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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains pitolisant hydrochloride equivalent to 4.45 mg of pitolisant.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

White, round, biconvex film-coated tablet, 3.7 mm diameter, marked with “5” 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).

- to improve wakefulness and reduce excessive daytime sleepiness (EDS) in adult patients with obstructive sleep apnoea (OSA) whose EDS has not been satisfactorily treated by, or who have not tolerated, OSA primary therapy, such as continuous positive airway pressure (CPAP).

4.2 Posology and method of administration

Treatment should be initiated by a physician experienced in the treatment of sleep disorders or in the treatment of OSA and cardiovascular risk. OSA disease should be annually reassessed.

Wakix is not a therapy for the underlying airway obstruction in patients with OSA. Primary OSA therapy should be maintained or periodically rechallenged in patients not tolerating primary OSA therapy.

Posology

Narcolepsy

Adults

Pitolisant 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 upon wakening.

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.

Improving wakefulness and reduce excessive daytime sleepiness (EDS) in OSA patients

Pitolisant 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 18 mg/day:

- 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 4.5 mg tablets) per day.
- Week 3: 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.

At any time, the dose can be decreased (down to 4.5 mg per day) or increased (up to 18 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 upon wakening.

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, hepatic status, individual response and tolerance.

Insomnia has been reported in higher rate in the elderly and dosing should be adjusted accordingly (see section 4.8).

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

Hepatic impairment
No dosage adjustment is required in patients with mild hepatic impairment.

In patients with moderate hepatic impairment (Child-Pugh B) the titration period should be two-week up-titration steps instead of one after initiation of treatment, due to expected longer half-life and higher exposure, and a dosage adjustment in patients with moderate hepatic impairment could eventually be considered depending on individual response and tolerance. The daily dose can be increased without exceeding a maximal dose of 18 mg (see section 5.2).

Pitolisant is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see section 4.3).

Poor metabolizers
By comparison to CYP2D6 extensive metabolisers, higher systemic exposure (up to 3 fold) is observed in CYP2D6 poor metabolisers and lower exposure (by 0.8-fold) is observed in CYP2D6 ultra-rapid metabolizers. No differences in systemic exposure is observed between CYP2D6 extensive and intermediate metabolizers.
In the up-titration scheme, dose increment should take into account this higher exposure in CYP2D6 poor metabolizers, and a dosage adjustment in patients with known poor CYP2D6 metabolizer genotype could be considered depending on

individual response and tolerance (see section 5.2). Furthermore, no dose recommendation can currently be given for CYP2D6 ultra-rapid metabolizers taking a CYP3A inducer, because the PK is currently unknown in this subpopulation.

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, hypertension, at risk of major adverse cardiovascular events (MACE), 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 and alternative should be used.

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 and alternative should be used.

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

(e.g. haloperidol, risperidone, erythromycine, clarithromycine, roxithromycine, loratadine, sildenafil) Combination with pitolisant should be made with a careful monitoring (see section 4.4).

Pharmacokinetic interactions

In subjects that are CYP2D6 intermediate, extensive (normal) or ultra-rapid metabolizers, CYP2D6 is the main enzyme involved in the biotransformation of pitolisant, CYP3A is involved to a lesser extent. In subjects that are CYP2D6 poor metabolizers or are CYP2D6 intermediate, extensive or ultra-rapid metabolizers taking CYP3A inducers, CYP3A is significantly involved in the biotransformation of pitolisant and CYP2D6 is involved to a lesser extent.

Medicinal products affecting pitolisant metabolism

- Enzyme inducers

CYP3A inducers will most likely have an effect on the pharmacokinetics of pitolisant in CYP2D6 poor metabolizers and CYP2D6 ultra-rapid metabolizers and their effect in these populations is currently unknown. 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.
Co-administration of pitolisant with rifampicin in multiple doses significantly decreases pitolisant mean C_{max} and AUC ratio about 0.6 fold and 0.5 fold, 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.

