Somnolence Epilepsy Bradykinesia Paresthesia	Loss of consciousness Tension headache Memory impairment Poor sleep quality
Eye disorders		Visual acuity reduced Blepharospasm	
Ear and labyrinth disorders	Vertigo	Tinnitus	
Cardiac disorders		Extrasystoles Bradycardia	
Vascular disorders		Hypertension Hypotension Hot flush	
Respiratory, thoracic and mediastinal disorders		Yawning	

Gastrointestinal disorders	Nausea Vomiting Dyspepsia	Dry mouth Abdominal pain Diarrhoea Abdominal discomfort Abdominal pain upper Constipation Gastrooesophageal reflux disease Gastritis Gastrointestinal pain Hyperacidity Paraesthesia oral Stomach discomfort	Abdominal distension Dysphagia Flatulence Odynophagia Enterocolitis
Skin and subcutaneous tissue disorders		Erythema Pruritus Rash Hyperhidrosis Sweating	Toxic skin eruption Photosensitivity
Musculoskeletal and connective tissue disorders		Arthralgia Back pain Muscle rigidity Muscular weakness Musculoskeletal pain Myalgia Pain in extremity	Neck pain Musculoskeletal chest pain
Renal and urinary disorders		Pollakiuria	
Pregnancy, puerperium and perinatal conditions			Abortion spontaneous
Reproductive system and breast disorders		Metrorrhagia	
General disorders and administration site conditions	Fatigue	Asthenia Chest Pain Feeling Abnormal Malaise Oedema Peripheral oedema	Pain Night sweats Sense of oppression
Investigations		Weight increased Weight decreased Hepatic enzymes increased	Creatine phosphokinase increased
		Electrocardiogram QT prolonged Heart rate increased Gamma-glutamyltransferase increased	General physical condition abnormal Electrocardiogram repolarisation abnormality Electrocardiogram T wave inversion

Description of selected adverse reactions

Headache and insomnia
During clinical studies, episodes of headache and insomnia have been reported (7.7 % to 8.4%). Most of these adverse reactions were mild to moderate. If symptoms persist a reduced daily dose or discontinuation should be considered.

Gastric disorders
Gastric disorders caused by hyperacidity have been reported during clinical studies in 3.5% of the patients receiving pitolisant. These effects were mostly mild to moderate. If they persist a corrective treatment with proton pump inhibitor could be initiated.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

Symptoms

Symptoms of Wakix overdose may include headache, insomnia, irritability, nausea and abdominal pain.

Management

In case of overdose, hospitalisation and monitoring of the vital functions are recommended. There is no clearly identified antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code: N07XX11.

Mechanism of action

Pitolisant is a potent, orally active histamine H3-receptor antagonist/inverse agonist which, via its blockade of histamine auto-receptors enhances the activity of brain histaminergic neurons, a major arousal system with widespread projections to the whole brain. Pitolisant also modulates various neurotransmitter systems, increasing acetylcholine, noradrenaline and dopamine release in the brain. However no increase in dopamine release in the striatal complex including nucleus accumbens was evidenced for pitolisant.

Pharmacodynamic effects

In narcoleptic patients with or without cataplexy, pitolisant improves the level and duration of wakefulness and daytime alertness assessed by objective measures of ability to sustain wakefulness (e.g. Maintenance of Wakefulness Test (MWT)) and attention (e.g. Sustained Attention to Response Task (SART)).

