Iowa PDL New Drug Review

Proprietary Name: Wakix®
Common Name: pitolisant
PDL Category: Central Nervous System Agents

Pharmacology/Usage: Pitolisant, the active ingredient of Wakix®, is an antagonist/inverse agonist of the histamine-3 (H3) receptor. The mechanism of action for its approved indication is not clear; however, its efficacy could be mediated through its activity as an antagonist/inverse agonist at histamine-3 (H3) receptors.

Indication: For the:

- Treatment of excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy.
- Treatment of excessive daytime sleepiness (EDS) in pediatric patients 6 years of age and older with narcolepsy.

There is no pregnancy category for this medication; however, the risk summary indicates that available data with use in pregnant women have not determined a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to Wakix® during pregnancy. Patients should be encouraged to enroll in the Wakix® pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call 1-800-833-7460. The safety and efficacy of use for treatment of cataplexy in the pediatric population with narcolepsy have not been established. The safety and efficacy for treatment of EDS in pediatric patients less than 6 years of age with narcolepsy have not been established.

Dosage Form: Film-Coated Tablets: 4.45mg and 17.8mg.

Recommended Dosage: For adults, the recommended dosage range is 17.8mg to 35.6mg QAM upon awakening. Titrate dosage as follows:

- Week 1: Initiate with a dosage of 8.9mg (two 4.45mg tablets) once daily.
- Week 2: Increase dosage to 17.8mg (one 17.8mg tablet) once daily.
- Week 3: May increase to the maximum recommended dosage of 35.6mg (two 17.8mg tablets) once daily.

Dose may be adjusted based on tolerability. If a dose is missed, patients should take the next dose the following day in the morning upon wakening. It may take up to 8 weeks for some patients to achieve a clinical response.

For pediatric patients 6 years and older, the recommended starting dosage is 4.45mg QAM upon awakening. Titrate dosage as follows:

- Week 1: Initiate with a dosage of 4.45mg (one 4.45mg tablet) once daily.
- Week 2: Increase dosage to 8.9mg (two 4.45mg tablets) once daily.
- Week 3: Increase dosage to 17.8mg (one 17.8mg tablet) once daily, which is the maximum recommended dosage for patients weighing <40kg.

- Week 4: For patients weighing ≥40kg, may increase to the maximum recommended dosage of 35.6mg (two 17.8mg tablets) once daily.

Dose may be adjusted per tolerability. If a dose is missed, take the next dose the following day in the morning upon awakening. It may take up to 8 weeks for some patients to achieve a clinical response.

Dosage reduction is recommended in patients known to be poor CYP2D6 metabolizers because these patients have higher pitolisant concentrations than normal CYP2D6 metabolizers. Refer to the prescribing information for additional information.

While no dosage adjustment is recommended with mild hepatic impairment, monitor patients with mild hepatic impairment. Monitor patients with moderate hepatic impairment and adjust the dosage of Wakix®. Refer to the prescribing information for additional information. Wakix® is contraindicated with severe hepatic impairment. Dosage adjustment is recommended in patients with eGFR <60ml/min/1.73m^2. Refer to the prescribing information for additional information. Wakix® is not recommended in patients with end stage renal disease (eGFR <15ml/min/1.73m^2).

Drug Interactions: Concomitant use of Wakix® with strong CYP2D6 inhibitors increases pitolisant exposure by 2.2-fold. Reduce the Wakix® dose by half.

Concomitant use of Wakix® with strong CYP3A4 inducers decreases exposure of pitolisant by 50%. Assess for loss of efficacy after starting a strong CYP3A4 inducer. For patients stable on Wakix® 8.9mg or 17.8mg QD, increase the dose of Wakix® to reach double the original daily dose over 7 days. If concomitant dosing of a strong CYP3A4 inducer is discontinued, decrease Wakix® dosage by half.

Wakix® increases the levels of histamine in the brain; thus, H1 receptor antagonists that cross the blood-brain barrier may reduce the efficacy of Wakix®. Avoid centrally acting H1 receptor antagonists with Wakix®.

