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Summary of the risk management plan (RMP) for Wakix (pitolisant)

This is a summary of the risk management plan (RMP) for Wakix, which details the measures to be taken in order to ensure that Wakix is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Wakix, which can be found on Wakix's EPAR page.

Overview of disease epidemiology

Wakix (pitolisant) is a medicine used to treat narcolepsy. Narcolepsy is a rare, long-term sleep disorder which affects the brain's ability to regulate the normal sleep-wake cycle. Narcolepsy is characterised by excessive daytime sleepiness, episodes of muscle weakness (cataplexy), hallucinations related to sleep, sleep paralysis, broken sleep at night, reduced attention span as well as non-sleep symptoms such as obesity, anxiety, and cognitive and emotional problems. Not all symptoms are present in all patients.

The prevalence of narcolepsy in European countries varies from 2 to 5 people in 10,000. The age of onset varies from early childhood to around 50 years.

Summary of treatment benefits

Wakix has been investigated in 2 main studies involving a total of 261 adults with narcolepsy, the majority of whom also had cataplexy. The studies compared Wakix with placebo (a dummy treatment). The main measure of effectiveness was based on how sleepy patients felt during daytime, assessed using the Epworth Sleepiness Scale or ESS. This is a standard scale used in patients with narcolepsy which ranges from 0 to 24.

The first study showed that Wakix was more effective than placebo at reducing daytime sleepiness: patients taking Wakix had an average reduction of 3 points more in the ESS scale than those taking placebo after 8 weeks of treatment. Results from this study also showed a decrease in the number of cataplexy attacks. The second study, however, did not show a difference between Wakix and placebo at reducing sleepiness or cataplexy.

When looking at sleepiness with an objective test called Maintenance of Wakefulness Test or MWT, the results of the two studies together showed that Wakix significantly improved wakefulness compared with placebo.

In a further study in 105 patients with narcolepsy and cataplexy, Wakix was also more effective than placebo at reducing the number of cataplexy attacks per week: the number of cataplexy attacks decreased from around 9 to around 3 per week in patients taking Wakix, while it remained at around 7 per week in patients taking placebo.

Unknowns relating to treatment benefits

No difference was reported according to age, sex, or medical history. There is limited experience with Wakix in people with kidney or liver impairment, severe heart and circulation disease or severe depression/anxiety.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Insomnia (difficulty sleeping)	Insomnia has been reported commonly in clinical studies (in up to 10 patients in 100 treated with Wakix mostly at a dose from 18 to 36 mg per day). Most cases were mild to moderate.	Wakix should be taken during breakfast in the morning. If symptoms of insomnia persist, the dose should be reduced.
Gastric (stomach) disorders caused by high levels of stomach acids (hyperacidity)	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.	Wakix should be given with caution in patients with acid-related gastric disorders or when given together with stomach irritants such as corticosteroids or NSAIDs (non-steroidal anti-inflammatory drugs). If acidity persists treatment with proton pump inhibitors may be started.
Anxiety and depression	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.	Wakix should be given with caution in patients with history of severe anxiety or severe depression.
Body weight increase	Weight increase has been reported uncommonly (in up to 10 patients in 1,000 treated with Wakix).	Wakix should be administered with caution in patients with severe obesity or severe anorexia. In case of significant weight change, treatment should be re-evaluated by the physician.
Side effects resulting from increased exposure to Wakix in patients with reduced kidney function (renal impairment)	In patients with reduced kidney function (stages 2 to 4 according to the international classification of chronic kidney disease), the amount of pitolisant (the active substance in Wakix) in the blood tended to increase by a factor of 2.5.	In patients with kidney impairment the maximum daily dose should be reduced to 18 mg.
Side effects resulting from increased	In patients with mild liver impairment (Child-Pugh A), the amount of pitolisant in the blood was not different to that in	No dose adjustments are need in patients with mild liver impairment. In patients with moderate liver impairment

Risk	What is known	Preventability
exposure to Wakix in patients with reduced liver function (hepatic impairment)	healthy volunteers. In patients with moderate liver impairment (Child-Pugh B), the amount of pitolisant in the blood increased by a factor of 2.4.	the maximum daily dose should be reduced to 18 mg. Wakix must not be used in patients with severe liver impairment.
Interaction with medicines known as CYP2D6 inhibitors	Medicines known as CYP2D6 inhibitors could significantly increase pitolisant blood level if given with Wakix. CYP2D6 inhibitors block the action of the CYP2D6 enzyme that is partly responsible for breaking down pitolisant in the body. They include paroxetine, fluoxetine, venlafaxine, quinidine, duloxetine, bupropion, terbinafine and cinacalcet.	Wakix should be given with caution if used together with CYP2D6 inhibitors. A dosage adjustment may need to be considered.

