ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ozawade 4.5 mg film-coated tablets
Ozawade 18 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Ozawade 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)

Ozawade 4.5 mg film-coated tablet

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

Ozawade 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

Ozawade is indicated 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 healthcare professional experienced in the treatment of OSA and cardiovascular risk. OSA disease should be annually reassessed.

Ozawade 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

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

Paediatric population
There is no relevant use of Ozawade in the paediatric population in Obstructive Sleep Apnoea (OSA).

CYP2D6 metabolizers phenotype (If known)
By comparison to CYP2D6 extensive metabolizers, higher systemic exposure (up to 3-fold) is observed in CYP2D6 poor metabolizers 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 the 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 impairment

Pitolisant should be administered with caution in patients with 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 (see section 4.5).

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 (6-12-times the therapeutic dose, that is 108 mg to 216 mg) produced mild to moderate prolongation of QTc interval (10-13 ms). 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 studies, 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).

Drug abuse, rebound effect

In a specific study, pitolisant showed no or very low signal suggestive of abuse at the current therapeutic dose of 36 mg and at doses up to 216 mg; consequently, potential for drug abuse or recreational drug with pitolisant is very low.

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Antidepressants

Tri or tetracyclic antidepressants with anti-histaminic H1-receptor properties (e.g. imipramine, clomipramine, mirtazapine) may impair the efficacy of pitolisant because they may decrease 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, diphenhydramine, 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

- 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 alone or combined with CY3A4 inhibitors significantly increases to the same extent 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) alone or combined with a CYP3A4 inhibitors (itraconazole, ketonazole) should be done with caution.

- 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.

- CYP3A4 inhibitors

Based on the in vitro biotransformation pathway, CYP3A4 inhibitors may have an impact on the pharmacokinetics of pitolisant and particularly in subjects that are CYP2D6 poor metabolizers.
The combination of pitolisant with grapefruit juice and itraconazole was evaluated in healthy volunteers. No clinically relevant pharmacokinetic drug-drug interaction was evidenced with any of these combinations. In CYP2D6 poor metabolizers, co-administration of pitolisant with paroxetine (a strong CYP2D6 inhibitor) combined with a CYP3A4 inhibitor may moderatly increase the exposure compared with administration with paroxetine alone confirming the minor clinical impact of CYP3A4 inhibition.
However, based on the biotransformation pathway caution should be exercised when pitolisant is co-administered with both CYP2D6 and CYP3A4 inhibitors whatever the CYP2D6 phenotype of the patients due to a significant decrease in clearance and an increase in exposure.

- 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, 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 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).

- Other

The combination of pitolisant with modafinil or sodium oxybate 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 reactions are headache 9.5%, insomnia (all types) 8.0%, anxiety 2.7%, nausea 2.3%, abdominal pain 1.9% and vertigo 1.7%.

Tabulated list of adverse reactions

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

	Common	**Uncommon**
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		Swelling of eyelid 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		Hot flush Hypertension Hypertensive crisis
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 Oedema peripheral

Description of selected adverse reactions

Headache and insomnia
During clinical studies in OSA indication, episodes of headache and insomnia have been reported (9.5 % and 8.0%) 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 presumably 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.

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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

Symptoms of pitolisant 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 an 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.

Clinical efficacy

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 studies: HAROSA I and HAROSA II.

HAROSA I studied the efficacy and safety of pitolisant in the treatment of EDS in patients with Obstructive Sleep Apnoea syndrome (OSA), and treated by Continuous Positive Airway Pressure (CPAP), but still complaining of EDS. This was a prospective, multicenter, randomized, double-blind study of pitolisant versus placebo, 12-week double-blind phase. 244 patients were analyzed (183 pitolisant, 61 placebo), 83% male, average of 53 years old, 12% over 65 years. Patients had EDS (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 EDS despite the efforts made beforehand to obtain an efficient nCPAP.

