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Original Article

The European Medicines Agency review of pitolisant for treatment of narcolepsy: summary of the scientific assessment by the Committee for Medicinal Products for Human Use

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ABSTRACT

On 31 March 2016, the European Commission issued a decision for a marketing authorisation valid throughout the European Union (EU) for pitolisant (Wakix) for the treatment of narcolepsy with or without cataplexy in adults. Pitolisant is an antagonist/inverse agonist of the human histamine H3 receptor. The dose should be selected using an up-titration scheme depending on individual patient response and tolerance and should not exceed 36 mg/day.

The main evidence of efficacy of pitolisant was based on two Phase III clinical trials. The improvement on excessive daytime sleepiness was shown against placebo in the Harmony I study (−3.33 points; 95% confidence interval (CI) [−5.83; −0.83]; $p = 0.024$) and in Harmony CTP (−3.41 points; 95% CI [−4.95; −1.87]; $p < 0.0001$). The daily cataplexy rate in Harmony I improved against placebo with a rate ratio (rR) of 0.38 whilst in the Harmony CTP the ratio of improvement on weekly cataplexy rate against placebo was 0.512. The most commonly reported adverse reactions were headache, insomnia and nausea. This article summarizes the scientific review leading to approval of pitolisant in the EU. The assessment report and product information are available on the European Medicines Agency website (http://www.ema.europa.eu).

1. Introduction

Narcolepsy is a rare sleep disorder characterized by excessive daytime sleepiness (EDS) and cataplexy. A deficit of hypocretin (orexin), a wake-stimulating peptide produced by the hypothalamus, is hypothesized to be the key underlying mechanism [1]. It is a chronic and often extremely incapacitating disease with negative impact on the quality of life of affected patients. The current therapeutic options are limited and rely on relief of symptoms. Pitolisant is a first-in-class drug acting on histamine H3 receptors. As pitolisant's mechanism of action is different from the currently available treatments, it can offer an alternative option for the patients and physicians.

In 2014, the European Medicines Agency (EMA) received an initial marketing authorisation application for pitolisant. The scientific review was conducted by the EMA's Committee for Medicinal Products for Human Use (CHMP). Based on this review, a marketing authorisation was issued in the European Union (EU) for pitolisant for the treatment of narcolepsy with or without cataplexy in adults. The detailed scientific assessment report and product information [including the summary of product characteristics (SmPC)] for this product are available on the EMA website (http://www.ema.europa.eu).

2. Mode of action

Pitolisant is a histamine H3 receptor (H3R) antagonist/inverse agonist. It triggers a long-lasting activation of histaminergic neurons in the brain, a neuronal system involved in the maintenance of wakefulness, attention and cognition. Pitolisant crosses the blood–brain barrier and elicits histamine release in the whole

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central nervous system accompanied by release of other wake-promoting neurotransmitters (dopamine, noradrenaline and acetylcholine) in cerebral cortex, presumably via an indirect mechanism. Dopamine release in nucleus accumbens is not affected, which differentiates it from other wake-promoting agents, eg, amphetamine-like psychostimulants.

In vivo studies in wild-type and orexin KO mice and in cats showed that pitolisant increased the duration of waking at the expense of slow wave sleep and paradoxical sleep with corroborating electroencephalogram changes at ≥10 mg/kg (p.o.), thereby supporting a proof-of-concept for its use in narcoleptic patients [2,3].

3. Non-clinical aspects

Safety pharmacology studies showed that pitolisant has the ability to prolong the QT interval in humans. In vitro, it blocked hERG currents with an IC_{50} of 1.3 μM and affected action potential parameters in rabbit Purkinje fibres at concentrations higher than 1 μM. In vivo, slight QTc prolongation was observed in telemetered dogs.

Pitolisant is extensively metabolized, including an active first-pass metabolism by CYP3A4 in gut, and is widely distributed in tissues. Pitolisant crosses the placenta and blood–brain barrier and was found in milk.

In general, low safety margins were determined in toxicity studies. The main target organ was the central nervous system, with hypoactivity, ptyalism, abnormal gait, tremors and clonic convulsions observed at the highest doses in repeated studies. Pitolisant is not genotoxic and did not show any neoplastic potential in studies conducted in rats and transgenic mice. Pitolisant has shown effects on reproductive function and embryofoetal development. Teratogenic effect was observed at maternally toxic doses in rats and in rabbits. At high doses, pitolisant induced sperm morphology abnormalities and decreased motility without any significant effect on fertility indexes in male rats. It also decreased the percentage of live conceptuses, increased post-implantation loss in female rats and caused a delay in postnatal development.