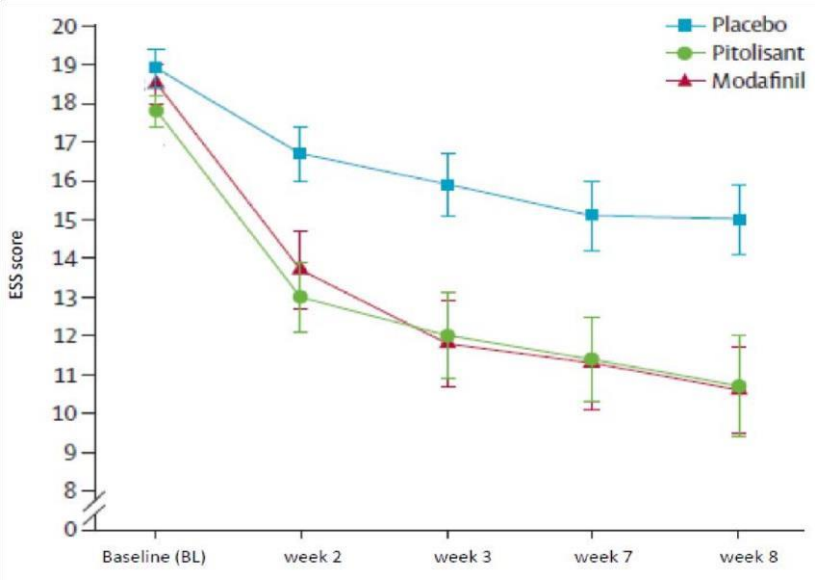
Clinical efficacy and safety

Narcolepsy (with or without cataplexy) is a chronic condition. The effectiveness of pitolisant up to 36 mg once a day, for the treatment of narcolepsy with or without cataplexy was established in two

main, 8 weeks, multicenter, randomized, double-blind, placebo-controlled, parallel group trials (Harmony I and Harmony CTP). Harmony Ibis, study with a similar design, was limited to 18 mg once a day. Long-term safety data of Wakix in this indication are available in the open label long-term study HARMONY III.

The pivotal study (Harmony 1), double-blind, randomized, vs placebo and modafinil (400 mg/day), parallel group studies with flexible dose adaptation, included 94 patients (31 patients treated with pitolisant, 30 with placebo and 33 with modafinil). Dosage was initiated at 9 mg once a day and was increased, according to efficacy response and tolerance to 18 mg or 36 mg once a day per 1-week interval. Most patients (60%) reached the 36 mg once a day dosage. To assess the efficacy of pitolisant on Excessive Daytime Sleepiness (EDS), Epworth Sleepiness Scale (ESS) score was used as primary efficacy criterion. The results with pitolisant were significantly superior to those in the placebo group (mean difference: -3.33; 95%CI [-5.83 to -0.83]; $p < 0.05$) but did not differ significantly from the results in the modafinil group (mean difference: 0.12; 95%CI [-2.5 to 2.7]). The waking effect of the two active substances was established at similar rates (Figure 1).

Figure 1: Changes in Epworth Sleepiness Scale Score (ESS) (mean ± SEM) from Baseline to week 8 in Harmony 1 study



The effect on Epworth was supported in two laboratory tests of vigilance and attention (Maintenance of Wakefulness Test (MWT) (p=0.044) and Sustained Attention to Response (SART) (p=0.053, almost but not significant)).

Cataplexy attacks frequency in patients displaying this symptom was decreased significantly (p=0.034) with pitolisant (-65%) compared to placebo (-10%). The daily cataplexy rate (geometric means) was 0.52 at baseline and 0.18 at final visit for pitolisant and 0.43 at baseline and 0.39 at final visit for placebo, with a rate ratio rR=0.38 [0.16 ; 0.93] (p=0.034).

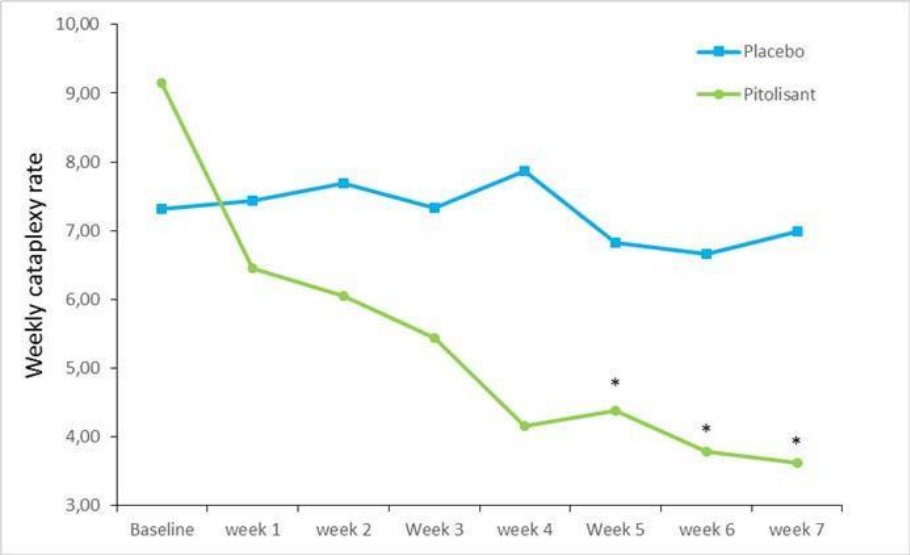
The second pivotal study (Harmony Ibis) included 165 patients (67 treated with pitolisant, 33 with placebo and 65 with modafinil). The study design was similar to study Harmony I except that the maximum dose for pitolisant reached by 75% of patients was 18 mg once a day instead of 36 mg in Harmony I. As an important unbalance led to comparison of results with or without cluster grouping of sites, the most conservative approach showed non-significant ESS score decrease with pitolisant compared to placebo (pitolisant-placebo=-1.94 with p=0.065). Results from cataplexy rate at 18 mg once a day were not consistent with those of the first pivotal study (36 mg once a day).