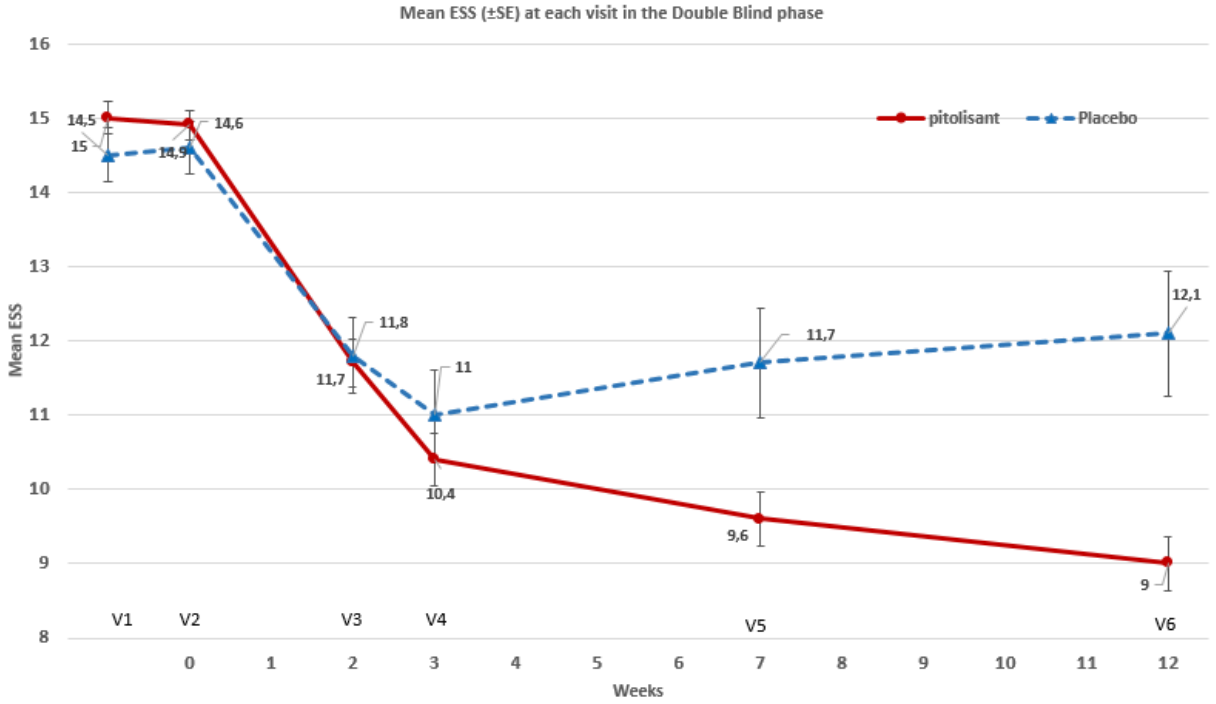
The primary efficacy variable was the change in Epworth Sleepiness Scale (ESS) Score between baseline and end of treatment. During the double-blind phase, the maximum dose prescribed was 18 mg for 79.8% of the patients in the active treatment group and for 88.5% of the patients in the placebo group. 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 1 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 EDS in patients with Obstructive Sleep Apnoea syndrome (OSA) refusing the Continuous Positive Airway Pressure (CPAP) therapy. This was a prospective, multicenter, 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 analyzed (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 EDS.

