PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR WAKIX

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

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

This summary of the RMP for Wakix 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 Wakix's RMP.

Wakix has been approved in accordance with Article 3(1) of Regulation (EC) No 726/2004 and Article 8(3) of Directive 2001/83/EC.

I The medicine and what it is used for

Wakix is authorised in adult, adolescents and children from the age of 6 years for the treatment of narcolepsy with or without cataplexy (see SmPC for the full indication). It contains pitolisant as the active substance and it is given by oral route.

Further information about the evaluation of Wakix's benefits can be found in Wakix's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *EPAR summary of Wakix*

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

Important risks of Wakix, together with measures to minimise such risks and the proposed studies for learning more about Wakix'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, 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 Wakix is not yet available, it is listed under ‘missing information’ below.

II.A. List of Important risks and missing information

Important risks of Wakix 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 Wakix. 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).

Summary of safety concerns	
Important identified risks	Insomnia Gastric disorders caused by hyperacidity Anxiety Depression and suicidal ideation Weight increase
Important potential risks	Proconvulsive potential QT-interval prolongation Misuse Drug dependence Rebound effect Fertility disorders Exposure during pregnancy and lactation Interaction with drugs displaying histamine H1 receptor antagonism activity.
Missing information	Long-term safety including paediatric patients Patients with severe depression and severe anxiety Patients with underlying severe cardiovascular diseases

II.B Summary of important risks

Identified risks

Insomnia	
Evidence for linking the risk to the medicine	Insomnia has been reported commonly in clinical studies (in up to 10 patients in 100 treated with Wakix mostly at dose from 18 to 36 mg per day). Most cases were mild to moderate.
Risk factors and risk groups	No specific risk group was identified during the clinical development. The frequency of insomnia is higher in elderly.
Risk minimisation measures	Routine risk minimisation • SmPC § 4.8 • PL Section 4 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

Gastric disorders caused by hyperacidity	
Evidence for linking the risk to the medicine	Wakix may increase the stomach acidity. Gastric disorders have been reported commonly (in up to 10 patients in 100 treated with Wakix) during clinical studies. However, no stomach ulcers were reported.
Risk factors and risk groups	No specific risk group was identified during the clinical development. The frequency of gastric disorders is similar between gender and age.
Risk minimisation measures	Routine risk minimisation • SmPC § 4.8 • SmPC § 4.4 • PL section 2 • PL section 4 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

Anxiety	
Evidence for linking the risk to the medicine	Anxiety and depression have been reported commonly (in up to 10 patients in 100 treated with Wakix). Uncertainty remains on the causal association between the risk of depression/anxiety and Wakix as psychiatric side effects are frequent comorbidities in narcolepsy.
Risk factors and risk groups	No specific risk group (age or gender) was identified during the clinical development. The prevalence of moderate to severe depression / anxiety ranged from 15% to 37% in the narcoleptic population (Vandeputte et al Sleep Med 2003). In Harmony III study (P09-10, n = 102 pitolisant-treated patients), 18 patients (17.6%) had medical history of depression or depressive syndrome at inclusion. Among them 9 (8.8%) had ongoing depression at study entry. These data are in accordance with the prevalence reported in the narcoleptic population.
Risk minimisation measures	Routine risk minimisation • SmPC § 4.8 • SmPC § 4.8 • SmPC § 4.4: • PL section 2 • PL section 4 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

Depression and suicidal ideation	
Evidence for linking the risk to the medicine	Anxiety and depression have been reported commonly (in up to 10 patients in 100 treated with Wakix). Uncertainty remains on the causal association between the risk of depression/anxiety and Wakix as psychiatric side effects are frequent comorbidities in narcolepsy. Suicidal events have been reported in non-interventional studies (PASS and EAP in US) with an incidence between 0.54% in the PASS and 0.30% in the EAP in US.
Risk factors and risk groups	No specific risk group (age or gender) was identified. The prevalence of moderate to severe depression / anxiety ranged from 15% to 37% in the adolescent-adult narcoleptic population (Vandeputte et al Sleep Med 2003) and about 25% of the narcoleptic children have been described with high levels of depressive symptoms [Innocente 2014]. Incidence of suicidal ideation is about 9 % in narcoleptic patient (Alasim et al, 2019). In Harmony III study (P09-10, n = 102 pitolisant-treated patients), 18 patients (17.6%) had medical history of depression or depressive syndrome at inclusion. These data are in accordance with the prevalence reported in the narcoleptic population. In PASS (n=364) and in the EAP in US (n=622), 2 patients and 3 patients, respectively reported suicidal events.
Risk minimisation measures	Routine risk minimisation • SmPC § 4.4 • SmPC § 4.8 • PL section 2 • PL section 4 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

Weight increase	
Evidence for linking the risk to the medicine	Weight increase has been reported uncommonly (in up to 10 patients in 1,000 treated with Wakix).
Risk factors and risk groups	No specific risk group (age or gender) was identified with pitolisant during the clinical development.
Risk minimisation measures	Routine risk minimisation • SmPC § 4.4 • SmPC § 4.8 • PL section 2 • PL section 4 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

Potential risks

Proconvulsive potentials	
Evidence for linking the risk to the medicine	Convulsions were reported at high doses in animal studies. In clinical trials, one case of worsening of epilepsy was reported in an epileptic patient. Caution is recommended in patients with severe epilepsy.
Risk factors and risk groups	Medical history of epilepsy.
Risk minimisation measures	Routine risk minimisation • SmPC § 4.4 • SmPC § 5.3 • PL section 2 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