- CYP2D6 inhibitors

CYP2D6 inhibitors will most likely have an effect on the pharmacokinetics of pitolisant in subjects that are CYP2D6 intermediate, extensive metabolizers or ultra-rapid metabolizers and taking no CYP3A inducers, but not in subjects that are CYP2D6 poor metabolizers or intermediate, extensive metabolizers or CYP2D6 ultra-rapid metabolizers and taking CYP3A inducers. A dosage adjustment during the combination could eventually be considered depending on individual response and tolerance.

Co-administration of pitolisant with paroxetine significantly increases pitolisant mean C_{max} and $AUC_{0—72h}$ ratio about 1.5 fold and 2 fold, 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.

Other

In a clinical multiple dose study, the combination of pitolisant with probenecid decreases the AUC of pitolisant by about 0.7 fold. The underlying mechanism is unknown. A dosage adjustment during the combination could eventually be considered depending on individual response and tolerance.

Medicinal products that pitolisant may affect metabolism

- CYP3A4 and CYP2B6 substrates

A clinical induction study showed that pitolisant is a weak inducer of CYP3A (0.2-fold reduction in midazolam exposure). 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.

Pitolisant might decrease the exposure to oral contraceptives and an additional further reliable contraceptive method should be used (see section 4.6).

- 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. Pitolisant may be a clinically relevant inhibitor of OCT1 based on in vitro data and a clinically relevant interaction may occur with substrates of OCT1 (e.g. metformin).

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).

<u>Other</u>

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 and no dose adjustment is necessary when pitolisant is co-administered with those current treatments of OSA symptoms.

Pitolisant decreases the olanzapine exposure by 0.3 fold.

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:

Narcolepsy and other indications

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 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 distension Dysphagia Flatulence

		Abdominal pain upper Constipation Gastroesophageal reflux disease Gastritis Gastrointestinal pain Hyperacidity Paraesthesia oral Stomach discomfort	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

Obstructive sleep apnoea

MedDRA System Organ Class	**Very Common**	**Common**	**Uncommon**

Infections and infestations			Herpes zoster Viral upper respiratory tract infection
Blood and lymphatic system disorders			Alanine aminotransferase increased Blood cholesterol increased Blood pressure increased Blood triglycerides increased Hepatic enzyme increased Transaminase increased
Metabolism and nutrition disorders			Alcohol intolerance Increased appetite Hypoglycaemia Weight decreased Weight increased
Psychiatric disorders		Insomnia (all types) Anxiety disorders Sleep disorders	Confusional arousal Depressed mood disorders and disturbances Fear Irritability Nervousness disorders Libido disorders Panic reaction Withdrawal syndrome
Nervous system disorders	Headache		Circadian rhythm sleep disorder Dizziness Dysgeusia Psychomotor hyperactivity Migraine Sleep paralysis Hypotonia
Eye disorders			Dry eye Photopsia
Ear and labyrinth disorders		Vertigo	Tinnitus
Cardiac disorders			Atrioventricular block first degree Palpitations Tachycardia

			Ventricular extrasystoles Electrocardiogram QT prolonged Heart rate increased
Vascular disorders		Hypertension	Hot flush
Respiratory, thoracic and mediastinal disorders			Yawning Cough Nocturnal dyspnoea
Gastrointestinal disorders		Nausea/vomiting Abdominal pain and discomfort Diarrhoea	Constipation Dry mouth Enterocolitis Faeces discoloured Gastrointestinal disorders Breath odour Flatulence Rectal haemorrhage Salivary hypersecretion
Skin and subcutaneous tissue disorders			Rash Hyperhidrosis Pruritus Erythema Cold sweat Night sweats Solar dermatitis
Musculoskeletal and connective tissue disorders			Limb discomfort Muscle spasms Myalgia Arthralgia Tendonitis
Renal and urinary disorders			Pollakiuria
General disorders and administration site conditions		Pain and Discomfort	Asthenia Pyrexia Thirst

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.