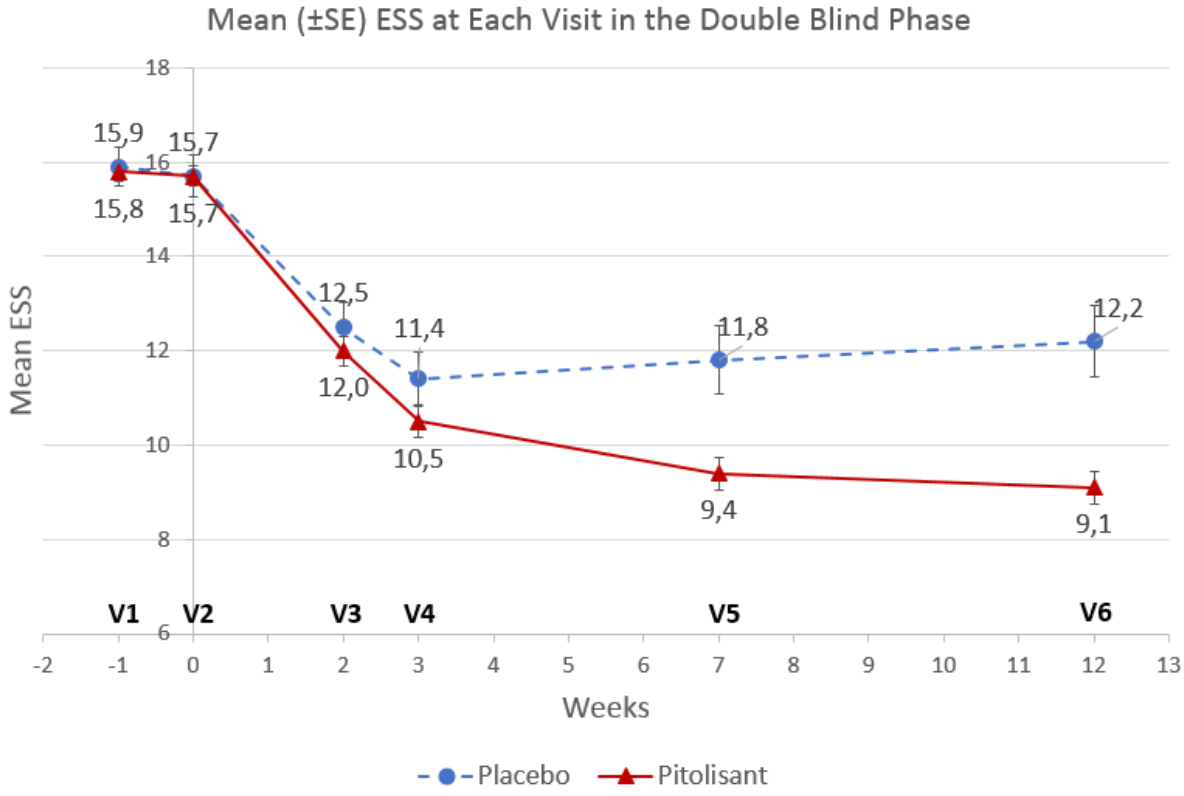
The primary efficacy variable was the change in Epworth Sleepiness Scale (ESS) score between baseline and end of treatment. During the double-blind phase, the maximum dose prescribed was 18 mg for 82.5% of the patient in the active treatment group and for 86.6% of the patients in the placebo group.

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 center 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 2 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 studies 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 pitolisant/placebo
2) treatment effect
3) difference pitolisant-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 studies. 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.

HAROSA III was a prospective, randomized, double-blind (12 weeks), placebo-controlled study in 361 patients with syndrome (OSA). Subjects complained of EDS despite treated by nCPAP therapy or had EDS and refused nCPAP therapy. Subjects were randomized to pitolisant (n=242) or placebo (n=119). Pitolisant was up titrated from 9 to 18 mg and then, depending on the patient's response, either remained stable or was further up titrated to 36 mg or was down titrated to 9 mg. Subjects were on a stable dose phase for 9 weeks. The primary efficacy endpoint was the change from baseline in Epworth Sleepiness Scale (ESS) score at end of treatment. Under pitolisant (36 mg OD) the ESS

improved from 14.5 points to 9.3 points on the ESS score, which was from 14.0 points to 11.8 points under placebo. The difference was 2.6 points ($p<0.001$). Improvement in EDS assessed by ESS score is of same magnitude as those observed in the other trials conducted in OSA patients. There was no difference in response between subjects with nCPAP and subjects who refused nCPAP.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Ozawade in all subsets of the paediatric population in Obstructive Sleep Apnoea (OSA) (see section 4.2 for information on paediatric use).