Improvement of the two objective tests of wakefulness and attention, MWT and SART, with pitolisant was significant versus placebo (p=0.009 and p=0.002 respectively) and non-significant versus modafinil (p=0.713 and p=0.294 respectively).

Harmony CTP, a supportive double blind, randomized, parallel group study of pitolisant versus placebo, was designed to establish pitolisant efficacy in patients with high frequency cataplexy in narcolepsy. The primary efficacy endpoint was the change in the average number of cataplexy attacks per week between the 2 weeks of baseline and the 4 weeks of stable treatment period at the end of study. 105 narcoleptic patients with high frequency weekly cataplexy rates at baseline were included (54 patients treated with pitolisant and 51 with placebo). Dosage was initiated at 4.5 mg once a day and was increased, according to efficacy response and tolerance to 9 mg, 18 mg or 36 mg once a day per 1-week interval. Most patients (65%) reached the 36 mg once a day dosage.

On the primary efficacy endpoint, Weekly Rate of Cataplexy episodes (WRC), the results with pitolisant were significantly superior to those in the placebo group ($p < 0.0001$), with a progressive 64% decrease from baseline to end of treatment (Figure 2). At baseline, the geometric mean of WRC was 7.31 (median=6.5 [4.5; 12]) and 9.15 (median=8.5 [5.5; 15.5]) in the placebo and pitolisant groups respectively. During the stable period (until the end of treatment), geometric mean WRC decreased to 6.79 (median=6 [3; 15]) and 3.28 (median=3 [1.3; 6]) in the placebo and pitolisant groups respectively in patients who had experienced at least one episode of cataplexy. The observed WRC in pitolisant group was about half of WRC in the placebo group: the effect size of pitolisant compared with placebo was summarized by the ratio rate rR(Pt/Pb), rR=0.512; 95%CI [0.435 to 0.603]; $p < 0.0001$). The effect size of pitolisant compared with placebo based on a model for WRC based on BOCF with centre as a fixed effect was 0.581, 95%CI [0.493 to 0.686]; $p<0.0001$.

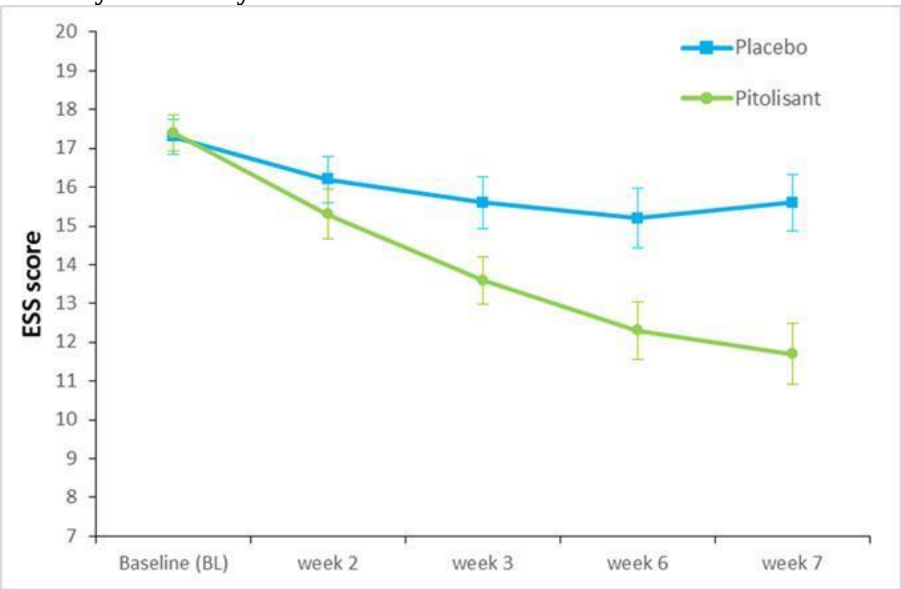
Figure 2: Changes in weekly cataplexy episodes (geometric mean) from Baseline to week 7 in Harmony CTP study



