NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pitolisant hydrochloride for treating excessive daytime sleepiness caused by obstructive sleep apnoea [ID1065]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pitolisant hydrochloride for treating excessive daytime sleepiness caused by obstructive sleep apnoea [ID1065]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Bioprojet (Lincoln Medical)
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submission from:**
   a. Sleep Apnoea Trust Association (SATA)
4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews Ltd
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   a. Graham Hill, Patient Expert nominated by Sleep Apnoea Trust Association (SATA)
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9. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews Ltd

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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Document B

Company evidence submission

May 2020

File name	Version	Contains confidential information	Date
		Yes	

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Abbreviations

AQ-20R	Airways Questionnaire
AE	Adverse events
AHI	Apnoea-Hypopnea Index
BDI-13 items	Beck Depression Inventory 13 items
BMI	Body mass index
BSC	Best supportive care
CGI-C	Clinical Global Impressions of Change
CGI-S	Clinical Global Impressions of Severity
CEAC	Cost-effectiveness acceptability curves
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CHD	Coronary heart disease
CSR	Clinical study report
CV	Cardiovascular
DIC	Deviance information criterion
DSA	Deterministic sensitivity analysis
DVLA	Driver and Vehicle Licensing Agency
EDS	Excessive daytime sleepiness
EMA	European Medicines Agency
EQ-5D	EuroQoL quality of life questionnaire.
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep Questionnaire
HRQOL	Health related quality of life
HTA	Health technology appraisal
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison

ITT	Intention to treat
LOCF	Last Observation Carried Forward
LSEQ	Leeds Sleep Evaluation Questionnaire
MAD	Mandibular advancement device
MID	Minimally important difference
MMSE	Minimal Mental State Examination
MSLT	Multiple sleep latency test
MWT	Maintenance of Wakefulness Test
ODI	Oxygen desaturation index
OLE	Open label extension
OLS	Ordinary least squares
OSA	Obstructive sleep apnoea
OSAHS	Obstructive sleep apnoea/hypopnoea syndrome
OSLER	Oxford Sleep Resistance test
PGIC	Physicians Global Impression of Change
PGOE	Patient's Global Opinion of the Effect
PLM	Periodic Limb Movement Disorders
PLMAI	PLM arousal index
PP	Per protocol
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QOL	Quality of life
RCT	Randomised controlled trial
RDI	Respiratory Disturbance Index
RTA	Road traffic accident
SAQLI	Sleep Apnoea Quality of Life Index
SD	Standard deviation
SBP	Systolic blood pressure

TEAE	Treatment emergent adverse events
TMJ	Temporomandibular joint
TMT	Trail Making Test Parts A&B
WTP	Willingness to pay

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Pitolisant will be marketed as Ozawave®, for excessive daytime sleepiness (EDS) in patients with obstructive sleep apnoea (OSA)[1] and is currently marketed as Wakix®, for the treatment of narcolepsy with or without cataplexy in adults[2].

The submission covers the full marketing authorisation for pitolisant (Ozawave). Pitolisant will be indicated for the treatment of EDS in patients with OSA and treated by continuous positive airway pressure (CPAP) but still complaining of EDS, or in patients with OSA refusing/not tolerating CPAP[1].

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such CPAP	As per scope In line with the clinical study programme, we will consider two subgroups 1. Patients receiving CPAP with residual EDS (HAROSA I study)[3] 2. Patients refusing CPAP with EDS (HAROSA II study)[4]	Pitolisant was investigated in two patient populations in two separate studies: 1. Patients receiving CPAP who had residual EDS (HAROSA I study)[3] 2. Patients refusing CPAP with EDS (HAROSA II study)[4]
Intervention	Pitolisant with or without primary OSA therapy	As per scope	
Comparator(s)	Established clinical management without pitolisant	As per scope Established clinical management includes optimised CPAP and lifestyle measures (losing weight, stopping smoking and limiting alcohol consumption). Mandibular advancement devices (MAD) are a potential treatment option for OSA and can be used in patients with mild or moderate disease.	We have included MAD as a scenario analysis in our economic modelling of patients with EDS who refuse CPAP as some patients may be offered MAD in this situation, although only if their disease is mild or moderate.

Outcomes	• EDS • Fatigue • Length of life • Adverse effects (AE) of treatment • ealth-related quality of life (HRQOL)	As per scope We will also consider Physicians Global Impression of Change (PGIC) and Patient's Global Opinion of the Effect (PGOE). We will consider specific AE related to the cardiovascular (CV) system.	Physician and patient rating of treatment is helpful to understand how treatment impacts on the physician and patient. Length of life will be assessed by deaths during treatment. The HAROSA studies for pitolisant are over 1 year and therefore, longer term changes in mortality will not be apparent from the clinical study programme. Some treatments for EDS are associated with changes in CV risk factors, for example, modafinil which is no longer approved for EDS due to OSA. It is important to understand the CV risk profile of pitolisant, particularly as many people with EDS due to OSA have underlying CV risk factors and/or CV comorbidities.
Subgroups to be considered	• Mild, moderate and severe obstructive sleep apnoea • People who cannot have or have refused CPAP • People not continuing CPAP	OSA patients with EDS who cannot have CPAP, refuse CPAP or who are unable to continue with CPAP will be considered as one subgroup.	There is a lack of data to separate out patients according to severity of OSA. Pitolisant is likely to be used in people with moderate and severe OSA.

B.1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	**Pitolisant (Ozawave)**
Mechanism of action	Pitolisant is a potent wakefulness promoting agent. Levels of histamine and other wake-promoting neurotransmitters are increased in the brain, resulting in improved wakefulness[5]. Pitolisant is an orally active histamine H3-receptor antagonist/inverse agonist which, via its blockade of histamine auto-receptors, enhances the activity of brain histaminergic neurones. Pitolisant also modulates various neurotransmitter systems, increasing acetylcholine, noradrenaline, and dopamine release in the brain. It should be noted that there is no increase in dopamine release in the reward centre of the brain (striatal complex including nucleus accumbens) with pitolisant[5].
Marketing authorisation/CE mark status	Submission to European Medicines Agency (EMA) November 2019
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Pitolisant is indicated for the treatment of EDS in patients with OSA and treated by CPAP but still complaining of EDS, or in patients with OSA refusing/not tolerating CPAP[1] Pitolisant is already licensed for the treatment of narcolepsy with or without cataplexy in adults under the brand name Wakix[2] Pitolisant should be administered with caution in patients with • History of psychiatric disorders such as severe anxiety or severe depression with suicidal ideation risk • Renal impairment or moderate hepatic impairment (Child-Pugh B) • Acid-related gastric disorders or when co-administered with gastric irritants such as corticosteroids or NSAIDs • Severe obesity or severe anorexia • Severe epilepsy[1] Treatment should be carefully monitored in patients with • Cardiac disease co-medicated with other QT-prolonging medicinal products or known to increase the risk of repolarization disorders, or co-medicated with medicinal products that significantly increase pitolisant Cmax and AUC ratio • Severe renal or moderate hepatic impairment[1] Women of childbearing potential should 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 woman patient is using hormonal contraceptives[1]
Method of administration and dosage	<u>For EDS due to OSA</u>

	Pitolisant should be used at the lowest effective dose, depending on individual patient response and tolerance, according to an up-titration scheme, without exceeding the dose of 18 mg/day[a]: Week 1: initial dose of 4.5 mg (one 4.5 mg tablet) per day. Week 2: the dose may be increased to 9 mg (two 4.5 mg tablets) per day. Week 3: 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. At any time the dose can be decreased (down to 4.5 mg per day) or increased (up to 18 mg per day) according to physician assessment and the patient's response The total daily dose should be administered as a single oral dose in the morning during breakfast[1] <u>For narcolepsy</u> Pitolisant should be used at the lowest effective dose, depending on individual patient response and tolerance, according to an up-titration scheme, without exceeding the dose of 36 mg/day: 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 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 oral dose in the morning during breakfast[2]
Additional tests or investigations	The presence of EDS should be confirmed by the Epworth Sleepiness Scale (ESS), a simple questionnaire-based scale scored out of 24. Scores of 11-12 indicate mild EDS, 13-15 moderate EDS and 16-24 severe EDS. There is no need for CV monitoring e.g. ECG monitoring
List price and average cost of a course of treatment	[redacted]

Please see Appendix C for the Summary of Product Characteristics. The European Public Assessment Report is not yet available

[a] The dosage in the clinical studies for pitolisant were 5 mg and 20 mg. The 5 mg tablet contains 5 mg of pitoilsant hydrochloride which equates to 4.45 mg of pitolisant as the active substance, the 20 mg tablet contains 20 mg of pitoilsant hydrochloride which equates to 17.8 mg of pitolisant as the active substance. The doses for labelling consider the active substance and have been rounded up to 4.5 mg and 18 mg, respectively.

B.1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Overview

Pathophysiology and symptoms

OSA is the most common cause of EDS[6]. In people with OSA, the walls of the upper airways relax and narrow during sleep, resulting in interrupted breathing[b] which leads to intermittent hypoxia, arousal from sleep and fragmented sleep[6]. The interrupted, fragmented sleep in patients with OSA is poor in both quality and quantity, resulting in EDS[6].

EDS is characterised by persistent sleepiness, fatigue and lethargy during the day[7]. People with EDS have uncontrollable daytime sleepiness that interferes with their daily life. Patients may doze off during their usual daily activities, for example, whilst having a conversation, reading, watching television or driving. This can be extremely debilitating and has a significant impact on QOL[6,8].

Cognitive function is impaired in around two-thirds of people with EDS, resulting in problems with memory and concentration which impact on work performance and reduced participation in and enjoyment of everyday activities[6,8].

People with EDS may also be depressed; around one-half of people with severe EDS have co-existing depression and that depression correlates with poor QOL[9].

The British Lung Foundation asked people about their experience of EDS[10]:

"It felt like I was semi-comatose, living in a fog."

"I woke up feeling exhausted. I could not concentrate at work, I was depressed."

"I sometimes even dozed off at the wheel."

Quality of life

People with EDS and OSA have a reduced QOL, with scores of 40.4 ± 9.9 on the SF-12 physical scale and 41.9 ± 11.1 on SF-12 mental scale[11]. The SF-12 scale is a 100-point scale with lower numbers indicating poorer QOL. Mapping these SF-12 scores to EQ-5D[12] results in a QOL score of 0.753 (where 1 indicates optimum QOL and 0 death). The impact of EDS on QOL is similar to that seen in patients in the first year post-stroke or in patients with chronic renal or chronic lung disease[11-13].

Additional work using a respiratory-specific HRQOL scale (Airways Questionnaire [AQ]-20R) revealed that greater EDS is associated with poorer respiratory-specific HRQOL, over and above the effects of OSA, respiratory comorbidity and generic physical HRQOL[14].

Impact on work

People with EDS have reduced productivity at work, take more long-term sick leave and leave work due to ill health compared to people without EDS.

[b] Complete blockage of the airway for 10 seconds or more is termed apnoea and a partial blockage of the airway resulting in an airflow reduction of >50% for 10 seconds or more is termed hypopnoea

The 2008 National Sleep Foundation Sleep in America survey (telephone poll) found that OSA was linked to difficulty in concentration, problems with organisation, mistakes at work, mood changes (impatience, avoidance of interactions, boredom), decreased productivity and failure to finish assigned tasks, absenteeism and falling asleep at work. All of which were significantly more likely in people with OSA compared to people without a sleep disorder[15]. Focus groups with 42 people with EDS due to OSA quantified the burden: all of the participants felt that their EDS had impacted on their work, including difficulty staying awake (69%), difficulty completing detailed tasks (52%) and a decrease in productivity (36%). Of the participants, 12% had experienced disciplinary action, including termination of employment (7%). Most of the people in this sample were also using CPAP or MAD (70%)[16].

A Norwegian study found that people with EDS due to OSA were twice as likely to leave work due to ill health (adjusted odds ratio: 2.03) and more likely to be on long term sick leave (adjusted odds ratio: 1.36)[14].

Impact on accidents

EDS is associated with an increased risk of accidents (particularly road traffic accidents [RTA]), indeed, the impact of EDS on RTAs is similar to that of drink driving[17]. A meta-analysis of six studies revealed that the odds ratio of the risk of a collision in drivers with OSA was 2.52[18]. It has been estimated that 40,000 RTAs/year in the UK are due to untreated OSA, given that these accidents result in injury or even fatality, the impact is considerable[10].

This increased risk of RTA is reflected in advice from the Driver and Vehicle Licensing Agency (DVLA) that anyone with excessive sleepiness due to OSA must not drive and must notify the DVLA. In order for patients to regain their driving licence they must have medical confirmation of control of their condition, improved sleep and treatment adherence[19]. For professional drivers (goods or passenger carrying vehicles) driving must cease until satisfactory control of symptoms has been achieved, with ongoing compliance with treatment, confirmed by consultant or specialist opinion. Regular, normally annual, driving licence review is required.

Mortality and morbidity

In addition to the impact of EDS on life and work, EDS also has an impact on morbidity and mortality. People with EDS are at increased risk of hypertension, coronary heart disease (CHD), arrhythmia, heart failure, and stroke[20-22], with a greater risk of CV disease in women than in men. This has an obvious impact on mortality, with patients with severe EDS at the highest risk[21,23].

Epidemiology

The British Lung Foundation estimate that there are 1.5 million people in the UK with OSA, of whom 45% (675,000 people) have moderate and severe OSA. Up to 85% of these patients are undiagnosed and therefore untreated[10].

OSA is common in middle-aged and older people. Estimates of prevalence vary according to definition and diagnostic techniques but around 17% of men and 9% of women aged 50-70 years have clinically significant moderate/severe OSA[24].

The prevalence of OSA increases steeply with increased body mass index (BMI)[24,25] and projections suggest that increased prevalence of obesity will contribute to higher overall rates of OSA in the future[26].

Data from the UK Sleep Survey, which surveyed people aged 18-100 years, found self-reported rates of sleep apnoea (defined as stopping breathing in the night) of 9% in men and 6% in women[25]. However, many people are unaware that they have OSA and OSA is undiagnosed in around 80% of patients[26]. A study which identified OSA in patients admitted to a UK hospital found a rate of observed apnoeas of 65%[27].

The co-existence of moderate/severe OSA and EDS is referred to as obstructive sleep apnoea/hypopnoea syndrome (OSAHS). It is difficult to make precise estimates of prevalence of OSAHS due to differences in diagnostic techniques[6], however, around 7% of men and 3% of women aged 50-70 years have co-existing EDS and moderate/severe OSA[24].

True rates of OSAHS are likely to be higher and are anticipated to increase over the next decades as rates of OSA rise.

1.3.2 Clinical pathway

Treatment of OSA, the most common underlying cause of EDS, has the potential to improve daytime wakefulness and reduce EDS[28].

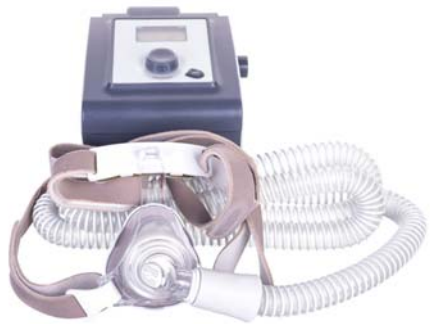
Technology appraisal guidance (TA139) published by NICE for the treatment of OSAHS in 2008 state that lifestyle measures (weight loss, smoking cessation, limiting alcohol consumption) are first-line treatment options for OSAHS[28].

NICE (TA 139) recommend CPAP for people with moderate or severe symptomatic OSAHS or for people with mild OSAHS with symptoms that impact on QOL and in whom lifestyle measures or other relevant treatment options have been unsuccessful or are considered inappropriate[28].

CPAP is the gold standard treatment for EDS due to OSA. CPAP involves wearing a mask attached to a CPAP machine during sleep. Air is blown into the airways, increasing air pressure in the throat and offsetting the negative suction pressure during intake of breath that leads to upper airway collapse in people with OSA. This prevents the airway from narrowing and keeps the upper airway open during sleep[29]. In order to be effective, the mask must be worn for the duration of sleep, which some patients may find uncomfortable or claustrophobic.

A Health Technology Appraisal (HTA) carried out by the Canadian Agency for Drugs and Technologies in Health in 2014 found that CPAP was generally more effective than lifestyle measures or MAD[30].

Figure 1: CPAP machine.



CPAP is effective in reducing EDS in many people, however, up to 55% will have residual EDS despite CPAP[31]. Co-morbidities such as narcolepsy, restless legs syndrome and depression increase the rate of EDS in people with OSA[32]. When confounding factors such as poor adherence and co-morbidities are taken into account, 6-9% of people using CPAP have residual EDS[32,33].

Residual EDS has also been reported in patients who are adherent with CPAP, suggesting that other mechanisms may be at play. It has been suggested that the nocturnal hypoxia seen in patients with OSA may lead to permanent damage to the sleep-wake axis in the brain[34].

The standard of care for residual EDS in OSA is optimisation of CPAP, which includes patient education, sleep hygiene, appropriate CPAP mask selection and use, and use of humidification, as well as assessment of whether residual CPAP is due to other co-morbidities (obesity, depression, diabetes, hypothyroidism) or other sleep disorders (behaviourally induced insufficient sleep, restless legs syndrome/periodic limb movement in sleep, or narcolepsy) and management of co-morbidities if present[35].

At present, there are no licensed treatment options to reduce EDS in patients adherent to CPAP with residual EDS.

Around one-third of patients are non-adherent with CPAP or refuse to use it because of discomfort, inconvenience or claustrophobia[36]. The only alternative treatment in patients unable to use CPAP is a MAD, although their use is limited.

A MAD is a gum shield-like device that holds the airways open during sleep. TA 139 states that the efficacy of MADs has been established in clinical trials, but these devices are traditionally viewed as a treatment option only for mild and moderate OSAHS[28]. MADs are an option for people with mild/moderate OSAHS unable to use CPAP or for those who snore or have mild OSAHS with normal daytime alertness[37]. A number of different MADs are available, most of which are custom made for the patient. Before a patient is fitted for a MAD, they must undergo a complete dental assessment; some patients may be unable to use a MAD due to dental or gum disease or because they wear dentures. MAD are associated with a number of side-effects including dry mouth, excessive salivation, pain, gagging or temporomandibular joint (TMJ) syndrome[38].

Surgical and interventional treatments for OSAHS have also been considered by NICE, but are not routinely recommended.

- Surgery involves resection of the uvula and redundant retrolingual soft tissue. TA 139 states that there is a lack of evidence of clinical effectiveness and that surgery is not routinely used in clinical practice[28].

- NICE IPG241 does not recommend soft-palate implants for OSAHS and states that they should not be used due to a lack of evidence for efficacy[39].

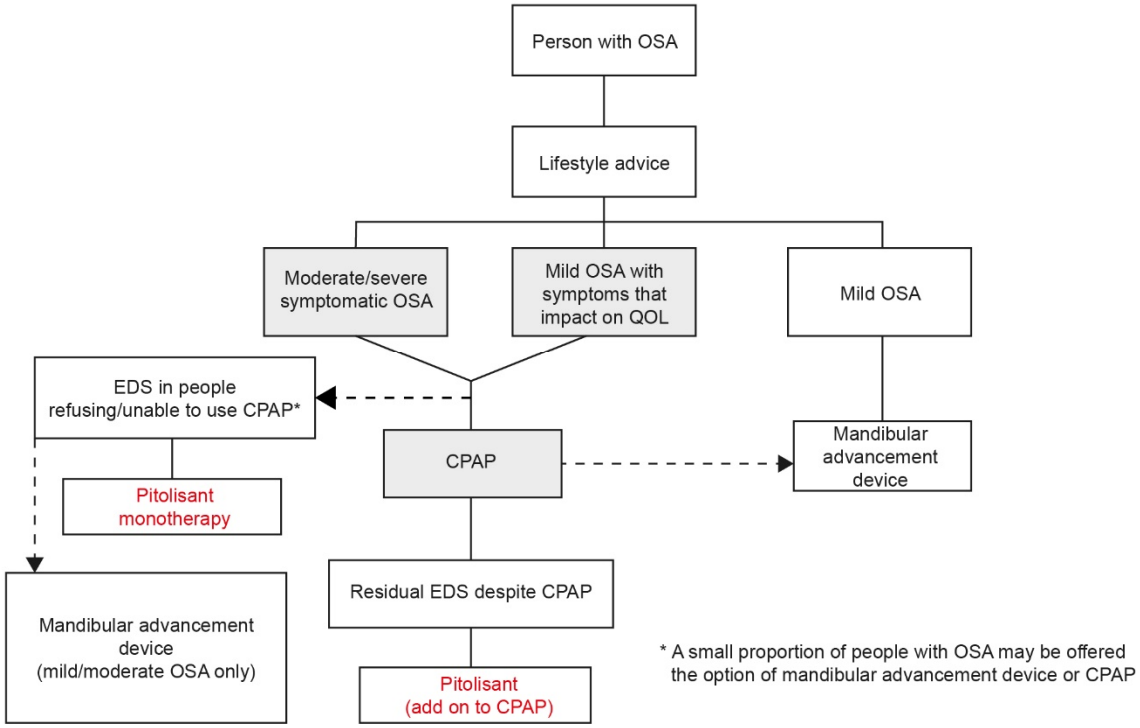
- NICE IPG241 does not recommend hypoglossal nerve stimulation for moderate to severe OSAHS due to a lack of evidence for efficacy and safety. Hypoglossal nerve stimulation should only be used with special arrangements for clinical governance, consent and audit[40].

At present, there are no licensed wakefulness promoting agents for EDS[41]. Modafinil was licensed for EDS due to OSA, however, in 2011 the European Medicines Agency (EMA)[42] concluded that the benefit-risk balance for modafinil was not positive under normal conditions of use for EDS associated with OSA and removed this indication from the

marketing authorisation. The EMA identified risks for the development of skin and hypersensitivity reactions, as well as neuropsychiatric reactions and considered that the CV risk profile should be further characterised. Existing data on CV risk means that there is a specific contraindication in patients with uncontrolled moderate to severe hypertension and in patients with cardiac arrhythmia in the Summary of Product Characteristics for modafinil.

Pitolisant is a new treatment option for people with EDS caused by OSA who have tried CPAP and have residual EDS on CPAP or are unable to tolerate or refuse CPAP.

Figure 2: Clinical pathway of care for treating EDS caused by OSA[28,37]



Grey shading is taken from NICE TA139 (Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome)

B.1.4 Equality considerations

None

B. 2. Clinical effectiveness

B.2.1 Identification and selection of relevant studies

The clinical evidence included in this submission was identified from a rigorous systematic review of multiple data sources to identify all relevant publications for the efficacy, safety and development of economic models for the use of pitolisant for the treatment of EDS in adults with OSA. Full details of the methodology followed for this review are reported in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

Two randomised controlled trials (RCT) provide evidence for pitolisant, both of which were followed by open label extensions (OLE).

HAROSA I (P09-08) was in patients with OSA treated with CPAP, but with residual EDS[3]. HAROSA I has been submitted for publication, but is not yet published, therefore, we have used the clinical study report (CSR) to populate this section[3].

HAROSA II (P09-09) was in patients with OSA and EDS who refused CPAP[43]. HAROSA II has been published as Dauvilliers Y, Verbraecken J, Partinen M, et al. Pitolisant for Daytime Sleepiness in Obstructive Sleep Apnea Patients Refusing CPAP: A Randomized Trial. Am J Resp Critical Care Med 2020: 10.1164/rccm.201907-1284OC[4] and we have used both the published paper and the CSR to populate this section.

Both studies were prospective, multicentre, randomised, double-blind, placebo-controlled trials carried out in patients aged over 18 years who suffered from EDS due to OSA. The populations of the two trials were similar, except in the HAROSA I trial, patients must have had previous nasal CPAP (nCPAP) therapy for at least 3 months[3], and still be experiencing EDS, whereas patients recruited into the HAROSA II study had refused nCPAP therapy and were experiencing EDS[4,43] . The intervention in both studies was pitolisant at different dosing regimens (5 mg, 10 mg or 20 mg per day) compared to matched placebo.

Both RCTs report the change in ESS between baseline and end of study treatment as the primary end-point. Both also report the following outcomes as secondary end-points: Pichot Fatigue scale, Clinical Global Impressions of Severity (CGI-S) or Change (CGI-C) and the patient's global opinion on the effect of investigational drugs, Epworth response, OSleR test, sleep diary, Leeds Sleep Evaluation Questionnaire (LSEQ), trail-making test (TMT) and EuroQoL quality of life questionnaire (EQ-5D).