During clinical studies in OSA indication, episodes of headache and insomnia have been reported (12.4 % and 8.9%) more frequently in women (headache and

insomnia) and in elderly (insomnia) patients. Most of these adverse reactions were mild to moderate (see section 4.2). Dosing should be adjusted accordingly.

Gastric disorders
Gastric disorders caused by hyperacidity have been reported during clinical studies in 3.5% of the patients receiving pitolisant. Higher rates of nausea are reported in women. 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) (see section 5.1)
The paediatric population has been studied in a double-blind multicentre randomised 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%).

Patients with low/normal Body Mass Index (BMI) (<25)
Headache, insomnia, nausea and anxiety have been reported in higher rates in patients with low/normal BMI. Dosing should be adjusted accordingly.

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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)).

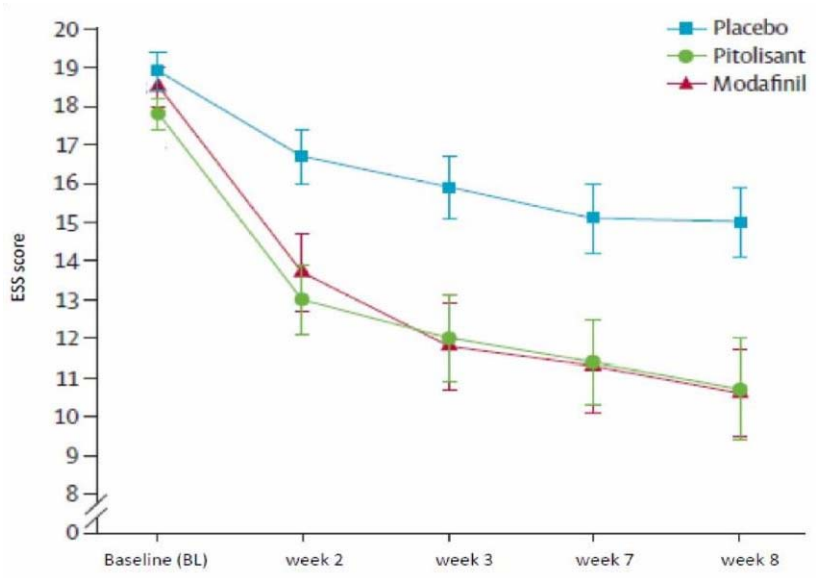
Clinical efficacy and safety

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).

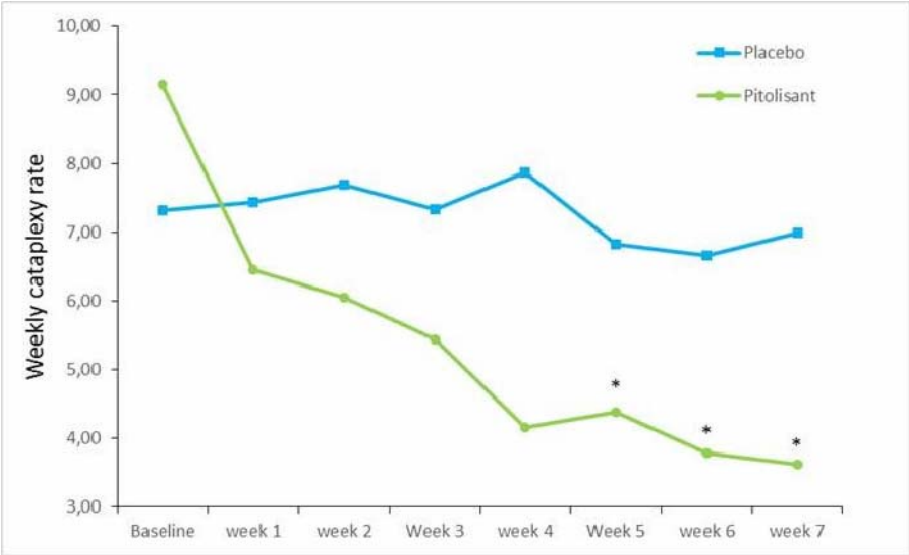
The second pivotal study (Harmony Ibis) included 165 patients (67 treated with pitolisant, 33 with placebo and 65 with modafinil). The study design was similar to study Harmony I except that the maximum dose for pitolisant reached by 75% of patients was 18 mg once a day instead of 36 mg in Harmony I. 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

