MTRAC
Midlands Therapeutics Review and Advisory Committee

Commissioning Support

Pitolisant *(Wakix®▼)*

For the treatment of narcolepsy with or without cataplexy (Type 1 and type 2 narcolepsy)

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of pitolisant:

- That the Summary of Product Characteristics (SPC) advises that treatment should be initiated by a physician experienced in the treatment of sleep disorders.
- Specialist advice was that the initial diagnosis of narcolepsy should be confirmed at a tertiary sleep clinic. They were also of the opinion that pitolisant was a suitable option following treatment with methylphenidate or modafinil.
- Once the patient's condition and drug dose are stable a RICaD (Rationale for Initiation, Continuation and Discontinuation) or other locally agreed transfer of care protocol may be appropriate on discharge of the patient from the tertiary care clinic. The Summary of Product Characteristics (SPC) for pitolisant advises that, as long-term efficacy data are limited, the continued efficacy of treatment should be regularly evaluated by the physician.

Strength of the evidence for efficacy

The evidence for the efficacy of pitolisant was considered to be relatively weak. Pitolisant was shown to lower excessive daytime sleepiness more than placebo, but non-inferiority to modafinil, another standard treatment for this condition, was not proven. The rate of cataplexy attacks was also shown to be significantly lower with pitolisant treatment compared with placebo over seven weeks of treatment. The outcomes used in the trials were appropriate and patient-centred, but the duration of treatment in the trials (7 or 8 weeks) was short for a chronic condition. According to the European licensing report, longer term data were available up to 12 months from an uncontrolled open label study that suggested that efficacy (less daytime sleepiness) was maintained over this period.

MTRAC considered pitolisant because it was a new licensed product that primary care prescribers may be asked to prescribe.

Description of technology

Pitolisant is the first in a new class of orally active histamine H3-receptor antagonist treatments for narcolepsy with or without cataplexy. It acts to promote wakefulness by enhancing the activity of brain histaminergic neurons and modulating various neurotransmitter systems, increasing acetylcholine, noradrenaline and dopamine release in the brain.

The dose of pitolisant should be titrated up to the lowest effective dose over three weeks depending on individual patient response. The recommended starting dose is 9 mg (two 4.5 mg tablets) in the first week. The dose can be doubled to one 18 mg tablet daily in the second week and to the maximum dose of 36 mg (two 18 mg tablets daily) in the third week if necessary; the dose can also be decreased to 4.5mg daily. Effective doses are in the range 4.5mg to 36mg per day, taken as a single dose in the morning during breakfast.[1]

See the pitolisant Summary of Product Characteristics (SPC) for full details.[1]

Background

Narcolepsy is a chronic neurological disorder in which there is a disruption in the usual patterns of non-rapid-eye-movement sleep and rapid-eye movement, or 'dreaming' sleep. This causes difficulty in staying asleep, and in staying awake and bouts of excessive daytime sleepiness (EDS), the first symptom of narcolepsy in 90% of cases. Other characteristic features, which represent intrusions of REM sleep into wakefulness, include cataplexy (episodes of reversible paralysis associated with emotion experienced by about 70% of patients with narcolepsy), sleep paralysis (generalised paralysis just before, or while falling asleep or waking), vivid hypnagogic or hypnopompic hallucinations on falling asleep or on waking, and disturbed nighttime sleep (DNS).[2]

It is estimated that narcolepsy affects at least 25,000 people in the UK, and is usually diagnosed between 20 and 40 years of age, although the symptoms often begin during adolescence.[3]

Current therapies for narcolepsy treat the symptoms of EDS, and/or nighttime wakefulness and include non-pharmacological measures such as advice on good sleep hygiene and avoidance of over-the-counter medications that could cause drowsiness. Pharmacological treatments include the stimulants methylphenidate, amphetamines or modafinil. Amphetamines and modafinil promote wakefulness by interfering with the dopamine reuptake transporter, producing higher synaptic concentrations of dopamine. Cataplexy can be reduced by tricyclic antidepressants, paroxetine, or venlafaxine. Sodium oxybate, a natural metabolite of γ-aminobutyrate, which acts as a neurotransmitter via its own receptors and via the stimulation of the $GABA_B$ receptors*, promotes non-fragmented sleep and is often effective in reducing both EDS and cataplexy.[3;4]

Clinical evidence for efficacy and safety

Two fully published, double-blind RCTs[5-7] compared pitolisant with modafinil and/or placebo in people with

* *Metabotropic transmembrane receptor for gamma-aminobutyric acid*

narcolepsy with or without cataplexy (81% of people in HARMONY I and all participants in HARMONY CTP had cataplexy and continued treatment with stable doses of sodium oxybate or antidepressants throughout the trials).

