ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Wakix 4.5 mg film-coated tablets
Wakix 18 mg film-coated tablets

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 (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, adolescents and children from the age of 6 years 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

Adults
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
Wakix should be used at the optimal dose, depending on individual patient response and tolerance, according to an up-titration scheme, without exceeding the dose of 36 mg/day (18 mg/day in children weighing less than 40 kg).
- Week 1: initial dose of 4.5 mg (one 4.5 mg tablet) per day.
- Week 2: the dose may be increased to 9 mg (two 4.5mg tablets) per day.
- Week 3: the dose may be increased to 18 mg (one 18 mg tablet) per day.
- Week 4: in children weighing 40 kg and above, 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 in children weighing 40 kg and above or 18 mg per day in children weighing less than 40 kg) 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.

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 in adults 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) substrates, 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 in adult patients 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:

MedDRA System Organ Class	**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	Loss of consciousness Tension headache Memory impairment Poor sleep quality

		Psychomotor hyperactivity Restless Legs Syndrome Somnolence Epilepsy Bradykinesia Paresthesia	
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 Gastroesophageal 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 Electrocardiogram QT prolonged Heart rate increased Gamma-glutamyltransferase increased	Creatine phosphokinase 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.

Paediatric population (Age 6 to 17)
The paediatric population has been studied in a double-blind multicentre randomized placebo-controlled trial; a total of 73 children and adolescents with narcolepsy with or without cataplexy were treated with pitolisant for 8 weeks.
Frequency, type and severity of adverse reactions in children and adolescents were similar to that of adults. The most frequent related adverse drug reactions (ADRs) reported in this population were headache (11%), insomnia (5.5%), hypertension (2.7%).

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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

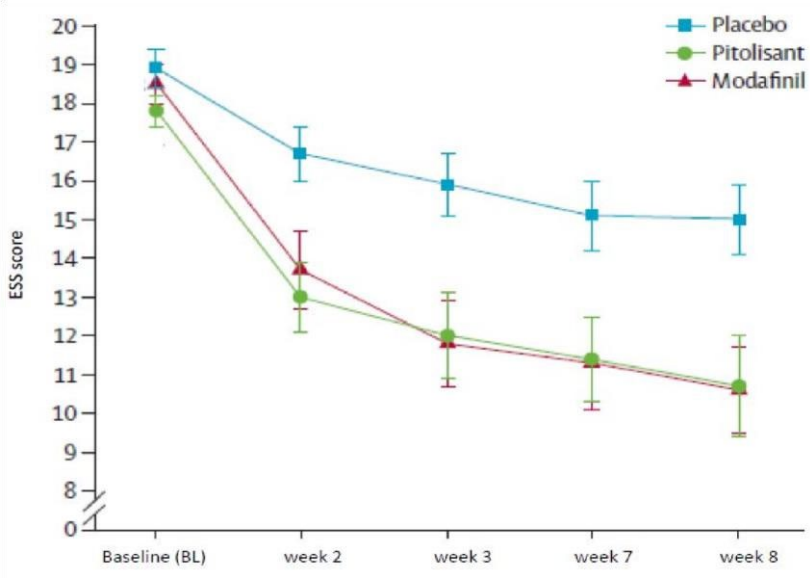
In narcoleptic patients with or without cataplexy, pitolisant improves the level and duration of wakefulness and daytime alertness assessed by objective measures of ability to sustain wakefulness (e.g. Maintenance of Wakefulness Test (MWT)) and attention (e.g. Sustained Attention to Response Task (SART)).

Clinical efficacy and safety

Adult population
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).