Table 3: Clinical effectiveness evidence

Study	HAROSA I[3]					HAROSA II[43]				
Study design	Prospective, multicentre, randomised, double-blind placebo-controlled study followed by open-label extension.									
Population	Patients aged at least 18 years with OSA treated with CPAP, with residual EDS Defined as having moderate or severe OSA, prior CPAP therapy for a minimum period of 3 months and experiencing EDS ≥12.					Patients aged at least 18 years with OSA and EDS refusing CPAP Defined as having moderate or severe OSA, refusing CPAP and experiencing EDS ≥12.				
Intervention(s)	Pitolisant (starting dose 5 mg, titrated up to 20 mg maximum dose as needed)									
Comparator(s)	Placebo									
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No		No			No	
Rationale for use/non-use in the model	Provides placebo-controlled evidence for pitolisant in patients with residual EDS despite CPAP on a background of current standard of care (optimised CPAP and lifestyle changes)					Provides placebo-controlled evidence for pitolisant in patients refusing CPAP on a background of current standard of care (lifestyle changes)				
Reported outcomes specified in the decision problem	**Change in ESS from baseline**									
All other reported outcomes	Pichot Fatigue scale. Clinical Global Impressions of Severity and Change (CGI-S and CGI-C). Patient's global opinion on the effect of investigational drugs. Epworth response. OSleR (Oxford Sleep Resistance) test. Sleep diary (sleepiness and sleep episodes). Mean wakefulness duration Mean daily alertness duration Mean daily number of sleep/sleepiness episodes Mean daily duration of sleep/sleepiness episodes decreased Leeds Sleep Evaluation Questionnaire (LSEQ). Trail Making Test (TMT) Parts A&B. EuroQoL (EQ-5D) QOL questionnaire. Amphetamine-like withdrawal symptoms									

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Trial methodology

A comparative summary of trial methodology for HAROSA I and HAROSA II are shown in Table 4. Patients in HAROSA I had OSA with residual EDS, despite CPAP whilst those in HAROSA II had OSA and EDS and had refused treatment with CPAP.

Patients in both studies had OSA with moderate to severe EDS. People were enrolled in the studies if they had normal mental capacity, no mental health or CV issues and were not severely obese. Patients were encouraged to maintain their usual behaviours around sleep and wakefulness.

The HAROSA I study[3] assessed 298 patients with OSA, with an ESS score ≥12, who had undergone nCPAP therapy for at least 3 months for ≥4 hours per day but still reported EDS. Of these, 244 were eligible for entry into the double-blind phase of the study and were the intention-to-treat (ITT) group. Patients were randomised on a balanced 3:1 basis to pitolisant or placebo using an electronic web randomisation server: 183 were randomised to pitolisant and the remaining 61 to the placebo group.

The HAROSA II study (2009-017251-94)[4,43] assessed 298 patients with OSA, with an ESS score ≥12, who refused nCPAP therapy and reported EDS. Of these, 268 were eligible for entry into the double-blind phase of the study and comprised the ITT group. Patients were randomised on a balanced 3:1 basis to pitolisant or placebo using an electronic web randomisation server: 201 patients were randomised to the pitolisant group and 67 to the placebo group.

All patients attended a screening visit (V0). Phone contact was made one week after the screening visit (T1). All patients were instructed to stop their current treatments at V1 and a baseline visit (V2) was used for randomisation at the end of this wash-out phase. After randomisation, patients were titrated up to the target dose over 3 weeks (V2 to V4) before starting a 9-week phase (V4-V6). Patients were instructed to take their dose of pitolisant or matched placebo once a day, in the morning before breakfast.

If patients did not want to participate in the OLE, an end-of-treatment visit was made (V7). If patients continued to the OLE, the treatment drug was titrated over 4 weeks to recommended dose (V6-V8) followed by a 36-week treatment phase. Two further visits (V9 and V10) were made after 3 months to check the daily dose. V11 was the evaluation visit and V12 was the end of the trial.

The primary outcome was the change in ESS score from baseline (V2) to the end of the RCT period (V6).

Table 4: Comparative summary of trial methodology

Trial number (acronym)	HAROSA I[3]	HAROSA II[43]
Location	38 centres in 9 European countries: Belgium (6), Bulgaria (6), Denmark (2), Finland (3), France (8), Germany (3), Macedonia (2), Spain (6), Sweden (2)	29 centres in 10 European countries: Belgium (2), Bulgaria (6), Denmark (1), Finland (3), France (5), Germany (1), Macedonia (3), Serbia (3), Spain (3), Sweden (2)
Trial design	Patients who fulfilled selection criteria were randomised to either pitolisant or placebo. The study was in two parts, a 12-week double-blind part starting with an escalating dose period followed by treatment with the selected dose. After 12 weeks, patients had the option of entering a 40-week double-blind period. Randomisation was centralised and performed via an electronic Web Randomisation Server.	
Inclusion criteria	Patients using CPAP therapy for a minimum period of 3 months and still complaining of EDS Polysomnography performed between visit 1 and visit 2 or during the last 12 months with • Apnoea-Hypopnea Index (AHI) ≤ 10. • Periodic Limb Movement Disorders (PLM) as defined by a PLM arousal index (PLMAI) ≤ 10 per hour	Patients refusing to be treated by nCPAP therapy, and still complaining of EDS Polysomnography performed between visit 1 and visit 2 or during the last 12 months with • AHI ≥15. • PLM as defined by PLMAI ≤ 10 per hour
Inclusion criteria (common to both studies)	Male and/or female outpatients of at least 18 years of age. Minimal Mental State Examination (MMSE) ≥ 28. Beck Depression Inventory 13 items (BDI-13 items): score < 16 and item G=0 ESS ≥ 12. BMI ≤ 40 kg/m². Female patients of child-bearing potential using a medically accepted method of birth control Patients had to be willing not to operate a car (if sleepy at the wheel) or heavy machinery Maintenance of behaviours which could affect diurnal sleepiness (e.g. caffeine consumption, nocturnal sleep duration).	
Exclusion criteria (all common to both studies)	Insomnia Co-existing narcolepsy Sleep debt not due to OSA (according to physician's judgment) Non-respiratory sleep fragmentation (restless legs syndrome) Shift workers – Professional drivers Refusal from the patient to stop any current therapy for EDS, or predictable risks for the patient to stop the therapy Psychiatric illness Acute or chronic disease preventing the improvement assessment [for example, severe Chronic Obstructive Pulmonary disease (COPD)] Current or recent (within 1 year) history of drugs, alcohol, narcotic, or other substance abuse or dependence	

	Any significant serious abnormality of the CV system, e.g. recent myocardial infarction, angina, hypertension or dysrhythmias (within the previous 6 months), Electrocardiogram Bazett's corrected QT interval longer than 450 milliseconds, history of left ventricular hypertrophy or mitral valve prolapse Severe co-morbid medical, or biological condition that could jeopardize the study participation, at the discretion of the Investigator (particularly, in the CV system and instable diabetes) Positive serology tests (Hepatitis, Hepatitis B surface Antigen and Human Immunodeficiency Virus) Pregnant or breast-feeding women Women with child-bearing potential and no efficient birth-control method Patient with a dominant arm deficiency impeding the achievement of the tests Patient using prohibited treatments Congenital galactose poisoning, glucose and galactose malabsorption, deficit in lactase (lactose in placebo) Patient participating in another study or being in a follow-up period in another study	
Settings and locations where the data were collected	Patients were outpatients during the study period Data was collected at up to 12 study visits which occurred in hospital: visit 1 selection visit prior to washout visit 2 inclusion and randomisation visit (week 0) visit 3 dose adjustment visit (week 2) visit 4 dose confirmation visit (week 3) visit 5 assessment of efficacy (week 7) visit 6 end of the double-blind period (week 12) visit 7 dose adjustment (week 14) visit 8 dose confirmation (week 16) visit 9 assessment (week 28) visit 10 assessment (week 41) visit 11 end of double-blind period (week 52) visit 12 end of study (week 53)	
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	**Double-blind period** 298 patients were screened for inclusion 244 were eligible 183 were randomised to pitolisant 61 were randomised to placebo **Stable dose during the double-blind period** Pitolisant: 20 mg=70.3%, 10 mg=21.1% and 5 mg =8.6% Placebo: 20 mg=81.4%, 10 mg=10.2% and 5 mg =8.5% **Open-label period** 199 patients participated in the double-blind period (151 from the pitolisant group and 48 from the placebo group)	**Double-blind period** 298 patients were screened for inclusion 268 were eligible 201 were randomised to pitolisant 67 were randomised to placebo **Stable dose during the double-blind period** Pitolisant: 20 mg=75.4%, 10 mg=15.7% and 5 mg =8.9% Placebo: 20 mg=81.5%, 10 mg=10.8% and 5 mg =7.7% **Open-label period** 236 patients participated in the double-blind period (181 from the pitolisant group and 55 from the placebo group)

	Stable dose during the open-label period Pitolisant to pitolisant: 20 mg=77.4%, 10 mg=17.3% and 5 mg =5.3% Placebo to pitolisant: 20 mg=78.6%, 10 mg=19.0% and 5 mg =2.4%	**Stable dose during the open-label period** Pitolisant to pitolisant: 20 mg=76.3%, 10 mg=12.2% and 5 mg =11.5% Placebo to pitolisant: 20 mg=78.3%, 10 mg=15.2% and 5 mg =6.5%
Mode of administration and titration scheme	Patients were instructed to take the study treatment with a glass of water when they woke up, every morning before breakfast Pitolisant/placebo dose starting at 5 mg from day 1 to day 7, 10 mg from day 8 to day 14 and 20 mg from day 15, dose was maintained or reduced at day 21 according to tolerability and dose stable thereafter	
Permitted and disallowed concomitant medication	**Disallowed medication** All drugs indicated for somnolence All hypnotic drugs Tricyclic antidepressants such as clomipramine, imipramine, desmethylimipramine and protriptyline displaying histamine H1 receptor antagonist activity that could affect the activity of pitolisant Centrally-acting antihypertensive drugs e.g. clonidine Any formulation containing codeine Psychostimulants (Amphetamine and amphetamine-like CNS stimulants, methylphenidate, modafinil or other) H1 antihistamine products Drugs containing dextropropoxyphene Drugs containing sodium oxybate Surgical intervention for OSA were also prohibited treatments	
Primary outcomes (including scoring methods and timings of assessments)	Primary outcome was change in ESS between baseline and end of treatment ESS is a simple questionnaire which asks the participant about eight common situations and the likeliness of sleep/dozing whilst in the situation e.g. sitting and reading, watching television, sitting in a public place, as a passenger in a car, lying down to rest, talking to someone, sitting quietly after lunch and whilst driving but stopped in traffic. Each situation is scored from 0 would never doze to 3 high chance of dozing. The overall ESS score ranges from 0 (no daytime sleepiness) to a maximum of 24 (severe daytime sleepiness) A score of 0-10 is normal, 11-12 mild EDS, 13-15 moderate and 16-24 severe[6] The minimal important difference (MID) for the ESS is 2 points in patients with OSA and EDS[44] ESS was measured at all study visits except visit 7 (dose adjustment at the start of the double-blind period)	
Other outcomes used in the economic model/specified in the scope	Fatigue, AE and QOL are included in the scope and will be reported	
Pre-planned subgroups	AE were analysed by sex and age group	

2.3.2 Baseline characteristics

Baseline characteristics are shown below in Table 5.

Patients in HAROSA I were middle aged, obese and predominantly male, with most people in full time employment. Patients had had a diagnosis of OSA for around 4 years and had an ESS indicating moderate EDS. Just over one-half of patients had pre-existing CV disease (138/244, 56%). Patients were well matched in both groups, except for professional activity, since more patients in the placebo arm were in employment than in the pitolisant arm.

Patients in HAROSA II were also middle aged, obese and predominantly male, with most people in full time employment. Patients had had a diagnosis of OSA for around 1 year and had an ESS indicating moderate to severe EDS. Just over one-half of patients had pre-existing CV disease (145/268, 54%). Patients were well matched in both groups.

Table 5: Baseline characteristics: double-blind period

	HAROSA I[3]		**HAROSA II[43]**	
	Pitolisant (n=183)	Placebo (n=61)	Pitolisant (n=201)	Placebo (n=67)
Age (years) **Mean (standard deviation),**	53.8 (10.5)	51.0 (10.6)	51.9 (10.6)	52.1 (11.0)
Gender **Male, n (%)** **Female, n (%)**	149 (81.4%) 34 (18.6%)	53 (86.9%) 8 (13.1%)	151 (75.1%) 50 (24.9%)	51 (76.1%) 16 (23.9%)
BMI **Mean (SD)**	32.66 (5.22)	32.17 (4.28)	32.8 (4.6)	33.0 (4.3)
Professional activity **Yes, n (%)** **No, n (%)**	117 (63.9%) 66 (36.1%)	50 (82.0%) 11 (18.0%)	139 (69.2%) 62 (30.8%)	49 (73.1%) 18 (26.9%)
Days of work per week **Mean (SD)**	5.1 (0.5)	5.0 (0.6)	5.0 (0.5)	5.1 (0.2)
Medical history **Any significant** **CV**	152 (83.1%) 111 (60.7%)	46 (75.4%) 27 (44.3%)	142 (70.6%) 110 (54.7%)	47 (70.1%) 35 (52.2%)
Time since OSA diagnosis (months) **Mean (SD)**	44.84 (44.07)	48.99 (57.08)	12.1 (25.0)	11.5 (23.2)
ESS **Mean (SD)**	14.9 (2.7)	14.6 (2.8)	15.7 (3.1)	15.7 (3.6)
Baseline Pichot Fatigue Scale score **Mean (SD)**	13.2 (7.2)	11.4 (7.2)	13 (6.5)	11.1 (5.9)

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

HAROSA I and HAROSA II used identical statistical analysis methods for the primary analysis, as detailed in Table 6. The study groups in HAROSA I and HAROSA II were determined by the treatment received, with no additional planned subgroup analyses.

Efficacy analysis were also carried out on the per protocol (PP) population, which was defined as all patients in the intention to treat (ITT) population without protocol violations or premature discontinuation of the double-blind period.

Table 6: Statistical analysis for the HAROSA studies[3,43]

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
The primary efficacy end-point, change in ESS score between beginning of treatment (visit 2) and end of the double-blind period (Last Observation Carried Forward [LOCF])	Analysis was carried out on the ITT population, which was defined as all randomised patients ANCOVA methodology was used to perform statistical analysis and all statistical tests were performed two-sided, at the 5% level of significance The final LOCF ESS score was primarily analysed using an ANCOVA model adjusting for ESS and BMI at visit 2 (randomisation visit) and study site as random effect	The sample size was calculated after considering results from exploratory studies on pitolisant, which provided an estimate of the ESS residual variability to standard deviation (SD) of 6. The MID was fixed to ESS = 3, corresponding to an effect size of 0.5. The correlation between final and baseline ESS was conservatively estimated to r = 0.4 By assuming ANCOVA at 0.95 confidence level as the main confirmatory test, a difference of at least Delta = 3 should have been detected with a power of 90% in using at least 60 patients in the placebo group and 180 patients in the pitolisant treatment group	During the double-blind period missing data for the primary efficacy variable and for response were allocated following the LOCF, defined as the last available assessment at V2, V3, and V4.

The figures in Appendix D illustrate patient flow through the studies for both the double-blind and open label periods.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality of the trials was assessed and recorded using the Cochrane Risk of Bias tool-2[c], as shown in Table 7 below. Both trials were considered to be high quality, with low risk of bias. The full quality assessment is reported in Appendix D1.3.

[c] Available from https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

Table 7: Summary of quality assessment of included pitolisant trials

Trial acronym	HAROSA I[3]	HAROSA II[4,43]
Overall risk of bias	Low	Low

2.5.1 Describe the methods used for assessing risk of bias and generalisability of individual trials (including whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

We used the *Systematic reviews: CRD's guidance for undertaking reviews in health care* published by the University of York Centre for Reviews and Dissemination to assess risk of bias at the study level.

HAROSA I and HAROSA II both had a low risk of bias, as shown in Table 8.

Table 8: Quality assessment results for the HAROSA studies

Trial acronym	HAROSA I[3]	HAROSA II[4,43]
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)		

2.5.2 Consider how closely the trials reflects routine clinical practice in England.

The trials are in patients with EDS, either residual EDS whilst using CPAP or EDS in patients refusing CPAP.

In the UK, clinicians work hard to optimize CPAP treatment and encourage patients to adhere to treatment[35]. Newer CPAP machines include technology so that patients can be remotely monitored by the clinic[45] and this has improved adherence to CPAP[46,47]. However, a proportion of patients either have residual EDS whilst on CPAP or refuse treatment with CPAP as per the HAROSA trial populations.

At present, pharmaceutical treatment options for these patients are limited to wakefulness promoting agents (modafinil, dexamphetamine, methylphenidate, sodium oxybate) which are not licensed for use in the UK for OSAHS and are not recommended for use[41,42]. Clinical opinion suggests that dexamphetamine, methylphenidate, sodium oxybate are never used in the UK and that modafinil is rarely used, due to concerns over AE[35].

MADs are an alternative option for people with mild/moderate OSAHS refusing to use CPAP[37]. MADs are less effective than CPAP[30] and their use is limited in clinical practice.

The HAROSA I and II studies consider pitolisant versus placebo which reflects routine UK practice, since other wakefulness promoting agents or MADs are not used in routine clinical practice.

The demographics of the patient population in HAROSA I and II is very similar to that seen in UK clinical practice: predominantly middle aged, obese men, most of whom are still working[35].

B.2.6 Clinical effectiveness results of the relevant trials

2.6.1 Daytime sleepiness

The ESS is the standard measure of daytime sleepiness. It is measured using a simple questionnaire, scored from 0, indicating no daytime sleepiness, to a maximum of 24. A score over 10 indicates excessive daytime sleepiness, over 12 moderate daytime sleepiness and over 15 severe daytime sleepiness[6].

Pitolisant significantly reduced daytime sleepiness with an ESS decrease of -5.52 in patients receiving CPAP (HAROSA I) and -6.30 in patients refusing CPAP (HAROSA II). There was a significant placebo-controlled treatment effect on ESS, adjusted for ESS and BMI at baseline, of -2.6 in HAROSA I and -2.8 in HAROSA II, p<0.001 for both studies, see Table 9 for details.

The MID for the ESS is 2 points in patients with OSA and EDS[44], indicating that the difference is both clinically and statistically significant.

Table 9: Reduction in ESS, mean (SD), during the 12-week double-blind period (ITT population)[3,43]

	Baseline	**12 weeks (LOCF)**	**Baseline**	**12 weeks (LOCF)**	**Difference**
HAROSA I	Pitolisant (n=183)		Placebo (n=61)		
	14.9 (2.7)	9.42 (4.66)	14.6 (2.8)	11.87 (5.70)	-5.52 (4.41) vs -2.75 (5.90) Mean difference: 2.77 p<0.001 **Treatment effect of -2.6 (95% CI: [-3.9; -1.4]) (p<0.001)**
HAROSA II	Pitolisant (n=201)		Placebo (n=67)		
	15.7 (3.1)	9.4 (4.6)	15.7 (3.6)	12.1 (5.8)	-6.3 (4.5) vs -3.6 (5.5) Mean difference: 2.7 p<0.001 **Treatment effect of -2.8 (95% CI: [-4.0;-1,5]) (p<0.001)**

Pitolisant works within 5 weeks to increase wakefulness and reduce daytime sleepiness, by week 5 of treatment mean ESS was in the normal range (≤ 10), see Figure 3 for HAROSA I

and Figure 4 for HAROSA II. Mean ESS was maintained in the normal range for the duration of the double-blind period.

Figure 3: HAROSA I – ESS mean score at each visit (±SE) in the 12-week double-blind period, n=244 (ITT population)[3]

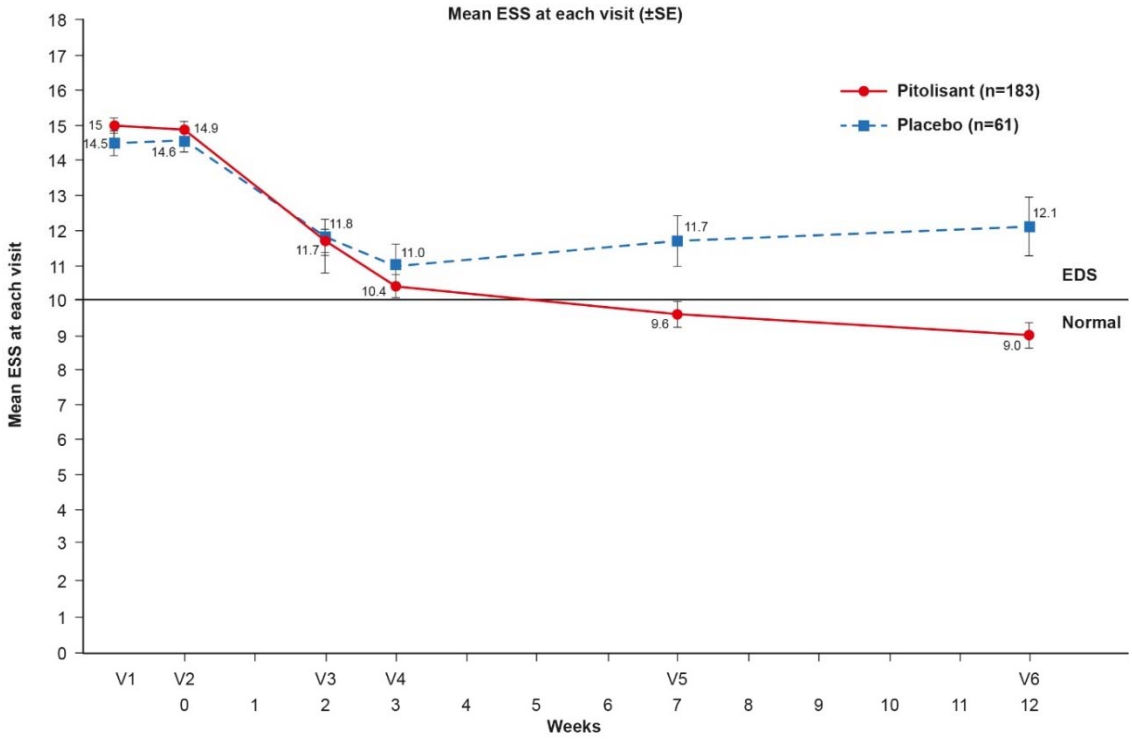
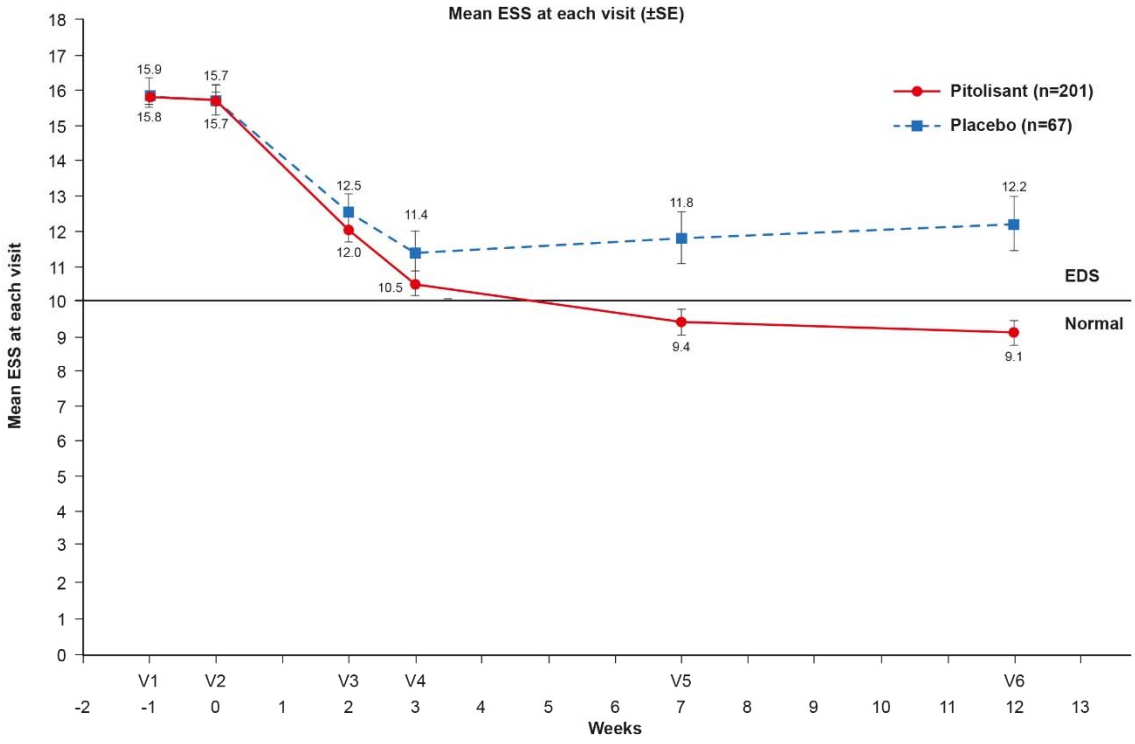


Figure 4: HAROSA II – ESS mean score (±SE) at each visit in the 12-week double-blind period, n=268 (ITT population)[43]



Patients had the option to continue in the open-label period for 40 weeks, during which all patients received pitolisant. In HAROSA I, 151 (83%) patients in the pitolisant arm and 48 (79%) of patients in the placebo arm chose to continue or start treatment with pitolisant. In HAROSA II, figures were 181 (90.5%) and 55 (82%) respectively.

