NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pitolisant hydrochloride for treating excessive daytime sleepiness caused by obstructive sleep apnoea

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pitolisant hydrochloride in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: May 2021

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using pitolisant hydrochloride in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 24 June 2021.

Second appraisal committee meeting: To be confirmed.

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Pitolisant hydrochloride is not recommended, within its marketing authorisation, to improve wakefulness and reduce excessive daytime sleepiness in adults with obstructive sleep apnoea whose sleepiness has not been satisfactorily treated by primary obstructive sleep apnoea therapy such as continuous positive airway pressure (CPAP), or who cannot tolerate it.

1.2 This recommendation is not intended to affect treatment with pitolisant hydrochloride that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Excessive daytime sleepiness caused by obstructive sleep apnoea is usually treated with a primary obstructive sleep apnoea therapy such as CPAP. Some people might not tolerate CPAP so they are offered mandibular advancement devices.

Clinical trial evidence suggests that pitolisant hydrochloride reduces excessive daytime sleepiness, with and without CPAP. But there is uncertainty about the evidence because of the way the trials were done. They excluded some people who might be eligible for pitolisant hydrochloride in the NHS. There are also concerns about how they assessed quality of life, so it is uncertain if pitolisant hydrochloride improves quality of life. And there may be a placebo effect in the standard care group (primary obstructive sleep apnoea therapy) that has not been considered and explored sufficiently.

There are concerns about how the trial data have been modelled to take account of a potential placebo effect in the standard care group, and how health-related quality of life was assessed. There is also uncertainty about the assumptions around reduced cardiovascular risk. So, the cost-effectiveness estimates for pitolisant

hydrochloride are uncertain. They are also likely to be higher than what NICE normally considers an acceptable use of NHS resources. So pitolisant hydrochloride is not recommended.

2 Information about pitolisant hydrochloride

Anticipated marketing authorisation indication

2.1 On 20 May 2021 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product pitolisant hydrochloride (Ozawade), intended to improve wakefulness and reduce excessive daytime sleepiness (EDS) in adult patients with obstructive sleep apnoea (OSA) whose EDS has not been satisfactorily treated by, or who have not tolerated, OSA primary therapy, such as continuous positive airway pressure (CPAP).

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics.

Price

2.3 The proposed list price for pitolisant hydrochloride is commercial in confidence.

3 Committee discussion

The appraisal committee considered evidence submitted by Lincoln medical, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

It recognised that there were remaining areas of uncertainty associated with the analyses presented and took these into account in its decision making. It discussed the following issues, which were outstanding after the technical engagement stage:

exclusion criteria in the clinical trials, relevance of mandibular devices, reliability of an indirect treatment comparison, length of follow up in the clinical trials, effect on cardiovascular events, the mapping algorithm, the probability of road traffic accidents and adjustment for a possible placebo effect.

The condition

Excessive daytime sleepiness caused by obstructive sleep apnoea affects quality of life

3.1 The patient expert explained that obstructive sleep apnoea can affect people's physical and mental wellbeing. Excessive daytime sleepiness affects daily life including education, employment, maintaining a social life and the ability to drive. Symptoms of sleep apnoea such as snoring can disrupt a partner's sleep, affecting their own quality of life. The patient expert said that a better understanding of the condition among GPs could improve consistency in arriving at a diagnosis sooner. The clinical experts noted that obstructive sleep apnoea can be associated with high blood pressure, which is associated with heart disease and stroke. The committee concluded that excessive daytime sleepiness caused by obstructive sleep apnoea affects quality of life.

Pitolisant hydrochloride would typically be offered in addition to CPAP, but some people cannot tolerate CPAP

3.2 The clinical experts advised that most people with excessive daytime sleepiness caused by obstructive sleep apnoea are referred to sleep clinics. Initial treatment includes lifestyle advice about weight loss. For people with mild symptomatic obstructive sleep apnoea, mandibular devices are considered. For adults with moderate or severe obstructive sleep apnoea, NICE guidance on obstructive sleep apnoea recommends CPAP. The patient expert explained that CPAP is usually well tolerated but some people struggle to use it regularly because it is big, noisy and can affect sleep. The clinical experts explained that CPAP is not tolerated by some people because they feel claustrophobic wearing a mask,

particularly when they have certain mental health issues. People with neurodegenerative conditions may also not tolerate CPAP, and some people have anatomical variations that make CPAP unsuitable for them. The clinical and patient experts also explained that some people using CPAP will have residual excessive daytime sleepiness. They noted that pitolisant hydrochloride is a potential treatment option that people would welcome for improving excessive sleepiness, although it does not treat the underlying causes of obstructive sleep apnoea. The committee concluded that because pitolisant hydrochloride does not treat underlying airway obstruction it would likely be used as an addition to CPAP, but it acknowledged that some people cannot tolerate CPAP.

