**Pending CCG approval**

NHS
Pan Mersey
Area Prescribing Committee

# PITOLISANT tablets (Wakix® ▼)

**The Pan Mersey Area Prescribing Committee recommends the prescribing of PITOLISANT tablets (Wakix® ▼), by specialists working in a regional and national tertiary commissioned sleep service only, for the treatment of Narcolepsy with or without cataplexy in those who are contraindicated or have not tolerated other standard treatments.**

**RED**

**Pitolisant is indicated in adults for the treatment of narcolepsy with or without cataplexy.**[1]

Within Aintree University Hospital NHS Foundation Trust sleep service, pitolisant will be prescribed in line with the Narcolepsy Pathway:

- As a 3rd line agent to modafanil and dexamphetamine or methylphenidate (+/- TCA / SSRI antidepressants) where the drugs don't provide an effective reduction in excessive daytime sleepiness (EDS).
- Where the patient is intolerant of / contraindicated to the above agents.
- **Its use will not be in combination with sodium oxybate.**

Following initiation, monitoring will be undertaken monthly at outpatient follow up appointments with an initial trial of 3 months.

If insufficient benefit is seen at this point, pitolisant treatment will be discontinued.

The lowest effective dose should be used.

**Pitolisant may reduce the effectiveness of hormonal contraceptives. The patient should be informed of this by the specialist prior to initiating treatment and advised to seek immediate advice about effective non-hormonal contraceptive alternatives.**

**CCG's will require assurance for the use of this drug via process such as Blueteq (or similar).**

**Note**: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

Supporting information

# PITOLISANT tablets (Wakix® ▼)

## Effectiveness

Pitolisant is a potent, orally active histamine H3-receptor antagonist/inverse agonist which, via its blockade of histamine auto-receptors enhances the activity of brain histaminergic neurons, a major arousal system with widespread projections to the whole brain.[2]

Two fully published double-blind RCT's compared pitolisant with modafanil and / or placebo in patients with or without cataplexy (Harmony I and Harmony CTP trial).[3,4]

Harmony I (pitolisant / placebo/ modafinil)
•Statistically and clinically superior to placebo for improving EDS measured by the ESS. (P<0.05)
•Pitolisant 10 mg to 40 mg per day was not shown to be non-inferior to modafinil 100 mg to 400 mg per day for excessive daytime sleepiness measured by the ESS.
•For time awake in a darkened room, pitolisant 10–40 mg per day was statistically superior to placebo (p<0.05), there was no statistically significant difference compared with modafinil 100 mg to 400 mg per day (p=0.173) measured by the maintenance of wakefulness test

Harmony CTP looked at the safety and efficacy of pitolisant on cataplexy in patients with narcolepsy.
•Pitolisant 5 mg to 40 mg per day reduced the weekly cataplexy rate by about half compared with placebo (p<0.0001); from a baseline of 9.15 to 2.27 attacks per week in the pitolisant group, and 7.31 to 4.52 attacks per week in the placebo group
•75% reduction in cataplectic attacks.
•Secondary outcomes of ESS and MWT monitored. Again, significantly greater than with placebo.
•There were no serious adverse events, but one case of severe nausea in the pitolisant group. The most frequent adverse events in the pitolisant group (headache, irritability, anxiety, and nausea) were mild or moderate except one case of severe nausea. No withdrawal syndrome was detected following pitolisant treatment; one case was detected in the placebo group

No head to head RCT's are possible with sodium oxybate / pitolisant.
RCT's that compared the safety and efficacy and of medical treatments for narcolepsy were analysed using network meta-analysis. Modafinil, sodium oxybate pitolisant had similar efficacy in reducing excessive day time sleepiness. Only sodium oxybate and pitolisant were shown with a comparable beneficial effect on cataplexy. Overall, pitolisant was found with the best P score on the Benefit / Risk ratio.[5]

## Safety

EMA reviewed that overall data available demonstrate that pitolisant has a positive effect on the two major symptoms of narcolepsy, excessive daytime sleepiness and cataplexy. In addition, pitolisant works differently from currently available treatments and therefore offers an alternative treatment option. The safety profile of Wakix is considered acceptable, with no major safety concerns identified. The Agency's Committee for Medicinal Products for Human Use (CHMP) therefore decided that Wakix's benefits are greater than its risks and recommended that it be approved for use in the EU

Pitolisant is contraindicated in severe hepatic impairment (Child Pugh C) and Breastfeeding. It should be administered with caution in people with moderate hepatic impairment or renal impairment, a history of psychiatric disorders, acid related gastric disorders or taking concomitant gastric irritants, severe obesity or anorexia, severe epilepsy, cardiac disease, taking concomitant QT-prolonging medicines or CYP2D6 inhibitors.