*p<0.0001 vs placebo

The effect of pitolisant on EDS was also assessed in this population using the ESS score. In the pitolisant group, ESS decreased significantly between baseline and the end of treatment compared to placebo with an observed mean change of -1.9 ± 4.3 and -5.4 ± 4.3 (mean ± sd) for placebo and pitolisant respectively, ($p<0.0001$) (Figure 3). This effect on EDS was confirmed by the results on Maintenance of Wakefulness Test (MWT). The geometric mean of the ratios ($MWT_{Final}/MWT_{Baseline}$) was 1.8 (95%CI 1.19; 2.71, p=0.005). The MWT value in the pitolisant group was 80% higher than in the placebo group.

Figure 3: Changes in Epworth Sleepiness Scale Score (ESS) (mean ± SEM) from Baseline to week 7 in Harmony CTP study



The open-label, long-term Phase III study (HARMONY III) assessed the long term safety of pitolisant in patients suffering from narcolepsy (with or without cataplexy) over 12 months and with an extension of up to 5 years. 102 narcoleptic patients with or without cataplexy were included in the 12 months follow-up period. 68 patients completed the first 12 months period. 45, 38, 34 and 14 patients completed the 2, 3, 4 and 5 year follow-up periods, respectively.
The maximal dose received during the study was 36 mg / day in 85% of patients. After 12 months of treatment, improvements in EDS assessed by ESS score of remaining patients is of same magnitude as those observed in the other trials conducted in narcoleptic patients. The decrease in mean ESS score (SD) was -3.62 (4.63) after 1 year.
After 12 months of treatment with pitolisant, frequency of symptoms such as sleep attacks, sleep paralysis, cataplexy and hallucinations has been improved.
No major safety concern was identified. The safety results observed were similar to those reported in previous trials where pitolisant at 36 mg once daily was given for up to 3 months only.

5.2 Pharmacokinetic properties

The exposure to pitolisant in healthy volunteers was assessed in studies involving more than 200 subjects that received doses of pitolisant in single administration up to 216 mg and for a duration up to 28 days.

Absorption

Pitolisant is well and rapidly absorbed with peak plasma concentration reached approximately three hours after administration.

Distribution

Pitolisant exhibits high serum protein binding (>90%) and demonstrates approximately equal distribution between red blood cells and plasma.

Biotransformation

The metabolisation of pitolisant in humans is fully characterized. The major non-conjugated metabolites are hydroxylated derivatives in several positions and cleaved forms of pitolisant leading to inactive major carboxylic acid metabolite found in urine and serum. They are formed under the action of CYP3A4 and CYP2D6. Several conjugated metabolites were identified, the major ones (inactive)

being two glycine conjugates of the acid metabolite of pitolisant and a glucuronide of a ketone metabolite of monohydroxy desaturated pitolisant.

On liver microsomes, pitolisant and its major metabolites do not significantly inhibit the activities of the cytochromes CYP1A2, CYP2C9, CYP2C19, CYP2C8, CYP2B6, CYP2E1 or CYP3A4 and of uridine diphosphate glucuronosyl transferases isoforms UGT1A1, UGT1A4, UGT1A6, UGT1A9 and UGT2B7 up to the concentration of 13.3 µM, a level considerably higher than the levels achieved with therapeutic dose. Pitolisant is an inhibitor of CYP2D6 with moderate potency (IC_{50} = 2.6 µM).

Pitolisant induces CYP3A4, CYP1A2 and CYP2B6 *in vitro*. Clinically relevant interactions are expected with CYP3A4 and CYP2B6 substrates and by extrapolation, UGTs, CYP2C and P-gp substrates (see section 4.5).

In vitro studies indicate that pitolisant is neither a substrate nor an inhibitor of human P-glycoprotein and breast cancer resistance protein (BCRP). Pitolisant is not a substrate of OATP1B1, OATP1B3. Pitolisant is not a significant inhibitor of OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2K at the tested concentration. Pitolisant shows greater than 50% inhibition towards OCT1 (organic cation transporters 1) at 1.33 µM, the extrapolated IC_{50} of pitolisant is 0.795 µM (see section 4.5).

Elimination

Pitolisant has a plasma half-life of 10-12 hours. Upon repeated administrations, the steady state is achieved after 5-6 days of administration leading to an increased serum level around 100%. Inter individual variability is rather high, some volunteers showing outlier high profile (without tolerance issues).