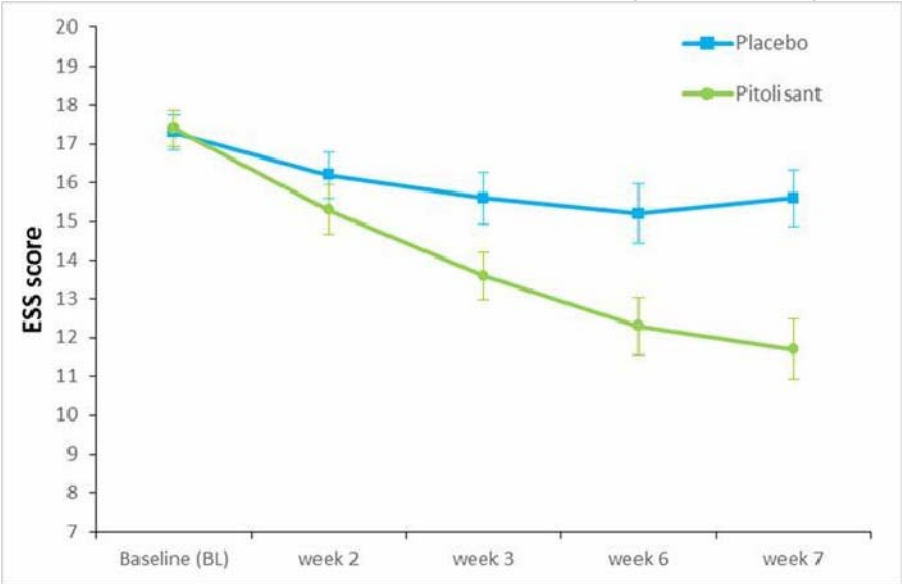


*p<0.0001 vs placebo

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.

The efficacy of pitolisant in the treatment of Excessive Daytime Sleepiness (EDS) in patients with Obstructive Sleep Apnoea (OSA) has been studied in two pivotal clinical trials: HAROSA I and HAROSA II.

HAROSA I studied the efficacy and safety of pitolisant in the treatment of Excessive Daytime Sleepiness in patients with Obstructive Sleep Apnoea syndrome (OSA), and treated by Continuous Positive Airway Pressure (CPAP), but still complaining of Excessive Daytime Sleepiness (EDS). This was a prospective, multicentre, randomized, double-blind study of pitolisant versus placebo, 12-week double-blind phase. 244 patients were analysed (183 pitolisant, 61 placebo), 83% male, average of 53 years old, 12% over 65 years. Patients had excessive daytime sleepiness (an Epworth Sleepiness Scale [ESS] score greater than or equal to 12) and were submitted to nCPAP therapy for a minimum period of 3 months and still complaining of Excessive Daytime Sleepiness despite the efforts made beforehand to obtain an efficient nCPAP.