Wakefulness continued to improve over the long-term, with further benefit during the open-label period of the study. By the end of the 52-week study period, those patients who had received pitolisant for the duration of the study had ESS scores well within the normal range (8.1 in patients receiving CPAP and 7.7 in patients refusing CPAP). Figure 5 and Figure 6 illustrate that wakefulness is maintained over the long-term with pitolisant.

Table 10: Reduction in ESS, mean (SD), during the 40-week open-label period (ITT population)[3,43]

	Entry into open-label	40 weeks (LOCF)	Difference	Entry into open-label	40 weeks (LOCF)	Difference
HAROSA I	Pitolisant then pitolisant (n=151)			Placebo then pitolisant (n=48)		
	9.4 (4.8)	8.1 (4.7)	-1.21 (3.12)	12.0 (6.0)	7.9 (5.1)	-4.07 (5.29)
HAROSA II	Pitolisant then pitolisant (n=181)			Placebo then pitolisant (n=55)		
	9.3 (4.6)	7.7 (4.5)	-1.6 (3.4)	12.2 (5.6)	7.0 (4.0)	-5.2 (5.4)

Figure 5: HAROSA I – ESS mean score (±SE) during the overall study period (open-label ITT population), n=199[3]

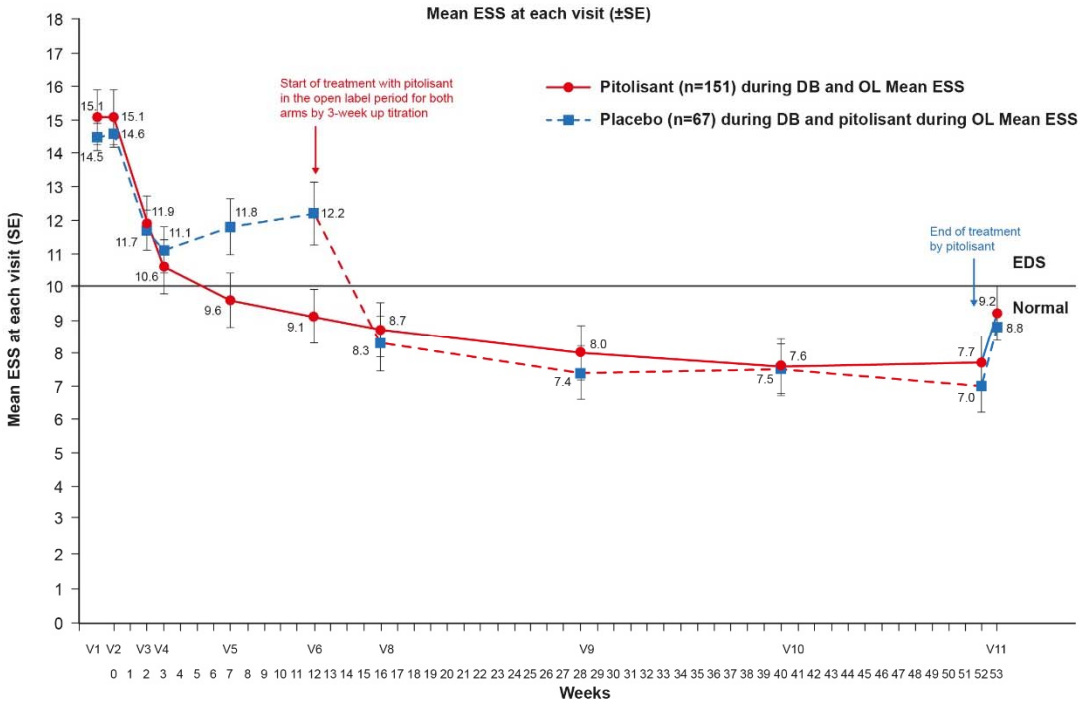
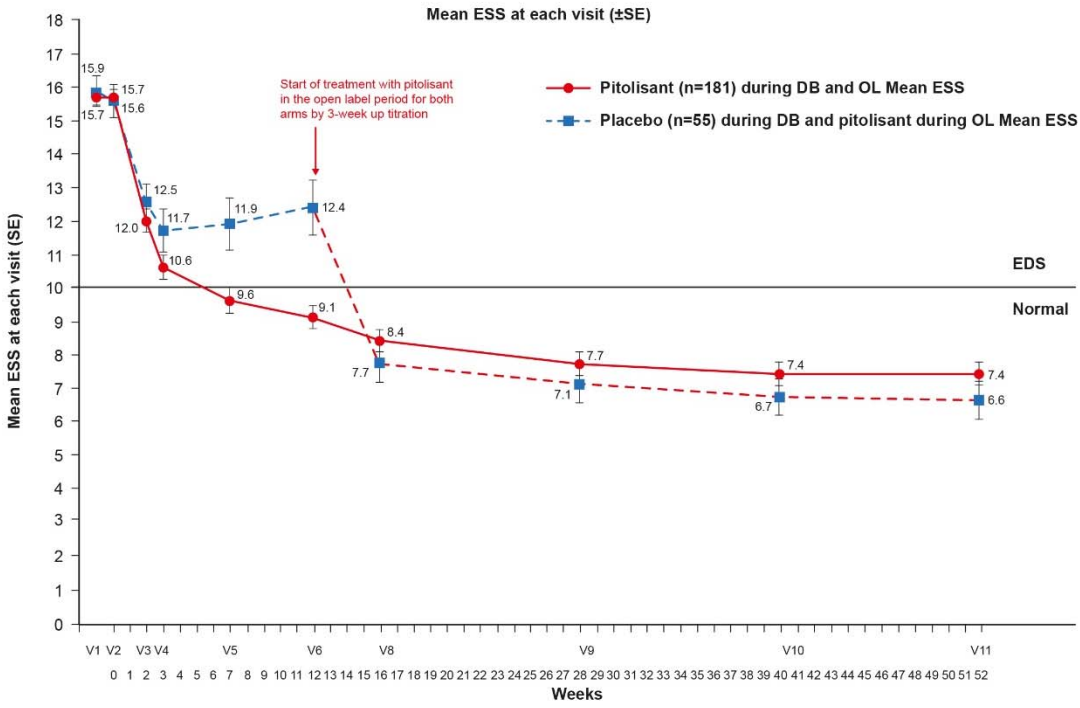


Figure 6: HAROSA I – ESS mean score (±SE) during the overall study period (open-label ITT population), n=236[43]



2.6.2 Fatigue

The reduction in fatigue is shown in Table 11 (double-blind period) and Table 12 (open-label period).

In HAROSA I, mean score on the Pichot fatigue scale decreased in both groups, although the difference was not significant (p=0.707). By the end of the open-label period; Pichot fatigue scale had fallen further still to 7.4 in patients receiving pitolisant then pitolisant and 7.0 in those receiving placebo then pitolisant.

In HAROSA II, mean score on the Pichot fatigue scale decreased in both groups, there was a significant improvement in fatigue with pitolisant by the end of the 12-week double-blind period, p=0.005. By the end of the open-label period; Pichot fatigue scale had fallen further still to 7.6 in patients receiving pitolisant then pitolisant and 7.4 in those receiving placebo then pitolisant.

Table 11: Reduction in Pichot Fatigue Score, mean (SD), during the 12-week double-blind period (ITT population)[3,43]

	Baseline	12 weeks (LOCF)	Baseline	12 weeks (LOCF)	Difference
HAROSA I	Pitolisant (n=183)		Placebo (n=61)		
	13.2 (7.2)	9.4 (6.9)	11.4 (7.2)	8.6 (6)	-3.8 (5.6) vs -2.9 (5.9) **Treatment difference 0.9, NS**
HAROSA II	Pitolisant (n=201)		Placebo (n=67)		
	13 (6.5)	9.2 (6.6)	11.1 (5.9)	10.5 (6.1)	-3.6 (5.6) vs -1 (6.3) **Treatment difference 2.6, p=0.005**

Table 12: Reduction in Pichot Fatigue Score, mean (SD), during the 40-week open-label period (ITT population)[3,43]

	Entry into open-label	40 weeks (LOCF)	Difference	Entry into open-label	40 weeks (LOCF)	Difference
HAROSA I	Pitolisant then pitolisant (n=151)			Placebo then pitolisant (n=48)		
	9.7 (7.1)	7.4 (6.2)	-1.6 (5.8)	8.9 (6.2)	7.0 (6.2)	-1.2 (5.8)
HAROSA II	Pitolisant then pitolisant (n=181)			Placebo then pitolisant (n=55)		
	9.2 (6.7)	7.6 (5.5)	-1.4 (5.9)	10.6 (6.1)	7.4 (4.7)	-2.9 (6.2)

2.6.3 Physician and patient rating of treatment

The benefit in wakefulness and relief of daytime sleepiness is reflected in Physicians Global Impression of Change (PGIC) and Patient's Global Opinion of the Effect (PGOE) of treatment.

During the double-blind period there was a statistically significant difference in the proportion of Physicians and Patients who rated the treatment effect as improved, see Table 13.

By the end of the open-label period both physicians and patients rated the treatment effect as further improved over the double-blind period. In HAROSA I, 90.8% of physicians with patients originally randomised to pitolisant and 90.2% originally randomised to placebo rated the treatment effect as improved (67.7% and 58.5% as very much or much improved). Figures for HAROSA II were 92.5% and 95.7% with 70.4% and 78.7% rating treatment effect as very much or much improved, respectively. A similar picture was seen for PGOE for both HAROSA I (89.3% and 87.8% improved, 68.7% and 65.8% very much or much improved) and HAROSA II (93.1% and 94.1%, 76.7% and 81.3% very much or much improved.

Table 13: Physicians Global Impression and PGOE of treatment (ITT population)[3,43]

	Physicians Global Impression of Change			Patient's Global Opinion of the Effect		
	Pitolisant	**Placebo**		**Pitolisant**	**Placebo**	
HAROSA I	78.0% assessed as improved (11.0% very much improved, 42.2% much improved, and 24.9% minimally improved)	53.4% assessed as improved (6.9% very much improved, 27.6% much improved, and 19.0% minimally improved)	p<0.001	76.4% assessed as improved (marked effect 33.3%, moderate effect 27.6%, minimal effect 15.5%)	56.9% assessed as improved (marked effect 25.9%, moderate effect 10.3%, minimal effect 20.7%)	p=0.005
HAROSA II	84.2% assessed as improved (11.1% very much improved, 44.2% much improved, and 28.9%	56.3% assessed as improved (4.7% very much improved, 29.7% much improved, and 21.9%	p<0.001	86.3% assessed as improved (marked effect 30.0%, moderate effect 33.7%, minimal effect 22.6%)	60.9% assessed as improved (marked effect 21.9%, moderate effect 18.8%, minimal effect 20.3%)	p<0.001

	minimally improved)	minimally improved)				

2.6.4 Death

There were no deaths in HAROSA I.

There were two deaths in HAROSA II, one during the double-blind period in a patient taking pitolisant (cardiopulmonary failure, unlikely to be related to pitolisant) and one in the open-label period in a patient who took placebo in the double-blind period (sudden death syndrome, unlikely to be related to placebo).

2.6.5 HRQOL

In HAROSA I, there was no difference in EQ-5D or VAS during the double-blind phase.

In HAROSA II, there was a significant improvement in the pain/discomfort domain (no problems 54.7% versus 40.6%, p=0.044) and a trend towards improvement in QOL on the VAS in the pitolisant arm (7.3 mm improvement versus 1.8 mm improvement, p=0.044).

B.2.7 Subgroup analysis

There were no subgroup analyses.

B.2.8 Meta-analysis

Meta-analysis was not carried out since the two HAROSA studies considered different populations: HAROSA I considered the impact of pitolisant in patients with residual EDS despite CPAP treatment, whereas HAROSA II considered patients with EDS refusing CPAP. Both studies had a low risk of bias.

In both populations, pitolisant improved wakefulness and reduced daytime sleepiness significantly more than placebo. The standard measure of EDS is ESS, there was a placebo-controlled treatment effect of -2.6 (95% CI: [-3.9; -1.4]) (p<0.001) on ESS in HAROSA I and -2.8 (95% CI: [-4.0;-1,5]) (p<0.001) in HAROSA II.

At the end of the double-blind period mean ESS was within the normal range (<10) in the pitolisant arm of both studies. Patients entering into the open-label period, who all received pitolisant during the open-label period, had further improvements in wakefulness and reduced daytime sleepiness, which continued until the end of the 40-week open-label period.

By the end of the open-label period mean ESS was well within the normal range (≤10). In HAROSA I, mean ESS was 8.1 in patients originally randomised to pitolisant and 7.9 in patients originally randomised to placebo. In HAROSA II, mean ESS was 7.7 and 7.0 respectively.

B.2.9 Indirect and mixed treatment comparisons

Indirect treatment comparison (ITC) was not carried out for the base case since the HAROSA studies compare treatment with pitolisant plus BSC versus placebo plus BSC, this ties in with the scope which asks us to compare pitolisant with established clinical management without pitolisant.

However, an ITC was carried out to compare pitolisant with MADs in people with OSAHS to be used in a scenario analysis in the economic modelling, full details of the ITC are in Appendix D with a summary below.

2.9.1 Summary of trials used to carry out the ITC

Table 14:Summary of the trials used to carry out the ITC

Study	Active arms			Placebo arms		
	MAD	CPAP	Pitolisant	Placebo tablet	Placebo MAD	Placebo Conservative management
Aarab et al. 2011[48]	Yes	Yes			Yes	
Barnes et al. 2004[49]	Yes	Yes		Yes		
Gotsopoulos et al. 2002[50]	Yes				Yes	
Hans et al. 1997[51]	Yes	Yes				
Lam et al. 2007[52]	Yes	Yes				Yes
Blanco et al. 2005[53]	Yes				Yes	
Johnston et al. 2002[54]	Yes				Yes	
Petri et al 2008[55]	Yes				Yes	Yes
HAROSA II study[4]			Yes	Yes		

2.9.2 Results of the ITC

All selected studies were similar in terms of the variables that might be considered as potential treatment effect modifiers (demographic and clinical baseline characteristics), except for Blanco et al[53] . In Blanco et al the percentage of men (92.85%) was significantly higher than that observed in the rest of the studies, this discrepancy could be explained by the small size (n=15) of the study.

Additionally, there was a significant heterogeneity between study results, with two small studies (Blanco 2005[53] and Hans 1997[51]) reporting much larger treatment differences in ESS compared to the other studies (-8.5 and -4.3 respectively, compared to differences in the range of -0.94 to -2.8 for the other six studies).

Treatment duration ranged from 4-26 weeks and is a potential source of heterogeneity, given that treatment duration is considered a potential treatment effect modifier. However, there was not a clear correlation between the ESS effect size and treatment duration in the studies.

We carried out a base case ITC comparing HAROSA II with all eight MAD studies and a scenario analysis comparing HAROSA II with six MAD studies (excluding Blanco et al and Hans et al). Both random effect and fixed effects analyses were carried out.

We elected to use the fixed effect results from the scenario analysis excluding Blanco et al and Hans et al, because the scenario yielded a better fit than the base case (posterior mean of residual variance and deviance information criterion [DIC] were significantly lower).

In the scenario analysis, the posterior mean of the residual deviance was similar in both fixed and random effect models, whereas the number of parameters used to fit the random effect model was higher than in the fixed effect model. The DIC was lower in the fixed effect model, suggesting that the fixed effect model best fits the data. Therefore, we elected to use this output in the economic model, results are shown below in Table 15.

Table 15: Results of the ITC comparing pitolisant with MAD

Treatment	Median difference in ESS score	95% CrI	
MAD versus best supportive care (BSC)	-1.334	-1.977	-0.6932
Pitolisant versus BSC	-2.8	-4.046	-1.553
Pitolisant versus MAD	-1.466	-2.866	-0.06304

B.2.10 Adverse reactions

The safety population was defined as patients who received at least one dose of study medication, irrespective of the outcome, and for whom at least one valid post-baseline evaluation is available.

2.10.1 Discontinuations due to adverse events

Pitolisant was well tolerated with <2% of patients discontinuing treatment due to adverse AE in the double-blind phase.

Table 16: Treatment emergent AE (TEAE) leading to discontinuation in the double-blind period (safety population)[3,43]

	Pitolisant (n=183)	Placebo (n=61)	Absolute risk (95% CI)	Relative risk (95% CI)
HAROSA I	4 (1.1%)	2 (3.3%)		0.67 (0.13-3.55), NS
	Pitolisant (n=200)	Placebo (n=67)	Absolute risk (95% CI)	Relative risk (95% CI)
HAROSA II	3 (1.5%)	2 (3.0%)		0.50 (0.09-2.94), NS

Over the course of 1 year, discontinuations due to AE were 5.3% in HAROSA I (patients using CPAP) and 2.2% in HAROSA II (patients refusing CPAP).

This is supported by Patient's Overall Evaluation of Tolerance, which was measured at the end of the double-blind period. In HAROSA I, 88.9% of patients randomised to pitolisant and 91.7% of patients randomised to placebo rated the tolerability of treatment as good. In HAROSA II, 100% of patients in both arms rated the tolerability of treatment as good.

At the end of the open-label period of the studies, discontinuations due to AE were 8/151 (5.3%) in patients receiving pitolisant followed by pitolisant and 2/48 (4.2%) in patients receiving placebo followed by pitolisant in HAROSA I (patients using CPAP). Rates were slightly lower in HAROSA II (patients refusing CPAP) at 4/181 (2.2%) and 1/55 (1.8%), respectively.

This is also supported by Patient's Overall Evaluation of Tolerance measured at the end of the open-label period. In HAROSA I, 95.7% of patients receiving pitolisant followed by

pitolisant and 95.5% receiving placebo followed by pitolisant rated tolerability of treatment as good. In HAROSA II, more patients rated tolerability of treatment as good – 99.4% and 100% respectively.

2.10.2 Adverse events during the double-blind period

Pitolisant was well tolerated in both the HAROSA studies, see Table 17.

There was no significant difference in the incidence of TEAEs of special interest, treatment-related TEAEs and TEAEs leading to study drug withdrawals (HAROSA I: p=0.118, p=0.256 and p=0.625, respectively and HAROSA II: p=0.440, p=0.377, p=0.540 and p=0.998, respectively).

The most frequently reported TEAE in each group was headache, in HAROSA I (14.8% in the pitolisant arm versus 11.5% in the placebo arm) and in HAROSA II (8.5% versus 10.4%)

TEAE of special interest were defined as anxiety, depression, drug abuse and misuse, drug dependence, fertility disorders, gastric disorders caused by hyperactivity, insomnia, proconvulsive potential, QT-interval prolongation, rebound effect and weight increase. As illustrated in Table 17 insomnia was the only TEAE of special interest reported by more than 2% of patients in the pitolisant arm (9.3% versus 3.3% in HAROSA I and 5.5% versus 3.0% in HAROSA II).

TEAE were almost all mild to moderate in severity. In HAROSA I, 15/215 events were severe in the pitolisant arm (one headache, one insomnia and 13 others) and 3/41 events were severe in the placebo arm. In HAROSA II, rates were 5/59 events (one insomnia and four others) and 3/17 events (one insomnia, one headache and one other), respectively.

Rates of serious TEAE were low in both studies. In HAROSA I two patients (1.1%) of patients randomised to pitolisant experienced a serious TEAE (irritable bowel syndrome and musculoskeletal pain). In HAROSA II, two patients (1.0%) of patients randomised to pitolisant experienced a serious TEAE (electrocardiogram QT prolonged and cardiopulmonary failure leading to death). All serious TEAE were considered unlikely to be treatment-related.

Table 17: TEAE in the double-blind period (safety population), n=244 for HAROSA I and n=267 for HAROSA II[3,43]

	HAROSA I				HAROSA II			
	Pitolisant (n=183)	**Placebo (n=61)**	**Absolute risk reduction (95% CI)**	**Relative risk (95% CI)**	**Pitolisant (n=200)**	**Placebo (n=67)**	**Absolute risk reduction (95% CI)**	**Relative risk (95% CI)**
Overview								
Any TEAE	86 (47.0%)	20 (32.8%)	-0.14 (-0.28-0.00)	1.433 (0.97-2.12)	59 (29.5%)	17 (25.4%)	-0.04 (-0.16-0.08)	1.16 (0.73-1.85)
Any TEAE of special interest	25 (13.7%)	4 (6.6%)	-0.07 (-0.15-0.01)	2.083 (0.75-5.70)	17 (8.5%)	4 (6.0%)	-0.03 (-0.09-0.04)	1.42 (0.50-4.08)
Any treatment-related TEAE	49 (26.8%)	12 (19.7%)	-0.07 (-0.19-0.05)	1.36 (0.78-2.38)	48 (24.0%)	13 (19.4%)	-0.05 (-0.16-0.07)	1.24 (0.72-2.14)
Any serious TEAE	2 (1.1%)	0 (0.0%)	-	-	2 (1.0%)	0 (0.0%)	-	-
TEAE by system organ class and preferred term reported by ≥2% of patients in any arm								
Ear and labyrinth disorders					4 (2.0%)	2 (3.0%)	0.01 (-0.04-0.05)	0.67 (0.13-3.58)
Vertigo					4 (2.0%)	2 (3.0%)	0.01 (-0.04-0.05)	0.67 (0.13-3.58)
Cardiac disorders	5 (2.7%)	0 (0.0%)	-	-				
Gastrointestinal disorders	21 (11.5%)	6 (9.8%)	-0.02 (-0.10-0.07)	1.167 (0.49-2.75)	11 (5.5%)	4 (6.0%)	0.00 (-0.06-0.07)	0.92 (0.30-2.80)
Diarrhoea	6 (3.3%)	1 (1.6%)	-0.02 (-0.06-0.02)	2.00 (0.25-16.27)				
Nausea					5 (2.5%)	1 (1.5%)	-0.01 (-0.05-0.03)	1.68 (0.20-14.08)
General disorders and administration site conditions					5 (2.5%)	0 (0.0%)	-	-
Infections and infestations	27 (14.8%)	7 (11.5%)	-0.03 (-0.13-0.06)	1.29 (0.59-2.80)	8 (4.0%)	4 (6.0%)	0.02 (-0.04-0.08)	0.67 (0.21-2.15)
Nasopharyngitis	5 (2.7%)	5 (8.2%)	0.05 (-0.02-0.13)	1.80 (0.73-4.47)	1 (0.5%)	2 (3.0%)	0.02 (-0.02-0.07)	0.17 (0.02-1.82)
Influenza	6 (3.3%)	0 (0.0%)		-				
Investigations	5 (2.7%)	2 (3.3%)	-	0.83 (0.17-4.19)	2 (1.0%)	4 (6.0%)	0.05 (-0.01-0.11)	0.17 (0.03-0.89)
Musculoskeletal and connective tissue disorders	18 (9.8%)	1 (1.6%)	-0.08 (-0.14 - -0.03)	6.00 (0.82-44.01)	4 (2.0%)	2 (3.0%)	0.01 (-0.04-0.05)	0.67 (0.13-3.58)
Back pain	6 (3.3%)	0 (0.0%)	-	-	1 (0.5%)	2 (3.0%)	0.02 (-0.02-0.07)	0.17 (0.02-1.82)

Arthralgia	4 (2.2%)	0 (0.0%)	-	-				
Nervous system disorders	35 (19.1%)	9 (14.8%)	-0.04 (-0.15-0.06)	1.30 (0.66-2.54)	19 (9.5%)	8 (11.9%)	0.02 (-0.06-0.11)	0.80 (0.37-1.73)
Headache	27 (14.8%)	7 (11.5%)	-0.03 (-0.13-0.06)	1.29 (0.59-2.80)	17 (8.5%)	8 (11.9%)	0.03 (-0.05-0.12)	0.71 (0.32-1.57)
Dizziness	5 (2.7%)	1 (1.6%)	-0.01 (-0.05-0.03)	1.67 (0.20-13.99)				
Psychiatric disorders	23 (12.6%)	3 (4.9%)	-0.08 (-0.15-0.00)	2.56 (0.79-8.22)	19 (9.5%)	3 (4.5%)	-0.05 (-0.11-0.01)	2.12 (0.65-6.95)
Insomnia	17 (9.3%)	2 (3.3%)	-0.06 (-0.12-0.00)	2.83 (0.67-11.91)	11 (5.5%)	2 (3.0%)	-0.03 (-0.08-0.03)	1.84 (0.42-8.10)
Respiratory, thoracic and mediastinal disorders	7 (3.8%)	3 (4.9%)	0.01 (-0.05-0.07)	0.78 (0.21-2.91)	4 (2.0%)	0 (0.0%)	-	-
Nasal congestion	1 (0.5%)	2 (3.3%)	0.03 (-0.02-0.07)	0.17 (0.02-1.81)				
Skin and subcutaneous tissue disorders	7 (3.8%)	2 (3.3%)	-0.01 (-0.06-0.06)	1.17 (0.25-5.47)				
TEAE of special interest								
Insomnia	17 (9.3%)	2 (3.3%)	-0.06 (-0.12-0.00)	2.83 (0.67-11.91)	11 (5.5%)	2 (3.0%)	-0.03 (-0.08-0.03)	1.84 (0.42-8.10)
Initial insomnia					1 (0.5%)	0 (0.0%)	-	-
Abdominal pain upper	2 (1.1%)	1 (1.6%)	0.01 (-0.03-0.004)	0.67 (0.06-7.22)	1 (0.5%)	0 (0.0%)		
Abdominal discomfort	2 (1.1%)	0 (0.0%)	-	-				
Gastroesophageal reflux disease	2 (1.1%)	0 (0.0%)	-	-	1 (0.5%)	0 (0.0%)	-	-
Dyspepsia					0 (0.0%)	1 (1.5%)	-	-
Anxiety	2 (1.1%)	0 (0.0%)	-	-	2 (1.0%)	0 (0.0%)	-	-
Depression					0 (0.0%)	1 (1.5%)	-	-
Electrocardiogram QT prolonged	0 (0.0%)	1 (1.6%)	-	-	2 (1.0%)	0 (0.0%)	-	-
Weight increased	1 (0.5%)	0 (0.0%)	-	-				

CV risk factors

Given that modafinil, an earlier treatment for EDS associated with OSA, was removed from the market due to increased CV risk[42], we present the impact of pitolisant on CV risk factors in Table 18 and Table 19.

