Northern Treatment Advisory Group

Northern (NHS) Treatment Advisory Group

Treatment Appraisal: Decision Summary

Date	5th November 2018 (updated 22nd February 2022 to reference NICE TA for Solriamfetol)
Appraisal & Details	Following appeal the Northern (NHS) Treatment Advisory Group considered a review of its appraisal of **Pitolisant (Wakix®) for the treatment of narcolepsy with or without cataplexy in adults.**
Recommendation	**The Northern (NHS) Treatment Advisory Group recommends the use of Pitolisant as a treatment option only in narcoleptic patients with residual severe daytime sleepiness who have an Epworth score of 14 or over if they have already tried Modafinil and Dexamfetamine or Methylphenidate, and where therapy will make a substantial difference to their quality life. Prescription of this medication will be limited to Sleep Centres with adequate expertise in managing narcolepsy and using this medication: The James Cook University Hospital, Department of Sleep Medicine and Royal Victoria Infirmary.** Patients with resistant narcolepsy are often unable to study effectively or work in sedentary occupation that involves typing or computer work, for example, and use of Pitolisant would be expected to significantly improve or even allow this type of activity. Improvement in social activities, such as being able to watch a film all the way through, is also something that is reviewed in clinic. Eligible patients will be given a month's trial of Pitolisant at 18mg a day with a view to increasing to 36mg a day for a further month if there has been a partial response as assessed by a reduction in Epworth score. After a two month trial of Pitolisant patients will be reviewed and Pitolisant will only be continued with there has been an improvement in quality of life and the patient has an Epworth score less than 10. The Committee felt the evidence base for Pitolisant was stronger in the single agent setting. Therefore this recommendation does not support the use of Pitolisant in combination regimens unless other stimulants used on a when required basis. In the absence of clear and objective improvement in narcolepsy then Pitolisant should be discontinued. Solriamfetol is another treatment option for narcolepsy used in the same place of the treatment pathway as Pitolisant. On the 5th January 2022 NICE issued TA758: Solriamfetol for treating excessive daytime sleepiness caused by narcolepsy. Solriamfetol is recommended by NICE as an option for treating

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	excessive daytime sleepiness in adults with narcolepsy with or without cataplexy. This is only if Modafinil and either Dexamfetamine or Methylphenidate have not worked well enough or are not suitable. The NICE TA supersedes the previous NTAG recommendation for Solriamfetol for narcolepsy from December 2020. No NICE TA for Pitolisant for narcolepsy is currently planned.
Clinical evidence summary	Two small randomised controlled trials (RCT s) of Pitolisant 5–40 mg per day in adults with narcolepsy with or without cataplexy showed that compared with placebo, Pitolisant improved excessive daytime sleepiness, improved time awake in a darkened room and reduced the weekly cataplexy rate. Pitolisant was also compared with modafinil in a non-inferiority analysis. Non-inferiority to Modafinil was **not** shown. The long-term safety and efficacy data for Pitolisant are limited. There is no data showing how Pitolisant compares to other treatments for narcolepsy or how effective it is in patients who cannot tolerate or do not respond to current treatment options.
Safety	The most common adverse events in the Pitolisant groups were insomnia headache, nausea, anxiety, irritability, dizziness, depression, tremor, sleep disorders, fatigue, vomiting, vertigo, dyspepsia, weight increase and upper abdominal pain. The most serious adverse drug reactions are abnormal weight decrease and spontaneous abortion. No participants in the Pitolisant groups had withdrawal syndrome during the withdrawal phase. The EPAR states that some uncertainties remain with regard to the effects of pitolisant on depression, weight and appetite, ulcer formation, and more generally on adverse events that might occur after long-term exposure.
Patient Perspective	Narcolepsy is a disabling sleep disorder characterised by excessive daytime sleepiness. Patients are often unable to stay awake or asleep for long periods of time. Around 70% of people with narcolepsy also have cataplexy, which is a sudden loss of muscle tone triggered by strong emotions. Episodes can last from seconds to minutes and occur with varying frequency. Patients will be pleased that there is another treatment option available for a difficult to treat condition. However they will also want to know that Pitolisant will be of benefit in the long term and that there are no long term adverse effects; there is currently insufficient published information available to confirm this.
Cost analysis summary	The company anticipate that Pitolisant will be used initially for people with narcolepsy who either cannot tolerate current treatments or have not responded to these. It is estimated that narcolepsy affects 0.05% of the population with approx. 31,000 cases in the UK. About 5,000 of these are thought to receive treatment. Of the treated population, it is estimated that about