In the **HARMONY I trial**[6] (n = 95; 8 weeks' duration) pitolisant (flexible dosing in range 5 to 40 mg as hydrochloride; equivalent to 9 to 36 mg daily pitolisant) was compared with modafinil (flexible doses of 100mg, 200mg or 400mg). Doses were titrated for 3 weeks, followed by 5 weeks at stable dose. All patients received a placebo in the final week (withdrawal phase). The primary outcome, the change in Epworth Sleepiness Score (ESS) from baseline to the end of the trial was shown to be clinically and significantly better with pitolisant treatment than placebo. Non-inferiority to modafinil was not proven. The proportion of people who had improvement in excessive daytime sleepiness assessed by the modified clinical global impression of change (CGI-C) rating was 56% (14/25) in the placebo group, 73% (19/26) in the pitolisant group and 86% (24/28) in the modafinil group (no statistical analysis reported). The maintenance of wakefulness test (MWT) was another secondary outcome and showed significantly greater improvement for pitolisant versus placebo, but no significant difference versus modafinil. The test involved staying awake in a darkened room and this increased from a baseline of 7.4 minutes to 9.7 minutes in the pitolisant group, and from a baseline of 8.8 minutes to 15.1 minutes in the modafinil group after 8 weeks of treatment.

In the **HARMONY CTP trial**[7] (n = 106; 7 weeks), participants were randomised to pitolisant or placebo. During the 3-week titration phase pitolisant hydrochloride was given at flexible doses of 5 mg, 10 mg or 20 mg per day, followed by four weeks at stable doses of up to 40 mg/day (equivalent pitolisant doses: 4.5 mg, 9 mg and 18 mg, up to 36 mg/day). All patients received a placebo in the final week (withdrawal phase). The primary outcome in this trial was the change in the rate of cataplexy, which was lowered significantly more with pitolisant compared with placebo. The mean weekly cataplexy rate reduced by 75% (from 9.15 to 2.27 attacks per week) in the pitolisant group and by 38% (from 7.31 to 4.52 attacks per week) in the placebo group; a rate ratio of 0.51 (95% CI 0.44 to 0.60, p<0.0001) with pitolisant compared with placebo. The changes in the ESS and the MWT were secondary outcomes in this trial. The change from baseline with pitolisant for both outcomes were shown to be significantly greater than with placebo.

No participants in the placebo or pitolisant group had withdrawal syndrome during the withdrawal phase, compared with 3 participants in the modafinil group.

Quality of life was assessed using the European quality of life questionnaire (EQ-5D) and values were found to be much the same for all three groups in HARMONY I[6], and not significantly different between pitolisant and placebo in HARMONY CTP[7]. Patient global impression on treatment improved only slightly more for pitolisant and modafinil than for participants receiving placebo.

Adverse events

In the HARMONY I trial[6], the most frequent adverse event in all groups was headache. Participants in the pitolisant group also reported insomnia, abdominal discomfort and nausea; abdominal discomfort, nausea, diarrhoea, dizziness, anxiety and irritability were reported in the modafinil group. In the HARMONY CTP trial[7], pitolisant-treated participants reported irritability, anxiety, and nausea, whereas the most frequent adverse event in the placebo group was somnolence.

Considerations for cost impact

The manufacturer estimates (in the NICE evidence summary of pitolisant) that there are approximately 30,000 people in the UK with narcolepsy, about 5,000 of whom receive pharmacological treatment. Of these, they estimate that about 50% of people who are currently being treated may have issues with their existing medicines and may be eligible for treatment with pitolisant; equating to 2,500 people over a 5-year period (source: Lincoln Medical Ltd, October 2016).

Estimated cost of a years' treatment with pitolisant and potential alternatives (excluding VAT; prices taken from MIMS January 2018, Drug Tariff [Feb 2018]):

- Pitolisant (Wakix®▼) 4.5 to 36mg £3,772 - £7,543
- Generic methylphenidate 20 to 30mg £97 - £145
- Generic modafinil 200 to 400mg £105 - £222
- Modafinil: (Provigil®) 200 to 400mg £1,280 - £2,560
- Generic dexamfetamine 10 to 60mg £622 - £3,731
- Sodium oxybate (Xyrem®) 4.5 to 9g £6,570 to £13,140

References

1. Wakix 4.5 mg / 18mg film-coated tablets. EMC 2016 www.medicines.org.uk/emc/medicine/32397
2. Thorpy MJ, Dauvilliers Y. Clinical and practical considerations in the pharmacologic management of narcolepsy. Sleep Medicine 2015; 16:9-18.
3. Narcolepsy. NHS Choices 2016 http://www.nhs.uk/Conditions/Narcolepsy
4. Strambi LF. A need for new treatments in narcolepsy. Lancet Neurol 2013; 12(11):1039-1040.
5. Narcolepsy with or without cataplexy in adults: pitolisant. NICE 2017 www.nice.org.uk/advice/es8
6. Dauvilliers Y et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. Lancet Neurol 2013; 12(11):1068-1075.
7. Szakacs Z et al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2017; 16(3):200-207.