The tables show that treatment with pitolisant does not result in any clinically relevant changes in either blood pressure or heart rate.

Table 18: Blood pressure and heart rate changes: HAROSA I[3]

	Pitolisant (n=183)		**Mean change**	**Placebo (n=61)**		**Mean change**
	Baseline	12 weeks		Baseline	12 weeks	
Systolic blood pressure (mmHg) Mean (SD)	129.3 (12.9)	128.7 (12.0)	-0.6 (10.8)	130.2 (11.8)	129.1 (12.0)	-1.8 (10.1)
Diastolic blood pressure (mmHg) Mean (SD)	80.3 (8.9)	79.9 (8.3)	-0.4 (7.3)	80.6 (6.9)	81.4 (9.0)	0.6 (9.0)
Heart rate Mean (SD)	70.9 (11.9)	70.0 (11.5)	-0.9 (9.6)	71.3 (9.6)	70.3 (10.4)	-1.4 (9.1)

Table 19: Blood pressure and heart rate changes: HAROSA II[43]

	Pitolisant (n=200)		**Mean change**	**Placebo (n=67)**		**Mean change**
	Baseline	12 weeks		Baseline	12 weeks	
Systolic blood pressure (mmHg) Mean (SD)	128.2 (11.6)	127.4 (11.4)	-0.7 (11.6)	127.2 (7.2)	128.5 (10.1)	1.3 (9.3)
Diastolic blood pressure (mmHg) Mean (SD)	80.1 (6.6)	79.8 (6.4)	-0.2 (7.5)	80.3 (5.1)	80.4 (5.2)	0.2 (5.9)
Heart rate Mean (SD)	74.2 (10.2)	73.5 (9.8)	-0.3 (9.7)	72.9 (10.2)	73.7 (10.8)	0.3 (8.4)

2.10.3 Adverse events during the open-label period

There were no new safety signals in the open-label period, headache continued to be the most frequently reported TEAE (ranging from 8.8% to 14.6%). The majority of TEAE continued to be mild to moderate in severity: in HAROSA I 17 events in pitolisant followed by pitolisant arm and nine events in placebo followed by pitolisant arm, in HAROSA II 7 and 4 respectively.

Insomnia was the only TEAE of special interest reported by more than 2% of patients in all study groups (ranging from 3.9% to 8.3%).

Treatment with pitolisant during the long-term extension did not result in any clinically relevant changes in either blood pressure or heart rate.

Drug withdrawal was reported by two patients in HAROSA I (one in the pitolisant followed by pitolisant arm and one in the placebo followed by pitolisant arm). It was not reported in HAROSA II.

Rates of serious TEAE were low. In HAROSA I, 11 serious TEAE were reported in nine patients (6.0%) in the pitolisant followed by pitolisant arm and one event (2.1%) in the placebo followed by pitolisant arm. Only one serious TEAE was considered to be possibly related to the study treatment (hypertension) in a patient in the pitolisant followed by pitolisant arm. In HAROSA II, one serious TEAE was reported (sudden death syndrome) which was considered to be unlikely to be related to pitolisant.

At the end of the open-label period, patients were assessed for withdrawal symptoms using the Amphetamine-like Withdrawal Symptoms Questionnaire. Patients were interviewed twice during the week after the abrupt interruption of pitolisant by means of a questionnaire checking their feeling of specific symptoms that could be part of a withdrawal syndrome (once by telephone 3 days after treatment interruption and once in person 7 days after treatment interruption). The combination of dysphoria (a state of generalised unhappiness, restlessness, dissatisfaction, or frustration) plus two additional symptoms (from fatigue, vivid and unpleasant dreams, insomnia or hypersomnia, increased appetite and psychomotor retardation or agitation) was recorded as withdrawal.

Amphetamine-like withdrawal symptoms were rare, occurring in <1% of the total study population[3,43]. In HAROSA I 10 patients (7.7%) in the pitolisant followed by pitolisant arm and one patient (2.4%) in the placebo followed by pitolisant arm reported withdrawal symptoms. Of the patients who reported symptoms, only four reported them at 3-days post-treatment interruption during the telephone call. The others reported them at 7-days after treatment interruption, which is long after drug withdrawal. Patients reported fatigue and excessive sleepiness are both symptoms of untreated EDS. In contrast, withdrawal symptoms were not reported in HAROSA II.

Pitolisant has a low risk of abuse. A Human Abuse Potential study, which is mandatory for FDA approval, has also been carried out and is described in detail in Appendix F. The study, in 38 people who were non-dependent recreational stimulant users, randomised participants in a 4-period, double-blind, crossover design to receive single doses of pitolisant 35.6 mg (therapeutic dose for narcolepsy), pitolisant 213.6 mg (supratherapeutic dose), phentermine 60 mg (a mild stimulant), and placebo[56]. The primary end-point was maximum effect (Emax) on the 100-point Drug Liking ("at this moment") visual analogue scale. Pitolisant demonstrated a significantly lower potential for abuse versus phentermine and an overall profile similar to placebo; indicating a low risk of abuse for pitolisant. The proven low risk of abuse means that pitolisant is not a controlled or scheduled drug, which has benefits to the healthcare professionals prescribing and dispensing it.

Table 20: AE in the open-label period (safety population), n=199 for HAROSA I and n=236 for HAROSA II[3,43]

	HAROSA I		HAROSA II	
	Pitolisant then pitolisant (n=151)	Placebo then pitolisant (n=48)	Pitolisant then pitolisant (n=181)	Placebo then pitolisant (n=55)
Overview				
Any TEAE	83 (55.0%)	23 (47.9%)	52 (28.7%)	18 (32.7%)
Any TEAE of Special Interest	17 (11.3%)	10 (20.8%)	15 (8.3%)	5 (9.1%)
Any treatment-related TEAE	44 (29.1%)	15 (31.3%)	43 (23.8%)	11 (20.0%)
Any serious TEAE	9 (6.0%)	1 (2.1%)	0 (0.0%)	1 (1.8%)
TEAE by system organ class and preferred term reported by ≥2% of patients in any arm				
Cardiac disorders	2 (1.3%)	2 (4.2%)		
Ear and labyrinth disorders	5 (3.3%)	0 (0.0%)		
Eye disorders	1 (0.7%)	2 (4.2%)		
Gastrointestinal disorders	11 (7.3%)	4 (8.3%)	7 (3.9%)	2 (3.6%)
General disorders and administration site conditions	10 (6.6%)	1 (2.1%)		
Infections and infestations	26 (17.2%)	7 (14.6%)	6 (3.3%)	4 (7.3%)
Bronchitis	6 (4.0%)	0 (0.0%)		
Influenza	8 (5.3%)	3 (6.3%)	3 (1.7%)	2 (3.6%)
Nasopharyngitis	7 (4.6%)	3 (6.3%)		
Rhinitis	0 (0.0%)	2 (4.2%)		
Injury, poisoning, and procedural complications	6 (4.0%)	2 (4.2%)		
Investigations	3 (2.0%)	3 (6.3%)		
Musculoskeletal and connective tissue disorders	21 (13.9%)	5 (10.4%)	7 (3.9%)	3 (5.5%)
Back pain	7 (4.6%)	2 (4.2%)		
Nervous system disorders	27 (17.9%)	9 (18.8%)	20 (11.0%)	7 (12.7%)
Headache	17 (11.3%)	7 (14.6%)	16 (8.8%)	5 (9.1%)
Psychiatric disorders	16 (10.6%)	6 (12.5%)	15 (8.3%)	5 (9.1%)
Insomnia	10 (6.6%)	4 (8.3%)	7 (3.9%)	4 (7.3%)
Respiratory, thoracic and mediastinal disorders	7 (4.6%)	0 (0.0%)	3 (1.7%)	2 (3.6%)
Skin and subcutaneous tissue disorders	9 (6.0%)	1 (2.1%)		
Surgical and medical procedures	6 (4.0%)	0 (0.0%)		
TEAE of special interest				
Insomnia	10 (6.6%)	4 (8.3%)	7 (3.9%)	4 (7.3%)
Middle insomnia			1 (0.6%)	0 (0.0%)
Abdominal pain upper	1 (0.7%)	1 (2.1%)	2 (1.1%)	0 (0.0%)
Abdominal discomfort	1 (0.7%)	1 (2.1%)		
Gastroesophageal reflux disease				
Dyspepsia	2 (1.3%)	0 (0.0%)		
Anxiety	1 (0.7%)	0 (0.0%)	5 (2.8%)	1 (1.8%)

Mood altered	1 (0.7%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Depression	1 (0.7%)	1 (2.1%)		
Electrocardiogram QT prolonged	0 (0.0%)	1 (2.1%)		
Weight increased	0 (0.0%)	1 (2.1%)		
Drug withdrawal syndrome	1 (0.7%)	0 (0.0%)		
Withdrawal syndrome	0 (0.0%)	1 (2.1%)		

B.2.11 Ongoing studies

We searched clinicaltrials.gov to identify ongoing studies of relevant interventions in patients with excessive daytime sleepiness due to OSA. The results are shown in Table 21. There was only one study of pitolisant, which is due to report in 2020.

Table 21: Ongoing studies in OSA with EDS

Principal investigator, and location	Year (expected completion date)	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention (and version(s))	Comparator(s)	Outcomes
Rodriguez P. Bulgaria, Macedonia [NCT02739568]	2020	Double-blind placebo-controlled RCT	Adults with EDS due to OSA despite ≥4 hours/day CPAP or refusing CPAP with BMI ≤40 kg/m^2	Pitolisant	Placebo	ESS score ESS responder rate Reduction of sleepiness Improvement in vigilance QOL (EQ-5D) LSEQ, Pichot Fatigue Scale improvement Trail-making test improvement CGI improvement
Farkas R. USA [NCT03845023]	December 2019	Placebo-controlled phase 2 RCT	Men aged 25 to 65 years or women aged 25 to 70 years with OSA and ESS score ≥4 if not using CPAP	AD036, 3 doses (Not reported)	Placebo	Proportion with ≥50% reduction in AHI Oxygen desaturation index ESS
Not reported, [NCT04091425]	2020	Placebo-controlled crossover RCT	Patients with OSA and EDS despite ≥4 hours CPAP per day with ESS ≥10	TAK-925 IV infusion (2 doses)	Placebo	Safety Pharmacokinetics

B.2.12 Innovation

We believe that pitolisant has substantial health-related benefits that we may find challenging to include in economic modelling.

People with EDS have uncontrollable daytime sleepiness that interferes with their daily life. Despite sleeping at night, patients may doze off during their usual daily activities e.g. whilst having a conversation, reading, watching television or driving. Alertness and focus are also affected in around two-thirds of people with EDS, resulting in problems with memory and concentration which impact on work performance and reduced participation in and enjoyment of everyday activities[6,8].

These symptoms can be extremely debilitating and have a significant impact on QOL[6,8]. However, data from HAROSA I and HAROSA II did not show an improvement in QOL[3,43]. The lack of impact on QOL is consistent with other studies in OSA treated with CPAP[57], MADs[58,59] or modafinil[60,61].

Clinical opinion, systematic reviews and work carried out by the Assessment Group for the NICE CPAP HTA indicate that generic instruments to measure QOL, including the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and the EuroQol (EQ-5D) do not capture benefit in QOL in patients with EDS[35,62,63]. These instruments have not been specifically designed to assess aspects of QOL in patients with OSA or EDS and sleep is not included as a specific dimension. Therefore, the true benefits of treatment are unlikely to be captured by the modelling.

As discussed earlier, most people with EDS as a result of OSA are working (~70% in the clinical trials for pitolisant), which reflects UK clinical practice[35]. We believe that the improvement in wakefulness and reduction in daytime sleepiness will allow patients to improve productivity at work and reduce long-term absenteeism, both of which are not captured in the economic modelling carried out for this submission. In the case of individuals for whom driving is a key element of their employment, control of EDS allows people to regain their driving licence and return to employment.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Pitolisant, due to its wake-promoting effects, enables people with EDS due to OSA to remain awake and alert during the day. Two well conducted, large placebo-controlled clinical studies, one in people with residual sleepiness despite CPAP and one in people refusing CPAP, have shown that pitolisant acts quickly to increase wakefulness and reduce daytime sleepiness and that wakefulness is sustained over the long-term[3,4].

The two studies: HAROSA I in patients with residual EDS despite CPAP[3] and HAROSA II in patients with EDS refusing to receive CPAP[4,43] were identical in design. A 12-week placebo-controlled period (double-blind period) followed by a 40-week OLE when all patients who wished were switched to pitolisant (open-label period). Patients originally randomised to pitolisant were therefore exposed to active treatment for 1 year.

In the HAROSA studies, pitolisant resulted in a clinically meaningful placebo-controlled improvement in ESS, the standard measure of sleepiness[44], by -2.6 points, (95% CI -3.9; -1.4), $p<0.001$ in patients using CPAP and by -2.8 (-4.0;-1,5), $p<0.001$ in patients unable/unwilling to use CPAP[3,4]. By week 5 of treatment, mean ESS was in the normal range (≤ 10) from a baseline of 14.9 in patients using CPAP and a baseline of 15.7 in patients refusing to use CPAP. A score of >12 denotes abnormal sleepiness[3,4].

Wakefulness continued to improve over the long-term, with further benefit seen after 3 months of treatment[3,4]. By the end of the 52-week study period, those patients who had received pitolisant for the duration of the study had ESS scores well within the normal range (8.1 in patients receiving CPAP and 7.7 in patients refusing CPAP)[3,4].

For patients refusing CPAP there was also a significant improvement in fatigue (treatment difference 2.6 as measured by the Pichot Fatigue Scale, p=0.005). A trend towards improvement in fatigue was seen in patients using CPAP (treatment difference 0.9). Fatigue continued to improve during the open-label phase in both patient populations.

At the end of the 1-year study period, pitolisant resulted in significant improvements in clinician-rated and patient-rated assessment, with around 90% of clinicians and patients rating pitolisant as improving symptoms[3]. Symptoms were improved very much/much in 68% of clinicians and 69% patients participating in the study using CPAP and in 70% and 77% participating in the study without CPAP.

At present, there are no licenced wakefulness-promoting agents in the UK. Modafinil was licenced for EDS due to OSA, however, concerns over serious side effects including psychiatric disorders, CV symptoms, and serious skin and multi-organ hypersensitivity reactions led the EMA's Committee for Medicinal Products for Human Use to conclude that the benefits of modafinil could only be considered to outweigh the risks when used to treat narcolepsy. Therefore, in January 2011, the committee concluded that the benefit/risk profile not adequate for OSA, shift work sleep disorder and idiopathic hypersomnia and recommended that these indications be removed from the product information[42].

A meta-analysis of studies using modafinil and armodafinil showed that compared with placebo, these agents reduced the ESS by 2.51 points (95% CI, 2.00–3.02)[64]. However, their use is limited by serious AE.

In the HAROSA studies, pitolisant was well tolerated with <2% of patients discontinuing treatment due to AE in the double-blind phase[3]. Over the course of 1 year, discontinuations due to AE were 5.3% in the study using CPAP and 2.2% in the study without CPAP[3,4].

Headache was the most common AE, affecting 14.8% of patients receiving pitolisant in the study using CPAP and 8.5% in the study without CPAP during the double-blind phase of the studies. A similar proportion of patients receiving placebo experienced headache too (11.5% and 10.4% respectively)[3,4]. Rates of headache did not increase during the open label phase of the studies[3,43].

CV AE were reported in <5% of patients taking pitolisant in HAROSA I and not at all in HAROSA II[3,4,43]. Treatment with pitolisant does not result in any clinically relevant changes in either blood pressure or heart rate[3,4,43]. CV monitoring, e.g. ECG monitoring is not required for patients taking pitolisant[1].

Pitolisant is not a psychostimulant and does not increase dopamine levels in the reward centres of the brain, therefore, we would not anticipate potential for addiction. To assess this, patients who did not wish to enter into the open label phase were assessed for withdrawal symptoms after pitolisant was stopped at the end of the double-blind period. As expected, no patients had amphetamine-like withdrawal symptoms[3,43]. Human and animal studies confirm the lack of withdrawal symptoms and have shown that there is no potential for addiction with pitolisant[56,65]. This means that unlike many other treatments used for EDS, pitolisant is not a controlled or scheduled drug, which has benefits to the healthcare professionals prescribing and dispensing it.

The TEAE reported in the HAROSA studies are similar to those reported in the HARMONY 3 study, which is a pragmatic, open-label, multicenter study which evaluated the effect of pitolisant (18 or 36 mg once daily) in 102 adults with narcolepsy over the long-term (up to 5 years). Data from year 1 has been reported; the most common AE were headache (11.8%), insomnia (8.8%), weight gain (7.8%), anxiety (6.9%), depression (4.9%), and nausea (9%)[66]. It should be noted that the maximum dose for EDS is 18 mg which is considerably lower than the maximum dose for narcolepsy, therefore we might expect lower rates of AE in patients receiving pitolisant for EDS.

2.13.1 Strengths

The evidence-base for pitolisant is from two relatively large placebo-controlled studies: one study in patients with residual EDS despite using CPAP (HAROSA I, n=183 randomised to pitolisant, n=61 randomised to placebo) and study with EDS in patients refusing CPAP (HAROSA II, n=201 randomised to pitolisant, n=67 randomised to placebo). It is noteworthy that two studies (one study in each patient population) was carried out, rather than one study including patients from both populations.

The studies were assessed to have a low risk of bias and demonstrated a statistically significant placebo-controlled reduction in EDS (as measured by ESS) over the 12-week double-blind period of -2.6 in HAROSA I and -2.8 in HAROSA II. This is a clinically meaningful difference in ESS[44].

There was further improvement in ESS during the 40-week open-label period with the final ESS score well below the threshold for EDS in both studies.

The studies were placebo-controlled, given the lack of an alternative licensed treatment for EDS placebo was a valid and pragmatic comparator. It is also interesting to note the strong placebo effect, which can be seen in Figure 3 and Figure 4, which show the ESS mean score at each visit in the 12-week double-blind period. At the beginning of the study (weeks 1-3) the decrease in ESS is similar, after week 3 the curves diverge with ESS in the pitolisant arm showing a further decrease and ESS in the placebo arm beginning to rise.

2.13.2 Limitations

The HAROSA studies considered pitolisant versus placebo. Current clinical practice is to ensure that patients undertake lifestyle changes (weight loss, alcohol reduction, smoking cessation) and that CPAP is optimised in all patients receiving CPAP. We can't be sure that lifestyle measures and CPAP were optimised in all the study participants, however, the placebo-controlled design helps to mitigate any differences.

Like most clinical trials, the study population excluded certain patient groups, including significant serious CV disease and psychiatric illness. This means that evidence is not available for these patient groups. However, safety data from the two pivotal trials did not indicate any CV or psychiatric issues. With regard to CV disease, just over half of patients enrolled in the HAROSA studies had non-serious underlying CV disease.

Patients were also excluded if they had restless legs syndrome, depression or BMI >40. These co-morbidities all increase the risk of EDS, excluding them from the study populations is a sensible approach to ensure the baseline risk of EDS is similar across the included patients.

The studies were not designed to consider different doses and the results presented are for the mixed pitolisant dose population. Most patients were on the maximum dose of 20 mg

(approximately 75%), with the remainder on 10 mg (approximately 20%) or 5 mg (approximately 5%). It would have been helpful to be able to present the response to treatment by dose. We know from the HARMONY studies with pitolisant in narcolepsy, that around one-quarter of patients obtain good results with lower doses[67].

The relatively short duration of the double-blind period means that comparative data is only available for 12 weeks. The longer-term follow-up over 40 weeks provides us with data for 1 year, which indicates that the efficacy of pitolisant is maintained long-term with minimal side-effects. Clearly, longer term data would be beneficial since patients receiving pitolisant for EDS resulting from OSA are likely to be on treatment indefinitely.

ESS is subjective and does not correlate well with objective measures of sleep[68]. ESS measures the propensity to fall asleep during the day which is different from measures of sleep deprivation which look at ability to remain alert (psychomotor vigilance) (OSLER), perceived quantity of sleep at night (sleep diary), aspects of sleep and early morning behaviour (LSEQ), cognitive function (TMT) and fatigue (Pichot Fatigue Scale). Therefore, it is not unexpected that during the 12-week double-blind period secondary end-points including OSLER test, Sleep diary (sleepiness and sleep episodes), LSEQ, TMT Parts A&B, Pichot Fatigue scale and QOL did not show a significant improvement with pitolisant in both studies.

The lack of impact on QOL is consistent with other studies in OSA treated with CPAP[57], MADs[58,59] or modafinil[60,61]. Clinical opinion, systematic reviews and work carried out by the Assessment Group for the NICE CPAP HTA indicate that generic instruments to measure QOL, including the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and the EuroQol (EQ-5D) do not capture benefit in QOL in patients with EDS[35,62,63]. These instruments have not been specifically designed to assess aspects of QOL in patients with OSA or EDS and sleep is not included as a specific dimension.

Patients in HAROSA II had noticeably lower rates of AE than those in HAROSA I in the double-blind period (see Table 17). The reasons for this are unclear, but expert opinion suggests that it may be that patients refusing CPAP in HAROSA II are particularly motivated to stay on treatment and focus less on AE, since there is no other treatment option for them and their EDS is more severe at baseline (15.7 versus 14.9)[35]. HAROSA II also included more patients from Eastern Europe than HAROSA I, who may be more stoic with regards to AE. Indeed, analysis of multinational Alzheimer's disease clinical trials revealed that AE rates were lower in Eastern Europe than in North America and Western Europe/Israel[69].

HAROSA II has been published (January 2020) and HAROSA I was submitted for publication in April 2020 and publication is anticipated later in 2020. No abstracts have been published or presented and there is little information in the public domain.

2.13.3 Internal validity

Internal validity of the evidence for pitolisant is high, both the HAROSA studies were placebo-controlled, therefore, we can be certain that there is no other explanation for the beneficial effect of pitolisant on ESS.

2.13.4 External validity

External validity of the evidence for pitolisant is high for a number of reasons.

- The primary end-point of both HAROSA studies was change in EDS as measured using the ESS. ESS is the gold standard for measuring sleepiness and is used in all clinical

trials in EDS. The ESS questionnaire is highly relevant to patients, since it assesses the likelihood of dozing off or falling asleep in everyday situations (sitting and reading, watching television, in public, in a car, whilst chatting to someone, sitting quietly or lying down to rest). Mean ESS was normalised in the pitolisant arm by the end of the double-blind period in both HAROSA studies, indicating that pitolisant in effective in reducing EDS as measured by a decrease in ESS.

