

**January
2016**

Pitolisant hydrochloride for obstructive sleep apnoea

LAY SUMMARY

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

Obstructive sleep apnoea is caused by a repetitive relaxing of the throat muscles during sleep which leads to the airway becoming repeatedly blocked off. Difficulties in breathing during the night causes patients to wake up suddenly, have an interrupted nights' sleep, and feel sleepy during the daytime. Obstructive sleep apnoea is often linked to being overweight, smoking, drugs, drinking alcohol, and a poor sleeping routine. However, if changing these factors does not improve symptoms, patients may be advised to use a CPAP (continuous positive airway pressure) machine at night time, but not all patients are able to tolerate CPAP therapy.

Pitolisant hydrochloride is a new drug that may improve daytime sleepiness in patients with obstructive sleep apnoea. It is taken once daily as a tablet. Pitolisant hydrochloride is currently being studied to see how well it works and whether it is safe to use in people with obstructive sleep apnoea.

If pitolisant hydrochloride drug licensed for use in the UK, it would be the first drug for obstructive sleep apnoea that could be taken as a tablet. It could be particularly helpful for people who still suffer excessive daytime sleepiness despite CPAP therapy, or for patients who do not wish to use a CPAP machine.

NIHR HSRIC ID: 7512

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

NIHR Horizon Scanning Research & Intelligence Centre,
University of Birmingham. Email: nihrhsc@contacts.bham.ac.uk
Web: www.hsrc.nihr.ac.uk



**National Institute for
Health Research**

TARGET GROUP

- Obstructive sleep apnoea (OSA): moderate to severe; patients experiencing excessive diurnal sleepiness - second line; patients receiving or declining nasal continuous positive airway pressure (CPAP) therapy.

TECHNOLOGY

DESCRIPTION

Pitolisant hydrochloride (WAKOSA; BF2.649; tiprolisant) is an inverse agonist of histamine receptor type 3, which strengthens histaminergic transmission in the brain and increases wakefulness. Pitolisant is intended for patients with moderate to severe OSA who are already receiving, declining or intolerant to treatment with nasal CPAP therapy. In the phase III clinical trial, pitolisant hydrochloride is administered orally at 5-20mg once daily for a duration of 12 weeks¹.

Pitolisant hydrochloride does not currently have a Marketing Authorisation in the EU for any indication.

Pitolisant hydrochloride is also in phase III clinical trials for the treatment of:

- Excessive daytime sleepiness in narcolepsy patients, with and without cataplexy (as an add-on therapy to both sodium oxybate and modafinil).
- Excessive daytime sleepiness in patients with Parkinson's disease.

It is in phase II clinical trials for the treatment of:

- Narcolepsy (with or without cataplexy) in children.
- Photosensitivity in epilepsy.
- Attention-deficit hyperactivity disorder.

INNOVATION and/or ADVANTAGES

If licensed, pitolisant hydrochloride will offer an additional treatment option for patients with moderate or severe OSA who experience excessive daytime sleepiness, despite CPAP treatment.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

OSA is partial or complete upper airway occlusion during sleep². Symptoms include regular arousal from sleep, sleep fragmentation and excessive daytime sleepiness (EDS)². OSA is associated with neuropsychological impairment, metabolic and cardiovascular co-morbidities and increased mortality². Risk factors for OSA include alcohol consumption, drugs, smoking, obesity, poor sleep schedule and sleep position. OSA often occurs with symptoms of EDS, when it is termed obstructive sleep apnoea syndrome³.

Patients with OSA are broadly categorised into having mild, moderate and severe disease; the severity is measured using the frequency of apnoeas (a ten second period where no or almost no respiratory airflow can occur) and hypopnoeas (a ten second period where the cross-sectional area of the lumen of the upper respiratory tract is reduced and airflow is reduced by at least 50% from baseline leading to oxygen desaturation and/or arousal from sleep) per hour of sleep⁴. Moderate OSA is defined as experiencing between 15 and 30 sleep obstructive-related breathing events per hour. Severe OSA is defined as experiencing more than 30 sleep obstructive-related breathing events per hour. Severity of daytime sleepiness symptoms is measured using the Epworth Sleepiness Scale (ESS).

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

- The National Service Framework for long-term conditions (2005).

CLINICAL NEED and BURDEN OF DISEASE

OSA is the third most common respiratory disorder in UK (after asthma and chronic obstructive pulmonary disease)³. In the UK, 4% of middle-aged men and 2% of middle-aged women are estimated to be affected by obstructive sleep apnoea syndrome⁵. The prevalence increases with age³.

In 2014, there were 24,107 admissions for sleep apnoea (G47.3) in England, resulting in 24,237 bed days and 24,892 finished consultant episodes⁶. During 2014, 61 deaths from sleep apnoea were registered in England and Wales (G47.3)⁹.

Previous estimates suggested that in the UK, 20,000 of the probable 180,000 patients with obstructive sleep apnoea syndrome were using CPAP in 2006³. The company suggest that this figure is likely to be an underestimate of current CPAP use. The population likely to be eligible to receive pitolisant could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal guidance. Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome (TA139) March 2008.
- NICE interventional procedure guidance. Soft-palate implants for obstructive sleep apnoea (IPG241). November 2007.

Other Guidance

- Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical Guidance for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults. 2009⁷.

CURRENT TREATMENT OPTIONS

First line treatments for OSA concentrate on targeting the known risk factors by making lifestyle changes - for example, losing weight, smoking cessation and decreasing alcohol consumption.

