PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR OZAWADE® (PITOLISANT)

This is a summary of the risk management plan (RMP) for Ozawade®. The RMP details important risks of Ozawade®, how these risks can be minimised, and how more information will be obtained about Ozawade®'s risks and uncertainties (missing information).

Ozawade®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ozawade® should be used.

This summary of the RMP for Ozawade® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ozawade®'s RMP.

I The medicine and what it is used for

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

It contains pitolisant as the active substance and it is given by oral route.

Further information about the evaluation of Ozawade®'s benefits can be found in Ozawade®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/ozawade.

II Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Ozawade®, together with measures to minimise such risks and the proposed studies for learning more about Ozawade®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Ozawade® is not yet available, it is listed under 'missing information' below.

II.A. List of Important risks and missing information

Important risks of Ozawade® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ozawade®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Important identified risks	None
Important potential risks	Long term risks of body weight increase Cardiovascular events including QT-interval prolongation Adverse effects on reproductive function Adverse effects on embryofoetal development
Missing information	Long-term safety

II.B Summary of important risks

Identified risks

None

Potential risks

Long term risks of body weight increase	
Evidence for linking the risk to the medicine	Weight increase has been reported uncommonly (in up to 40 patients in 1,513 treated with pitolisant).
Risk factors and risk groups	No specific risk group (age or gender) was identified with pitolisant during the clinical development. However the prevalence of obesity is high in population with sleep disorders.
Risk minimisation measures	Routine risk minimization measures • SmPC § 4.4 • SmPC § 4.8 • PL section 2 • PL section 4 Medicinal product subject to special medical prescription Treatment should be initiated by a healthcare professional experienced in the treatment of OSA and cardiovascular risk

Cardiovascular events including QT-interval prolongation	
Evidence for linking the risk to the medicine	Pitolisant has not been studied in patients with underlying severe cardiovascular disease. Pitolisant produces QT prolongation at doses higher than the therapeutic dose. In clinical trials, no effects on the heart were identified at therapeutic doses. Patients with heart disease, treated with other QT-prolonging medicines or known to be at risk of arrhythmias (irregular heartbeat), treated with medicines that increase the amount of pitolisant in the blood or with severe kidney or moderate liver impairment should be carefully monitored.
Risk factors and risk groups	No specific risk group (age or gender) was identified with pitolisant during the clinical development. However the prevalence of cardiovascular disease is high in population with sleep disorders. Interaction with medicinal products increasing the QT interval on the ECGs. Administration to patients with long QT-syndrome or electrolyte imbalance.
Risk minimisation measures	Routine risk minimization measures • SmPC § 4.4 • SmPC § 4.5 • SmPC § 4.8 • SmPC § 5.3 • PL section 2 • PL section 4 Medicinal product subject to special medical prescription Treatment should be initiated by a healthcare professional experienced in the treatment of OSA and cardiovascular risk.
Additional pharmacovigilance activities	Cardiovascular risk and Long-term safety PASS (P21-02) See section II.C of this summary for an overview of the post-authorisation development plan

Adverse effects on reproductive function	
Evidence for linking the risk to the medicine	No data on fertility are available in humans. Studies in animals have shown effect on semen parameters, without a significant impact on reproductive performance in males and reduction on the percentage of live fetuses in treated females.
Risk factors and risk groups	Patient with medical history of fertility disorders.
Risk minimisation measures	Routine risk minimization measures • SmPC § 4.3 • SmPC § 4.6 • SmPC§ 4.8 • SmPC § 5.3 • PL Section 2 Medicinal product subject to special medical prescription Treatment should be initiated by a healthcare professional experienced in the treatment of OSA and cardiovascular risk

Adverse effects on embryofoetal development	
Evidence for linking the risk to the medicine	Pregnancy There are no data on the use of pitolisant in pregnant women. Studies in animals have shown reproductive toxicity, including teratogenicity (causing birth defects). Ozawade is not recommended during pregnancy and in women of childbearing potential not using contraception. Ozawade may reduce the effectiveness of hormonal contraceptives; therefore an alternative method of contraception should be used. Breastfeeding Animal studies have shown that pitolisant can pass into breast milk. Therefore breastfeeding is contraindicated during treatment with Ozawade.
Risk factors and risk groups	Child bearing potential women without effective contraceptive method.
Risk minimisation measures	Routine risk minimization measures • SmPC § 4.3 • SmPC § 4.4 • SmPC § 4.5 • SmPC § 4.6 • SmPC § 5.3 • PL Section 2 Medicinal product subject to special medical prescription Treatment should be initiated by a healthcare professional experienced in the treatment of OSA and cardiovascular risk

Missing information

Long-term safety	
Risk minimisation measures	Routine risk minimization measures • SmPC § 4.8 and • SmPC § 4.4 • PL section 2 • PL section 4 Medicinal product subject to special medical prescription Treatment should be initiated by a healthcare professional experienced in the treatment of OSA and cardiovascular risk
Additional Pharmacovigilance activity	Cardiovascular risk and Long-term safety PASS (P21-02) See section II.C of this summary for an overview of the post-authorisation development plan

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorization

Not applicable.

II.C.2 Other studies in post-authorisation development plan

Category 3 study:

P21-02: A multi-center, observational post-authorization safety study to compare the cardiovascular and long-term safety of OZAWADE in patients with obstructive sleep apnoea treated or not by CPAP and exposed or not to OZAWADE according to the therapeutic indication in the SmPC, when used in routine medical practice.

Purpose of the study:
The primary objective of the PASS will assess the cardiovascular risk (Cardiovascular events including QT-interval prolongation) in OSA patients treated with OZAWADE compared with OZAWADE-unexposed patients with OSA. The second primary objective is to collect information on long-term safety of pitolisant in patients with obstructive sleep apnoea treated with OZAWADE according to the agreed therapeutic indication in the SmPC.