- The population of the HAROSA studies is relevant to the English population[35]. Although the study excluded patients with serious CV disease (defined as recent myocardial infarction, angina, hypertension or dysrhythmias [within the previous 6 months], QT interval longer than 450 ms, history of left ventricular hypertrophy or mitral valve prolapse) and psychiatric illness, safety data from the two pivotal trials did not indicate any CV or psychiatric issues. It should also be noted that 56% of patients in HAROSA I and 54% of those in HAROSA II entered the studies with a history of non-serious CV disease.

However, the recent COVID-19 epidemic means that we were unable to seek the usual level of clinician input. We sought early advice (before the final scope) from an established clinician through several telephone conversations, which was incredibly helpful. To ensure robust advice from around England, we contacted a number of other clinicians were keen to support this work. However, the advent of COVID-19 and the impact on their workload, meant that these clinicians have been unable to work with us.

This has led to several areas of uncertainty, which we have attempted to validate using desk research.

- Use of MADs in clinical practice: guidance from NICE suggests that MADs are only suitable for patients with mild or moderate OSAHS. Given that MADs are not prescribed we have been unable to identify the true extent of their use in clinical practice. It should also be noted that MADs were not explicitly included in the scope for pitolisant[70].

- Our original SLR was carried out using the draft scope which did not include MAD as a comparator. Due to short time-lines we have carried out an additional SLR identifying SLR of MAD for efficacy and safety to inform our modelling. It should be noted that MAD were included in our original SLR for QOL, costs and healthcare interventions and previously published cost-effectiveness studies.

- The proportion of patients with EDS who refuse CPAP: we have robust data from clinical papers and clinician input that around 10-20% of patients suitable for CPAP refuse it[35,71]. There is some uncertainty around the proportion of refusers who had EDS, with estimates ranging from 95% to 50%, we have made a conservative assumption and assumed 50%[33,35].

2.13.5 Life expectancy

There are a paucity of studies looking at life expectancy in people with OSA and EDS. One US-based longitudinal cohort study in older people aged over 65 years found that those with sleep disordered breathing and EDS had a reduction in life expectancy (measured as difference in median survival) of around 5 years less than those with either sleep disordered breathing alone, EDS alone or neither[23]. Another long-term longitudinal study (Wisconsin Longitudinal Study) from the US found that there was a reduction in life expectancy of around 4 years over 10 years in older people with EDS at age 60[72]. These data are difficult to interpret since people with OSA and EDS commonly have co-morbidities e.g. obesity, diabetes, which may also impact on life expectancy.

The 18-year follow-up of a large prospective population-based cohort study (Wisconsin Sleep Cohort Study) also suggests that mortality is increased in people with OSA[73]. After correction for multiple confounders, this study estimated all-cause mortality rates as follows: no OSA: 2.85/1,000 person-years, mild OSA: 5.54/1,000 person-years, moderate OSA: 5.42/1,000 person-years and severe OSA: 14.6/1,000 person years. The British Lung Foundation suggests that people with moderate to severe OSA are likely to have EDS as a result of their condition[10] – if this is the case then people with severe OSA have all-cause mortality rates of over 5-times higher than people without OSA.

There is also now a reasonable body of evidence to suggest that people who have a short duration of sleep are at higher risk of CV morbidity and stroke and that the presence of OSA is associated with reduced life expectancy[20-22,74].

Furthermore, mortality is increased in motor vehicle drivers with EDS due to RTA[18].

2.13.6 Epidemiology

Narcolepsy

Pitolisant is already licensed for the treatment of narcolepsy with or without cataplexy in adults.

Ohayon et al reported on the results of a population survey carried out in five European countries between 1994 and 1999 and identified a point prevalence for moderate or severe narcolepsy of 0.047%[75]. However, given the small number of patients involved, there is significant uncertainty around the precision of this estimate. A database study carried out in the USA by the same lead author looked a much larger population over the period 2008-1010[76]. The total population at risk in the final year assessed (2010) was 176.2 million; in this group, the authors identified 77,616 patients with a diagnosis of narcolepsy. This yields a point prevalence of 0.044%. The US result provides considerable reassurance for the validity of the European estimate, giving an estimated prevalence of moderate and severe narcolepsy in England of 56 million x 0.047% = 26,309.

A significant proportion of patients with narcolepsy remain undiagnosed and therefore untreated. Clinician advice sought for the sodium oxybate submission to Scottish Medicines Consortium[77] suggests that only around 20% of patients (n=5,262) will have received a formal diagnosis. This represents the baseline population who would be potentially eligible for treatment with pitolisant for narcolepsy

EDS due to OSA

In 2014 the British Lung Foundation estimated that there were 1.5 million people in the UK with OSA, of whom 45% (675,000 people) have moderate and severe OSA and are eligible for CPAP[10].

A significant proportion of patients with OSA remain undiagnosed and therefore untreated. The British Lung Foundation suggest that in 2014, in the UK, around half of all eligible adults were receiving CPAP. Assuming that use is uniformly spread throughout the UK, this would equate to 284,367 people in England.

Within this population, evidence suggests that 6-9% of people have residual EDS[32,33]. Therefore, we can estimate that there are between 17,100 and 25,600 people in England with moderate to severe OSA receiving CPAP have residual EDS and are eligible for treatment with pitolisant. We have assumed a mid-point estimate of 21,300.

Estimating the number of patients with EDS who refuse CPAP is more difficult due to the paucity of published data. Data from the US suggests that 17% of patients refuse CPAP, defined as refusal to use or continue CPAP[71]. Expert opinion from the UK suggests that around 5% of patients refuse CPAP without trying it and a further 5-10% take the CPAP machine home, but do not engage with treatment[35]. Given that newer CPAP machines include technology so that patients can be remotely monitored by the clinic[45] which has improved engagement with CPAP[35], we have assumed that 15% of eligible patients refuse CPAP. Therefore, we can estimate that 42,655 will refuse CPAP. Of these, clinical opinion suggests that 95% to 50% will have EDS[33,35]. We have taken a conservative approach and used 50% in our estimates, suggesting that there are 21,300 patients with EDS due to OSA who refuse CPAP who would be suitable for treatment with pitolisant.

The total patient population suitable for treatment with pitolisant for EDS due to OSA in England is therefore around 42,600.

Overall population for pitolisant

The overall population is therefore, 5,262 for narcolepsy and 42,600 for EDS due to OSA, giving a total of 47,862.

B. 3. Cost effectiveness

B.3.1 Published cost-effectiveness studies

Details of identification of the studies and a description of the identified studies is reported in in Appendix G.

Eleven studies were identified, of which four were UK-based. Details of the UK-based studies can be found below in Table 22. Details of the remaining studies can be found in Appendix G (Table 29 and Table 30).

Table 22: Summary list of published cost-effectiveness studies: UK based studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Guest[78]	2008	Markov model with 7 health states: event-free uncontrolled OSA, event-free controlled OSA, stroke, RTA, CV event, survival after stroke, RTA or CVD event and dead, with a 14-year time horizon and 1-year cycle length	55 years with severe OSA and EDS	QALYs after 14 years of CPAP or no treatment: CPAP = 8.09 (95% CI 7.17 to 8.44) No treatment = 7.22 (95% CI 6.48 to 7.93)	Expected discounted health care costs over 14 years following CPAP or no treatment: Clinician visits for OSA: CPAP = £682.22, No treatment = £0 Devices: CPAP = £1794.52, No treatment = £0 Diagnostic sleep studies: CPAP = £123.60, No treatment = £0 Resources required to manage CV events: CPAP = £546.50, No treatment = £1044.67 Resources required to manage strokes: CPAP = £4961.12, No treatment = £7203.58 Resources required to manage RTAs: CPAP = £1546.29, No treatment = £2396.77 Total: CPAP = £9672.25, No treatment = £10,645.02	Cost per QALY gained Year 1 = >£25,000 Year 2 = approximately £10,000 Dominant by year 13.

Weatherly[79,80]	2009	Markov state-transition cohort model that compared the cost-utility of CPAP with dental devices and conservative management in OSA in the UK over a lifetime horizon from the perspective of the NHS and Personal Social Services. The health states were OSA, OSA post CHD event, OSA post-stroke and dead, with RTAs as additional events and cost and utility data came largely from previous NICE submissions.	50-year-old men or women with confirmed OSA	Total QALYs in 50-yr old men: Conservative management = 11.93 Dental device = 12.26 CPAP = 12.39 Total QALYs in 50-yr old women: Conservative management = 12.71 Dental device = 13.02 CPAP = 13.15	**Costs in 50-yr old men** **Conservative management** Treatment costs = £21 RTA costs = £2,201 CVD event costs = £5,918 Total costs = £8,140 **Dental device** Treatment costs = £1,726 RTA costs = £1,138 CVD event costs = £5,932 Total costs = £8,787 **CPAP** Treatment costs = £2,465 RTA costs = £904 CVD event costs = £5,931 Total costs = £9,301 **Costs in 50-yr old women** **Conservative management** Treatment costs = £21 RTA costs = £2,139 CVD event costs = £5,840 Total costs = £7,999 **Dental device** Treatment costs = £1,824 RTA costs = £1,108 CVD event costs = £5,829 Total costs = £8,762	**ICER in 50-yr old men** Dental device: ICER = £2,000/QALY vs conservative management CPAP: ICER = £3,899/QALY vs dental device overall **ICER in 50-yr old women** Dental device: ICER = £2,432/QALY vs conservative management CPAP: ICER = £4,335/QALY vs dental device

					CPAP Treatment costs = £2,608 RTA costs = £878 CVD event costs = £5,820 Total costs = £9,306	
Sharples[81]	2014	A critique of an economic evaluation conducted as part of an RCT evaluating the cost-utility of three non-adjustable MADs in patients with OSA of any severity, from the NHS perspective in the UK. The model compared treatment with no treatment with a 4-week time horizon with outcomes based on ESS and FOSQ measures of sleepiness.	Patients attending or newly referred to a hospital with OSA and ESS ≥9	The 4-week QALY is calculated as a 4-week proportion of the 52-week year, i.e. QALY = (4 × utility score)/52 Mean baseline QALYs based on SF-6D scores: No treatment = 0.053 SP2 = 0.057 bMAD = 0.053 SP1 = 0.052 Total utility (based on EQ-5D-3L) over 4 weeks, mean (SE): No treatment = 0.0649 (0.0017) SP1 = 0.0658 (0.0017) SP2 = 0.0658 (0.0019) bMAD = 0.0667 (0.0017)	Unit costs were taken from NHS supply prices, NHS Agenda for Change pay scales 2011/12, NHS Reference Costs, and manufacturer costs. Total costs over 4 weeks reported as mean (SE): No treatment = £78.50 (£19.97) SP1 = £74.64 (£10.47) SP2 = £63.43 (£8.05) bMAD = £104.89 (£24.39)	ICERs were negative for SleepPro1 and SleepPro2 compared to no treatment. ICER (based on EQ-5D-3L): bMAD = £14,876/QALY ICER (based on SF-6D): bMAD = £30,743/QALY
Sharples[81]	2014	adaptation of an existing cost-utility model to compare non-adjustable MADs, CPAP and conservative management in patients with OSA from the NHS	50-year-old men who drive with newly diagnosed or existing OSA of any severity; baseline ESS score = 11.9	ESS scores were mapped to EQ-5D-3L and SF-6D values using regression analyses, indicating a unit fall in ESS score is associated with an increase in utility, based	Mean costs: Intervention: Conservative management = £36, MAD = £3206, CPAP = £3524 RTA: Conservative management = £1963,	Base case ICER: MADs vs Conservative management = £6687 CPAP vs MADs = 15,367

		and personal social services perspective in the UK. The MADs used were Sleep Pro 1, Sleep Pro 2 and a bespoke MAD. The Markov model had 4 health states: OSA, OSA after CHD event, OSA after stroke and dead, with three events: CVD events, stroke and RTAs. The model had a 4-year time horizon and 1-year cycle length and applied a 3.5% discount rate		on a SF-6D (n = 294) value of 0.0095 (95% CI 0.0070 to 0.0123) and based on an EQ-5D-3L (n = 94) value of 0.0097 (95% CI 0.0019 to 0.0175).	MAD = £713, CPAP = £716 CV Event: Conservative management = £4118, MAD = £4103, CPAP = £4074 Total costs: Conservative management = £6116 MAD = £8022 CPAP = £8307	

B.3.2 Economic analysis

In order to inform prior NICE guidance on the use of CPAP in OASHS, a de novo economic model from the perspective of the NHS was developed by the University of York. This was subsequently published in 2009 by McDaid et al[80]. A subsequent economic analysis carried out by Sharples et al comparing MADs to CPAP used the same fundamental model structure, extending it to include efficacy data for MADs derived from a systematic review[81].

Given that the underlying model was developed to specifically meet the needs of NICE and has become the de facto default approach for assessing these technologies in the UK, we would have needed a powerful reason to re-design the model for the purposes of this submission. The structure, health states, assumptions and many of the input parameters within the York model were therefore incorporated unaltered into our own economic analysis.

The previously published versions of the York model[80,81] did not incorporate any assessment of pharmaceutical treatment options, but the structure was not device-specific and therefore adaptation of the structure to incorporate efficacy data for pitolisant was achieved without complication. The full range of input parameters was re-evaluated, with appropriate updates being made. Other than this, the results obtained should be directly comparable with the two previous iterations of the model.

3.2.1 Patient population

Pitolisant is likely to be granted a licence for the treatment of EDS in patients with OSA and treated by CPAP but still complaining of EDS, or in patients with OSA refusing/not tolerating CPAP[1].

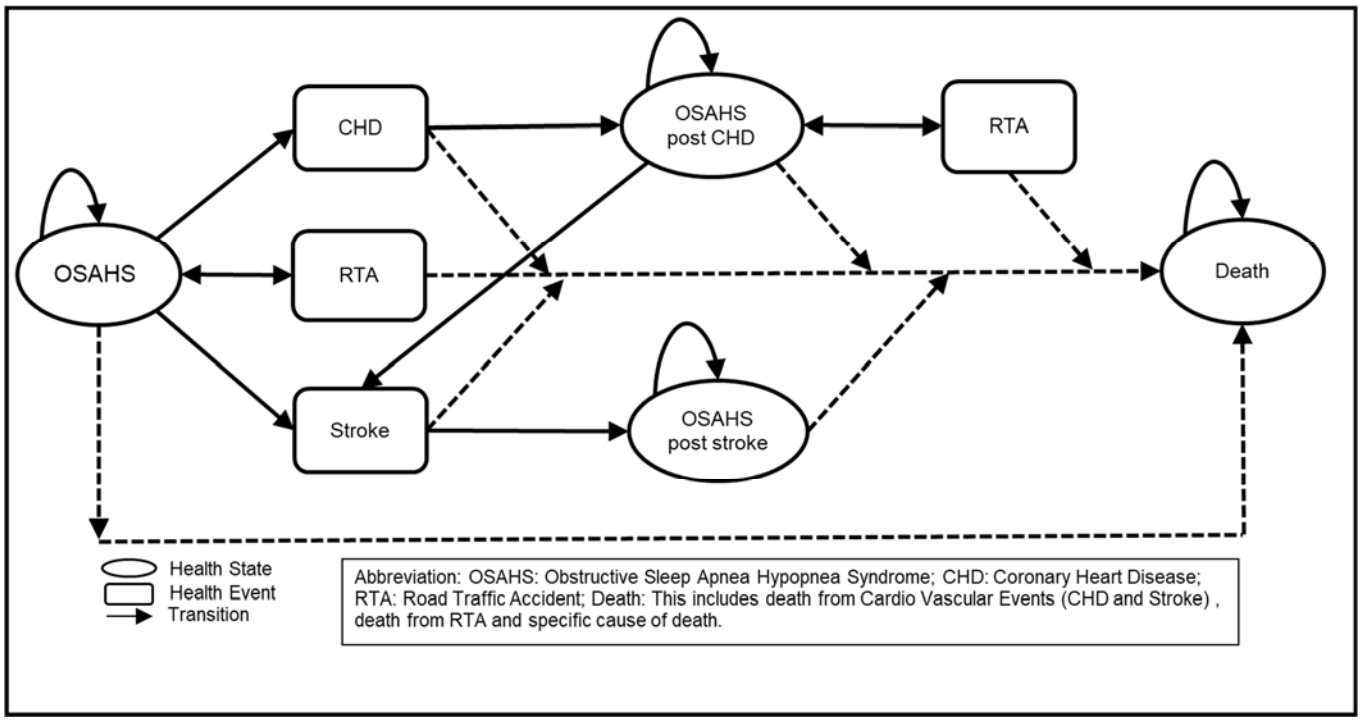
For the economic model, the base case analysis is based on the licence, which reflects the two key studies for pitolisant

- HAROSA I: adult patients with moderate or severe OSAHS, with residual EDS despite treatment with CPAP for a minimum period of 3 months
- HAROSA II: adult patients with EDS due to OSA who refuse the use of CPAP

3.2.2 Model structure

Figure 7 provides a diagrammatic representation of the model. Elliptical boxes represent health states and square boxes represent events. Arrows show the direction of transitions between health states and the occurrence of events. All members of the cohort started in the OSAHS state and could stay in that state, unless a transition occurred, until death.

Figure 7: Pitolisant model structure



Patients could move into the post-CHD state if they experienced an acute CHD event and survived. This state allowed for the increased morbidity and mortality associated with having had a CHD event. If they did not survive, they moved to the absorbing death state. If they did survive, they could remain in this post-CHD state until death or they experienced a fatal or non-fatal RTA or suffered a stroke. If they survived a RTA, they remained in the same health state post-event. If they survived a stroke, they moved to the post-stroke state, where they were again able to remain until death. They were not able to move back to a CHD state once they had suffered a stroke.

Patients could suffer a stroke while in the initial OSAH state, in which case, if they survived, they would move to the post-stroke health state and be subject to the increased risk of mortality and morbidity following their event. It was assumed that patients in the post-stroke state would stop driving, and therefore, were not able to experience fatal or non-fatal RTA.

Patients in the initial OSAHS state may at some point experience a RTA and, provided it was not fatal, would stay in the OSAHS state until another transition or death.

Movements between states were determined by a set of transition probabilities, derived from various sources. In the base case, transitions relating to the risk of CHD and stroke were informed by the QRISK 3[82], QStroke[83] and Framingham predictive models[84,85], utilising information on baseline characteristics of the patients in the pitolisant treatment groups in HAROSA I and HAROSA II.

Table 23: Features of the economic analysis

Factor	Chosen values	Justification
Time horizon	25 years	Given that OSAHS is a chronic disease, it is appropriate to use a long-term time horizon, in order to capture the long-term impact of treatments on the incremental cost-effectiveness ratio (ICER). A time horizon of 25 years was deemed reasonable given that the average age of patients with OSAHS is around 55 years old in the model. Summing the average age of the cohort and the time horizon gives a number close the life expectancy for men in the UK (75% of patients in the model are male), which is around 80 years.
Cycle length	1 year	Standard for similar models, Sharples et al, 2014[81] and McDaid et al, 2009[80]
Treatment waning effect?	Lifetime effect	It was assumed that patients are on pitolisant treatment for the rest of their life.
Source of utilities	Brazier et al, 2002[86]	Algorithm that allows us to map the improvement in ESS score to HRQOL
Source of costs (see Section 3.5)	Cost of pitolisant from manufacturer Cost of MAD – updated costing based on published manufacturer estimates Cost of outcomes (RTA, CHD + stroke) sourced from the literature	Sources chosen were to ensure consistency with previous UK models (NICE[28], Sharples et al, 2014[81]) for comparative purposes

3.2.3 Intervention technology and comparators

Table 24 lists the intervention technology (pitolisant) and the comparators: BSC for the base case and MAD for a scenario analysis for patients with EDS due to OSA refusing CPAP.

Pitolisant should be used at the lowest effective dose, depending on individual patient response and tolerance, according to an up-titration scheme, without exceeding the dose of 18 mg/day[d].

Table 24: Intervention technology and comparators

Treatment	Dosage regimen
Pitolisant (oral)	4.5, 9 and 18 mg per day
BSC	-
MAD (scenario analysis)	Bespoke MADs supplied by the NHS

[d] The dosage in the clinical studies for pitolisant were 5 mg and 20 mg. The 5 mg tablet contains 5 mg of pitoilsant hydrochloride which equates to 4.45 mg of pitolisant as the active substance, the 20 mg tablet contains 20 mg of pitoilsant hydrochloride which equates to 17.8 mg of pitolisant as the active substance. The doses for labelling consider the active substance and have been rounded up to 4.5 mg and 18 mg, respectively.

B.3.3 Clinical parameters and variables

The source of evidence for each parameter in the model were retrieved from systematic literature reviews, meta-analysis and RCTs (HAROSA I and HAROSA II).

The HAROSA I and HAROSA II studies provided evidence on intermediary outcomes in terms of ESS score but did not measure the treatment effects in terms of their impact on utility, risk of CV events (CHD and stroke) or RTAs.

Baseline ESS was estimated by using ESS score in the placebo arm of each study after 12 weeks of double blind treatment (11.9 in HAROSA I and 12.1 in HAROSA II), see Table 9.

3.3.1 Estimating the risk of CV events

HAROSA I and HAROSA II provided information on the effect of pitolisant on ESS score. The implications of a decrease in ESS on CV events must be estimated to use in the economic model.

The Framingham (UK version), QRISK 3 and QStroke[82-85,87] equations provide a link between risk factors such as blood pressure and the incidence of non-fatal CV events.

The risk of CHD and stroke were predicted using the UK version of the Framingham risk equations[87], and this was used in the base case of the model. The baseline risk equations for Framingham score were estimated separately for men and women using the characteristics of patients treated with pitolisant in HAROSA I and HAROSA II as presented in Table 25 below. When data were not available, plausible assumptions were used. The weighted average risk of CV events was then computed relatively to the distribution of men and women in the HAROSA I and HAROSA II studies.

Table 25: Ten-year risk of CHD and stroke for patients in pitolisant arm (baseline risk)

Characteristics	HAROSA I	HAROSA II
Age	54	52
Total cholesterol (mg/dl)	169	169
HDL cholesterol (mg/dl)	42	42
Systolic blood pressure (mmHg)	129	127
Atrial fibrillation present?	No	No
On antihypertensive treatment?	No	No
History of smoking in past year?	Yes	Yes
History of diabetes?	No	No
History of CHD, congestive heart failure or peripheral vascular disease?	No	No
Left ventricular hypertrophy on ECG?	No	No
10-year probability of CHD event	13.5% (Male); 9.1% (Female)	12% (Male); 8.1% (Female)
Annual probability of CHD event (Weighted average)	1.3%	1.2%
10-year probability of stroke	5.2% (Male); 2.5% (Female)	4.6% (Male); 2.1% (Female)
Annual probability of stroke event (Weighted average)	0.5%	0.4%

A scenario analysis has been included using QRISK 3 and QStroke. The published risk equations predict the risk of CV events and stroke using QRISK 3 (10-year risk) and QStroke (1-year risk) as a function of systolic blood pressure (SBP).

The QRISK 3 equation estimates the overall risk of CV events. In order to estimate the specific risk of CHD, the risk of stroke or transient ischaemic attack obtained from the QStroke equation was subtracted from the risk of CV events obtained from the QRISK 3 equation.

The baseline risk equations for QRISK 3 and QStroke were estimated separately for men and women using the characteristics of patients treated with pitolisant in HAROSA I and HAROSA II as presented in Table 26 and Table 27 below. When data were not available, plausible assumptions were used. The weighted average risk of CV events was then computed relatively to the distribution of men and women in the HAROSA I and HAROSA II studies.

Table 26: Ten-year risk of CV events for patients in the pitolisant arms of the HAROSA studies (baseline risk)

Characteristics	HAROSA I	HAROSA II
Age	54	52
Ethnicity	White or not stated	White or not stated
Smoking status	Moderate smoker	Moderate smoker
Diabetes status	none	none
Cholesterol/HDL ratio	5	5
Systolic blood pressure (mmHg)	129	127
Standard deviation of at least two most recent systolic blood pressure readings (mmHg)	12	11
Height (cm)	173	171
Weight (kg)	98	97
Ten-year probability of CV events	12.7% (Male), 7.5% (Female)	10.9% (Male), 6.3% (Female)
Annual probability of CV events (Weighted average)	1.2%	0.1%

Table 27: One-year risk of stroke for patients in pitolisant arms of the HAROSA studies (baseline risk)

Characteristics	HAROSA I	HAROSA II
Age	54	52
Ethnicity	White or not stated	White or not stated
Smoking status	Moderate smoker	Moderate smoker
Diabetes status	none	none
Cholesterol/HDL ratio	4	4
Systolic blood pressure (mmHg)	129	127
Height (cm)	173	171
Weight (kg)	98	97
Annual probability of stroke	0.3% (Male), 0.2% (Female)	0.2% (Male), 0.2% (Female)
Weighted average	0.275%	0.2%

It was assumed that the risk of CV events was independently predicted by the difference in ESS score. In addition, the baseline risk of CV events in the model were based on the risks observed in patients treated with pitolisant, the baseline risks were subsequently used to estimate the incremental or decremental risk of CV events in patients receiving BSC or MAD depending on the direction and size of the difference in ESS score.

