National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Bioprojet	It is important to refer this topic to NICE for appraisal, because there are some OSA patients treated with CPAP (5 to 10%), with good adherence, that have residual Excessive Daytime Sleepiness (EDS): in that case pitolisant could benefit these patients.	Comment noted. No action required.
	British Thoracic Society	This does not seem high priority for NICE, there are a number of existing, cheaper stimulants available, although none are licensed for the indication of excessive daytime sleepiness in OSA after CPAP or if CPAP intolerant The potential benefit from pitolisant as a stimulant is a long half life therefore potentially few side effects of dependency and lower abuse potential. But there are increasing concerns about the recognised effects on increasing pulse, hypertension and vascular risk. To date this has been shown for all stimulants without any data to date to prove pitolisant is safer in this regard. Pitolisant to date seems well tolerated with a good side effect profile and shows modest benefit in narcolepsy, similar to modafinil.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	British Thoracic Society	Weight gain is so strongly associated with OSA that weight loss as a key lifestyle issue rather than simply “diet”. Sedative medication and in particular opioids and benzodiazepines can worsen or cause OSA, so possibly “reducing sedative drugs” rather than just “drugs” Reference 6 seems inappropriate as this is narcolepsy and not OSA, so “other causes of EDS including narcolepsy”	Comment noted. The background section of the scope has been updated. These comments do not necessitate any change to the draft remit.
Timing Issues	Bioprojet	The need for this assessment is important but not urgent. Given that pitolisant is yet to be filed with the regulatory authorities and unlikely to be available until late 2020, there are no immediate time pressures on this review. However, currently the guidelines in development for OSA do not include any pharmacological agent in development and therefore this appraisal presents an opportunity to address that gap.	Comment noted. No action required.
	British Thoracic Society	No obvious urgency	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Thoracic Society	See above but further information on role of weight, other sleep disorders and sedative drugs	Comment noted. The background section of the scope has been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
The technology/ intervention	Bioprojet	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. Pitolisant also modulates various neurotransmitter systems, increasing acetylcholine, noradrenaline and dopamine release in the brain. However, there is no increase in dopamine release in the striatal complex, including the nucleus accumbens shown with pitolisant. That means that pitolisant reduces the symptoms of EDS and also residual EDS, with the minimal risk of abuse.	Comment noted. No action required.
	British Thoracic Society	Yes except about 50% of patients discontinue pitolisant due to lack of benefit in the follow up narcolepsy studies and this should be included	Comment noted. Details about treatment benefit and compliance are not included in the technology section of the scope.
Population	Bioprojet	The population that could benefit from pitolisant is the OSA patient with good adherence to CPAP treatment, presenting with a residual EDS. This appears to represent approximately 5 to 10% of the OSA patient population, so 15,000 to 30,000 patients in UK.	Comment noted. Pitolisant hydrochloride will be appraised within its marketing authorisation.
	British Thoracic Society	Those with EDS due to other causes that have evidence based therapies eg restless legs syndrome should be excluded. Those on sedative medication should have this reduced where possible. Depression is considered a common cause of sleepiness despite CPAP and so should be excluded given there are existing NICE approved therapies.	Comment noted. Pitolisant hydrochloride will be appraised within its marketing authorisation.

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		Those with EDS on CPAP are different than those with EDS due to refusal to wear CPAP as the latter gave far greater vascular risk so this would be the key separation. There are concerns about CPAP refusers being in the same group as those with excessive daytime sleepiness despite CPAP; these are two different patient groups and many would opt not to use/refuse CPAP if a tablet was an option. Also – what tests are required to define this group? ESS? Multiple sleep latency tests? Should therapy be discussed by MDT?	Comment noted. Any subgroup of the population who would be expected to respond differently for treatment can be considered separately. Comment noted. This section of the scope aims to provide a brief overview of the background for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal.
Comparators	Bioprojet	There is no licenced comparator or commercialised drug available to treat residual EDS in OSA patients. Modafinil is sometimes prescribed for this cohort of patients, but lost its indication in 2010 because of several serious side effects.	Comment noted. Treatments used off label can be considered as comparators. Therefore, modafinil could potentially still be considered a relevant comparator if used in established NHS clinical

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			practice. However, the scope has been updated to include established clinical management without pitolisant hydrochloride as the comparator.
	British Thoracic Society	CPAP is the current standard of care for moderate or severe OSA. Other options for people who cannot use CPAP are surgery including bariatric, Hypoglossal nerve stimulation (NICE GL), non invasive ventilation, mandibular advancement devices Currently stimulants are not standard treatment for EDS despite CPAP following licence change for modafinil and few would routinely use dexamphetamine due to side effect profile. Sodium oxybate can exacerbate central apnoeas and oxygen desaturations for some, while modafinil and methylphenidate have been used for EDS despite CPAP	Comment noted. This scope aims to define relevant treatments for people with EDS caused by OSA, not treatments for OSA. Comment noted. The comparators listed in the scope aims to be inclusive. A rationale should be provided for excluding any comparators from the evidence submission, which can be considered by the appraisal committee.
Outcomes	Bioprojet	EDS is a key symptom of OSA and can occur even with regular use of CPAP. EDS was measured with very common and well documented parameters: Epworth Score (ESS) and Maintenance of Wakefulness Test (MWT).	Comment noted. The outcomes section of the

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			scope has been updated.
	British Thoracic Society	Need measurement of blood pressure and cardiovascular events as the most likely harms. BMI should be measured as some get appetite suppression with stimulants Side effect profile including skin rashes, StevensJohnson syndrome Measures of AHI or ODI	Comment noted. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes if appropriate.
Economic analysis	British Thoracic Society	Long term follow up should encompass drop out rates	Comment noted. Any issues relating to the long-term treatment compliance, can be considered by the appraisal committee.
Equality and Diversity	British Thoracic Society	No concerns	Comment noted. No action required.
Other considerations	British Thoracic Society	This is an opportunity for NICE to provide guidance on all stimulants and narcolepsy. There are no guidelines and clearly wide variation in practice.	Comment noted. No action required.
Innovation	Bioprojet	Pitolisant is an innovative treatment since it targets the histamine pathway, via the H3 receptor. Because of this unique mode of action, it is the only drug to relief OSA patients with residual EDS in order to improve their quality of life, with minimal side effects, no requirement to monitor ECGs, as well as having low risk of abuse potential and withdrawal symptoms.	Comment noted. The appraisal committee will consider the innovative nature of the technology.

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	British Thoracic Society	We would not expect the technology to make a significant and substantial impact and it might even discourage CPAP use	Comment noted. No action required.
Questions for consultation	British Thoracic Society	Pitsolisant costs more than the other current stimulants so duration of patent?	Comment noted. The cost-effectiveness of pitolisant hydrochloride will be considered in any future appraisal.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

None.