Mandibular advancement devices are sometimes used as an alternative to CPAP but their availability varies across the country

3.3 The clinical experts explained that people who decline CPAP or cannot tolerate it may be offered a mandibular advancement device, which helps prevent the airway closing. They highlighted that there is variation in practice because the devices are not available at every sleep clinic across the country. About 20% of people who do not have CPAP might be offered a mandibular advancement device. The company stated that mandibular devices are generally used earlier in the treatment pathway than CPAP, so someone who declines CPAP is likely to have already been offered a mandibular device. Although availability varies across the country, the committee concluded that mandibular advancement devices are sometimes offered to people who decline CPAP or cannot tolerate it.

Pitolisant hydrochloride is likely to be prescribed in secondary care

3.4 The clinical experts highlighted that pitolisant hydrochloride would likely be prescribed in specialist sleep clinics (secondary care) because of the need to monitor adherence to CPAP. They highlighted that additional monitoring would be needed if pitolisant hydrochloride were recommended. They were uncertain if prescribing could move to primary

care in the future. The committee concluded that pitolisant hydrochloride is likely to be prescribed in secondary care.

Clinical evidence

Pitolisant hydrochloride improves excessive daytime sleepiness, with and without CPAP

3.5 HAROSA 1 and HAROSA 2 were randomised trials of patients having either pitolisant hydrochloride plus standard care or placebo plus standard of care, for a 12-week double-blind period. After 12 weeks all patients in the trial were offered pitolisant hydrochloride for 40 weeks (the open-label phase). In HAROSA 1, patients had been using nasal CPAP therapy for at least 3 months and were experiencing excessive daytime sleepiness before starting the trial. HAROSA 2 included only people who had not used CPAP and were experiencing excessive daytime sleepiness. The primary outcome of the trials was reduction in Epworth Sleepiness Scale (ESS) scores. The results showed a reduction in ESS scores from baseline to week 12 in both trials. In people who used CPAP the ESS score reduced by 5.52 points. In people who had not used CPAP, the ESS score reduced by 6.30 points. In terms of quality of life, patients in HAROSA 1 reported no difference in EQ-5D or Visual Analogue Scale during the double-blind phase of the trials. However, there was an improvement in the pain and discomfort dimension in the population of HAROSA 2 ('no problems' reported by 54.7% of patients at baseline compared with 40.6% at week 12, p=0.044). The clinical experts explained that an ESS reduction of 2 or more points could be considered a clinically relevant reduction, but noted that there is no clinical consensus about this because it will vary between individuals. The committee concluded that pitolisant hydrochloride improves excessive daytime sleepiness, with or without CPAP.

It would be appropriate to explore a potential placebo effect in the HAROSA trials

3.6 The ESS score improved from baseline to week 12 in the placebo group in both of the HAROSA trials. The clinical experts suggested this could be because of potential observation bias from the Hawthorne effect (that is, patients reported an improvement in ESS because of more frequent contact with trial investigators than they would have with clinicians in clinical practice). However, they highlighted that there could be other reasons for the improvement. The company's analyses did not adjust for this placebo effect. The committee concluded that it would be appropriate to explore approaches to adjust for the placebo effect in the clinical trials (see section 3.14).

The HAROSA trials are broadly generalisable to NHS practice but exclude some patients who might be eligible for pitolisant hydrochloride

3.7 The HAROSA trials had exclusion criterion that stated people with psychiatric illness could be excluded from the trial. The company clarified that people with depression were only excluded if the investigating clinician felt that it would make study participation challenging for them, rather than for any particular concern about comorbid conditions. A Beck Depression Inventory (13-item short form) score of less than 16 was an inclusion criterion, meaning that people with mild (score 5 to 7) and moderate (score 8 to 15) depression were included in the HAROSA trials. The company stated that the trials included people with depression and anxiety. 18% of patients in HAROSA 1 and 5% in HAROSA 2 had a pre-existing psychiatric illness. The committee noted the company's submission, which stated that about half of people with severe excessive daytime sleepiness have co-existing depression. The clinical experts estimated that about half of people referred to sleep clinics might having antidepressant therapy of some kind. The committee accepted that some people with depression were included in the trials, but the proportions are lower than might be expected in the NHS. This might affect the

generalisability of the trial data. The effect of this on the clinical effectiveness estimates was unknown. The committee concluded that the HAROSA trials were broadly generalisable for decision making but underrepresent people with psychiatric illness.