Loke et al[88]. conducted a meta-analysis which included nine prospective studies (n=8,400) and investigated the association between OSAHS and the risk of CV disease. The results suggested an association between OSAHS and stroke (OR: 2.24, 95%CI: 1.57 to 3.19) and CHD (OR: 1.56, 95%CI 0.83 to 2.91).

Sharples et al[81]. conducted a meta-analysis which investigated the association between CPAP and the reduction in ESS score relative to BSC. This meta-analysis suggested that the use of CPAP significantly reduced the ESS score compared with BSC (effect size ESS: -2.23, 95% CI: -2.75 to -1.71).

We assumed that the increased risk of CV events reported by Loke et al[88]. was matched by the risk reduction observed in patients treated with CPAP, as previously assumed in NICE guidance (TA139)[28]. We also assumed that this reduction was uniquely and independently explained by the difference in terms of ESS score between CPAP and its comparators (BSC and MAD).

Given the paucity of direct evidence related to the relative risk of CV events between pitolisant and its comparators (BSC and MADs), we estimated the relative risk of stroke and CHD between pitolisant and BSC by taking the ratio of ESS scores for pitolisant and CPAP treatment, both compared with BSC, applied to the odds ratio for stroke and CHD reported by Loke et al[88]. The same approach has been applied to estimate the relative risk of CVEs between pitolisant and MAD. This reflects the approach adopted by Sharples et al[81] in their economic model exploring the cost effectiveness of MADs.

Given that QRISK 3 and the Framingham study provided a 10-year risk of CV events, this was converted into a constant yearly probability to match the cycle length used in the model. In order to derive the 1-year probability of CV events, it was assumed that survival followed an exponential distribution.

3.3.2 Estimating the risk of RTAs

We used an indirect approach to estimate the impact of pitolisant on fatal and non-fatal RTAs because of the lack of direct evidence.

The impact of CPAP on RTAs has been extensively reported in the literature[89,90]. Meta-analysis to assess the association between the treatment of OSAHS with CPAP and the risk of RTAs suggested that the risk of RTAs is significantly reduced in patients treated with CPAP (OR: 0.168, 95%CI: 0.1 to 0.23) compared to patients treated with BSC.

The risk of non-fatal RTA was reported in the Department for Transport report *Reported Road Casualties Great Britain: 2018 Annual Report*[91]. We assumed that the risk of non-fatal RTA observed in patients treated with pitolisant was similar to the risk observed in the general public in Great Britain and used this as the baseline risk in the model. The incremental risk of non-fatal RTAs for patients in the BSC and MAD groups was estimated using the same approach used to estimate the risk of CV events.

Table 28 below reports the risk of non-fatal RTAs applied to each treatment arm.

Table 28: Risk of non-fatal RTAs

Parameter	Probability	95% CI	Source
Annual probability of non-fatal RTA in pitolisant + BSC group (baseline population estimate)	0.36%		Department for Transport, 2018[91]
Annual probability of non-fatal RTA in BSC (HAROSA I, placebo arm)	2.89%	1.94% - 5.45%	Computed from the baseline estimate
Annual probability of non-fatal RTA in BSC (HAROSA II, placebo arm)	4.32%	2.68% - 9.17%	
Annual probability of non-fatal RTA in MAD (scenario analysis)	0.98%	0.81% - 1.32%	

We assumed that the ESS score was an independent predictor of the risk of RTAs. In order to derive the relative risk of RTAs for patients treated with pitolisant compared with patients treated with the comparators (BSC and MAD), the ratio of ESS scores for pitolisant and CPAP treatments – both compared with BSC - was applied to the odds ratio for RTA of CPAP with BSC. The same approach was applied to derive the relative risk of RTAs between pitolisant and MAD.

3.3.3 Estimating mortality rates

Table 29 reports annual rates of fatal CHD, stroke and RTAs.

Table 29: Parameters associated with fatal CHD, stroke and RTAs

Parameter	Probability	95% CI	Source
Annual probability of death following CHD	2.12%	2.08%-2.15%	Smolina et al, 2012[92]
Annual probability of death following stroke	4.91%	4.67%-5.13%	Crichton et al, 2016[93]
Annual probability of fatal CHD (death occurring within 30 days in event of acute CHD)	10.2%	-	Read et al, 2019[94]
Annual probability of fatal stroke (death occurring within 30 days in event of acute stroke)	26.4%	-	Seminog et al, 2019[95]
Annual probability of fatal RTA with pitolisant (baseline)	0.006%	-	Department for Transport, 2018[91]
Annual probability of fatal RTA with BSC (HAROSA I, placebo arm)	0.044%	-	Computed from the baseline estimate
Annual probability of fatal RTA with BSC (HAROSA II, placebo arm)	0.066%	-	
Annual probability of fatal RTA with MAD	0.015%	-	

The mortality rate for individuals who have not experienced CHD or stroke (by age and sex) was taken from the 2017-2018 UK life tables[96]. For each age band, the all-cause hazard was reduced by the proportion of patients dying of CHD and stroke.

For patients in post-CHD and post-stroke health states, the annual probability of death was computed from the 30-day mortality from Read et al[94] for CHD and Seminog et al[95] for stroke, with longer-term risk of death taken from Smolina et al[92] for CHD and Crichton et al[93]

for stroke. Annual rates were estimated assuming an exponential distribution of the risk of death following CV events.

The risk of fatal RTA was reported in the Department of Transport report *Reported Road Casualties Great Britain: 2018 Annual Report*[91]. It was assumed that the risk of fatal RTA seen in patients treated with pitolisant was similar to the risk observed in the general public in Great Britain and used as a baseline risk in the model. The incremental risk of fatal RTAs for patients in BSC and MAD groups was estimated using the same approach applied to estimate the risk of CV events.

B.3.4 Measurement and valuation of health effects

3.4.1 HRQOL data from clinical trials

An analysis linking the short-term outcome measures of clinical effectiveness to a preference-based measure of HRQOL in terms of utility was required. The HAROSA I and HAROSA II studies provided evidence intermediary outcomes in terms of ESS score but did not measure the treatment effect of pitolisant in terms of its impact on utility.

Therefore, a model was required to map the available clinical data to long-term outcomes, HRQOL and costs in order to estimate the long-term cost-effectiveness of treatment with pitolisant relative to its comparators (BSC and MAD) in the model.

3.4.2 Mapping

The NICE reference case indicates that the measure of health outcome used in the cost-effectiveness analysis should be quality adjusted life years (QALYs) calculated with utility values derived from validated generic, preference-based measures of HRQOL.

Across published RCTs in OSAHS the ESS score is the gold standard measurement of EDS and the most frequently reported efficacy measure. Previously published economic models have mapped the mean change in ESS score to utility change[80,81], an approach used by NICE in the assessment of the cost effectiveness of CPAP (NICE TA139)[28].

Of the two models, the population assessed within the York model[80] is the best match for those eligible for treatment with pitolisant. The mapping regression models developed in this publication are shown Table 30 (mapping from EQ-5D) and Table 31(mapping from SF-6D).

In accordance with the NICE reference case, the EQ-5D version was used for the base case, with the SF-6D mapping being offered in a scenario analysis. ESS score changes derived from the pivotal pitolisant RCTs (HAROSA I and HAROSA II) were used to map incremental utility versus BSC, with the same approach being adopted using the results of the ITC comparing pitolisant versus MAD, to populate the output of the MAD scenario.

Table 30: Ordinary least squares (OLS model) for mapping ESS scores to utility based on EQ-5D-3L

OLS model for utility based on EQ-5D-3L			
Utility	**Coefficient**	**SE**	**95% CI**
ESS	-0.01	0.004	-0.018 to -0.002
Baseline ESS	0.003	0.003	-0.004 to 0.01
Constant	0.893	0.029	0.836 to 0.949

Table 31: OLS model for mapping ESS scores to utility based on SF-6D

OLS model for utility based on SF-6D			
Utility	**Coefficient**	**SE**	**95% CI**
ESS	-0.01	0.001	-0.012 to -0.007
Baseline ESS	0.005	0.001	0.003 to 0.007
Constant	0.807	0.011	0.784 to 0.829

The utility decrements associated with stroke, CHD and age were based on the regression analysis reported by Sullivan et al[12]. and are reported in Table 32 below. This mirrors the approach used by McDaid et al in the York model[80]. Utility decrements/increments are applied to the baseline utility, based on patients receiving BSC, to reflect the utility associated with being in any health state in the model. In the absence of specific data, it was assumed that patients in the period following an acute CHD or stroke event would have similar utilities to that seen in the post-CHD and post-stroke health states. This was a conservative assumption as we should normally expect patients in acute state to have a lower utility than the utility observed in the post-event states.

Table 32: Utility scores used in the base case analysis

Utility	**Mean**	**Source**
OSAHS BSC – baseline (HAROSA I and HAROSA II)	Baseline ESS x -0.01 + 0.893	Estimated from prediction equation (Table 30)[80]
OSAHS treated with pitolisant – change from baseline (HAROSA I and HAROSA II)	$\Delta ESS_{Pitolisant\text{-}BSC}$ x -0.01	Estimated from prediction equation (Table 30)[80]
OSAHS treated with MAD – change from baseline (HAROSA II), used in scenario analysis	$\Delta ESS_{Pitolisant\text{-}MAD}$ x -0.01	Estimated from prediction equation (Table 30)[80]
CHD (absolute decrement)	-0.064	Sullivan et al, 2006[12].
Stroke (absolute decrement)	-0.052	Sullivan et al, 2006[12].
Non-fatal RTA	0.62	Currie et al, 2005[97]
Age (annual decrement)	-0.0007	Sullivan et al, 2006[12].

The utility associated with experiencing an RTA was based on EQ-5D measures from the Health Outcomes Data Repository, as reported by Jenkinson et al[98].

The EQ-5D-3L was the HRQOL instrument used in the base case analysis.

3.4.3 HRQOL studies

Appendix H describes how systematic searches for relevant health-related quality-of-life data were carried out and the relevant results.

A total of 24 relevant studies were found in populations with OSA. In 13 studies, patients also were specified to have EDS, usually defined as an ESS score of ≥9 or 10. The most commonly-used QOL tools were SF-36 and EQ-5D. Other tools used were EQ-VAS, SF-12, SF-6D, 15D and standard gamble interviews.

The quantitative results of these studies are presented in Tables 33-38; Appendix H.

EQ-5D assessments were carried out as part of the HAROSA I and HAROSA II studies. However, only the results of the VAS element of the questionnaire were presented by the authors, which cannot be considered a substitute for the summary index derived from the full health state profile, as it is not calibrated to societal valuation norms. For this reason, the study-specific data could not be used to populate the economic model. The ESS mapping approach adopted instead (described in paragraph 3.4.2) reflects the approach adopted in previous NICE submissions, specifically TA139[28].

3.4.4 Adverse reactions

There was no evidence of a specific AE signal associated with pitolisant versus placebo in the HAROSA pivotal trials (See paragraph 2.10.2). Of particular note, given reported CV risk issues associated with other treatments in this therapeutic area, the use of pitolisant is not associated with any change in SBP, diastolic blood pressure or heart rate.

For the base case comparisons, all other aspects of care were identical:

- Pitolisant + CPAP + BSC versus CPAP + BSC care
- Pitolisant + BSC versus BSC alone

We therefore did not include an element of AE impact on either utilities or costs in our model.

For the scenario comparison versus MAD it is possible, although unlikely, that there are significant technology-specific AE impacts associated with the MAD device. In the absence of evidence, however, we once again assumed that the utility and cost impact of any effects would be negligible compared to the long-term benefits of treatment and therefore did not factor this into the model.

3.4.5 HRQOL data used in the cost-effectiveness analysis

The utility values for the health states were based on OLS models for mapping ESS scores and utility based on EQ-5D-6L and SF-6D as reported in McDaid et al[80].

The baseline utility in the economic model was estimated based on the mean ESS score of patients in the BSC treatment group, and the approaches used to derive the utility estimates are described above in section 3.4.2.

Table 33 below reports the predicted utility in associated with the OSAHS, post-CHD, post-stroke and RTA health states.

Table 33: Summary of utility values for cost-effectiveness analysis

State	**Utility value: mean (standard error)**	**95% confidence interval**	Reference in submission (section and page number)	Justification
Health states with pitolisant - HAROSA I (EQ-5D-3L)				
OSAHS	0.803 (0.066)	0.673; 0.932	3.4.2	Derived from OLS regression model mapping ESS scores and utility (EQ-5D-3L)
Post-CHD	0.75 (0.066)	0.621; 0.880	3.4.2	
Post-stroke	0.739 (0.066)	0.610; 0.869	3.4.2	
Health states with pitolisant - HAROSA II (EQ-5D-3L)				
OSAHS	0.802 (0.066)	0.673; 0.932	3.4.2	

Post-CHD	0.750 (0.066)	0.620; 0.880	3.4.2	Derived from OLS regression model mapping ESS scores and utility (EQ-5D-3L)
Post-stroke	0.739 (0.066)	0.609; 0.869	3.4.2	
Health states with BSC – HAROSA I (EQ-5D-3L)				
OSAHS	0.777 (0.076)	0.628; 0.927	3.4.2	Derived from OLS regression model mapping ESS scores and utility (EQ-5D-3L)
Post-CHD	0.725 (0.077)	0.575; 0.875	3.4.2	
Post-stroke	0.714 (0.077)	0.564; 0.864	3.4.2	
Health states with BSC – HAROSA II (EQ-5D-3L)				
OSAHS	0.775 (0.077)	0.624; 0.927	3.4.2	Derived from OLS regression model mapping ESS scores and utility (EQ-5D-3L)
Post-CHD	0.723 (0.077)	0.571; 0.874	3.4.2	
Post-stroke	0.712 (0.077)	0.560; 0.863	3.4.2	
Scenario analysis: Health states with MAD – HAROSA II (EQ-5D-3L)				
OSAHS	0.789 (0.072)	0.649; 0.930	3.4.2	Derived from OLS regression model mapping ESS scores and utility (EQ-5D-3L)
Post-CHD	0.737 (0.071)	0.597; 0.877	3.4.2	
Post-stroke	0.726 (0.071)	0.586; 0.866	3.4.2	

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Appendix I describes how relevant cost and healthcare resource data were identified.

The costs included in the model were costs associated with the interventions, the cost associated with NHS healthcare related to OSAHS (CHD, stroke, fatal and non-fatal RTAs).

The cost of CHD events (acute CHD events and post-CHD) and fatal CV events were taken from an evaluation of cardiac medication published by Briggs et al[99], as per the work carried out by McDaid et al[80] and Sharples et al[81]. Given that the costs were reported in prices related to 2006, they were uprated to the 2018/2019 prices using the NHS cost inflation index[100].

The cost of acute stroke and post-stroke were obtained from Xu et al[101], an analysis of data from the Sentinel Stroke National Audit programme based on stroke care in England, Wales and Northern Ireland in 2015-16. They reported the mean health care cost at 1 year (£13,452) and 5 years (£17,963). In order to estimate the ongoing cost of stroke beyond year 1, the year 1 health care cost (£13,452) was subtracted from the 5-year health care cost (£17,963), with the result (£4,511) being divided by four to yield a figure of £1,128 for years 2-5. It was assumed that the ongoing cost remained constant over the following years.

Breakdown of the above costs in terms of acute cost of CHD and stroke and the ongoing cost of CHD and stroke is presented in Table 34 below.

The costs of fatal and non-fatal RTAs were computed using data obtained from the Department of Transport report *Reported Road Casualties Great Britain: 2018 Annual Report*[91], and they are also reported in Table 34 below.

Table 34: Mean cost associated with CHD, stroke and RTAs

Parameters	Mean cost	95% CI	Source
Cost of fatal CV events	£3,813	£2,902 to £4,724	Briggs et al, 2007[99]
Year 1 cost of CHD	£12,619	£11,559 to £13,679	Briggs et al, 2007[99]
Ongoing cost of CHD (years 2-5)	£933	£649 to £1,217	Briggs et al, 2007[99]
Year 1 cost of stroke	£13,452	£4,391 to £26,902	Xu et al, 2017[101]
Ongoing cost of stroke (years 2-5)	£1,128	£468 to £2,630	Xu et al, 2017[101]
Fatal RTA per patient	£6,289	-	Computed
HAROSA I: Non-fatal RTA per patient	£4,745	-	Computed
HAROSA II: Non-fatal RTA	£4,745	-	Computed

3.5.1 Intervention and comparators' costs and resource use

Table 35 below shows the treatment costs for pitolisant and MADs.

Table 35: Cost of pitolisant and MAD

Treatment	Dose regimen	PAS discount	Mean cost per year
Pitolisant (list price)	5, 10 and 20 mg per day	None	[redacted]
MAD	-	N/A	£687

Pitolisant costs are based on the manufacturer's proposed list price of [redacted]

For the BSC comparator arm, a zero incremental cost was assumed. In both the pivotal studies, all patients received BSC in addition to their randomised treatment – in combination with CPAP in HAROSA I or alone in HAROSA II. Consequently, any associated BSC (or CPAP) expenditure will not be a determinant of the incremental cost of pitolisant and was therefore not modelled.

. Three types of MAD are available:

- Thermoplastic device – self fitted
- Semi-bespoke device – patient-administered dental impression sent to manufacturer
- Bespoke device – in-clinic dental assessment, followed by specialist manufacture

Our clinical advisers inform us that NHS Sleep Clinics that provide funded MADs would be expected to follow the full bespoke model. The specific costs of provision of MADs are not specified within the NHS tariff, nor is it listed in the NHS reference costs. We therefore used the approach adopted in a previously published model (Sharples et al)[81] to estimate the cost of a bespoke MAD.

The authors of this model quote a manufacturer of the bespoke MAD, who estimated that a grade 6-8 technician in an NHS maxillofacial laboratory would be expected to take on average 7 hours to produce the MAD from the patient's dental mould. According to PSSRU[100], the current cost per hour of a band 8d professional ranges from £112-£115. In the absence of a specific value for a maxillofacial technician, we applied the lowest of these

estimates. Table 36 below outlines the overall estimated costs for a bespoke MAD, applying updated costs to the approach adopted in the TOMADO study.

Table 36: Cost estimate for bespoke MAD

Item	Unit cost	Total cost	Source
Assessment and measurement: Maxillofacial consultant – first appointment	£147	£147	NHS Tariff – Outpatient attendance prices 2019-2020[102]
Manufacturing cost 7 hours band 8d	£112	£784	PSSRU. Unit costs of health and social care[100]
Total device cost		**£931**	
Follow-up (x1 per year) Maxillofacial consultant – follow-up appointment	£66	£66	NHS Tariff – Outpatient attendance prices 2019-2020[102]
Annualised cost of MAD **Assumes 18-month device lifespan**		**£687**	Total device cost x 12/18 + Follow-up cost

3.5.2 Health-state unit costs and resource use

Health state costs are summarised in Table 37.

Table 37: Health state unit costs

Health state	Cost	Source
OSAHS	No incremental cost assigned	See para 3.5.1
CHD event (year 1 cost of CHD)	£12,619	Briggs et al, 2007[99]
Post-CHD event (years 2-5 cost of CHD)	£933	Briggs et al, 2007[99]
Stroke event (year 1 cost of stroke)	£13,452	Xu et al, 2017[101]
Post-stroke event (years 2-5 cost of stroke)	£1,128	Xu et al, 2017[101]
RTA	Serious: £17,323 Slight: £1,494 Blended estimate (HAROSA I): £4,815 Blended estimate (HAROSA II): £4,745	Department for Transport, 2018[91]
Death	Transition from model HS to death: CHD/stroke: £3,813 RTA: £6,289 Background mortality: no incremental cost assigned	Briggs et al, 2007[99] Department for Transport, 2018[91] Assumed no difference attributable to treatment

3.5.3 Adverse reaction unit costs and resource use

No costs assigned (see paragraph 3.4.4).

3.5.4 Miscellaneous unit costs and resource use

No additional costs.

B.3.6 Summary of base-case analysis inputs and assumptions

3.6.1 Summary of base-case analysis inputs

A summary of base-case analysis inputs is shown below in Table 38.

Table 38: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution used in OWSA: CI (distribution)	Distribution used in PSA	Reference to section in submission
Discount rate - cost	0.035	0.028 - 0.042 (20% variation)	BETA	
Discount rate - utility	0.035	0.028 - 0.042 (20% variation)	BETA	
Efficacy inputs				
CPAP + BSC + pitolisant vs CPAP + BSC (HAROSA I): ESS effect size	-2.6	95% CI: -3.9 to -1.4	NORMAL	Section 2.6.1
Pitolisant + BSC vs BSC alone (HAROSA II): ESS effect size	-2.8	95% CI: -4 to -1.5	NORMAL	Section 2.6.1
Pitolisant + BSC vs MAD + BSC (HAROSA II): ESS effect size	-1.466	95% CrI: -2.866 to -0.063	NORMAL	Section 2.9.2
Transition from OSAHS to RTA and fatal RTA pitolisant (baseline)				
CPAP + BSC + pitolisant: TP from OSAHS to RTA	0.0036	0.0029 - 0.0043 (20% variation)	BETA	Section 3.3.2
CPAP + BSC + pitolisant: TP from OSAHS to fatal RTA	0.0001	0.0000 - 0.0001 (20% variation)	BETA	Section 3.3.3
Transition probabilities pitolisant (HAROSA I)				
CPAP + BSC + pitolisant (HAROSA I): TP from OSAHS to acute CHD	0.0093	0.0074 - 0.0111 (20% variation)	BETA	Section 3.3.1
CPAP + BSC + pitolisant (HAROSA I): TP from OSAHS to acute stroke	0.0028	0.0022 - 0.0033 (20% variation)	BETA	Section 3.3.1
Transition probabilities BSC (HAROSA I)				
CPAP + BSC (HAROSA I): TP from OSAHS to acute CHD	0.0156	95% CI: 0.0075 - 0.0322	BETA	Section 3.3.1
CPAP + BSC (HAROSA I): TP from OSAHS to acute stroke	0.0070	95% CI: 0.0047 - 0.0106	BETA	Section 3.3.1
CPAP + BSC (HAROSA I): TP from OSAHS to RTA	0.0289	95% CI: 0.0194 - 0.0545	BETA	Section 3.3.2
CPAP + BSC (HAROSA I): TP from OSAHS to fatal RTA	0.0004	95% CI: 0.0004 - 0.0005	BETA	Section 3.3.3
Transition probabilities pitolisant (HAROSA II)				
Pitolisant + BSC (HAROSA II): TP from OSAHS to acute CHD	0.0082	0.0066 - 0.098 (20% variation)	BETA	Section 3.3.1
Pitolisant + BSC (HAROSA II): TP from OSAHS to acute stroke	0.002	0.0016 - 0.0024 (20% variation)	BETA	Section 3.3.1
Transition probabilities BSC (HAROSA II)				
BSC + placebo (HAROSA II): TP from OSAHS to acute CHD	0.0143	95% CI: 0.0065 - 0.0314	BETA	Section 3.3.1