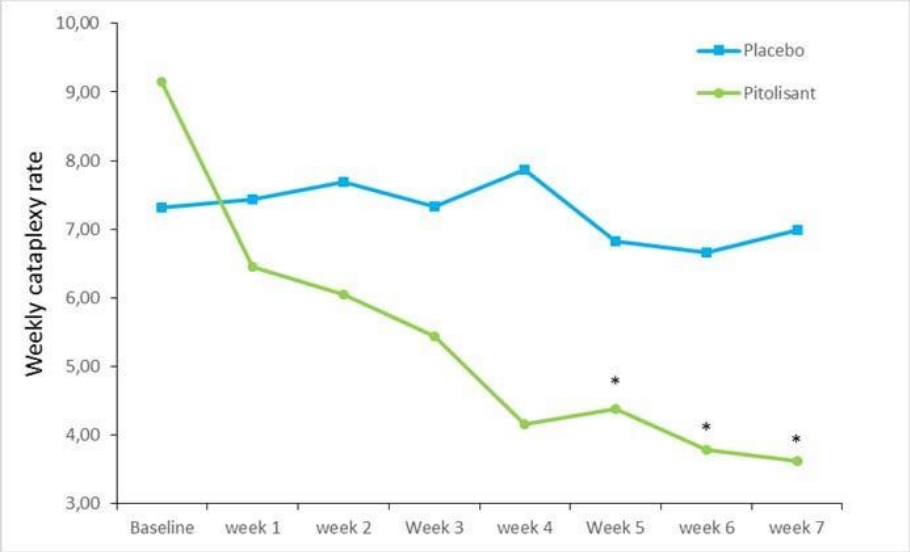
Improvement of the two objective tests of wakefulness and attention, MWT and SART, with pitolisant was significant versus placebo (p=0.009 and p=0.002 respectively) and non-significant versus modafinil (p=0.713 and p=0.294 respectively).

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.

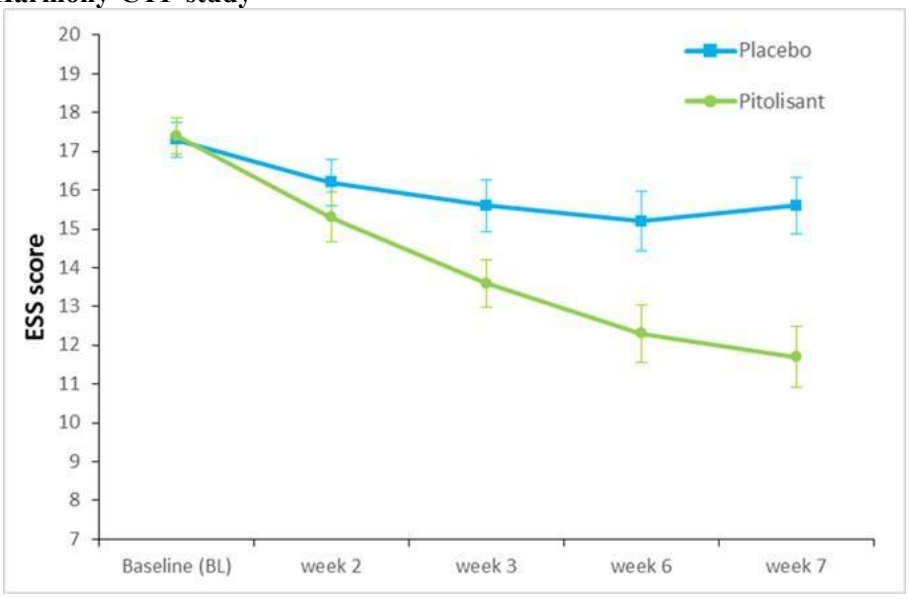
Figure 2: Changes in weekly cataplexy episodes (geometric mean) from Baseline to week 7 in Harmony CTP study



*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.