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	50% of patients may not tolerate or not respond to their existing medicines and therefore may be eligible for treatment with pitolisant. The cost of 30 days treatment with Pitolisant at dose of 4.5mg to 36mg once daily is £310 to £620 excluding VAT. The cost of 30 days treatment with other medicines use for narcolepsy is £7.52 to £314 for stimulants such as Modafinil, Dexamfetamine or Methylphenidate, and for £540 to £1080 Sodium Oxybate (all excluding VAT) (source = Drug Tariff, October 2018)
Financial impact PbR: likely In-tariff.	Using the estimates provided specialists, approximately 315 patients across the North East and Cumbria receive treatment for their narcolepsy with 50% of these (148) potentially eligible for treatment with Pitolisant. Approx 50% of these patients (74) continue on long-term Pitolisant, and it is estimated that 2 new patients remain on therapy each month. The potential cost impact of Pitolisant in the NE&C region for 74 patients is therefore £430,976 pa.

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Pitolisant for Narcolepsy Treatment Pathway

- Patients diagnosed with narcolepsy (aged 18 and over) will normally receive Modafinil as a first line treatment for excessive sleepiness, provided there are no contraindications.
- When Modafinil is not effective or tolerated, Dexamfetamine/Methylphenidate will be considered as the main second line option, provided there are no contraindications.
- If Dexamfetamine/methylphenidate treatment is not effective or tolerated, Pitolisant will be considered as a third line option, provided there are no contraindications.
- Nacroleptic patients with residual severe daytime sleepiness who have an Epworth score of 14 or over should be eligible to Pitolisant if they have already tried Modafinil and Dexamfetamine or Methylphenidate, and where therapy will make a substantial difference to their quality life.
- Patients with resistant narcolepsy are often unable to study effectively or work in sedentary occupation that involves typing or computer work, for example, and use of Pitolisant would be expected to significantly improve or even allow this type of activity. Improvement in social activities, such as being able to watch a film all the way through, is also something that is reviewed in clinic.
- Ineffective or non-tolerated treatments should be stopped prior to the commencement of Pitolisant.
- Clinician experience suggests that patients may also benefit from/need an additional low dose Amphetamine taken flexibly as a “rescue” therapy i.e. Pitolisant would give them background improved alertness through the day but for a drive or a meeting, for example, many would normally take an amphetamine dose to give them an hour or two of increased wakefulness/alertness.
- Patients with significant pre-existing medical conditions such as uncontrolled hypertension, history of stroke, TIA, myocardial infarction, coronary artery disease or severe depression, bipolar disorder, treatment resistant epilepsy for whom Modafinil, Dexamphetamine, Methylphenidate are contraindicated, will be offered Pitolisant.
- Patients who developed severe allergic reaction or other significant adverse effects to Modafinil, Dexamfetamine, Methylphenidate or Sodium Oxybate, will be offered Pitolisant.
- Pregnant and breastfeeding women and women of childbearing age, who are actively trying to become pregnant and not using adequate contraception will not be offered Pitolisant.

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- Children under age 16 will not be offered Pitolisant since the medication is not licenced for use in children.
- Prescription of this medication will be limited to Sleep Centres with adequate expertise in managing narcolepsy and using this medication : The James Cook University Hospital, Department of Sleep Medicine (Dr Paul Reading and Dr Adrienn Petreczky) and Royal Victoria Infirmary (Dr Kirstie Anderson)
- Eligible patients will be given a month's trial of Pitolisant at 18mg a day with a view to increasing to 36mg a day for a further month if there has been a partial response as assessed by a reduction in Epworth score. After a two month trial of Pitolisant patients will be reviewed and Pitolisant will only be continued if there has been an improvement in quality of life and the patient has an Epworth score less than 10.
- In the absence of clear and objective improvement in narcolepsy then Pitolisant should be discontinued.
- Prospective data will be collected about the use of this medication in each centre over the period of the following 12 months as a part of the audit cycle and submitted to NTAG to provide evidence for safety and potential cost efficacy. It will also monitor adherence to prescription guidelines.