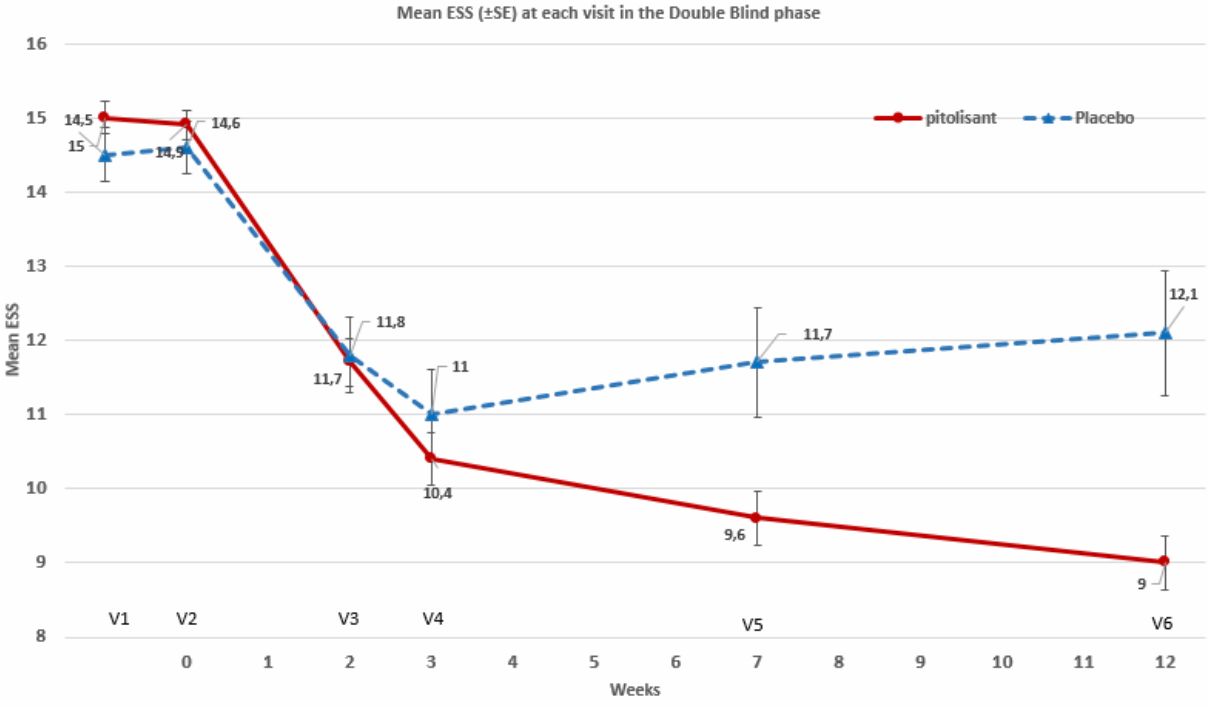
The primary efficacy variable was the change in Epworth Scale Score (ESS) between baseline and end of treatment. During the double-blind phase, the maximum dose prescribed was 18 mg for 79.8% of the patient in the active treatment group and for 88.5% of the patients in the placebo group. The maximum dose is reached after a three-week titration, starting with 4.5 mg.

After 12 weeks DB treatment, a significant improvement of the ESS was reported with pitolisant compared to placebo (table 1).

Table 1: overview of Efficacy results after 12 weeks in HAROSA I

Parameters	Treatment group (n)	Baseline score (at V2)	Final score (at V6)	Change	Difference from placebo 95% CI	P-value
ESS (SD)	Placebo (61)	14.6 (2.8)	12.1 (6.4)	-2.75	2.6[-3.9;-1.4]	P<0.001
	Pitolisant (183)	14.9 (2.7)	9 (4.8)	-5.52		

Figure 4 Changes in Epworth sleepiness scale (ESS) score in P09-08 study Double-Blind Phase - ITT Population (N=244)



HAROSA II studied the efficacy and safety of pitolisant in the treatment of Excessive Daytime Sleepiness in patients with Obstructive Sleep Apnoea syndrome (OSA) refusing the Continuous Positive Airway Pressure (CPAP) therapy. This was a prospective, multicentre, randomized, double-blind study of pitolisant versus placebo, 12-week double-blind phase followed by a 40-week open-label extension phase. 268 patients were analysed (201 pitolisant, 67 placebo), 75% male, average of 52 years, 12% over 65 years. Patients had an Epworth Sleepiness Scale [ESS] score greater than or equal to 12 and were refusing to be treated by nCPAP therapy, and still complaining of Excessive Daytime Sleepiness.