Paediatric population
The effectiveness of pitolisant up to 36 mg once a day has been studied for the treatment of narcolepsy with or without cataplexy in children from 6 to less than 18 years old in an 8-week, multicenter, randomized, double-blind, placebo-controlled, parallel group trial. It included 110 patients (72 patients in the pitolisant group, 38 in the placebo group). Dosage was initiated at 4.5 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. Patients weighing less than 40 kg remained at a maximum dose of 18 mg. Most patients (60%) reached the 36 mg once a day dosage. 35 patients (31.8%) were aged 6 to 11 years and 75 patients (68.2%) were aged 12 to less than 18 years. To assess the efficacy of pitolisant on Excessive Daytime Sleepiness (EDS) and cataplexy (CTP), the Ullanlinna Narcolepsy Scale (UNS) total score was used as primary efficacy criterion, assessed as the change from baseline to the end of double-blind period. The estimate LS means difference (SE) [95% CI] of UNS between treatment groups (pitolisant minus placebo) was -3.69 (1.37) [-6.38; -0.99], p=0.0073. Secondary endpoints included the paediatric daytime sleepiness scale (PDSS), the UNS-cataplexy (CTP) subscore, and the weekly rate of cataplexy (WRC). The estimate LS means difference (SE) [95% CI] of the PDSS total score between treatment groups (pitolisant minus placebo) was -3.41 (1.07) [-5.52; -1.31], p=0.0015. In the subgroup of patients with type 1 narcolepsy, who had no minimum level of cataplexy required at inclusion (N=61 in the pitolisant group; N=29 in the placebo group), the estimate LS means difference (SE) [95% CI] of the UNS-CTP subscore between treatment groups (pitolisant minus placebo) was -1.77 (0.78) [-3.29; -0.24], p=0.0229, and the rate ratio between the WRC in the pitolisant group and the WRC in the placebo group, adjusted for baseline, was in favor of pitolisant (0.42 [95% CI: 0.18; 1.01], p=0.0540).

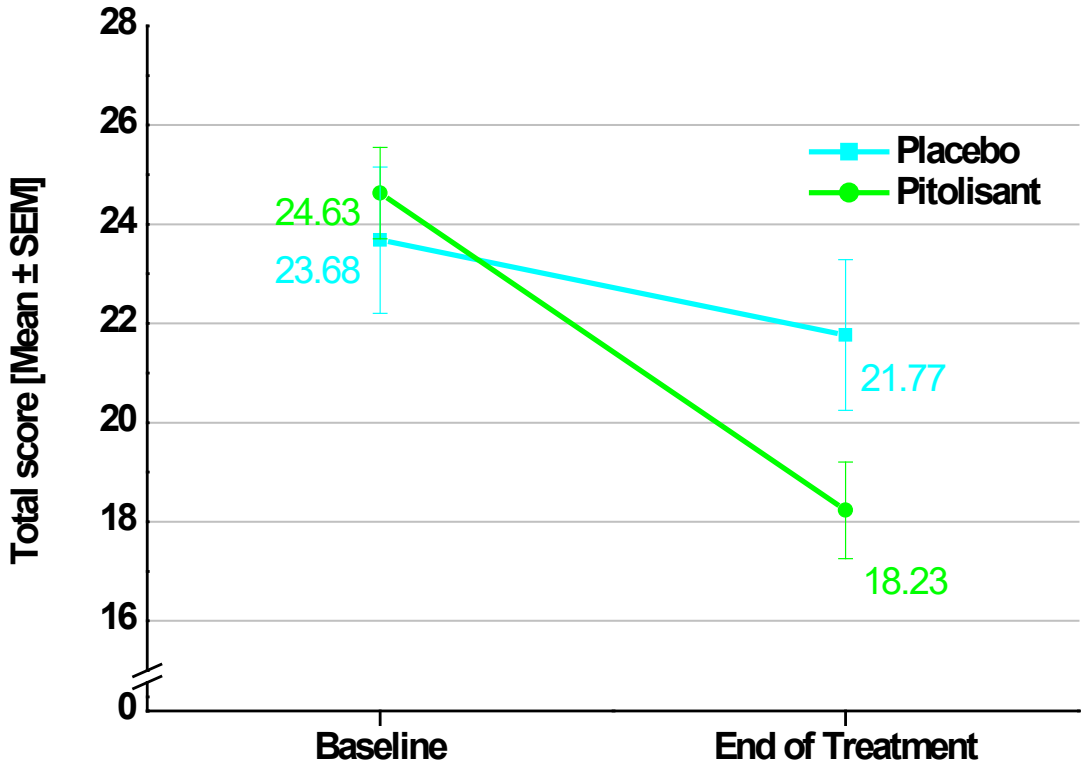
Table 1: overview of efficacy results after 8 weeks in phase 3 paediatric study