Compliance with CPAP is unlikely to be affected by treatment with pitolisant hydrochloride

3.8 The patient expert explained that some people with excessive daytime sleepiness may prefer to manage their symptoms with a medicine, rather than using CPAP. So they might use their CPAP less often when taking pitolisant hydrochloride, which could lead to a reduction in the combined benefits of CPAP and pitolisant hydrochloride. The clinical experts said that most sleep clinics can remotely monitor CPAP use. Some people, such as heavy goods vehicle drivers, regularly have their CPAP use monitored remotely. The clinical experts stated that people having pitolisant hydrochloride alongside CPAP may have their use monitored more frequently than in current practice. The committee concluded that CPAP use is unlikely to be affected by treatment with pitolisant hydrochloride because of regular monitoring.

It is acceptable to exclude mandibular advancement devices from the analyses in the absence of better data

3.9 The ERG report stated that the company should present a comparison of pitolisant hydrochloride with mandibular advancement devices for people who decline CPAP or cannot tolerate it. The committee recalled the clinical experts' comments on variable availability of mandibular advancement devices in the NHS (see section 3.3). The company provided an updated indirect treatment comparison between pitolisant hydrochloride and mandibular advancement devices, to assess efficacy based on change in ESS scores from baseline. This updated comparison suggested that pitolisant hydrochloride had a much larger effect on ESS than placebo only, but no effect compared with mandibular advancement devices and CPAP. The company highlighted that this analysis has

limitations. The committee recalled the company's comments that mandibular advancement devices should not be considered as a comparator for this appraisal because they would not be used in the same position in the treatment pathway as pitolisant hydrochloride (see section 3.3). The company also highlighted that it does not have direct data on the use of pitolisant hydrochloride with mandibular advancement devices and the marketing authorisation does not specifically consider their use alongside pitolisant hydrochloride. The committee noted its earlier conclusion that mandibular advancement devices are sometimes used by people who do not have CPAP, although their use varies across the country. It agreed that it was useful to consider an analysis that incorporated mandibular advancement devices as a comparator. However, the committee concluded that the company's base-case analysis that excluded mandibular devices was acceptable for decision making in the absence of better data.

The trial follow-up period is long enough to understand the side effects and clinical benefits of pitolisant hydrochloride

3.10 The clinical experts have experience using pitolisant hydrochloride with people who have narcolepsy. They commented that they could rapidly see the benefits as well as the side effects of the treatment. The company provided data from HARMONY, a study of patients taking pitolisant hydrochloride for narcolepsy for 1 year or more. The ERG expressed caution that the effectiveness of pitolisant hydrochloride in HARMONY does not directly correlate to obstructive sleep apnoea because the cause of sleepiness is different. The committee concluded that the HARMONY follow-up period is long enough for decision making about the clinical benefits and side effects of pitolisant hydrochloride.

The economic model

The company's model structure is acceptable for decision making but has limitations

3.11 The company's model was based on a model developed by McDaid et al. (2009) for NICE's technology appraisal of CPAP for the treatment of obstructive sleep apnoea. The ERG noted that pitolisant hydrochloride and CPAP treat different aspects of the condition, so this may not be the best approach for evaluating pitolisant hydrochloride. However, it stated that the relevant consequences of the comparisons can be adequately assessed using this model although it may be more complicated than necessary. It corrected some aspects of the company's model, which had small effects on the company's base-case incremental cost-effectiveness ratio (ICER). The committee agreed there are limitations with some of the company's assumptions, but the model is acceptable for decision making.

