NHS
Pan Mersey
Area Prescribing Committee

PITOLISANT tablets (Wakix® ▼) for narcolepsy with or without cataplexy

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 adult patients in accordance with the Aintree University Hospital Sleep Service Pathway for Narcolepsy.

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

The Pan Mersey Area Prescribing Committee recommends the prescribing of pitolisant, by specialists working in a regional and national tertiary commissioned sleep service only, for the treatment of narcolepsy with or without cataplexy in adult patients in accordance with the Aintree University Hospital Sleep Service Pathway for Narcolepsy.

Within Aintree University Hospital Sleep Service, pitolisant will be prescribed in line with the Narcolepsy Pathway:

Pitolisant will be used as a 4TH line treatment option to modafinil and dexamfetamine or methylphenidate (+/- TCA / SSRI antidepressants) or solriamfetol:

- If the above agents don't provide an effective reduction in excessive daytime sleepiness or are not suitable.
- Where the patient is intolerant of / contraindicated to the above agents.

Pitolisant will not be used in combination with sodium oxybate or solriamfetol.

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.

Women of childbearing potential have to use effective contraception during treatment and at least up to 21 days after treatment discontinuation. Pitolisant may reduce the effectiveness of hormonal contraceptives. Therefore, an alternative method of effective contraception should be used if the patient is using hormonal contraceptives.[2]

It is the responsibility of the initiating prescriber to ensure that the patient is using effective contraception prior to commencing treatment and is counselled appropriately. Confirmation that benefits, risks and contraception have been discussed and details of any action taken should be provided to primary care if primary care prescribing of contraception is requested.

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.

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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

Pitolisant is contraindicated in hypersensitivity to the active substance or to any of the excipients, severe hepatic impairment (Child Pugh C) and breastfeeding.

The most serious adverse drug reactions are abnormal weight decrease (0.09%) and spontaneous abortion (0.09%;). Suicidal ideation has been reported in patients with psychiatric history treated with pitolisant.[2]

Common adverse effects reported are insomnia, anxiety, irritability, depression, sleep disorder, vertigo, fatigue, headache, dizziness, tremor, nausea, vomiting, dyspepsia.[2]

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.

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

Cost (excludes VAT)[6]

Drug	Dose Schedule	Cost per annum (dm+d)- EXCLUDES VAT
Solriamfetol	75mg – 150mg daily	£2,130.24 - £2,983.68
Pitolisant 4.5mg and 18mg tablets	4.5mg-36mg daily	£3,871-£7,440
Sodium oxybate 500mg/ml oral solution	2.25g-9g daily	£3,024-£12,096
Clomipramine capsules	10mg-75mg daily	£38.76-£174.60
Venlafaxine 225mg M/R caps	225mg daily	£93.24
Modafanil 200mg tablets	400mg daily	£146.88
Dexamfetamine 10mg tablets	10-60mg daily	£593.52-£3,561.12
Methylphenidate 10mg tablets	10-60mg daily	£39.60 – £334.08
Methylphenidate M/R capsules	10-60mg daily	£300.00-£1,080

Patient factors[2]

Pitolisant should not be used during pregnancy unless the potential benefit outweighs the potential risk for foetus.

Must not be prescribed if breastfeeding (pitolisant is contraindicated).

Must not be prescribed in severe liver impairment (Childs Pugh C).

Pitolisant should be administered with caution in people with moderate hepatic impairment (Child-Pugh B) 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. No dosage adjustment is required in patients with mild hepatic impairment.

See implementation notes for use in women of childbearing potential.

Prescribe with caution in patients with psychiatric history - suicidal ideation has been reported.

Prescribing information[2]

- 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.
- Prescribing in moderate hepatic impairment (Child-Pugh B): Manufacturer advises to consider dose increase two weeks after initiation; maximum daily dose 18 mg.
- In patients with renal impairment, the maximum daily dose should be 18 mg.

Implementation notes

- Prescribing and monitoring will be undertaken by the specialist sleep clinic.
- **Women of childbearing potential have to use effective contraception during treatment and at least up to 21 days after treatment discontinuation. Pitolisant may reduce the effectiveness of hormonal contraceptives. Therefore, an alternative method of effective contraception should be used if the patient is using hormonal contraceptives.**[1]

  It is the responsibility of the initiating prescriber to ensure that the patient is using effective contraception prior to commencing treatment and is counselled appropriately. Confirmation that benefits, risks and contraception have been discussed and details of any action taken should be provided to primary care if primary care prescribing of contraception is requested.

References

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