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%) C_{max} 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 C_{max} and AUC_{0-24h} 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 (91.4-95.2%) 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 metabolism of pitolisant in humans is well characterized and represents the major route of elimination. The major non-conjugated metabolites are cleaved forms of pitolisant leading to inactive major carboxylic acid metabolites, three of which being major and in a lesser extent five hydroxylated/N-oxide derivatives in several positions found in urine and serum. By combining the contribution of enzyme determined *in vitro* with the exposure of the main metabolites identified in the mass balance study, the estimated overall contribution of CYP enzymes in pitolisant metabolism is of 60% for CYP2D6 and of ~ 30% for CYP3A4/3A5 when CYP2D6 phenotype is extensive metabolizer. Several conjugated metabolites were identified, the major ones (inactive) being two glycine conjugates of carboxylic acid metabolites of pitolisant and a glucuronide of a ketone metabolite of monohydroxy desaturated pitolisant.

Inhibition/Induction
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).
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. A clinical study was conducted to assess the effect of pitolisant on CYP3A4 and CYP2B6 using midazolam and bupropion as a CYP3A4 and a CYP2B6 model substrate, respectively. Pitolisant does not affect the pharmacokinetic of bupropion and consequently is not a CYP2B6 or a CYP1A2 inducer and should be considered a borderline/weak inducer at clinically relevant concentrations.

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. The elimination is mainly achieved via urine (approximately 90%) through pharmacologically inactive-non conjugated and glycine and glucuronide conjugated metabolites. A small fraction (2.3%) was recovered in faeces.

Linearity/non-linearity

A cross-study assessment of single-dose data shows that pitolisant exposures increase proportionally with doses between 18 and 216 mg pitolisant but slightly more than dose-proportionally over the clinical dose range of 4.5 to 18 mg.

Special populations

There are unlikely to be any clinically relevant differences in the PK of pitolisant due to sex. Pitolisant has not been studied in obese population with BMI >40 kg/m^2.

Elderly

In 68 to 80 years old healthy volunteers 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 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 (see section 4.2). The underlying mechanism is unknown.

Hepatic impairment

In patients with mild hepatic impairment (Child-Pugh A), AUC increased by a factor 1.4 while C_{max} remained unchanged, compared with normal healthy volunteers.
In patients with moderate hepatic impairment (Child-Pugh B), AUC increased by a factor 2.4, while C_{max} remained unchanged (see section 4.2). Pitolisant pharmacokinetics after repeated administration in patients with hepatic impairment has not been evaluated yet.

Race

All studies have been performed mainly in Caucasians (Caucasians = 270; Black = 38; Asian = 20; Other = 3). Based on the data provided by the Applicant, the exposure appears to be similar between the different races.

CYP2D6 phenotypes and CYP3A polymorphism

The exposure to pitolisant was higher in the CYP2D6 poor metabolizers 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 metabolizers compared to the extensive metabolizers.

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.

5.3 Preclinical safety data

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, rats presented some limited histopathological changes in some organs (liver, duodenum, thymus, adrenal gland and lung).

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, rats and monkeys. However, no definitive conclusion could be drawn on tolerance, dependence and self-administration studies.

Pitolisant was neither genotoxic nor carcinogenic.

Teratogenic effect of pitolisant was observed at maternally toxic doses (teratogenicity safety margins 7.3 and 2.6 in rats and in rabbits, respectively). 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 2.3). It caused a delay in post-natal development (safety margin of 2.3).

Pitolisant/metabolites were shown to cross the placenta barrier and secreted in breast milk in animals.

Juvenile toxicity studies
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E 460)
Crospovidone type A (E 1202)
Talc (E 553b)
Magnesium stearate
Colloidal anhydrous silica (E 551)

Coating

Poly(vinyl alcohol) (E 1203)
Titanium dioxide (E 171)
Macrogol 3350 (E 1521)
Talc (E 553b)

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).

Ozawade 4.5 mg
Available in packs containing 1 bottle of 30 tablets or 1 bottle of 90 tablets.

Ozawade 18 mg
Available in packs containing 1 bottle of 30 tablets or 1 bottle of 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local 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/1/21/1546/001
EU/1/21/1546/002
EU/1/21/1546/003
EU/1/21/1546/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22/07/2021

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

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

Ozawade 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**

The requirements for submission of periodic safety update reports 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ozawade 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
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/1/21/1546/001
EU/1/21/1546/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ozawade 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

Ozawade 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
90 tablets

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ozawade 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/1/21/1546/002
EU/1/21/1546/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ozawade 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

Ozawade 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

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

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 Ozawade is and what it is used for

Ozawade is a medicine that contains the active substance pitolisant.