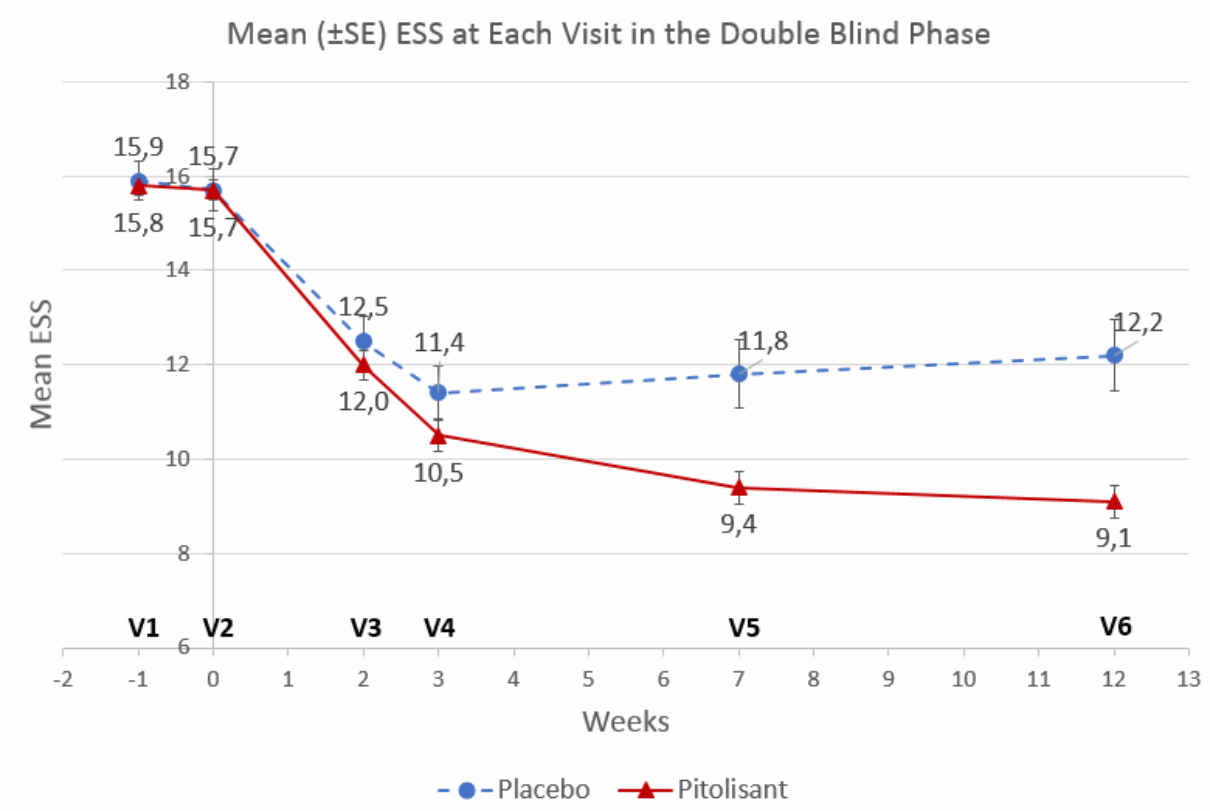
The primary efficacy variable was the change in Epworth Scale Score (ESS) between baseline and end of treatment. During the double-blind phase, the maximum dose prescribed was 18 mg for 82.5% of the patient in the active treatment group and for 86.6% of the patients in the placebo group.

After 12 weeks DB treatment, a significant improvement of the ESS was reported with pitolisant compared to placebo (ANCOVA model adjusting for ESS and BMI at V2 and study centre as random effect) (Table 2).