Drug dependence and abuse liability studies were conducted in mice, monkeys and rats [4] but their results did not allow definitive conclusions to be drawn. As pitolisant' s binding affinities for sigma 1 and 2 receptors are similar or higher than to H3R, the risk of abuse potential could not be excluded.

4. Clinical pharmacology

Pitolisant's absorption is rapid with C_{max} typically achieved between two and four hours after dosing. Exposure to pitolisant showed moderate to high interindividual variability and increased more than proportionally with a dose up to 216 mg after once-daily dosing. Drug exposure increased in patients with renal and hepatic impairment as well as in the elderly.

The metabolism pathways of pitolisant in humans are not fully characterized. The major hydroxylated metabolite is formed by CYP3A4 and CYP2D6. Pitolisant is a weak inhibitor of CYP2D6 and an inducer of CYP3A4, CYP1A2 and CYP2B6 in vitro. Clinically relevant interactions are expected with CYP3A4 and CYP2B6 substrates as well as with UDP-glucuronosyltransferases, CYP2C and P-gp substrates.

5. Clinical efficacy

The narcolepsy development program included eight phase II/III studies of which two (P07-03 [Harmony I] and P09-15 [Harmony Ibis]) were considered pivotal. Two further studies, P11-05 (Harmony CTP) and P09-10 (Harmony III), were considered supportive for the evaluation. The patients were aged 18–75 years and were predominantly Caucasian. The analysis of baseline characteristics did not show clinically relevant differences between treatment groups.

The pivotal studies were double-blind, eight-week, placebo-and modafinil-controlled trials. The dose could be titrated individually for each patient. The initiation dose and the maximum dose were 9 and 36 mg/day in the Harmony I study and 4.5 mg and 18 mg/day in Harmony Ibis. The number of enrolled patients was 94 in Harmony I and 165 in Harmony Ibis. Approximately 80% of patients had a history of cataplexy.

The primary endpoint in the pivotal studies was the comparison of final Epworth Sleepiness Scale (ESS) scores between pitolisant and placebo. A minimal clinically relevant difference of final ESS scores between pitolisant and placebo groups was pre-defined to be 3 points. The secondary endpoints included Maintenance Wakefulness Test (MWT), ESS Responder Rate and the number of daily cataplexy attacks.

In the Harmony I study, the mean ESS scores at baseline were 18.9 ± 2.5 (SD), 17.8 ± 2.5 and 18.5 ± 2.7 in the placebo, pitolisant and modafinil groups, respectively. By week eight, mean ESS score reductions 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 group (Fig. 1). In accordance with the ITT analysis of the primary endpoint, pitolisant was clinically and statistically significant compared to placebo (−3.33 points; 95% confidence interval (CI) [−5.83; −0.83]; $p < 0.05$) [5].

Superiority of pitolisant compared to placebo was also observed on MWT as pitolisant increased wakefulness maintenance time by 1.47 min ($p = 0.044$) compared to placebo.

Responder rate on ESS scores (defined as ESS ≤10) showed that pitolisant was significantly superior to placebo (odds ratio (OR) = 9.24 [3.82–22.35]; $p < 0.001$), and not statistically different from modafinil (OR = 1.06 [0.44; 2.54]; $p = 0.894$) (See Table 1).

In the Harmony Ibis study 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 group. The primary endpoint analysis showed non-significant ESS score decrease with pitolisant compared to placebo [−1.94 (−4.05, 0.07); $p = 0.065$].

Responder rate on ESS scores, according to the responder definition in this study ("ESS final ≤10 points or ESS baseline − ESS final ≥3 points"), showed that pitolisant was significantly superior to placebo (RR=0.60 [0.41–0.88]; $p = 0.008$). According to MWT results, pitolisant significantly increased the maintenance of

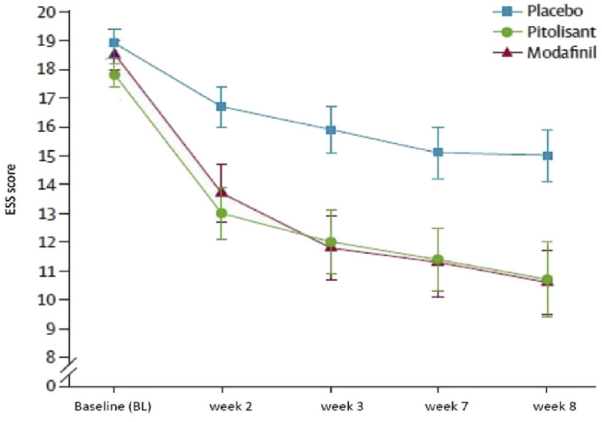

Fig. 1. Changes in Epworth Sleepiness Scale Score (ESS) (mean ± SEM) from Baseline to week 8 in Harmony 1 study [Dauvilliers, 2013].