The elimination is mainly achieved via urine (approximately 63%) through an inactive non conjugated metabolite (BP2.951) and a glycine conjugated metabolite. 25% of the dose is excreted through expired air and a small fraction (<3%) recovered in faeces where the amount of pitolisant or BP2.951 was negligible.

Linearity/non-linearity

When pitolisant dose is doubled from 27 to 54 mg, $AUC_{0-\infty}$ is increased by about 2.3.

Special populations

Elderly
In 68 to 80 years old patients the pharmacokinetics of pitolisant is not different compared to younger patients (18 to 45 years of age). Above 80 years old, kinetics show a slight variation without clinical relevance. Limited data are available in elderly. Therefore, dosing should be adjusted according to their renal hepatic status (see section 4.2 and 4.4).

Renal impairment
In patients with impaired renal function (stages 2 to 4 according to the international classification of chronic kidney disease, i.e. creatinine clearance between 15 and 89 ml/min), C_{max} and AUC tended to be increased by a factor of 2.5 without any impact on half-life (see section 4.2).

Hepatic impairment
In patients with mild hepatic impairment (Child-Pugh A), there was no significant changes in pharmacokinetics compared with normal healthy volunteers. In patients with moderate hepatic impairment (Child-Pugh B), AUC increased by a factor 2.4, while half-life doubled (see section 4.2). Pitolisant pharmacokinetics after repeated administration in patients with hepatic impairment has not been evaluated yet.

CYP2D6 poor metabolizers

The exposure to Pitolisant was higher in the CYP2D6 poor metabolisers after a single dose and at steady state; C_{max} and $AUC_{(0\text{-}tau)}$ was approximately 2.7-fold and 3.2-fold greater on Day 1 and 2.1-fold and 2.4-fold on Day 7. The serum Pitolisant half-life was longer in CYP2D6 poor metabolisers compared to the extensive metabolisers.

Race
The effect of race on metabolism of pitolisant has not been evaluated.

5.3 Preclinical safety data

After 1 month in mice, 6 months in rats and 9 months in monkeys, no adverse effect level (NOAEL) were 75, 30 and 12 mg/kg/day, p.o., respectively, providing safety margins of 9, 1 and 0.4, respectively when compared to the drug exposure at therapeutic dose in human. In rats, transient reversible convulsive episodes occurred at T_{max}, that may be attributable to a metabolite abundant in this species but not in humans. In monkeys, at the highest doses, transient CNS related clinical signs including emesis, tremors and convulsions were reported. At the highest doses, no histopathological changes were recorded in monkeys and rats presented some limited histopathological changes in some organs (liver, duodenum, thymus, adrenal gland and lung).

Pitolisant was neither genotoxic nor carcinogenic.

Teratogenic effect of pitolisant was observed at maternally toxic doses (teratogenicity safety margins < 1 in rats and in rabbits). At high doses, pitolisant induced sperm morphology abnormalities and decreased motility without any significant effect on fertility indexes in male rats and it decreased the percentage of live conceptuses and increased post-implantation loss in female rats (safety margin of 1). It caused a delay in post-natal development (safety margin of 1).

Pitolisant/metabolites were shown to cross the placenta barrier in animals.

Juvenile toxicity studies in rats revealed that the administration of pitolisant at high doses induced a dose related mortality and convulsive episode that may be attributable to a metabolite abundant in rats but not in humans.

Pitolisant blocked hERG channel with an IC_{50} exceeding therapeutic concentrations and induced a slight QTc prolongation in dogs.

In preclinical studies, drug dependence and drug abuse liability studies were conducted in mice, monkeys and rats. However, no definitive conclusion could be drawn on tolerance, dependence and self-administration studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Crospovidone, Talc, Opadry® II HP85F18422 white (containing polyvinyl alcohol, titanium dioxide, Macrogol 3350, talc), Magnesium stearate, Silica, colloidal anhydrous.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a temperature not higher than 30ºC. After first opening, the product may be used for up to 40 days when stored at temperature not higher than 30ºC.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a tamper evident, child-resistant, polypropylene screw cap fitted with desiccant (silica gel).

Bottle of 30 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. MANUFACTURER

Bioprojet Pharma, 9 rue Rameau 75002, Paris, France.

8. REGISTRATION HOLDER

Truemed LTD, 10 Beni Gaon Street, Netanya 4250499

9. REGISTRATION NUMBERS

Wakix 4.5mg 164-01-36119
Wakix 18mg 164-02-36120

Revised in December 2021 according to MOHs guidelines

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