BSC + placebo (HAROSA II): TP from OSAHS to acute stroke	0.0055	95% CI: 0.0035 - 0.0086	BETA	Section 3.3.1
BSC + placebo (HAROSA II): TP from OSAHS to RTA	0.0339	95% CI: 0.0221 - 0.0671	BETA	Section 3.3.2
BSC + placebo (HAROSA II): TP from OSAHS to fatal RTA	0.0005	0.0004 - 0.0006 (20% variation)	BETA	Section 3.3.3
Transition probabilities MAD (HAROSA II) used as a scenario analysis				
MAD + BSC: TP from OSAHS to acute CHD	0.0110	95% CI: 0.0073 – 0.0166	BETA	Section 3.3.3
MAD + BSC: TP from OSAHS to acute Stroke	0.0034	95% CI: 0.0027 – 0.0043	BETA	Section 3.3.1
MAD + BSC: TP from OSAHS to RTA	0.0117	95% CI: 0.0093 – 0.0167	BETA	Section 3.3.2
MAD + BSC: TP from OSAHS to fatal RTA	0.0002	0.0001 - 0.0002 (20% variation)	BETA	Section 3.3.3
Transition probabilities - Fatal CV events and death				
TP from acute CHD to fatal CV event	0.102	0.0816 – 0.1224 (20% variation)	BETA	Section 3.3.3
TP from acute stroke to fatal stroke	0.164	0.2112 – 0.3168 (20% variation)	BETA	Section 3.3.3
TP from post-CHD to death	0.021	95% CI: 0.0208 – 0.0215	BETA	Section 3.3.3
TP from post-stroke to death	0.049	95% CI: 0.0467 – 0.0513	BETA	Section 3.3.3
Utility based on EQ-5D				
Residual EDS (inadequate CPAP response, HAROSA I)				
CPAP + pitolisant (EQ-5D): Utility OSAHS	0.8026	95% CI: 0.6731 – 0.9321	BETA	Section 3.4.5
CPAP + pitolisant (EQ-5D): Utility CHD	0.7391	95% CI: 0.6096 - 0.8686	BETA	Section 3.4.5
CPAP + pitolisant (EQ-5D): Utility stroke	0.7502	95% CI: 0.6207 – 0.8797	BETA	Section 3.4.5
CPAP + BSC (EQ-5D): Utility OSAHS	0.7774	95% CI: 0.6275 – 0.9273	BETA	Section 3.4.5
CPAP + BSC (EQ-5D): Utility CHD	0.7139	95% CI: 0.5640 – 0.8638	BETA	Section 3.4.5
CPAP + BSC (EQ-5D): Utility stroke	0.7250	95% CI: 0.5751 – 0.8749	BETA	Section 3.4.5
CPAP refusers (patients with EDS due to OSA who refuse CPAP, HAROSA II)				
Pitolisant (EQ-5D): Utility OSAHS	0.8023	95% CI: 0.6726 – 0.9320	BETA	Section 3.4.5
Pitolisant (EQ-5D): Utility CHD	0.7388	95% CI: 0.6091 – 0.8685	BETA	Section 3.4.5
Pitolisant (EQ-5D): Utility stroke	0.7499	95% CI: 0.6202 – 0.8796	BETA	Section 3.4.5
BSC (EQ-5D): Utility OSAHS	0.7752	95% CI: 0.6235 – 0.9268	BETA	Section 3.4.5
BSC (EQ-5D): Utility CHD	0.7117	95% CI: 0.5600 – 0.8633	BETA	Section 3.4.5
BSC (EQ-5D): Utility stroke	0.7228	95% CI: 0.5711 – 0.8744	BETA	Section 3.4.5
MAD (EQ-5D): Utility OSAHS	0.7894	95% CI: 0.6492 – 0.9296	BETA	Section 3.4.5
MAD (EQ-5D): Utility CHD	0.7259	95% CI: 0.5857 – 0.8661	BETA	Section 3.4.5
MAD (EQ-5D): Utility stroke	0.7370	95% CI: 0.5968 – 0.8772	BETA	Section 3.4.5
Utility based on SF-6				
Residual EDS (inadequate CPAP response, HAROSA I)				
CPAP + pitolisant (SF-6D): Utility OSAHS	0.7185	95% CI: 0.6705 – 0.7665	BETA	Derived using OLS regression coefficient reported in section 2.4.2 Table 31
CPAP + pitolisant (SF-6D): Utility acute CHD	0.6550	95% CI: 0.6070 – 0.7030	BETA	
CPAP + pitolisant (SF-6D): Utility stroke	0.6661	95% CI: 0.6181 – 0.7141	BETA	
CPAP + BSC (SF-6D): Utility OSAHS	0.6937	95% CI: 0.6387 – 0.7488	BETA	
CPAP + BSC (SF-6D): Utility CHD	0.6302	95% CI: 0.5752 – 0.6853	BETA	

CPAP + BSC (SF-6D): Utility stroke	0.6413	95% CI: 0.5863 – 0.6964	BETA	
CPAP refusers (patients with EDS due to OSA who refuse CPAP, HAROSA II)				
Pitolisant (SF-6D): Utility OSAHS	0.7182	95% CI: 0.6701 – 0.7663	BETA	Derived using OLS regression coefficient reported in section 2.4.2 Table 31
Pitolisant (SF-6D): Utility CHD	0.6547	95% CI: 0.6066 – 0.7028	BETA	
Pitolisant (SF-6D): Utility stroke	0.6658	95% CI: 0.6177 – 0.7139	BETA	
Placebo (SF-6D): Utility OSAHS	0.6915	95% CI: 0.6358 – 0.7472	BETA	
Placebo (SF-6D): Utility CHD	0.6280	95% CI: 0.5723 – 0.6837	BETA	
Placebo (SF-6D): Utility stroke	0.6391	95% CI: 0.5834 – 0.6948	BETA	
MAD (SF-6D): Utility OSAHS	0.7055	95% CI: 0.6538 – 0.7572	BETA	
MAD (SF-6D): Utility CHD	0.6420	95% CI: 0.5903 – 0.6937	BETA	
MAD (SF-6D): Utility stroke	0.6531	95% CI: 0.6014 – 0.7048	BETA	
Absolute utility				
Utility RTA	0.6200	0.4960 - 0.7440 (20% variation)	BETA	Section 3.4.2
Costs				
Annual cost of pitolisant (list price)	[redacted]	Fixed parameter		Section B.1.2 and 3.5.1
Annual cost of MAD	£687	Fixed parameter		Section 3.5.1
Cost of fatal CV event	£3,813	95% CI: £2,902 - £4,724	GAMMA	Section B.3.5 and 3.5.2
Year 1 cost of CHD	£12,619	95% CI: £11,559 - £13,679	GAMMA	
Ongoing cost of CHD (years 2-5)	£933	95% CI: £649 - £1,217	GAMMA	
Year 1 cost of stroke	£13,452	95% CI: £4,391 - £26,902	GAMMA	
Ongoing cost of stroke (years 2-5)	£1,128	95% CI: £468 - £2,630	GAMMA	
Cost of RTA (HAROSA I)	£4,815	£3,852 - £5,778 (20% variation)	GAMMA	
Cost of RTA (HAROSA II)	£4,745	£3,796 - £5,694 (20% variation)	GAMMA	
Cost of fatal RTA	£6,289	£5,031 - £7,546 (20% variation)	GAMMA	

3.6.2 Assumptions

Table 39 lists the assumptions made in the economic model together with the justifications for each assumption.

Table 39: Assumptions made in the economic model

Assumption	Justification
Patients in OSAHS and post-CHD health states are assumed to have the same risk of experiencing an acute stroke as those without a prior event.	There was no available evidence in the literature, therefore, a conservative approach to estimate the risk of acute stroke when in the post-CHD health state seemed appropriate for the purpose of the model.
Patients experiencing a stroke event were assumed to stop driving, removing the excess risk of an OSAHS-induced RTA.	Evidence for the transition probability from post-stroke => RTA is lacking. Our view is that incorporating the possibility of patients driving again after recovering from stroke into the model would have a negligible impact on the ICER. Our rationale for this is that only a very small proportion of patients are involved in fatal or non-fatal RTA, coupled with the few patients that recover from

	stroke with no significant disability and are allowed to drive again.
Patients in OSAHS and post-CHD health states are assumed to have similar risk of fatal and non-fatal RTA.	Evidence for this transition is also lacking. However, it is plausible that a post-CHD event patient will drive again, so we elected to use a conservative approach, assuming no increase in risk in this population.
Patients treated with pitolisant have similar risk of CV events and fatal and non-fatal RTAs to the general population.	Evidence is lacking for this aspect of the model. Published models assessing the cost-effectiveness of CPAP for the treatment of OSAHS have made similar assumptions for CPAP[80,81] and we have consequently followed the same approach.
It was assumed that a 25-year lifetime horizon will approximate to a lifetime horizon.	This was deemed appropriate as the life expectancy for men in the UK is around 80 years (75% of the patients in the model are men). Given that the cohort of patients in the model have a mean age of 52.4 years in HAROSA I and 52 years in HAROSA II, most people would have reached the end of their life within 25 years of entry into the model.

B.3.7 Base-case results

Base case results are reported for two patient populations:

- Patients with residual EDS despite CPAP (inadequate CPAP response, HAROSA I)
- Patients with EDS due to OSA who refuse CPAP (CPAP refusers, HAROSA II)

The utility based on EQ-5D-3L was used in the base case analyses. Patients treated with MADs were considered in a scenario analysis.

3.7.1 Base-case incremental cost-effectiveness analysis results

For patients with residual EDS despite CPAP (HAROSA I population), pitolisant is associated with an ICER of £17,446/QALY) which is well below the conventionally accepted willingness to pay threshold (£30,000/QALY) when compared with BSC (see Table 40 and Table 41).

For patients with EDS due to OSA who refuse CPAP (HAROSA II), pitolisant is associated with an ICER of £16,896/QALY) which is well below the conventionally accepted willingness to pay threshold (£30,000/QALY) when compared with BSC (see

Table 42 and Table 43).

Table 40: Discounted costs and effects – patients with residual EDS despite CPAP (HAROSA I)

Base case result: Discounted costs and effects (HAROSA I)			
	Costs	**QALYs**	**ICER (Cost/QALY)**
Pitolisant + CPAP + BSC	£26,675	11.77	
CPAP + BSC	£9,743	10.80	
Increment	£16,932	0.97	£17,446

Table 41: Base case results – patients with residual EDS despite CPAP (HAROSA I)

Treatments	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pitolisant + CPAP + BSC	£26,675	14.81	11.77				
CPAP + BSC	£9,743	14.19	10.80	£16,932	0.62	0.97	£17,446
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 42: Discounted costs and effects – patients with EDS due to OSA who refuse CPAP (HAROSA II)

Base-case result: Discounted costs and effects - Pitolisant vs BSC (HAROSA II)			
	Costs	QALYs	ICER (Cost/QALY)
Pitolisant + BSC	£26,684	11.86	
BSC alone	£9,535	10.85	
Increment	£17,149	1.01	£16,896

Table 43: Discounted costs and effects – patients with EDS due to OSA who refuse CPAP (HAROSA II)

Treatments	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pitolisant + BSC	£26,684	14.92	11.86				
BSC alone	£9,535	14.29	10.85	£17,149	0.63	1.01	£16,896

Appendix J lists:

- **Clinical outcomes from the model**
- **Disaggregated results of the base case incremental cost effectiveness analysis**

B.3.8 Sensitivity analyses

3.8.1 Probabilistic sensitivity analysis

For the purposes of the probabilistic sensitivity analysis (PSA), all variables listed in Section 3.6.1 were tested across the stated range, using the distribution detailed in Table 38 . The cost of pitolisant was excluded from the PSA on the grounds that it is a fixed NHS price and not subject to parameter uncertainty.

All PSA simulations were run 1,000 times to generate estimated ICERs

Results: PSA

The probability of pitolisant being cost-effective at a willingness to pay (WTP) threshold of £30,000 per QALY is documented in Table 44 below.

Cost-effectiveness acceptability curves (CEAC) for pitolisant vs BSC patients with residual EDS despite CPAP (HAROSA I) and patients with EDS due to OSA who refuse CPAP (HAROSA II) are shown in Figure 8 and Figure 9. Cost-effectiveness scatter plots are also shown in Figure **10** and Figure 11.

Table 44: PSA results – probability of being cost effective at a WTP threshold of £30,000/QALY

Patients with residual EDS despite CPAP (HAROSA I)	**Pitolisant + CPAP + BSC**
CPAP + BSC	64%
Patients with EDS due to OSA who refuse CPAP (HAROSA II)	**Pitolisant + BSC**
BSC alone	66%

Figure 8: CEAC – patients with residual EDS despite CPAP (HAROSA I)

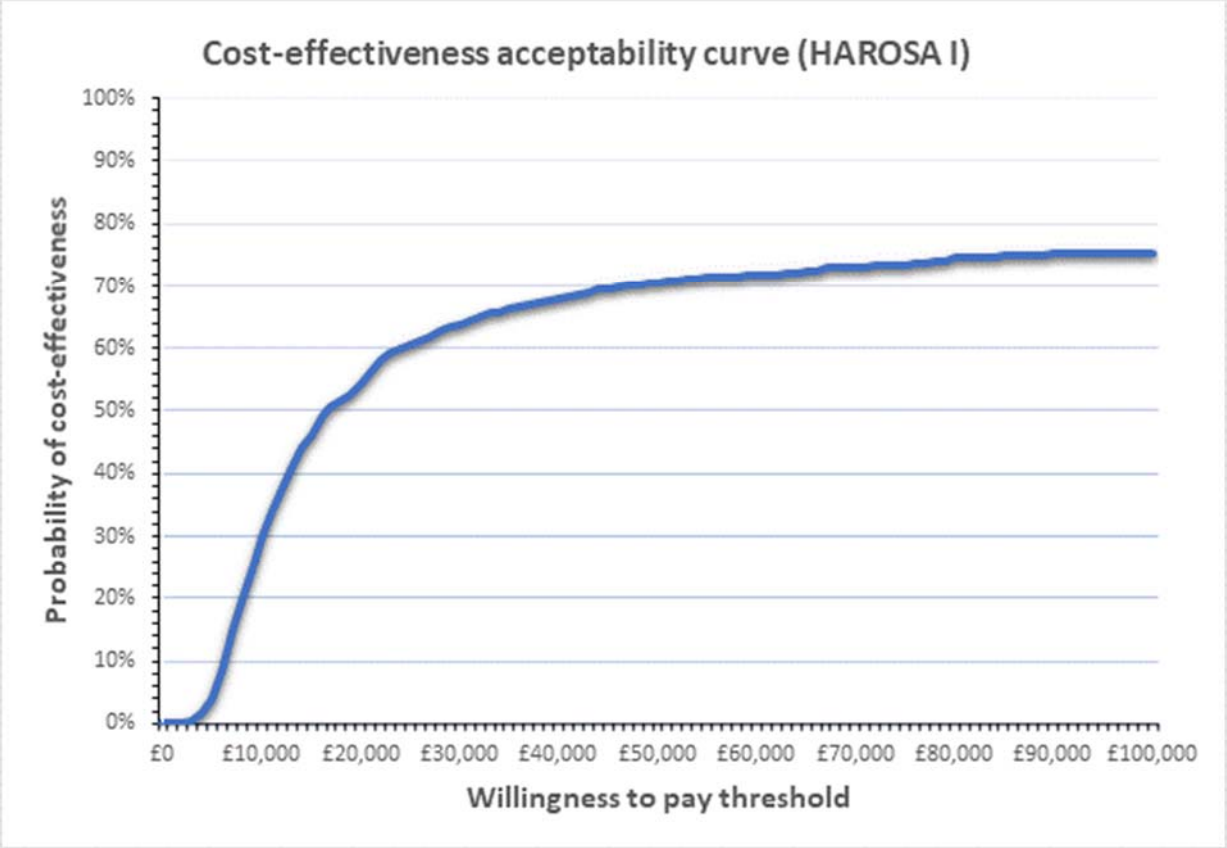


Figure 9: CEAC – patients with EDS due to OSA who refuse CPAP (HAROSA II)

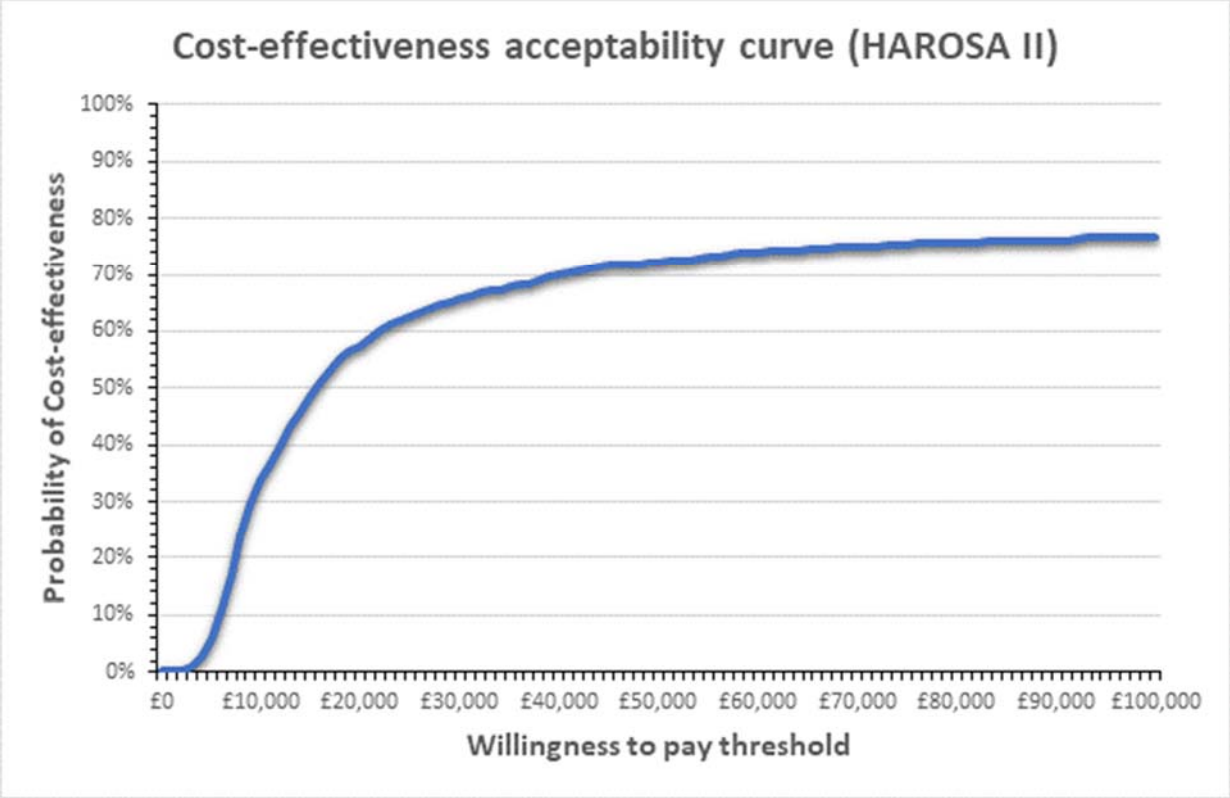


Figure 10: Cost-effectiveness scatter plot – patients with residual EDS despite CPAP (HAROSA I)

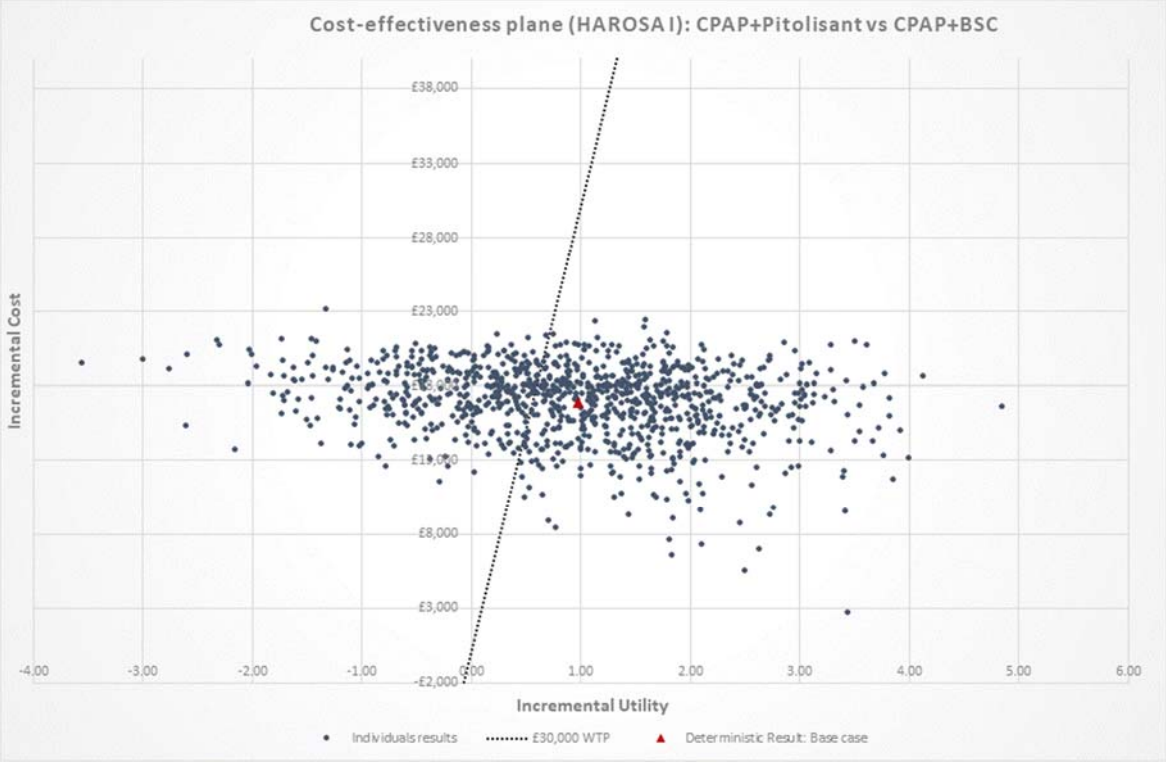
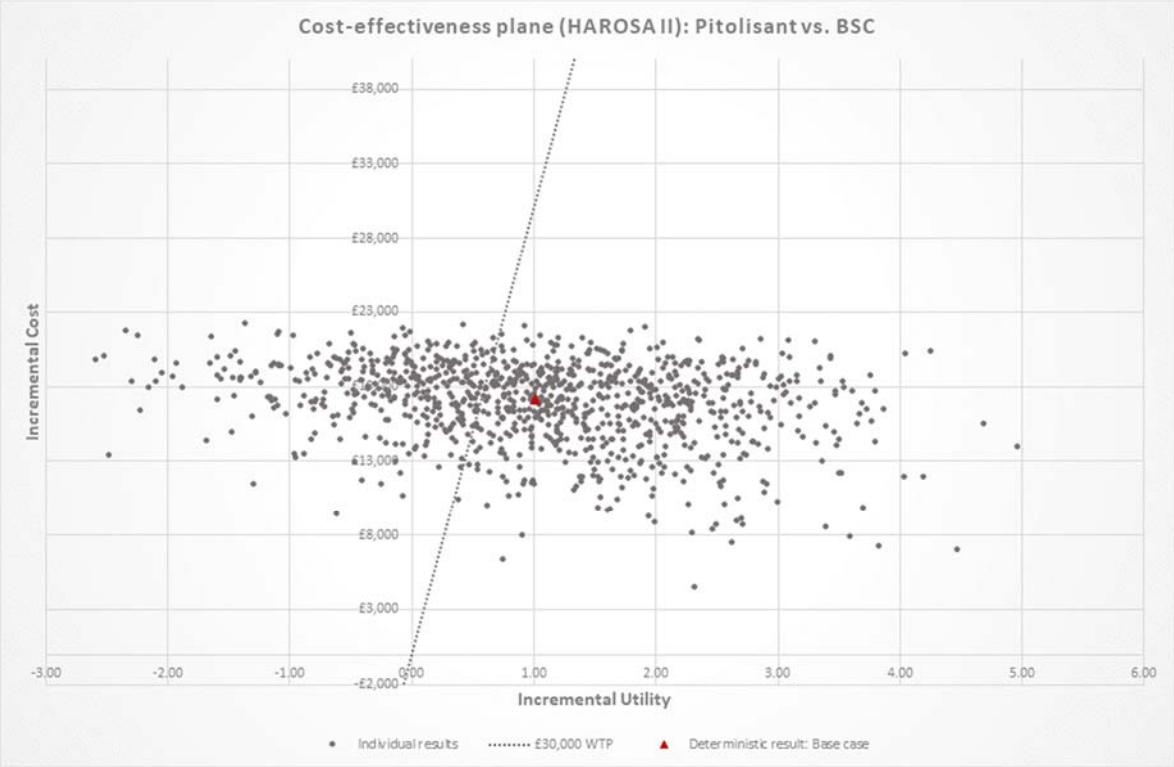


Figure 11: Cost-effectiveness scatter plot – patients with EDS due to OSA who refuse CPAP (HAROSA II)



3.8.2 Deterministic sensitivity analysis

For the purposes of the deterministic sensitivity analysis (DSA), all variables listed in section 3.6.1 were tested across the stated ranges. As per the PSA, the cost of pitolisant was excluded from the PSA on the grounds that it is a fixed NHS price and not subject to parameter uncertainty.

Results are shown below, the ten parameters associated with the greatest ICER spread are shown as tornado diagrams.

DSA results for patients with residual EDS despite CPAP (HAROSA I) are shown below in Table 45 with the corresponding tornado diagram in Figure 12.

DSA results for patients with EDS due to OSA who refuse CPAP (HAROSA II) are shown below in Table 46 with the corresponding tornado diagram in Figure 13.