Ozawade is used in adults with obstructive sleep apnoea to treat excessive daytime sleepiness. It is used when sleepiness occurs despite treatment with continuous positive airway pressure (CPAP) or in patients who have not tolerated CPAP.

Obstructive sleep apnoea (OSA) is a condition that causes you to stop breathing for at least 10 seconds during sleep. This can lead to excessive daytime sleepiness and a tendency to suddenly fall asleep in inappropriate situations (sleep attacks).

The active substance, pitolisant, works on receptors (targets) on cells in the brain that are involved in stimulating alertness. This effect helps to reduce daytime sleepiness and tiredness.

2. What you need to know before you take Ozawade

Do not take Ozawade 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 high levels may build up in patients whose liver function is severely reduced.
- Are breastfeeding.

Warnings and precautions

Talk to your doctor before taking Ozawade if any of the following apply to you:
- You have 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 to reduce inflammation, since gastric reactions can occur with Ozawade.

- You are very overweight or underweight, as your weight may increase or decrease while you are taking Ozawade.
- You have heart problems. Your doctor will need to check this regularly while you are taking Ozawade.
- You have severe epilepsy.

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

Ozawade does not replace your OSA primary treatment such as CPAP. You should continue to use such treatment as well as Ozawade.

Children and adolescents

Ozawade should not be taken by children or adolescents.

Other medicines and Ozawade

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

Tell your doctor or pharmacist if you are taking any of the following medicines:
- antidepressant medicines such as clomipramine, duloxetine, fluoxetine, imipramine, mirtazapine, paroxetine and venlafaxine
- bupropion, used either as an antidepressant or an aid to help stop smoking
- medicines for treating allergies called antihistamines such as pheniramine maleate, chlorpheniramine, diphenhydramine, promethazine, mepyramine, doxylamine
- rifampicin, an antibiotic used for treating tuberculosis and some other infections
- epilepsy medicines (to prevent fits) such as carbamazepine, phenobarbital and phenytoin
- heart medicines such as digoxin and quinidine
- St John's Wort (*Hypericum perforatum*), a herbal remedy for depression
- cinacalcet used for treating disorders of the parathyroid gland
- terbinafine, used for treating fungal infections
- diabetes medicines such as metformin and repaglinide
- medicines for treating cancer such as docetaxel and irinotecan
- cisapride, used for treating gastric reflux
- pimozide, used for treating some mental disorders
- halofantrine, used for treating malaria
- efavirenz, an antiviral medicine to treat HIV infection
- morphine, used for treating severe pain
- paracetamol, used for treating pain
- anticoagulant medicines (medicines that prevent blood clots) such as dabigatran and warfarin
- probenecid, used for treating gout
- medicines for treating pain, inflammation and fever such as acetylsalicylic acid (aspirin), diclofenac, ibuprofen, meloxicam and naproxen
- hormonal contraceptive (birth control medicine), see also under 'Pregnancy', below.

Pregnancy and breast-feeding

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

<u>Pregnancy</u>

You should not take Ozawade during pregnancy unless you and your doctor decide that you need to take it. There is not enough information on the risk of taking Ozawade during pregnancy. If you are a

woman, you have to use effective birth control during your treatment with Ozawade and for at least 21 days after stopping treatment. As Ozawade may reduce the effectiveness of a hormonal contraceptive (birth control medicine), an alternative method of effective contraception has to be used.

Breast-feeding

You must stop breastfeeding when you start taking Ozawade. Ozawade passes into milk in animals.

Driving and using machines

You may feel sleepy or your ability to concentrate may be impaired. Take care with activities that require attention such as driving a car and handling machinery. Talk to your doctor or your pharmacist if you are unsure about how your condition affects your ability to drive.

3. How to take Ozawade

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

Treatment is normally started with a dose of 4.5 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. The maximum daily dose is 36 mg.