Misuse	
Evidence for linking the risk to the medicine	Because Wakix affects the central nervous system, there is a potential risk for drug abuse and misuse, drug dependence and rebound effect (when the symptoms come back after stopping treatment).
Risk factors and risk groups	Persons wanted to increase their awakeness in special situations (working during the night, jet-lag,…).
Risk minimisation measures	Routine risk minimisation • SmPC § 4.2 • SmPC § 5.3 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

Drug dependence	
Evidence for linking the risk to the medicine	Because Wakix affects the central nervous system, there is a potential risk for drug abuse and misuse, drug dependence and rebound effect (when the symptoms come back after stopping treatment). In clinical studies, no signal of abuse and dependence was reported.
Risk factors and risk groups	Persons with history of drug abuse or drug dependence
Risk minimisation measures	Routine risk minimisation • SmPC § 4.2 • SmPC § 5.3 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

Rebound effect	
Evidence for linking the risk to the medicine	Because Wakix affects the central nervous system, there is a potential risk for drug abuse and misuse, drug dependence and rebound effect (when the symptoms come back after stopping treatment). In clinical studies, no signal of abuse and dependence was reported.
Risk factors and risk groups	Associated pathology with symptoms of somnolence (Obstructive sleep apnoea, Parkinson's disease, depression).
Risk minimisation measures	Routine risk minimisation • SmPC § 4.2 • SmPC § 4.4 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

Fertility disorders	
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 foetuses in treated females.
Risk factors and risk groups	Patient with medical history of fertility disorders.
Risk minimisation measures	Routine risk minimisation • SmPC § 4.6 • SmPC § 5.3 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

Exposure during pregnancy and lactation	
Evidence for linking the risk to the medicine	Pregnancy There are no data on the use of Wakix in pregnant women. Studies in animals have shown reproductive toxicity, including teratogenicity (causing birth defects). Wakix is not recommended during pregnancy and in women of childbearing potential not using contraception. Wakix 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 Wakix.
Risk factors and risk groups	Childbearing potential women without effective contraceptive method.
Risk minimisation measures	Routine risk minimisation • SmPC § 4.3 • SmPC § 4.4 • SmPC § 4.5 • SmPC § 4.6 • SmPC § 5.3 • PL Section 2 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

Interaction with drugs displaying histamine H1 receptor antagonism activity.	
Evidence for linking the risk to the medicine	Pitolisant stimulates wakefulness via the brain histamine system. All substances which block the brain histamine system could impair the effectiveness of Wakix. These include: • Tricyclic or tetracyclic antidepressants (e.g. imipramine, clomipramine, mirtazapine). • Anti-histamines (H1-receptor antagonists) that can pass into the brain (e.g. pheniramine maleate, chlorpheniramine, diphenydramine, promethazine, mepyramine).
Risk factors and risk groups	Association drugs displaying histamine H1 receptor antagonism activity could lead to inefficacy.
Risk minimisation measures	Routine risk minimisation • SmPC § 4.5 • PL Section 2. Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

QT-interval prolongation	
Evidence for linking the risk to the medicine	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	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 minimisation • SmPC § 4.4 • SmPC § 4.5 • SmPC § 4.8 • SmPC § 5.3 • PL sections 2 and 4 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

<u>Missing information</u>

Long term safety including paediatric patients	
Risk minimisation measures	Routine risk minimisation • SmPC § 4.8 • PL section 4 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.
Additional Pharmacovigilance activities:	PASS (Category 1): Study short name: **P15-11:** A multi-center, observational **post-authorization safety** study to document the drug utilisation of Wakix® and to collect information on the **safety** of Wakix® in adult population, when used in routine medical practice. **Open-label extension study** from the paediatric clinical trial (P11-06) (Category 3) **P11-06:** A randomized, double blind, placebo-controlled, parallel group, multicenter trial comparing the effects of

	pitolisant (BF2.649) or placebo for the treatment during 8 weeks (double-blind period) of narcoleptic children from 6 to less than 18 years with or without cataplexy. After 4-week of individual up-titration scheme from 5 to a maximum of 40 mg/d pitolisant (BF2.649) or placebo, the treatment will be administered at a stable dose for 4 weeks, followed by 1 week placebo period. Then, patients willing to continue will receive the study treatment (pitolisant) during a **prolonged open-label period.** See section II.C of this summary for an overview of post-authorisation development plan.

Patients with severe depression and severe anxiety	
Risk minimisation measures	Routine risk minimisation • SmPC § 4.4 • PL Section 2 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.
Additional Pharmacovigilance activities: PASS	Study short name: **P15-11:** A multi-center, observational **post-authorization safety** study to document the drug utilisation of Wakix® and to collect information on the **safety** of Wakix® when used in routine medical practice. See section II.C of this summary for an overview of Post-authorisation development plan.

Patients with underlying severe cardiovascular disease	
Risk minimisation measures	Routine risk minimisation • SmPC § 4.4 • PL Section 2 Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.

II.C Post-authorisation development plan

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

The following study is condition of the marketing authorisation:

P15-11: A multi-center, observational post-authorization safety study to document the drug utilisation of Wakix® and to collect information on the safety of Wakix® when used in routine medical practice

- To collect safety information on the long-term safety of Wakix in adult population, when used in real-life setting
- To document the drug utilization patterns of Wakix in routine medical practice

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

The open-label extension study from the paediatric study (P11-06) is appropriate to investigate long-term safety of Wakix in the paediatric population.