Women of childbearing potential have to use effective contraception during treatment and for at least 21 days after discontinuation. Pitolisant may reduce the effectiveness of hormonal contraceptives and alternative methods of contraceptives should be used

The most serious adverse drug reactions are abnormal weight decrease (0.09%) and spontaneous abortion (0.09%;)[2]

Common adverse effects reported are insomnia, anxiety, irritability, depression, sleep disorder, vertigo, fatigue, headache, dizziness, tremor, nausea, vomiting, dyspepsia

For full information, refer to the SPC.

Current treatments (stimulants and sedatives) are controlled drugs and wide spread abuse is known. These have many cautions and contraindications, varying tolerability and significant safety risks. Pitolisant is potentially a safer alternative to have in the treatment pathway before sodium oxybate.

From discussions with the North East Narcolepsy Centre, approximately 60% of patients respond to this drug, not due to ADR but ineffectiveness.

Studies have demonstrated that this drug does not have any potential for drug abuse.[7]

## Cost (excludes VAT)[6]

| Drug | Dose Schedule | Cost per annum (dm+d)- EXCLUDES VAT |
|---|---|---|
| Pitolisant 4.5mg and 18mg tablets | 4.5mg-36mg daily | £3,720.00-£7,440.00 |
| Sodium oxybate 500mg/ml oral solution | 2.25g-9g daily | £3,240.00-£12,960.00 |
| Clomipramine capsules | 10mg-75mg daily | £16.77-£41.60 |
| Venlafaxine 225mg M/R caps | 225mg daily | £612.43 |
| Modafanil 200mg tablets | 400mg daily | £181.68 |
| Dexamfetamine 10mg tablets | 10-60mg daily | £477.36-£2,864.16 |
| Methylphenidate 10mg tablets | 10-60mg daily | £41.04-£246.24 |
| Methylphenidate M/R capsules | 10-60mg daily | £300.00-£807.84 |

## Patient factors

- Must not be prescribed if pregnant
- Must not be prescribed if breastfeeding
- Must not be prescribed in severe liver impairment (Childs Pugh C)
- Women of childbearing potential have to use effective contraception during treatment and for at least 21 days after discontinuation.
- Pitolisant may reduce the effectiveness of hormonal contraceptives and alternative methods of contraceptives should be used (see implementation notes).

Supporting information

# PITOLISANT tablets (Wakix® ▼)

**Prescribing information**

Prescribing information (Hospital only)

- 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.

  Dosing will be in schedules of 9 mg, 18 mg, 36 mg.

At any time, the dose can be decreased (down to 4.5 mg per day) or increased (up to 36 mg per day) according to the physician assessment and the patient's response. The total daily dose should be administered as a single dose in the morning during breakfast

**Implementation notes**

Prescribing and monitoring will be undertaken by the specialist sleep clinic.

Patients stopping therapy during the first 3 months due to lack of response will be reimbursed by Lincoln Medical under the reimbursement scheme.

Pitolisant may reduce the effectiveness of hormonal contraceptives. Women of child bearing potential should be informed of this by the specialist prior to initiating treatment and advised to seek immediate advice about effective non-hormonal contraceptive alternatives. The specialist sleep service will also write to the GP to inform them of the need for contraceptive review when necessary.

**References**


1. European Medicines Agency Summary of European public assessment report (EPAR) for Wakix 2018. Accessed 13 June 2018
2. Lincoln Medical. Summary of Product Characteristics. Wakix 4.5mg /18mg Tablets. July 2016. Accessed 06 June 2018 at: https://www.medicines.org.uk/emc/product/7402
3. Dauvilliers, Yves t al. Pitolisant versus placebo or modafanil in patients with narcolepsy: a double-blind, randomised trial. The Lancet Neurology , Volume 12 , Issue 11 , 1068 - 1075
4. Szakacs, zoltanpoluektov, Mikhail et al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. The Lancet Neurology , Volume 16 , Issue 3, 200 - 207
5. Lehert, P, Falissard, B. Multiple treatment comparison in narcolepsy: a network meta-analysis. Sleep Journal, 2018, 1-13
6. NHSBSA Dictionary of Medicines and Devices (dm+d browser). Accessed 19 March 2019
7. Uguen, M, et al. Preclinical evaluation of the abuse potential of Pitolisant, a histamine H3 receptor inverse agonist/antagonist compared with Modafinil