Taiwan Food and Drug Administration

Assessment Report

Trade Name：唯醒膜衣錠 4.5 毫克 / Wakix 4.5mg film-coated tablets

Active Ingredient：Pitolisant hydrochloride

License Number：MOHW-PI 028103

Applicant：信東生技股份有限公司

Approval Date：2021/06/18

Indication：治療成人猝睡症(伴隨或未伴隨猝倒現象)

Background Information

Trade Name	唯醒膜衣錠 4.5 毫克 / Wakix 4.5mg film-coated tablets
Active Ingredient(s)	Pitolisant hydrochloride
Applicant	信東生技股份有限公司
Dosage Form & Strengths	膜衣錠
Indication	治療成人猝睡症(伴隨或未伴隨猝倒現象) Indicated in adults for the treatment of narcolepsy with or without cataplexy.
Posology	Wakix 應以最低有效劑量開始治療，根據病人對藥物的反應和耐受性上調劑量，每日劑量不超過 36mg：第 1 週：每日 9mg(4.5mg 兩粒)的起始劑量。第 2 週：劑量可以增加至每日 18mg(18mg 一粒)或減少至每日 4.5mg(4.5mg 一粒)。第 3 週：劑量可以增加至每日 36mg(18mg 兩粒)。可根據醫師的評估與病患的反應，而隨時減少劑量至每日 4.5mg 或增加劑量至每日 36mg。每日總劑量應在早餐時一次服用。 Wakix 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 36 mg/day: - Week 1: initial dose of 9 mg (two 4.5 mg tablets) per day. - Week 2: 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. - Week 3: the dose may be increased to 36 mg (two 18 mg tablets) per day.
Pharmacological Category ATC Code	N07XX11

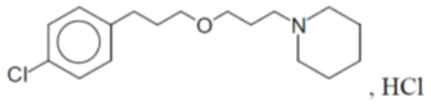
2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, pitolisant hydrochloride, is chemically designated as

1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride and has the following structure:



It is a white or almost white crystalline powder. The molecular formula and the molecular weight are $C_{17}H_{26}ClNO \cdot HCl$ and 332 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The structure of pitolisant hydrochloride is confirmed by UV spectrum, IR spectrum, nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry and elemental analysis. The specification for the drug substance includes tests for appearance, identification, appearance of solution, impurities, water content, particle size and assay.

2.1.2 Drug product

Wakix tablets are for oral administration and each film-coated tablet contains 5 mg or 20 mg of pitolisant hydrochloride (equivalent to 4.45 mg or 17.8 mg of pitolisant free base, respectively). The excipients used in the drug product comply with compendial monographs or in-house.

The specification for the drug product includes description, identification, assay, impurities, water content, disintegration time, dissolution, uniformity of mass, uniformity of dosage units and microbiological quality. Analytical methods are described well and validated.

Stability studies of drug product under long term condition (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Pitolisant is a potent and selective histamine H3R antagonist/inverse agonist and could effectively promote wakefulness in rodents and cats and orexin-knockout mice (a mouse model of narcolepsy). Furthermore, in the orexin-knockout mice, pitolisant significantly reduced the direct transitions from wake to REM sleep occurring during cataplexies. Safety pharmacology investigations suggest that pitolisant has no proarrhythmic properties. The pitolisant's effects on CNS and respiratory function only occurred at high doses, which provides sufficient safety margins compared to Human therapeutic doses (~40 mg/day).