	Placebo (n= 38)	**Pitolisant (n= 72)**
Ullanlinna Narcolepsy Scale (UNS)		
Total score		
Baseline mean (SD) End of treatment mean (SD) LS mean (SE) – change from baseline Estimate, 95% CI p-value	23.68 (9.08) 21.77 (9.25) -2.60 (1.35)	24.63 (7.80) 18.23 (8.14) -6.29 (1.14) -3.69 (-6.38; -0.99) 0.0073
Paediatric Daytime Sleepiness Score		
Baseline mean (SD) End of treatment mean (SD) LS mean (SE) – change from baseline Estimate, 95% CI p-value	20.00 (3.49) 17.96 (5.60) -2.11 (0.89)	20.16 (3.64) 14.57 (5.37) -5.53 (0.66) -3.41 (-5.52; -1.31) 0.0015
	Placebo (n= 29)	**Pitolisant (n= 61)**
UNS-Cataplexy Subscore*		
Baseline mean (SD) End of treatment mean (SD)	9.03 (4.33) 8.07 (4.62)	8.93 (3.96) 6.02 (4.00)

LS mean (SE) – change from baseline Estimate, 95% CI p-value	-1.12 (0.64)	-2.88 (0.44) -1.77 (-3.29; -0.24) 0.0229
Weekly cataplexy rate*		
Baseline mean (SD) LS mean (SE) Estimate, 95% CI p-value	13.44 (26.92) 5.05 (0.37)	8.63 (17.73) 2.14 (0.27) 0.42 (0.18; 1.01) 0.0540

*only measured in patients with type I narcolepsy

Figure 4 Change in the Mean Ullanlinna Narcolepsy Scale Total Score (mean ± SEM) from Baseline to the End of Treatment (Full Analysis Set)



Baseline=[V1 score (D-14) + V2 score (D0)]/2
End of treatment=[V6 score (D49) + V7 score (D56)]/2
SEM=standard error of the mean

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.

Paediatric population
The pharmacokinetics of pitolisant at the dose of 18 mg in children from 6 to less than 18 years with narcolepsy has been studied in a multi-centre, single dose trial. By comparison to adult patients exposure, in a Population PK analysis with a body weight-dependent model, systemic exposure to pitolisant at the dose of 18 mg as estimated by C_{max} and $AUC_{0\text{-}10h}$ are roughly 3-fold higher in children with a body weight below 40 kg and 2-fold higher in adolescents with a body weight above 40 kg compared to adults. Therefore, the dose titration should be initiated at the lowest dose of 4.5 mg and limited to 18 mg in children weighing less than 40 kg (see section 4.2).

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

Tablet core

Microcrystalline cellulose
Crospovidone type A
Talc
Magnesium stearate
Colloidal anhydrous silica

Coating

Poly(vinyl alcohol)
Titanium dioxide (E171)
Macrogol 3350
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Wakix 4.5 mg tablet

3 years

Wakix 18 mg tablet

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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 or 90 film-coated tablets.

Wakix 4.5 mg

Available in packs containing 1 bottle of 30 tablets.

Wakix 18 mg

Available in packs containing 1 bottle of 30 tablets or packs containing 1 bottle of 90 tablets or multi-packs containing 90 (3 bottles of 30) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bioprojet Pharma
9, rue Rameau
75002 Paris
France
Tel: +33 (0)1 47 03 66 33
Fax: +33 (0)1 47 03 66 30
e-mail: contact@bioprojet.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1068/001
EU/1/15/1068/002
EU/1/15/1068/003
EU/1/15/1068/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: *31/03/2016*
Date of latest renewal: *17/12/2020*

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Wakix 18 mg
Inpharmasci
ZI N°2 de Prouvy-Rouvignies
1 rue Nungesser
59121 Prouvy
France