The model should include a lifetime horizon and corrections for age decrements

3.12 The company's base-case analysis subtracted the age decrement from the total undiscounted quality-adjusted life years (QALYs) per cycle. So the age decrement was not weighted by the number of patients alive, and the difference between the treatment arms was not taken into account. The ERG corrected this by weighting the utility decrement by the proportion of patients alive in a specific cycle, then subtracting it from the total undiscounted QALYs per cycle. Although this had only a small effect on the ICER, the committee agreed with the ERG's approach. The ERG also suggested increasing the time horizon of the model from 25 years to 47 years, because many people in the cohort will live beyond 25 years. The committee agreed with the ERG's suggested changes to the time horizon and to calculating age decrements.

There is no direct evidence that pitolisant hydrochloride reduces cardiovascular events

3.13 The committee noted that the company did not provide an explanation about the biological mechanism by which pitolisant may reduce cardiovascular events. The company's model assumed that a reduction in ESS score was related to a reduction in cardiovascular disease risk (that is, patients could move into the post-coronary heart disease state if they experienced an acute cardiovascular event and survived). The modelling also assumed that pitolisant hydrochloride lowers the risk of cardiovascular events, which are more prevalent in people with EDS caused by OSA. The clinical experts explained that because of the lack of long-term clinical trials in obstructive sleep apnoea they rely on markers for cardiovascular risk, such as blood pressure. They stated that there is evidence that people using CPAP have a reduction in their blood pressure along with their daytime sleepiness, but there is no direct evidence to validate this assumption in the economic model. The ERG agreed with the clinical experts that it had not seen evidence that a reduction in ESS score with pitolisant hydrochloride would lead to a reduction in cardiovascular events. It was unaware of any reasonable mechanism by which a wakefulness drug would reduce cardiovascular risk, rather than this being a result of treating the underlying cause of excessive sleepiness (obstructive sleep apnoea). The committee noted that the HAROSA trials showed no changes in patient's blood pressure levels. In the absence of evidence of changes in cardiovascular markers the committee agreed with the ERG. It concluded that there is no direct evidence of clinical or biological mechanisms by which pitolisant hydrochloride has an effect on cardiovascular events.

Alternative modelling approaches should be explored to adjust for the placebo effect in the HAROSA trials

3.14 The committee recalled its discussion about the need to explore the effect of a placebo response on the clinical trial results (see section 3.6). It noted

the potential causes of such an effect and discussed ways to adjust for it. One way of adjusting for a placebo effect might be to remove the improvement in ESS scores observed in the placebo group from both the placebo and the pitolisant groups in the model (sometimes referred to as a centering approach). This could be combined with an approach that considers 'responders' and 'non-responders' separately, defined using individual patient data. It could also use a selection of response thresholds similar to those used in the ongoing NICE technology appraisal of solriamfetol for treating excessive daytime sleepiness. Restructuring the model in this way, and removing the effect observed in the placebo group from both groups, might reveal greater differences between the 2 groups. The committee concluded that approaches to account for the placebo effect shown in the HAROSA trials should be explored to understand the effect on the cost-effectiveness results.

The mapping algorithm used to inform the model is not appropriate

3.15 The company stated that advice from their clinical experts suggested that EQ-5D questionnaires may not adequately capture quality-of-life benefits in people with obstructive sleep apnoea. So the company's submission mapped ESS scores from the trials to EQ-5D rather than using values derived directly from the trials. The company stated this approach was consistent with that used in NICE's technology appraisal of CPAP for the treatment of obstructive sleep apnoea. The committee highlighted that if EQ-5D does not capture quality-of-life benefits adequately the results should not be mapped to EQ-5D, because it will remain insensitive. After technical engagement, the company provided an analysis using utility values calculated directly from EQ-5D data in the trials. These are academic-in-confidence and cannot be presented here. The ERG suggested that other measures, such as SF-6D, might be more sensitive in capturing quality-of-life benefits. The company provided a scenario analysis that mapped ESS scores to SF-6D, which increased the ICER from £29,698 to £34,034 per QALY gained. The committee agreed that the company's alternative scenario using SF-6D might be preferable, but

more understanding was needed to determine how well mapping to SF-6D captures quality-of-life benefits. It was concerned about the company's rationale for mapping ESS scores to EQ-5D because of the limitations in capturing quality-of-life benefits. The committee considered that using a mapping algorithm could be justified if evidence is provided that the questionnaires used in the trials, or the way they were applied, has not adequately captured quality of life. The committee would also require evidence that SF-6D captures quality-of-life benefits in a more sensitive way in people with obstructive sleep apnoea. The committee concluded that it preferred the EQ-5D utility values derived from the clinical trials and that more detailed evidence should be provided to explain why EQ-5D is insensitive to capturing changes in a person's quality of life.