2.2.2 Toxicological Studies

The pivotal repeated-dose toxicity studies included a 6-month study in rats and a 9-month study in monkeys. The main adverse effects of Pitolisant in both species were transient and reversible central nervous clinical signs (hypoactivity, ptyalism, abnormal gait to tremors, and clonic convulsions). Convulsions were not observed after discontinuation of

dosing and were not associated with microscopic findings in the brain. Additional target organs of toxicity after oral administration of pitolisant included liver, duodenum, thymus, adrenal gland, and lung in rats. Pitolisant and its metabolites were found to have no genotoxicity *in vitro* and *in vivo*. In addition, two carcinogenicity studies that achieved the maximum tolerated doses did not show Pitolisant's carcinogenic potential. Reproductive and developmental studies, including juvenile toxicity studies, indicate that pitolisant impaired reproductive function and embryofoetal development.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Pitolisant (Wakix film-coated tablets) is an orally active histamine H_3 receptor antagonist/inverse agonist, and is used to treat in adult patients of narcolepsy with or without cataplexy. The active ingredient of Wakix was pitolisant hydrochloride 5 mg and 20 mg (eq. to pitolisant 4.45 mg and 17.8 mg). The oral absorption of Wakix is about 90%. The T_{max} can reached at 3.5 hours (2 to 5 hours), $T_{1/2}$ was about 10 ~ 17 hours, following administering 20 mg pitolisant. Pitolisant exposure (C_{max} and AUC) increased proportionally in the dose range of 20 mg to 40 mg, but increased more than proportional within 10 mg ~ 240 mg. Steady state is reached by day 7, and accumulation ratio was 1.16 and 1.55 for C_{max} and AUC. High-fat meal decreased C_{max} and AUC of pitolisant by 30.5% and 13.5%, thus, Wakix can be taken regardless of food. The apparent volume of distribution of pitolisant is approximately 700 L (5 to 10 L/kg). The pitolisant human serum protein binding was high (91% ~ 96%) and concentration independent. The blood/plasma ratio < 1 at 10, 100 and 1000 nM concentrations. Pitolisant was extensively metabolized *in vivo*. CYP2D6 was the major metabolic enzyme and then was CYP3A4. The apparent oral clearance (CL/F) of pitolisant is 43.9 L/hr. Following a single oral radiolabeled pitolisant 17.8 mg dose, approximately 90% of the dose was excreted in urine (<2% unchanged) and 2.5% in feces, and there was no significant difference between CYP2D6 extensive metabolisers and CYP2D6 poor metabolisers.

2.3.2 Interaction Studies

Dose adjustment was not required when pitolisant co-administered with strong CYP3A4 inhibitor. Concomitant use of pitolisant with paroxetine (a strong CYP2D6 inhibitor) increased pitolisant the C_{max} and AUC of pitolisant by 1.5-fold and 2.2-fold, respectively. Therefore, the dose of WAKIX should be reduced by half during concomitant dosing. Rifampin (strong CYP3A4 inducer) decreased pitolisant C_{max} and AUC and by 39% and 48%,

thus, dose adjustment was required to avoid loss of efficacy. Pitolisant decreased the exposure of midazolam (3A4 substrate) by 22% and 17%. Therefore, reduced effectiveness of sensitive CYP3A4 substrates may occur when used concomitantly with WAKIX.

2.3.3 Special Populations

Elderly subjects showed higher exposure than young subjects, but the data was limited, the dose in elderly population should be adjusted according their physiological status. The exposure of pitolisant in patients with all degrees of renal impairment were higher than healthy subjects with normal renal function (C_{max}: ↑ 55% ~ 156%; AUC: ↑ 78% ~ 100%).Thus, the maximum daily dose in renal impairment patients should be 18 mg. The mild hepatic impairment patients did not need to adjust dose, but in patients with moderate hepatic impairment, the maximum dose should reduce by half (18 mg/day). Patients with severe hepatic impairment were contraindication due to lack of data.

Overall, the pharmacokinetic studies met the minimum requirements to support the marketing authorization of WAKIX. It is recommended to approve the NDA of WAKIX from the PK/PD perspective.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The sponsor provides two pivotal studies [Harmony 1] and [Harmony 1BIS] and a supportive study [Harmony CTP] to support the efficacy of Wakix for the claimed indication. The efficacy results are summarized below.