The most commonly used treatment for patients with moderate to severe OSA is continuous positive airway pressure (CPAP) delivered via a nasal mask^{2,4}. CPAP generates positive pressure through airflow which prevents upper airway collapse⁴. CPAP is recommended as a treatment option for patients with moderate or severe obstructive sleep apnoea syndrome or patients with mild OSAS if the symptoms are affecting their quality of life and ability to complete daily activities, and if other treatment options (such as lifestyle changes) have not been successful or are inappropriate⁷. CPAP is not tolerated by all individuals².

Custom made oral appliances can also be worn to enlarge the upper airway and/or decrease the collapsibility of the upper airway⁶.

EFFICACY and SAFETY

Trial	HAROSA1, NCT01071876, BF2.649; pitolisant or placebo; phase III.	HAROSA2, NCT01072968; BF2.649; pitolisant or placebo; phase III.
Sponsor	Bioprojet.	Bioprojet.
Status	Completed but unpublished.	Completed but unpublished.
Source of information	Trial registry ⁸ , company.	Trial registry ¹ , company.
Location	France.	France.
Design	Randomised, placebo-controlled.	Randomised, placebo-controlled.
Participants	n=244; adults; OSA; patients who have been treated with nasal CPAP but complaining of EDS; ESS score >11; no insomnia without OSA; no co-existing narcolepsy; no sleep debt not due to OSA; no other acute or chronic cases of severe disease.	n=268; adults; OSA; patients who are complaining of EDS but refuse nasal CPAP; ESS score >11; no insomnia without OSA; no co-existing narcolepsy; no sleep debt not due to OSA; no other acute or chronic cases of severe disease.
Schedule	Randomised to pitolisant 5mg, 10mg, 20mg or placebo (all oral), once daily, followed by 9 month open label extension phase, in which patients in pitolisant groups continue their treatment dose.	Randomised to pitolisant 5-20mg oral daily; or placebo oral daily.
Follow-up	Active treatment for 12 weeks, 1 year follow up.	Active treatment for 12 weeks, 1 year follow up.
Primary outcome/s	ESS score at 12 weeks.	ESS score at 12 weeks.
Secondary outcome/s	Quality of life as assessed by EQ-5D.	Quality of life as assessed by EQ-5D.
Expected reporting date	Late 2016.	Late 2016.

ESTIMATED COST and IMPACT

COST

The cost of pitolisant is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers

- | | |
|--|--|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input checked="" type="checkbox"/> Other: <i>pitolisant hydrochloride has the potential to improve ease of access as it is administered orally, so improving patient convenience².</i> | <input type="checkbox"/> No impact identified |

Impact on Health and Social Care Services

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services: | <input type="checkbox"/> Need for new services |
| <input checked="" type="checkbox"/> Other: <i>Pitolisant hydrochloride may be a treatment option for those with residual EDS despite adequate control of OSA with CPAP therapy^a.</i> | <input type="checkbox"/> None identified |

Impact on Costs and Other Resource Use

- | | |
|--|---|
| <input checked="" type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input type="checkbox"/> Other reduction in costs |
| <input type="checkbox"/> Other | <input type="checkbox"/> None identified |

Other Issues

- | | |
|--|--|
| <input checked="" type="checkbox"/> Clinical uncertainty or other research question identified: <i>The phase III trials are short term, long-term data on safety and efficacy would be of value^a.</i> | <input type="checkbox"/> None identified |
|--|--|

REFERENCES

- 1 ClinicalTrials.gov. Efficacy and safety of BF2.649 in treatment of excessive daytime sleepiness in patients with obstructive sleep apnea (OSA) refusing the nasal continuous positive airway pressure (nCPAP) therapy. www.clinicaltrials.gov/ct2/show/NCT01072968 Accessed 21 January 2016.
- 2 Mason M, Welsh EJ and Smith I. Drug therapy for obstructive sleep apnoea in adults (review). Cochrane Database of Systematic Reviews 2013;5.
- 3 McMillan A, Bratton DJ, Faria R *et al.* A multicentre randomised controlled trial and economic evaluation of continuous positive airway pressure for the treatment of obstructive sleep apnoea syndrome in older people: PREDICT. Health Technology Assessment, No. 19.40. Southampton (UK)2015.

^a Expert comments.

- 4 National Institute for Health and Clinical Excellence. Final Scope for the appraisal of continuous positive airways pressure (CPAP) for the treatment of obstructive sleep apnoea/hypopnoea syndrome (OSAHS). Technology appraisal TA139. London:NICE; March 2008.
- 5 Steier J, Martin A, Harris J *et al*. Predicted relative prevalence estimates for obstructive sleep apnoea and the associated healthcare provision in the UK. *Thorax* 2013;69(4)390-392.
- 6 Health & Social Care Information Centre. Hospital Episode Statistics for England, Admitted Patient Care, 2014-15. www.hscic.gov.uk.
- 7 Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical Guidance for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults. *Journal of Clinical Sleep Medicine* 2009;5:263-276.
- 8 ClinicalTrials.gov. BF2.649 in patients with obstructive sleep apnea syndrome (OSA) and treated by nasal continuous positive airway pressure (nCPAP), but still complaining of excessive daytime sleepiness (EDS). www.clinicaltrials.gov/ct2/show/NCT01071876 Accessed 21 January 2016.
- 9 Office for National Statistics. Deaths registered in England and Wales (series DR), 2014. www.ons.gov.uk.