Wakix 4.5 mg
Patheon
40 Boulevard de Champaret
38300 Bourgoin-Jallieu
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): A multi-center, observational post-authorization safety study to document the drug utilisation of Wakix and to collect information on the safety of Wakix when used in routine medical practice	Final report: 1Q 2025

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Wakix 4.5 mg film-coated tablets
pitolisant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bioprojet Pharma
9, rue Rameau
75002 Paris
France

12. MARKETING AUTHORISATION NUMBER

EU/1/15/1068/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Wakix 4.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Wakix 4.5 mg film-coated tablets
pitolisant
oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 tablets

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Wakix 18 mg film-coated tablets
pitolisant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bioprojet Pharma
9, rue Rameau
75002 Paris
France

12. MARKETING AUTHORISATION NUMBER

EU/1/15/1068/002 30 film-coated tablets
EU/1/15/1068/004 90 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Wakix 18 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON FOR MULTIPACK OF 90 (3 x 30) TABLETS - WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Wakix 18 mg film-coated tablets
pitolisant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets. Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bioprojet Pharma
9, rue Rameau
75002 Paris
France

12. MARKETING AUTHORISATION NUMBER

EU/1/15/1068/003 90 film-coated tablets (3 bottles of 30)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Wakix 18 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACK OF 90 (3 x 30) TABLETS WRAPPED IN TRANSPARENT FOIL – INCLUDING BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Wakix 18 mg film-coated tablets
pitolisant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 90 (3 bottles of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bioprojet Pharma
9, rue Rameau
75002 Paris
France

12. MARKETING AUTHORISATION NUMBER

EU/1/15/1068/003 90 film-coated tablets (3 bottles of 30)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Wakix 18 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Wakix 18 mg film-coated tablets
pitolisant
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 tablets
90 tablets

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Wakix 4.5 mg film-coated tablets
Wakix 18 mg film-coated tablets
pitolisant

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet?

1. What Wakix is and what it is used for

Wakix contains the active ingredient pitolisant. It is a medicine used to treat adults, adolescents and children over the age of 6 years with narcolepsy, with or without cataplexy.

Narcolepsy is a condition that causes excessive daytime sleepiness and a tendency to suddenly fall asleep in inappropriate situations (sleep attacks). Cataplexy is the onset of sudden muscle weakness or paralysis without losing consciousness, in response to a sudden emotional reaction such as anger, fear, joy, laughter or surprise.

The active substance, pitolisant, attaches to receptors on cells in the brain that are involved in stimulating alertness. This helps to combat daytime sleepiness and cataplexy and promote wakefulness.

2. What you need to know before you take Wakix

Do not take Wakix if you

- Are allergic to pitolisant or any of the other ingredients of this medicine (listed in section 6).
- Have severe liver problems, as pitolisant is normally broken down in the liver and excess levels may build up in patients whose liver function is severely reduced.
- Are breastfeeding.

Warnings and precautions

Talk to your doctor before taking Wakix if any of the situations mentioned below apply to you:

- You ever had anxiety or depression with suicidal thoughts.
- You have liver or kidney problems, as your dose may need to be adjusted.
- You have a gastric ulcer or you take medicines that can irritate your stomach such as medicines against inflammations, since gastric reactions have been reported with Wakix.
- You are obese or anorexic, as you may have change of your body weight (increase or decrease) while taking Wakix.
- You have heart problems. Your doctor will need to check this regularly while you are taking Wakix.
- You have severe epilepsy.

If any of these apply to you, talk to your doctor or pharmacist before taking Wakix.

Other things to talk to your doctor or pharmacist about:

Some people with history of psychiatric disorders have reported having suicidal thoughts while taking this medicine. Tell your doctor straight away if you notice that you are becoming depressed or have suicidal thoughts (see section 4). You may want to consider asking a family member or close friend to help you look out for signs of depression or other changes in your behaviour.

Children

Wakix should not be taken by children less than 6 years old.

Other medicines and Wakix

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Wakix can affect the way other medicines work and other medicines can affect the way Wakix works. Your doctor may need to adjust your doses.