It might take a few days before you feel the medicine starting to work and you may usually feel the maximum benefit after a few weeks.

Do not change the Ozawade dose 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.

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

If you take more Ozawade than you should

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

If you forget to take Ozawade

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 Ozawade

You should continue to take Ozawade for as long as instructed by your doctor. Do not stop taking Ozawade 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.

Common side effects (may affect up to 1 in 10 people):
- Headache
- Difficulty sleeping, sleeping problems, feeling anxious
- Feeling of "spinning" (vertigo)
- Feeling sick, abdominal (belly) discomfort

Uncommon side effects (may affect up to 1 in 100 people):
- Viral upper respiratory tract infection (common cold), cold sores
- Change in bleeding analyses, abnormal blood values related to the function of the liver, raised blood pressure, increase of cholesterol level in the blood
- Alcohol intolerance, increased appetite, low blood sugar level, body weight change
- Irritability, confusional state, fear, panic reaction, altered or increased sexual interest, feeling depressed, feeling nervous
- Loss of balance, trouble of sleep rhythm, impairment of the taste, sudden and unpredictable phases of mobility and immobility, migraine, sleep paralysis, loss of the ability to perform physical activities
- Swelling of eyelid, dry eye, presence of flashes of light or floaters in the vision
- Ringing or buzzing in the ear
- Irregular heart rhythm, palpitation, fast heart rate, abnormal heart rate
- Hot flush, high blood pressure, sudden rise in blood pressure
- Yawning, cough, difficulty to breath at night
- Diarrhoea, constipation, dry mouth, disorders of the digestive tract, inflammation of the digestive tract, discoloration of the faeces, odour of the breath, flatulence, rectal bleeding, high secretion of saliva
- Skin eruption, itching of the face, redness of the skin, cold sweats, excessive sweating, sweating at night, abnormal high sensitivity of the skin to sunlight
- Discomfort of arms and legs, spasms of muscles, pain of the muscles, joint pain, pain of the tendons
- Frequent urination
- Pain and discomfort, tiredness (fatigue), feeling hot, feeling thirsty, oedema of legs or hands

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 Ozawade

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 Ozawade contains

The active substance is pitolisant.

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

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

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

What Ozawade looks like and contents of the pack

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

Ozawade is available in a bottle of 30 tablets or 90 tablets.
Ozawade 4.5 mg: Available in packs containing 1 bottle of 30 tablets or packs containing 1 bottle of 90 tablets.
Ozawade 18 mg: Available in packs containing 1 bottle of 30 tablets or packs containing 1 bottle of 90 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

Bioprojet Pharma
9, rue Rameau
75002 Paris
France

Manufacturer

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

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Bioprojet Benelux
0032(0)78050202

Lietuva
Bioprojet Pharma
0033 (0)1 47 03 66 33

info@bioprojet.be

България
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Česká republika
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Danmark
Zambon Sweden, filial of Zambon Nederland B.V.
+46 (0)10 33 50 800
contact@zambongroup.com

Deutschland
Bioprojet Deutschland GmbH
030/3465 5460-0
info@bioprojet.de

Eesti
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Ελλάδα
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

España
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

France
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Hrvatska
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Ireland
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Ísland

contact@bioprojet.com

Luxembourg/Luxemburg
Bioprojet Benelux
0032(0)78050202
info@bioprojet.be

Magyarország
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Malta
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Nederland
Bioprojet Benelux N.V.
088 34 34 100
info@bioprojet.nl

Norge
Zambon Sweden, filial of Zambon Nederland B.V.
+46 (0)10 33 50 800
contact@zambongroup.com

Österreich
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Polska
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Portugal
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

România
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Slovenija
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Slovenská republika

Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Italia
Bioprojet Italia srl
+39 02 84254830
info@bioprojet.it.it

Κύπρος
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Latvija
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Suomi/Finland
Bioprojet Pharma
0033 (0)1 47 03 66 33
contact@bioprojet.com

Sverige
Zambon Sweden, filial of Zambon Nederland B.V.
+46 (0)10 33 50 800
contact@zambongroup.com

This leaflet was last revised in

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/EAA languages on the European Medicines Agency website.