Table 2: overview of Efficacy results after 12 weeks in HAROSA II

Parameters	Treatment group (n)	Baseline score (at V2)	Final score (at V6)	Change	Difference from placebo 95% CI	P-value
ESS (SD)	Placebo (67)	15.7 (3.6)	12.2 (6.1)	-3.6	-2.8 [-4.0;-1.5]	P<0.001
	Pitolisant (201)	15.7 (3.1)	9.1 (4.7)	-6.3		

Figure 5 Changes in Epworth sleepiness scale (ESS) score in P09-09 study Double-Blind Phase - ITT Population (N=268)



In an extended analysis the two HAROSA trials were compared and combined, showing significant improvements by pitolisant compared with placebo on the main parameters (ESS, OSleR test, Pichot Fatigue Scale and CGI).

Table 3: Main efficacy results in pooled analysis HAROSA I – HAROSA II

	Mean	95% CI	p
OSleR Test [1]	1.18	1.02, 1.35	P=0.022
Pichot fatigue scale [2]	-1.27	-2.30, -0.23	P=0.017
CGI [3]	-0.63	-0.84, -0.47	P<0.001

1) mean ratio P20/placebo
2) treatment effect
3) difference P20-placebo

Open-label data

Patients who participated in the double-blind 12 weeks period of HAROSA I and HAROSA II studies, could participate in the 40 week open-label phase. The primary objective of the open-label phase was long-term safety and effectiveness of pitolisant up to 18 mg/day. Maintenance of effect of pitolisant in EDS in OSA patients has not been established in blinded, placebo-controlled trials. In HAROSA I, 1.5% of patients discontinued study participation during the open-label phase, due to lack of efficacy and 4.0% due to adverse events. In HAROSA II, 1.3% of patients discontinued study participation during the open-label phase due to lack of efficacy and 2.5% due to adverse events.

<u>Paediatric population</u>

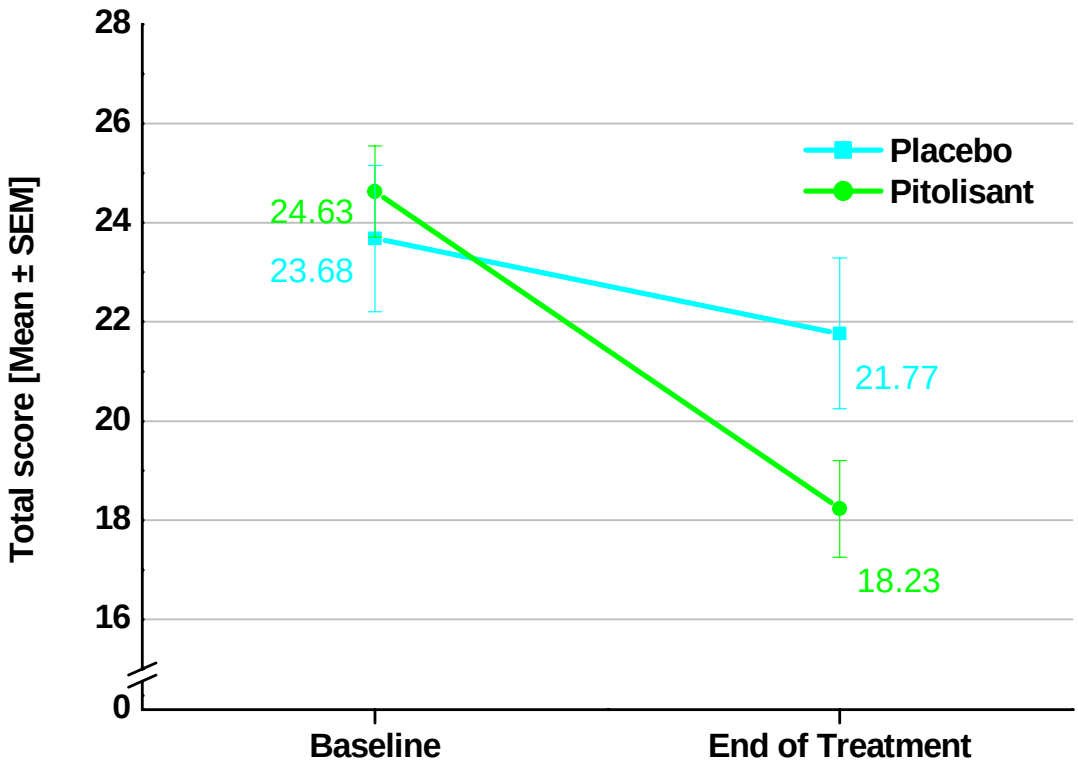
The effectiveness of pitolisant up to 36 mg once a day has been studied for the treatment of narcolepsy with or without cataplexy in children from 6 to less than 18 years old in an 8-week, multicentre, randomised, double-blind, placebo-controlled, parallel group trial. It included 110 patients (72 patients 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 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-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 favour of pitolisant (0.42 [95% CI: 0.18; 1.01], p=0.0540).