In particular, you should be cautious if you take Wakix together with some antidepressants (e.g. imipramine, clomipramine and mirtazapine) and some medicines to treat allergic conditions (anti-histamines, e.g. pheniramine maleate, chlorpheniramine, diphenydramine, promethazine, mepyramine, doxylamine).

Tell your doctor or pharmacist if you are taking any of the following medicines: rifampicin (an antibiotic), phenytoin, carbamazepine and phenobarbital (mainly used to control seizures), quinidine, digoxin (used to treat abnormal heart rhythms), paroxetine, fluoxetine, venlafaxine, duloxetine (antidepressants), St John's Wort (*Hypericum perforatum*) a herbal remedy for depression, bupropion (antidepressant or aid to smoking cessation), cinacalcet (for treatment of disorders of the parathyroid gland), terbinafine (used to treat fungal infections), metformin, repaglinide (used to treat diabete), docetaxel, irinotecan (used to treat cancer), cisapride (used to treat gastric reflux), pimozide (used to treat some mental disorders), halofantrine (to treat malaria), efavirenz (antiviral medicine to treat HIV), morphine, paracetamol (used to treat pain), dabigatran (used to treat problems of the veins), warfarin (used to treat heart diseases), probenecid (used to treat gout and gouty arthritis).Pitolisant can be used with modafinil or sodium oxybate.

Wakix may reduce the effectiveness of hormonal contraceptives, an alternative method of effective contraception has to be used (see section "Pregnancy).

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

Wakix should not be used during pregnancy unless your doctor says so. There is not enough information available to know whether any particular risk is associated with the use of Wakix during pregnancy. If you are a woman, you have to take a contraceptive during your treatment with Wakix and at least up to 21 days after treatment discontinuation. As Wakix may reduce the effectiveness of hormonal contraceptive, an alternative method of effective contraception has to be used.

Breast-feeding

Wakix passes into breast milk in animal. Patients taking Wakix must stop breastfeeding.

Driving and using machines

You should be cautious with activities that require attention such as driving a car and handling machinery. If you are unsure whether your condition has a negative effect on your ability to drive, talk to your doctor.

3. How to take Wakix

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults
Treatment is normally started with a dose of 9 mg once per day, and gradually increased over three weeks to the most appropriate dose. At any time, your doctor can increase or decrease your dose depending on how well the medicine works for you and how well you tolerate it.

It might take a few days before you feel the benefit of the medicine and the maximum benefit is usually felt after a few weeks.
Do not change doses of Wakix on your own. Any change in dosage must be prescribed and monitored by your doctor.

For a dose of 4.5 mg, take one 4.5 mg tablet.
For a dose of 9 mg, take two 4.5 mg tablets.
For a dose of 18 mg, take one 18 mg tablet.
For a dose of 36 mg, take two 18 mg tablets.

Adolescents and children over the age of 6
Treatment is normally started with a dose of 4.5 mg once per day, and gradually increased over three to four weeks to the most appropriate dose (see above).
If your weight is less than 40 kg, you should not take more than 18 mg per day.

Take Wakix once a day by mouth, in the morning with your breakfast.
Do not take a dose of Wakix in the afternoon since you may have difficulty sleeping.

If you take more Wakix than you should

If you take too many tablets of Wakix, contact your nearest hospital casualty department or tell your doctor or pharmacist immediately. You may experience headaches, stomach pain, feeling sick or irritable. You may also have difficulty sleeping. Take this leaflet and any remaining tablets with you.

If you forget to take Wakix

If you forget to take your medicine take the next dose at the usual time, do not take a double dose to make up for the forgotten one.

If you stop taking Wakix

You should continue to take Wakix for as long as instructed by your doctor. Do not stop taking Wakix suddenly on your own.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you notice any side effects, contact your doctor.