[Harmony 1]

Study subjects are patients diagnosed with narcolepsy with or without cataplexy. The primary efficacy endpoint is ESS change between the pitolisant group and the placebo group during an 8-week treatment period. By study end, mean ESS score reductions from baseline were -3.4 ± 4.2 in the placebo group, -5.8 ± 6.2 in the pitolisant group and -6.9 ± 6.2 in the modafinil one. The primary analysis was conducted using a linear mixed effects model, featuring analysis of covariance ANCOVA shows a significant improvement (p=0.024).

[Harmony 1BIS]

Study subjects are patients diagnosed with narcolepsy with or without cataplexy. The primary efficacy endpoint is the ESS change between the pitolisant, placebo and modafinil treatment groups, during an 8-week treatment period. By study end, mean ESS score reductions from baseline were -3.6 ± 5.6 in the placebo group, -4.6 ± 4.6 in the pitolisant group and -7.8 ± 5.9 in the modafinil one. The primary analysis was

conducted using a linear mixed effects model, featuring analysis of covariance ANCOVA shows a significant improvement (p=0.030).

[Harmony CTP]

Study subjects are patient diagnosed with narcolepsy with cataplexy. The primary endpoint is the change in the average number of cataplexy attacks per week between the baseline and the stable treatment period. At baseline, WRC were 7.31 and 9.15 for placebo and Pitolisant, respectively (ITT). During the stable period, they were 6.79 and 3.28. The Weekly Rate of Cataplexies observed in pitolisant group was about half of WRC in the placebo group (rR = 0.512) and the difference was statistically significant (95%CI 0.435, 0.603; p<0.0001).

2.4.2 Safety Results

There were 342 narcoleptic patients who received pitolisant treatment in the clinical developmental program. The proportion of TEAE were 52.3% in pitolisant group, 55.1% in modafinil group, and 41.1% in the placebo group. The most common AEs were headache, insomnia, nausea, weight anxiety, and irritability. The incidence of headache, insomnia, nausea increased with higher dose (9mg, 18mg, and 36mg).

There were no deaths event in the narcolepsy clinical trials. The proportion of serious AE were 3.8% in pitolisant group, 2.0% in modafinil group, and 1.3% in the placebo group All were considered by investigators as unrelated to studied treatment except for a case of pregnancy/miscarriage were causality was noted as possible. The proportion of AE leading to discontinuation were 5% in pitolisant group, 5.1% in modafinil group, and 3.2% in the placebo group. Other AEs of special interest was depression. The incidence rate of depression is similar between pitolisant, modafinil and placebo groups (0.006, 0.006 and 0.004 TEAE/patient-months). In narcoleptic studies, four patients reported symptoms associated with abuse potential (1.2%). When compared to placebo and modafinil groups (3.8% and 3.0% respectively), it showed that pitolisant did not increase abuse potential.

In the long-term study Harmony III, the most frequently reported preferred terms were headache (8% of TEAEs), insomnia (6.6%), anxiety (4.7%), weight increase (4.0%) and depression-like symptoms (3.3%).

2.5 Bridging Study Evaluation

The pitolisant exposure in six healthy male Chinese subjects was higher than 13 healthy male Caucasian subjects (C_{max}:↑15%; AUC:↑20%). Due to lack of multiple dose PK parameters comparison data form healthy subjects and target patients between Asian and non-Asian population, the ethnic difference was still unclear from

PK point of view.

There was no clinical data to evaluate ethnic sensitivity except the safety profile for single dose pitolisant use in 6 healthy male Chinese subjects. Narcolepsy was a rare disease, which means that to enroll further more Asian patient is difficult. Moreover, pitolisant showed its clinical benefit not only for the excessive daytime sleepiness, but also for cataplexy. Thus, the clinical reviewers suggest to waive further bridging study.

2.6 Conclusion

This NDA is approvable.

3. Post-Marketing Requirements

No post-marketing requirements