Concomitant use of drugs that prolong the QT interval may add to the QT effects of Wakix® and increase the risk of cardiac arrhythmia. Avoid the use of Wakix® in combination with other drugs known to prolong the QT interval.

Wakix® is a borderline/weak inducer of CYP3A4. Thus, reduced effectiveness of sensitive CYP3A4 substrates may occur when used concomitantly with Wakix®. The effectiveness of hormonal contraceptives (e.g., ethinyl estradiol) may be reduced when used with Wakix® and effectiveness may be reduced for 21 days after discontinuation of therapy. Patients using hormonal contraception should be advised to use an alternative non-hormonal contraceptive method during Wakix® treatment and for at least 21 days after discontinuation of treatment.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Wakix®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included headache (3%), insomnia (4%), nausea (3%), upper respiratory tract infection (2%), musculoskeletal pain (2%), anxiety (4%), heart rate increased (3%), hallucinations (3%), irritability (1%), abdominal pain (2%), sleep disturbance (1%), decreased appetite (3%), cataplexy (1%), dry mouth (1%), and rash (1%).

Wakix® prolongs the QT interval. The use of Wakix® should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong the QT interval. Wakix® should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval. The risk of QT prolongation may be greater in patients with hepatic or renal impairment due to higher concentrations of pitolisant. Monitor patients with renal or hepatic impairment for increased QTc.

Contraindications: In patients with:

- Known hypersensitivity to pitolisant or any component of the formulation.
- Severe hepatic impairment.

Manufacturer: Harmony Biosciences, LLC.

Analysis: The efficacy of Wakix® for the treatment of EDS in adults with narcolepsy was assessed in 2 multicenter, randomized, double-blind, placebo-controlled studies that included patients ≥18 years of age who met the International Classification of Sleep Disorders (ICSD-2) criteria for narcolepsy (with or without cataplexy) and who had an Epworth Sleepiness Scale (ESS) score ≥14. EDS was assessed using the ESS, an 8-item questionnaire by which patients rate their perceived likelihood of falling asleep during usual daily life activities. Each of the 8 items on the ESS is rated from 0 (would never doze) to 3 (high chance of dozing); the maximum score is 24. Both studies included an 8-week treatment period, which included a 3-week dose titration phase followed by a 5-week stable dose phase. These studies compared Wakix® with placebo and an active control.

In study 1, patients (N=95) received Wakix®, placebo or active control. The median age of patients in this study was 37 years, while more were Caucasian (90%) and male (54%). In addition, about 80% of the population had a history of cataplexy. Results suggested that Wakix® demonstrated statistically significantly greater improvement on the primary endpoint, the least squares mean final ESS score, compared to placebo.

In study 2, patients (N=166) were randomized to receive Wakix®, placebo, or active control. The median age of patients in this study was 40 years, while more were Caucasian (90%) and about 50% were male. In addition, 75% of the population had a history of cataplexy. Results of this study suggested that Wakix® demonstrated statistically significantly greater improvement on the primary endpoint, the least squares mean final ESS score, compared to placebo.

Results of both studies are presented in the table below, which was adapted from the prescribing information. Note that only placebo data was found in the prescribing information.

Study	Treatment group (N)	Baseline ESS Score, mean	Final ESS Score, LS mean at week 8	Placebo subtracted difference at week 8
Study 1	Wakix® (N=31)	17.8	12.4	-3.1
	Placebo (N=30)	18.9	15.5	
Study 2	Wakix® (N=66)	18.3	13.3	-2.2
	Placebo (N=32)	18.2	15.5	

The efficacy of Wakix® for the treatment of EDS in pediatric patients 6 years of age an older with narcolepsy was assessed in one multicenter, randomized, double-blind, placebo-controlled study that included pediatric patients 6 to 17 years of age who met the International Classification of Sleep Disorders (ICSD-3) criteria for narcolepsy (with or without cataplexy) and who had a Pediatric Daytime Sleepiness Scale (PDSS) score ≥15 (Study 4). EDS was assessed with the PDSS, an 8-item questionnaire in which patients report their frequency of EDS-related symptoms. Each of the 8 items on the PDSS is rated from 0 (never) or 4 (very often, always); the maximum scores is 32, with higher scores representing greater severity of symptoms. This study included an 8-week treatment period, which included a 4-week dose titration phase followed by a 4-week stable dose phase.