A utility decrement for road traffic accidents is not acceptable

3.16 The ERG explained that it agreed to keep the road traffic accidents (RTA) utility in the model, on the basis that people taking pitolisant hydrochloride would be more alert when driving. But it adjusted the utility by lowering the effect of RTAs using a disutility of the exceedance submitted by the company. It stated that there is no direct evidence to prove that pitolisant hydrochloride would reduce the incidence of RTAs because this was not measured in the HAROSA trials. It also stated that the model assumes that people with EDS who take pitolisant hydrochloride and drive have the same risk of an RTA as the general population driving in the UK, which is not a plausible assumption. The committee concluded that people with obstructive sleep apnoea and excessive daytime sleepiness are banned from driving so it agreed not to include a utility decrement for road traffic accidents.

Cost-effectiveness estimates

Pitolisant hydrochloride is not a cost-effective use of NHS resources

3.17 The committee considered the cost-effectiveness estimates for pitolisant hydrochloride with and without CPAP, plus standard care, compared with

standard care alone. The company provided cost-effectiveness estimates for 2 populations in line with the marketing authorisation. For people with residual excessive daytime sleepiness despite using CPAP, the deterministic ICER for pitolisant hydrochloride plus CPAP and best support care, compared with CPAP plus best support care alone, was estimated to be £29,698 per QALY gained (the probabilistic ICER was £29,824 per QALY gained). For people who decline or have not tolerated CPAP, the ICER for pitolisant hydrochloride plus best support care compared with best support care alone was estimated to be £29,803 per QALY gained (the probabilistic ICER was £29,932 per QALY gained). The committee preferred the ERG's base-case analysis, which included the following assumptions:

- a time horizon of 47 years (see section 3.12)
- correction for an age decrement (see section 3.12)
- no reduction in cardiovascular events in the base-case analysis (see section 3.13)
- reduction in the effect of RTAs on the ICER is reasonable (see section 3.16).

For people with residual excessive daytime sleepiness despite CPAP, this increased the ICER for pitolisant hydrochloride plus CPAP and best supportive care compared with CPAP and best supportive care alone to £67,557 per QALY gained. For people who refuse or do not tolerate CPAP, the ICER was estimated to be £62,923 per QALY gained. This ICER might increase further if an alternative approach to mapping utility values, such as SF-6D, is used (see section 3.15). The committee noted that the effect on the ICER of adjusting for the placebo effect seen in the HAROSA trials was unknown and would depend on the approach taken (see section 3.14). It concluded that the cost-effectiveness analyses were highly uncertain, and the most plausible ICER is likely to be above what NICE considers a cost-effective use of NHS resources.

Other factors

3.18 The clinical expert noted that people with mental health or neurodegenerative conditions struggle to use CPAP regularly, making it difficult to control excessive daytime sleepiness caused by their obstructive sleep apnoea. The marketing authorisation for pitolisant hydrochloride includes people with obstructive sleep apnoea whose excessive daytime sleepiness has not been satisfactorily treated by primary obstructive sleep apnoea therapy, such as CPAP. The committee agreed with the clinical experts that people who struggle with CPAP may be disadvantaged and that this should be taken into account in its decision making.

Conclusion

Pitolisant hydrochloride is not recommended for treating excessive daytime sleepiness caused by obstructive sleep apnoea

3.19 The committee recognised that excessive daytime sleepiness caused by obstructive sleep apnoea is a debilitating condition that negatively affects many aspects of daily life (see section 3.1). It acknowledged that pitolisant hydrochloride with standard care was more effective than standard care alone in reducing excessive daytime sleepiness, as measured by the ESS (see section 3.5). It agreed there was substantial uncertainty in the company's analyses, including:

- insufficient evidence of the impact of pitolisant hydrochloride in cardiovascular events (see section 3.13)
- needing an alternative approach to explore the placebo effect (see section 3.14)
- the mapping algorithm used to inform the model is not appropriate (see section 3.15).

The committee agreed that it would like to see analyses that include an alternative approach to adjusting for the placebo effect.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
April 2021

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Anne Murray-Cota

Technical lead

Christian Griffiths

Technical adviser

Gavin Kenny

Project manager

ISBN: [to be added at publication]