Common side effects (may affect up to 1 in 10 people):
- Difficulty in sleeping, feeling anxious, feeling irritable, feeling depressed, sleeping problems
- Headaches, feeling of "spinning" (vertigo), loss of balance, trembling
- Feeling sick, vomiting, indigestion
- Tiredness (fatigue)

Uncommon side effects (may affect up to 1 in 100 people):
- Sweating
- Decrease or increase of appetite
- Oedema
- Feeling jittery, nervousness, seeing or hearing things that are not really there
- Changing emotions
- Abnormal dreams
- Tension
- Difficulty in falling asleep at the beginning of the night or in the middle of the night or at the end of the night, difficulty in staying asleep, excessive sleepiness, somnolence
- State of indifference with lack of emotion
- Nightmare
- Feeling restless and unable to keep still
- Panic reaction
- Suicidal thoughts
- Altered or increased sexual interest
- Sudden and transient episode of muscle weakness, uncontrollable muscle spasms or movement of one leg
- Disturbance in attention
- Migraine
- Epilepsy
- Weakness
- Movement disturbance, slow body movement
- Sensation of tingling, tickling, pricking, or burning of the skin
- Sudden and unpredictable phases of mobility and immobility
- Feeling unsteady
- Reduced visual acuity, abnormal contraction or twitch of the eyelid
- Hearing of sound when no external sound is present
- Abnormal heart beat, slow or fast heart rate, raised or decrease blood pressure, hot flush
- Yawning
- Dry mouth
- Diarrhoea, abdominal pain, discomfort or pain in the belly (abdomen), constipation, heartburn, stomach pain and discomfort, gastritis, excessive acidity of the gastrointestinal tract
- Itching, skin condition of the face where the nose and cheeks are unusually red, excessive sweating
- Joint pain, back pain, muscle rigidity, muscle weakness, pain of the muscle and the bones, pain in the toes and in the fingers
- Abnormal urination
- Irregular uterine bleeding

- Loss of strength or extreme tiredness, chest pain, malaise, oedema
- Weight increase, weight decrease, abnormal reading (ECG) of the heart, abnormal blood values related to the function of the liver.

Rare side effects (may affect up to 1 in 1000 people):
- Loss of appetite, increased appetite
- Abnormal behaviour, confusional state, depressed mood, excitability, feelings of emotional and mental discomfort, feeling of seeing or hearing things that are not really there when you sleep
- Loss of consciousness, tension headache, trouble of the memory, poor sleep quality
- Abdominal discomfort, difficulty or pain in swallowing, flatulence, inflammation of the digestive tract
- Infection of the skin, abnormally high sensitivity to sunlight
- Neck pain, chest pain
- Spontaneous abortion
- Pain, night sweats, sense of oppression
- High blood level of the enzyme creatinine phosphokinase, abnormal general physical condition, modification of the electrical registration of the heart (ECG)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Wakix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Wakix contains

The active substance is pitolisant.

Wakix 4.5 mg tablet
Each tablet contains pitolisant hydrochloride, equivalent to 4.45 mg of pitolisant

Wakix 18 mg tablet
Each tablet contains pitolisant hydrochloride, equivalent to 17.8 mg of pitolisant.

The other ingredients are microcrystalline cellulose, crospovidone Type A, talc, magnesium stearate, colloidal anhydrous silica, poly(vinyl alcohol), titanium dioxide (E 171), macrogol 3350.

What Wakix looks like and contents of the pack

Wakix 4.5 mg comes in a white, round, film-coated tablet of 3.7 mm, biconvex marked with “5” on one side.
Wakix 18 mg comes in a white, round, film-coated tablet of 7.5 mm, biconvex marked with “20” on one side.

Wakix is available in a bottle of 30 tablets or 90 tablets.
Wakix 4.5 mg: Available in packs containing 1 bottle of 30 tablets.
Wakix 18 mg: Available in packs containing 1 bottle of 30 tablets or packs containing 1 bottle of 90 tablets or multi-packs containing 90 (3 bottles of 30) tablets.
Not all pack sizes may be marketed.

Marketing Autorisation Holder

Bioprojet Pharma
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Manufacturer

Wakix 18 mg
Inpharmasci
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1 rue Nungesser
59121 Prouvy
France

Wakix 4.5 mg
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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.
This leaflet is available in all EU/EEA languages on the European Medicines Agency website.