Table 4: 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) LS mean (SE) – change from baseline Estimate, 95% CI p-value	9.03 (4.33) 8.07 (4.62) -1.12 (0.64)	8.93 (3.96) 6.02 (4.00) -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 6 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. The steady-state (geometric mean, CV%) Cmax and AUC of the therapeutic dose (18 mg) is 35.5 ng/mL (59.2%) and 378 ng x h/mL (86.3%), respectively.
Upon repeated administrations, the steady state is achieved after 5-6 days of administration leading to an increased serum level around 2-fold. Inter individual variability is rather high (Geom CV% of 59.2 and 86.3 for Cmax

and AUC0-24h respectively), some volunteers showing outlier high profile (without tolerance issues).
The pharmacokinetics of pitolisant is not influenced by concomitant food intake.

Distribution

Pitolisant exhibits high serum protein binding (>90%) and demonstrates approximately equal distribution between red blood cells and plasma. Pitolisant is widely distributed with an apparent volume of distribution of 5-10 L/kg.

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 $AUC_{(0-tau)}$ 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.

In subjects that are CYP2D6 intermediate, extensive (normal) or ultra-rapid metabolizers, CYP2D6 is the main enzyme involved in the biotransformation of pitolisant, CYP3A is involved to a lesser extent. CYP3A4 and CYP3A5 genetic polymorphisms are unlikely to have significant effect on the pharmacokinetic of pitolisant.
In these subjects, CYP2D6 inhibitors will have an effect on the pharmacokinetic of pitolisant, not CYP3A inhibitors. In subjects that are CYP2D6 ultra-rapid metabolizers, CYP3A inducers may lead to an even more

rapid elimination of pitolisant and lower exposures compared to the other subgroups. This may result in exposures below therapeutic concentrations.

In subjects that are CYP2D6 poor metabolizers or are CYP2D6 intermediate, extensive or ultra-rapid metabolizers taking CYP3A inducers, CYP3A is significantly involved in the biotransformation of pitolisant and CYP2D6 is involved to a lesser extent. Only under these conditions, genetic polymorphisms in CYP3A4 and 3A5 may have a significant effect on the pharmacokinetic of pitolisant.
In subjects that are CYP2D6 poor metabolizers, CYP3A inhibitors and inducers will have an effect on the pharmacokinetic of pitolisant and CYP2D6 inhibitors to a much lesser extent. In subjects that are CYP2D6 intermediate, extensive or ultra-rapid metabolizers taking a CYP3A inducer, a CYP3A inhibitor will lead to a decrease in the contribution of CYP3A to the overall metabolism. However, the exposure is most likely similar to that in subjects that are not taking a CYP3A inducer. Thus, in this subpopulation, CYP3A inhibition is unlikely to affect the pharmacokinetic of pitolisant.

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.

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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

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 film-coated tablets.

Available in packs containing 1 bottle of 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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e-mail: BioprojetUKLtdie@eu.propharmagroup.com

8 MARKETING AUTHORISATION NUMBER(S)

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01/01/2021

10 DATE OF REVISION OF THE TEXT

10/03/2026