Important potential risks

Risk	What is known
Increased possibility of fits (proconvulsive potential)	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.
Fertility, exposure during pregnancy and breastfeeding	<u>Pregnancy</u> 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. <u>Breastfeeding</u> Animal studies have shown that pitolisant can pass into breast milk. Therefore breastfeeding is contraindicated during treatment with Wakix. <u>Fertility</u> 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.
Drug abuse and misuse, drug dependence, rebound effect	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.
Interaction with medicines displaying histamine H1 receptor antagonism activity	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,

Risk	What is known
	mirtazapine). • Anti-histamines (H1-receptor antagonists) that can pass into the brain (e.g. pheniramine maleate, chlorpheniramine, diphenydramine, promethazine, mepyramine).
QT-interval prolongation (alteration in the electrical activity of the heart seen on the ECG)	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.
Patients with CYP2D6 genetic polymorphism (genetically altered activity of an enzyme called CYP2D6)	No data are available on patients with genetically altered activity of an enzyme called CYP2D6 that is partly responsible for breaking down pitolisant in the body. However, it is known that altering the activity of this enzyme can affect pitolisant levels, since giving Wakix with medicines that block the action of CYP2D6 increases by 2-fold the amount of pitolisant in the blood.

Missing information

Risk	What is known
Long-term safety	Data on the long-term safety of Wakix are currently limited. A study to collect information on long-term safety is planned.
Paediatric patients (children)	Wakix has not been studied in patients younger than 18 years. A paediatric investigational plan is in place to study the use of pitolisant in children aged 6 to less than 18 years.
Patients with underlying severe cardiovascular (heart and circulation) disease	Wakix has not been studied in patients with underlying severe cardiovascular disease.
Patients with severe depression and severe anxiety	Wakix has not been studied in patients with severe depression and severe anxiety.
Patients with kidney impairment	Wakix has not been studied in patients with severely reduced kidney function (creatinine clearance below 15 ml/min).
Patients with liver impairment	Wakix has not been studied in patients with severely reduced liver function (Child-Pugh C).
Pharmacokinetic interactions	There are limitations in the information on potential interactions with other medicines. Additional studies to collect information on pharmacokinetic interactions are planned.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in

lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Wakix can be found on Wakix's EPAR page.

This medicine has no need of additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
P15-11	To collect information on the long-term safety of Wakix when used in a real-life setting over 5 years. To monitor and document how Wakix is used in routine medical practice.	- Long-term safety - Patients with severe depression and severe anxiety	Protocol to be submitted to EMA after marketing authorisation approval	Start: 2016 Final results: 2023
P15-02	Assess the mass balance recovery, metabolite profile and metabolite identification of [14C]-pitolisant, at steady-state conditions, in healthy CYP2D6 phenotyped subjects.	- CYP2D6 polymorphism	Planned to start in April 2016	2016
P14-07	To evaluate the pharmacokinetic interaction of a single dose of 40 mg pitolisant with sodium oxybate (Xyrem 2.25 g twice 3 h apart), in 16 healthy male volunteers. To evaluate the PK interaction between a single dose 40 mg pitolisant and a 22 day 200 mg *q.d.* modafinil administration period, in 16 healthy male volunteers.	Pharmacokinetic interactions	End study: November 2015 (clinical phase)	2016
P15-15	Drug-drug interaction with CYP3A4, CYP2B6	Pharmacokinetic interactions	Draft protocol	2016

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	substrates and UGT2B7 inhibitor.			
P11-06	Evaluation of safety and efficacy of Wakix in children from 6 to less than 18 years with narcolepsy with/without cataplexy, followed by a prolonged open-label period.	Evaluate efficacy in children	Planned to start in Q1 2016	2018
P11-11	To evaluate pharmacokinetics and the safety and tolerability of Wakix in children from 6 to less than 18 years with narcolepsy.	Evaluate the therapeutic dose according to the pharmacokinetics of pitolisant in children.	Started	2016

Studies which are a condition of the marketing authorisation

The post-authorisation safety study (P15-11) to collect information on long-term safety is a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable.

This summary was last updated in 12-2015.