In study 4, pediatric patients (N=110) aged 6 to 17 years were randomized to receive Wakix® or placebo. The median age of patients in this study was 13 years, while 56% were male and 82% had a history of cataplexy. Race and ethnicity were not collected in this study. Results suggested that Wakix® demonstrated statistically significantly greater improvement on the least squares mean change from baseline to the end of treatment in final PDSS total

score compared to placebo, of -3.41 points. Study 4 also included global assessments, which demonstrated positive trends supporting PDSS total score of improvement in favor of Wakix®.

The efficacy of Wakix® for the treatment of cataplexy in adults with narcolepsy was assessed in two multicenter, randomized, double-blind, placebo-controlled studies (Study 3 and Study 1) that included patients ≥18 years of age who met the International Classification of Sleep Disorders (ICSD-2) criteria for narcolepsy with cataplexy with at least 3 cataplexy attacks per week and an ESS score of ≥12 in study 3; and included patients meeting the ICSD-2 criteria for narcolepsy (with or without cataplexy) and an ESS score of ≥14 in study 1.

Study 3 included a 7-week treatment period, which included a 3-week dose titration phase followed by a 4-week stable dose phase where patients (N=105) were randomized to receive Wakix® or placebo. The median age in the study was 37 years, while 51% were male. Race was not collected in this study. Results suggested that Wakix® demonstrated statistically significantly greater improvement on the primary endpoint, the change in geometric mean number of cataplexy attacks per week from baseline to the average of the 4 week stable dosing period for Wakix® as compared with placebo.

Study 1 was described above. In the subset of patients with a history of cataplexy (N=49), Wakix® demonstrated statistically significantly greater improvement on the secondary endpoint, the change from baseline in geometric mean daily rate of cataplexy at week 8 for Wakix® compared with placebo.

Results of both studies are presented in the table below, which was adapted from the prescribing information.

Study	Endpoint	Treatment group (N)	Baseline rate mean	Final Rate mean	Rate Ratio (Wakix® to placebo)
Study 3	Final mean weekly rate of cataplexy over 4-week stable dosing period (primary endpoint)	Wakix® (N=54)	9.1	2.3	0.51
		Placebo (N=51)	7.3	4.5	
Study 1	Final mean daily rate of cataplexy at week 8 (secondary endpoint)	Wakix® (N=25)	0.4	0.1	0.07
		Placebo (N=24)	0.3	0.2	

Place in Therapy: Wakix® is a histamine-3 (H3) receptor antagonist/inverse agonist indicated for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy. It is also indicated for the treatment of EDS in pediatric patients 6 years of age and older with narcolepsy. It is contraindicated in severe hepatic impairment and has a warning regarding QT interval prolongation. Wakix® should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong the QT interval. It should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de points or sudden death. Monitor patients with hepatic or renal impairment for increased QTc. In the phase 3 studies assessing efficacy as compared with placebo, Wakix® demonstrated statistically significantly greater improvements on the primary endpoint as compared with placebo. Per the full text study by Dauvilliers et al[2] for Study 1, modafinil was included as an active comparator. Results demonstrated pitolisant was superior to placebo (difference -3.0) but not non-inferior to modafinil (difference 0.12, p=0.250) for the primary endpoint of differences in mean ESS score at endpoint.

Summary

There is no evidence to suggest that Wakix® is safer or more effective than other currently preferred, more cost-effective medications. It is therefore recommended that Wakix® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Wakix [package insert]. Plymouth Meeting, PA: Harmony Biosciences, LLC; 2025.
[2] Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomized trial. Lancet Neurol. 2013; 12(11): 1068-1075.