Table 45: DSA – patients with residual EDS despite CPAP (HAROSA I)

List parameters	Lower	Base case	Upper	ICER: Lower Bound	ICER: Upper Bound	Difference
CPAP + Pitolisant vs CPAP + BSC (HAROSA I): ESS Effect Size	-3.90	-2.60	-1.40	£7,544	£41,640	£34,096
CPAP+BSC (EQ-5D-3L): Utility OSAHS	0.63	0.78	0.93	£6,523	-£25,862	£32,385
CPAP+Pitolisant (EQ-5D-3L): Utility OSAHS	0.67	0.80	0.93	-£24,206	£6,412	£30,618
CPAP+BSC (HAROSA I): TP from OSAHS to Acute CHD	0.01	0.02	0.05	£26,594	£9,698	£16,896

CPAP+BSC (EQ-5D-3L): Utility CHD	0.56	0.71	0.86	£13,315	£25,294	£11,979
CPAP+BSC (HAROSA I): TP from OSAHS to Acute Stroke	0.01	0.01	0.02	£22,003	£13,183	£8,820
CPAP+Pitolisant (EQ-5D-3L): Utility CHD	0.61	0.74	0.87	£21,624	£14,621	£7,004
CPAP+BSC (EQ-5D-3L): Utility Stroke	0.58	0.73	0.87	£15,171	£20,522	£5,351
Discount rate - Utility	0.03	0.04	0.04	£16,022	£18,944	£2,922
CPAP+Pitolisant (HAROSA I): TP from OSAHS to Acute CHD	0.01	0.01	0.02	£16,206	£18,826	£2,620
CPAP+BSC (HAROSA I): TP from OSAHS to RTA	0.02	0.03	0.06	£18,107	£15,768	£2,339
Discount rate - Cost	0.03	0.04	0.04	£18,509	£16,484	£2,025
Treatment cost of stroke	4391.430	13452.000	26901.600	£18,253	£16,248	£2,005
CPAP+Pitolisant (EQ-5D-3L): Utility Stroke	£1	£1	£1	£18,471	£16,528	£1,943
CPAP+Pitolisant (HAROSA I): TP from OSAHS to Acute Stroke	0.004	0.005	0.006	£16,614	£18,349	£1,735
Utility RTA	0.50	0.62	0.74	£16,772	£18,176	£1,404
Management cost of stroke	£468	£1,128	£2,630	£17,764	£16,721	£1,044
TP from Acute Stroke to Fatal Stroke	£0	£0	£0	£17,860	£17,051	£809
HAROSA I: Cost of RTA	3851.9258	4814.9072	5777.8887	£17,758	£17,134	£624
CPAP+BSC (HAROSA I): TP from OSAHS to FRTA	0.00	0.00	0.00	£17,607	£17,288	£319
TP from Acute CHD to Fatal CHD	£0	£0	£0	£17,592	£17,302	£291
Management cost of CHD	£649	£933	£1,217	£17,589	£17,303	£286
Treatment cost of CHD	11558.640	12619.000	13679.360	£17,526	£17,366	£160
Cost of fatal CVE	2901.6000	3813.0000	4724.4000	£17,473	£17,419	£54
CPAP + Pitolisant: TP from OSAHS to FRTA	0.00005	0.00006	0.00007	£17,424	£17,467	£43
TP from Post CHD to Death	£0	£0	£0	£17,457	£17,435	£22
Cost Fatal RTA	5030.9594	6288.6992	7546.4391	£17,452	£17,439	£13

Figure 12: DSA (tornado diagram) – patients with residual EDS despite CPAP (HAROSA I)

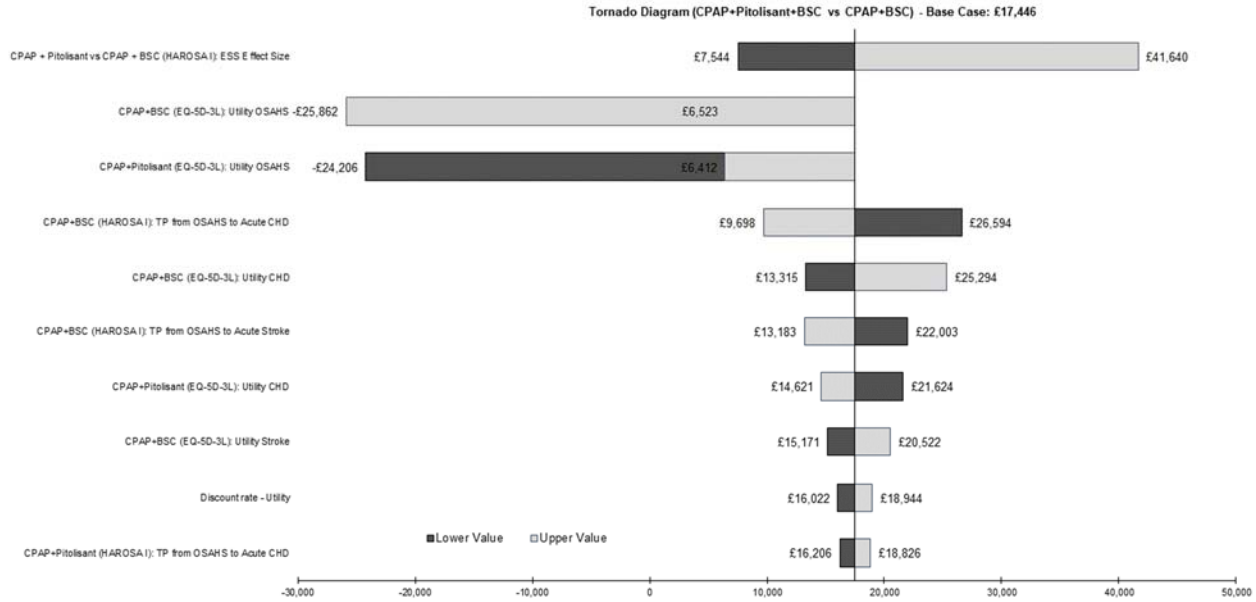
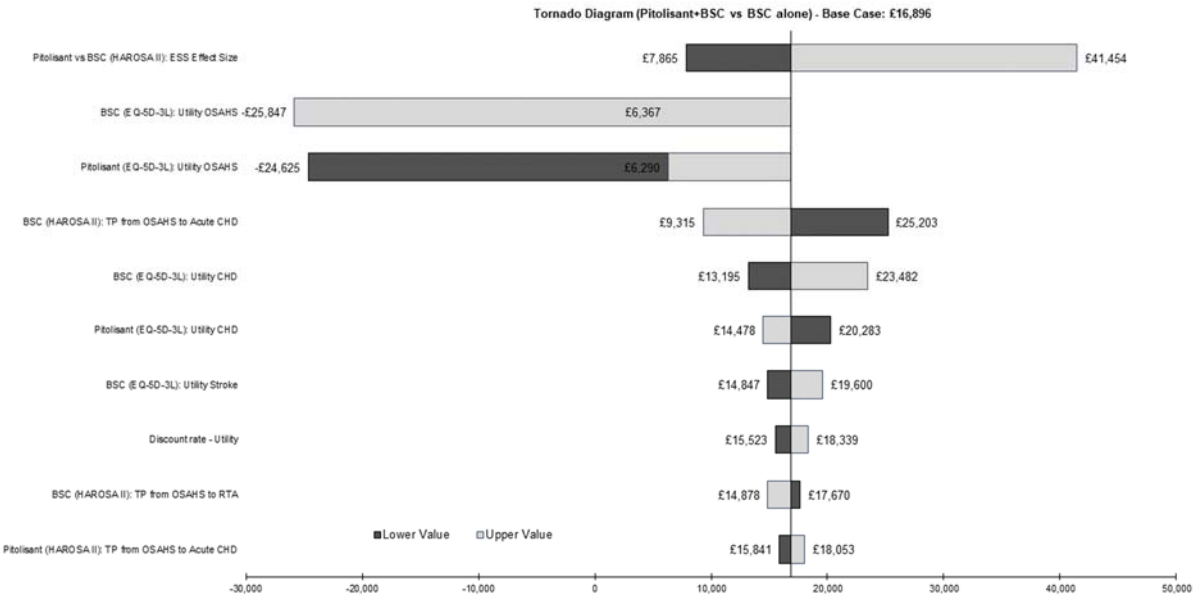


Table 46: DSA – patients with EDS due to OSA who refuse CPAP (HAROSA II)

List parameters	Lower	Base case	Upper	ICER: Lower Bound	ICER: Upper Bound	Difference
Pitolisant vs BSC (HAROSA II): ESS Effect Size	-4.00	-2.80	-1.50	£7,865	£41,454	£33,588
BSC (EQ-5D-3L): Utility OSAHS	0.62	0.78	0.93	£6,367	-£25,847	£32,214
Pitolisant (EQ-5D-3L): Utility OSAHS	0.67	0.80	0.93	-£24,625	£6,290	£30,916
BSC (HAROSA II): TP from OSAHS to Acute CHD	0.01	0.02	0.05	£25,203	£9,315	£15,888
BSC (EQ-5D-3L): Utility CHD	0.56	0.71	0.86	£13,195	£23,482	£10,287
Pitolisant (EQ-5D-3L): Utility CHD	0.61	0.74	0.87	£20,283	£14,478	£5,805
BSC (EQ-5D-3L): Utility Stroke	0.57	0.72	0.87	£14,847	£19,600	£4,753
Discount rate - Utility	0.03	0.04	0.04	£15,523	£18,339	£2,816
BSC (HAROSA II): TP from OSAHS to RTA	0.02	0.03	0.07	£17,670	£14,878	£2,792
Pitolisant (HAROSA II): TP from OSAHS to Acute CHD	0.01	0.01	0.01	£15,841	£18,053	£2,212
Discount rate - Cost	0.03	0.04	0.04	£17,939	£15,953	£1,985
Treatment cost of stroke	4391.43	13452.00	26901.60	£17,668	£15,750	£1,918
Pitolisant (EQ-5D-3L): Utility Stroke	0.620	0.750	0.880	£17,733	£16,134	£1,599
Utility RTA	£0	£1	£1	£16,162	£17,700	£1,539
Pitolisant (HAROSA II): TP from OSAHS to Acute Stroke	0.003	0.004	0.005	£16,200	£17,643	£1,443
Management cost of stroke	468.00	1127.75	2630.00	£17,200	£16,204	£996
TP from Acute Stroke to Fatal Stroke	£0	£0	£0	£17,277	£16,532	£745
HAROSA II: Cost of RTA	£3,796	£4,745	£5,694	£17,244	£16,548	£696
BSC (HAROSA II): TP from OSAHS to FRTA	0.0004	0.0005	0.0006	£17,064	£16,731	£333
Management cost of CHD	648.80	933.00	1217.20	£17,035	£16,757	£278
TP from Acute CHD to Fatal CHD	£0	£0	£0	£17,033	£16,762	£271

Treatment cost of CHD	£11,559	£12,619	£13,679	£16,974	£16,818	£156
CPAP + Pitolisant: TP from OSAHS to RTA	0.003	0.004	0.004	£16,841	£16,951	£109
TP from Post stroke to Death	0.0467	0.0491	0.0513	£16,848	£16,940	£92
Cost of fatal CVE	2901.60000	3813.00000	4724.40000	£16,922	£16,870	£52
CPAP + Pitolisant: TP from OSAHS to FRTA	£0	£0	£0	£16,876	£16,916	£40
TP from Post CHD to Death	0.0208	0.0212	0.0215	£16,906	£16,886	£21

Figure 13: DSA (tornado diagram) – patients with EDS due to OSA who refuse CPAP (HAROSA II)



3.8.3 Scenario analysis

Four scenario analyses were carried out, all of which explored the impact varying parameters on ICERs.

A. Comparison of pitolisant versus MAD in patients with EDS due to OSA who refuse CPAP (HAROSA II)

B. Use of SF-6D as the HRQOL instrument in the model

C. Use of QRISK 3 and QStroke to estimate baseline CV risk

D. Exclusion of costs and utilities of CV events from the model

Scenarios B-D were carried out for both populations: patients with residual EDS despite CPAP (HAROSA I) and patients with EDS due to OSA who refuse CPAP (HAROSA II).

Scenario A: comparison of pitolisant versus MAD in CPAP refusers (HAROSA II)

In the final scope issued by NICE in March 2020, the comparator technology was listed as: "*Established clinical management without pitolisant hydrochloride*". For patients with residual

EDS without CPAP, our clinical advisers suggested that BSC would be the usual alternative within the NHS, as outlined in paragraph B.1.3. This therefore constitutes the base case analysis for this patient population.

In patients who refuse CPAP, the majority would also be offered BSC, which therefore forms the base case analysis. However, our advisers suggest that in some NHS centres, where the severity of OASHS was mild or moderate, supply of bespoke MAD may be offered to some patients. We consequently ran a scenario analysis comparing pitolisant to MAD, in order to explore the potential impact of this minority comparator on the overall cost effectiveness of pitolisant.

The results are shown in Table 47.

Table 47: Scenario A – comparison of pitolisant versus MAD in patients with EDS due to OSA who refuse CPAP (HAROSA II), discounted costs and effects

Scenario A			
	Costs	**QALYs**	**ICER (Cost/QALY)**
Pitolisant + BSC	£26,684	11.86	
MAD + BSC	£14,984	11.40	
Increment	£11,699	0.46	£25,540

Scenario B: Use of SF-6D as the HRQOL instrument in the model

The utilities chosen for the base case were based on the analysis of EQ-5D-3L. A scenario analysis was carried out to explore the impact of using an alternative HRQOL instrument (SF-6D) on the ICERs.

Results for patients with residual EDS despite CPAP (HAROSA I) are shown below in Table 48 and for patients with EDS due to OSA who refuse CPAP (HAROSA II) in Table 49.

Table 48: Scenario B – use of SF-6D as the HRQOL instrument in patients with residual EDS despite CPAP (HAROSA I), discounted costs and effects

Scenario B, residual EDS (HAROSA I), base case ICER: £17,446			
	Costs	QALYs	ICER (Cost/QALY)
Pitolisant + CPAP + BSC	£26,675	10.53	
CPAP + BSC	£9,743	9.64	
Increment	£16,932	0.89	£19,125

Table 49: Scenario B – use of SF-6D as the HRQOL instrument in patients with EDS due to OSA who refuse CPAP (HAROSA II), discounted costs and effects

Scenario B, CPAP refuser (HAROSA II), base case ICER: £16,896			
	Costs	QALYs	ICER (Cost/QALY)
Pitolisant + BSC	£26,684	10.61	
BSC alone	£9,535	9.69	
Increment	17,149	0.92	£18,563

Scenario C: Use of QRISK 3 and QStroke to estimate baseline CV risk

We used the Framingham equation to estimate the baseline CV risk in the base case, which ensures consistency with previous models.

However, QRISK 3 and QStroke are more recent algorithms and may be regarded as more informative for the UK population.

Results for patients with residual EDS despite CPAP (HAROSA I) are shown in

Table 50 and for patients with EDS due to OSA who refuse CPAP (HAROSA II) in Table 51

Table 50: Scenario C – use of QRISK 3 and QStroke to estimate baseline CV risk in patients with residual EDS despite CPAP (HAROSA I), discounted costs and effects

Scenario C, residual EDS (HAROSA I), base case ICER: £17,446			
	Costs	QALYs	ICER (Cost/QALY)
Pitolisant + CPAP + BSC	£26,591	11.90	
CPAP + BSC	£8,485	11.05	
Increment	£18,106	0.85	£21,365

Table 51: Scenario C – use of QRISK 3 and QStroke to estimate baseline CV risk in patients with EDS due to OSA who refuse CPAP (HAROSA II), discounted costs and effects

Scenario C, CPAP refuser (HAROSA II), base case ICER: £16,896			
	Costs	QALYs	ICER (Cost/QALY)
Pitolisant + BSC	£26,585	12.01	
BSC alone	£7,970	11.15	
Increment	£18,615	0.86	£21,698

Scenario D: Exclusion of costs and utilities of CV events from the model

In the base case analysis, the impact of CV events in terms of costs and utilities was captured in the model. A scenario analysis looking exclusively at the impact of RTAs on the ICERs has been performed.

Results for patients with residual EDS despite CPAP (HAROSA I) are shown below in Table 52 and for patients with EDS due to OSA who refuse CPAP (HAROSA II in Table 53.

Table 52: Scenario D – exclusion of costs and utilities of CV events in patients with residual EDS despite CPAP (HAROSA I), discounted costs and effects

Scenario D, residual EDS (HAROSA I), base case ICER: £17,446			
	Costs	QALYs	ICER (Cost/QALY)
Pitolisant + CPAP + BSC	£26,156	12.41	
CPAP + BSC	£2,108	11.91	
Increment	£24,048	0.50	£48,550

Table 53: Scenario D – exclusion of costs and utilities of CV events in patients with EDS due to OSA who refuse CPAP (HAROSA II), discounted costs and effects

Scenario D, CPAP refuser (HAROSA II), base case ICER: £16,896			
	Costs	QALYs	ICER (Cost/QALY)
Pitolisant + BSC	£26,216	12.43	
BSC alone	£2,384	11.89	
Increment	£23,832	0.54	£44,019

3.8.4 Summary of sensitivity analyses results

DSAs identified three potentially important input parameters that exert the greatest effect on the ICERs for both base case comparisons:

1. The ESS effect size

2. Utility value associated with the OSAHS health state in the pitolisant arm

3. Utility value associated with the OSAHS health state in the BSC arm

The first two parameters are to some extent interdependent, in that if the mapping from ESS to utility were changed for the intervention arm, there would be a corresponding change in the mapping in the control arm. Thus, although the absolute utility values vary between arms, their relative values are unlikely to be materially altered if a different mapping were to be used. This is borne out by the results of Scenario B, where the use of an alternative utility algorithm yields very little difference in the ICER.

The third variable, the ESS effect size, was also identified as an important driver of the ICER. This is not surprising, since ESS drives the model itself in terms of RTA and CV events, this is in common with other iterations of the York model[80,81]. It is unclear whether the magnitude of this association is well defined and this is an area of uncertainty in any ICER generated from this core model.

Scenario A explores the use of MAD as a comparator and shows that this results in a significantly higher ICER. Given that this has a documented impact on ESS scores (albeit less than that seen with CPAP or pitolisant) and has a lower monthly cost, this result is unsurprising. It needs to be borne in mind, however, that MADs are not appropriate for the full range of patients in whom pitolisant is indicated and may therefore exert a lesser overall effect on a blended ICER than might be implied by this scenario.

Scenario C considers the use of QRISK 3 and QStroke algorithms to estimate baseline CV risk, rather than the Framingham equation used in the base case. QRISK 3 and QStroke are more recent algorithms, based on a UK population. The results are broadly comparable and below the £30,000 cost/QALY threshold, regardless of which algorithms were chosen.

Scenario D, which excludes the impact of treatment on cardiovascular risk, yields an ICER in excess of the £30,000/QALY threshold. Given the reduction in QALYs gained in the context of relatively constant costs of treatment, this outcome is as expected.

The final component examined was the probabilistic sensitivity analysis. Based on a willingness to pay threshold of £30,000/QALY, the proportion of simulations that yielded an acceptable ICER was 64% in patients with residual EDS despite CPAP (HAROSA I) and

66% in patients with EDS due to OSA who refuse CPAP (HAROSA II). This magnitude of spread is in keeping with results of other cost utility models, typically seen as representing a cost-effective treatment option for the NHS.

B.3.9 Subgroup analysis

There was insufficient data to carry out subgroup analysis.

B.3.10 Validation

3.10.1 Validation of cost-effectiveness analysis

This cost-effectiveness analysis was carried out by adapting and extending an established, published and peer-reviewed economic model that has previously been used to inform a NICE Technology Appraisal. The only significant components that have been altered are the efficacy inputs for pitolisant itself, combined with an updating of cost assumptions where required. In all other regards, the model mirrors the previously accepted and validated approach.

One limitation of this analysis is that it has been carried out in the context of the COVID-19 outbreak, which was already under way at the time that the final scope was issued by NICE, with significant variation form the previously issued draft that was used as the basis of our preliminary model design. Given that our specialist advisors are respiratory physicians, they have been unable to assist us in the validation of many of the inputs to this model, although we have been able to access the assistance of recently retired clinician. Whilst it is therefore possible that some of our assumptions are not an accurate reflection of current NHS practice, we have endeavoured to make conservative assumptions wherever this limitation arises.

B.3.11 Interpretation and conclusions of economic evidence

The results of this economic evaluation demonstrate that pitolisant is likely to offer a cost-effective treatment option for the NHS, when targeted at patients with OSAHS who either have residual symptoms despite using CPAP or who are unable or unwilling to use CPAP.

This is the first economic analysis that has been carried out for pitolisant, as this is a new agent that – at the time of carrying out the analysis – had not yet been licensed in this indication by the EMA. Consequently, there are currently no other published economic evaluations against which it can be compared. Having said that, the utility and cost outputs for the comparator arms are consistent with those seen for economic analyses of CPAP and MAD. This is as expected, as the previously published analyses also used the same core York model to assess cost utility.

The evaluation covers all relevant populations who would be expected to use pitolisant and is broadly consistent with both the proposed licensed indication and the target group identified in the NICE decision problem (Adults with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP).

There are perhaps two groups of patients not covered in this analysis:

- Those with mild OSAHS. However, as these patients would not be considered as eligible for NHS CPAP treatment unless their symptoms have an impact on their QOL and lifestyle measures or other relevant treatment options had been unsuccessful or are considered inappropriate, it is unlikely that they would fall within the intended treatment group, as identified above.

- Those patients using a MAD with residual EDS. Unfortunately, the clinical study programme for pitolisant did not consider this population and it is not possible to generate evidence to support economic modelling for this population. As discussed, NICE recommend MADs as an option for people with mild/moderate OSAHS unable to use CPAP or for those who snore or have mild OSAHS with normal daytime alertness[37]. We suggest that patients using MAD and experiencing residual EDS, would be more likely to switch to pitolisant rather than add on pitolisant to MAD because MADs are invasive and uncomfortable to wear overnight.

The key strength of this model is its transparency and reproducibility. It follows an approach that has been used by NICE before, thereby allowing cross-comparison with previous guidance. For the same reason, however, it shares the weaknesses of the previous NICE model. The risk of a patient progressing to a CV or RTA event is derived from a mapping against change in ESS score. Utilities are estimated using a similar approach. Whilst this is a well-established approach that has been used in the past, it is based on a relatively limited evidence base. Similarly, we have had to assume that a unit reduction in ESS will have the same effect on the extrapolated outcomes, regardless of the technology used to achieve those reductions. There is currently no evidence base to support this assumption and it warrants further investigation. However, given that changes in these parameters would tend to affect both arms of the comparison, the absolute incremental effect of any change is likely to be limited.

The conclusions of the analysis are both relevant and generalisable to clinical practice in England. CPAP is widely offered to people with moderate to severe OSAHS within the NHS and both the diagnostic criteria used and the treatment pathways followed are closely mirrored in the structure of this model.

B. 4. References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pitolisant hydrochloride for treating excessive daytime sleepiness caused by obstructive sleep apnoea [ID1065]

Response to clarification questions

June 2020

Section A: Clarification on effectiveness data

Search Methods

A1. Priority question: Regarding Appendix D: Identification, selection and synthesis of clinical evidence, Table 1. The ERG is currently unable to fully critique these searches due to the lack of hits per line for each strategy. Please provide full search strategies in their original format including hits per line.

Answer:

Table 1: Search strategies

Database	Search		Number of abstracts (16/01/2020)
Medline (via Embase)	1	('sleep disordered breathing'/exp OR 'sleep disordered breathing' OR 'sleep apnea':ab,ti OR osa:ab,ti OR 'sleep apnoea':ab,ti)	84217
	2	(pitolisant:ab,ti OR tiprosilant:ab,ti OR 'modafinil'/exp OR 'modafinil' OR modafinil:ab,ti OR 'dexamphetamine'/exp OR 'dexamphetamine' OR dexamphetamine:ab,ti OR 'methylphenidate'/exp OR 'methylphenidate' OR methylphenidate:ab,ti OR 'oxybate sodium'/exp OR 'oxybate sodium' OR 'sodium oxybate':ab,ti OR 'solriamfetol'/exp OR 'solriamfetol' OR solriamfetol:ab,ti OR 'pitolisant'/exp OR 'pitolisant' OR OR BF2.649 OR JZP-110)	37638
	3	1 AND 2	1099
	4	('quality of life'/exp OR 'quality of life' OR 'quality of life':ab,ti OR qol:ab,ti OR hqol:ab,ti OR hrqol:ab,ti OR hql:ab,ti OR hrql:ab,ti OR utilit*:ab,ti OR 'patient reported':ab,ti OR 'patient-reported':ab,ti OR euroqol:ab,ti OR 'eq 5d':ab,ti OR eq5d:ab,ti OR 'eq vas':ab,ti OR "health utilit* index":ab,ti OR hui:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR 'hui 2':ab,ti OR 'hui 3':ab,ti OR (('short form':ab,ti OR 'short-form':ab,ti OR shortform:ab,ti OR sf:ab,ti) AND (6:ab,ti OR 12:ab,ti OR 36:ab,ti)) OR 'time trade off':ab,ti OR 'time trade-off':ab,ti OR tto:ab,ti OR 'standard gamble':ab,ti OR 'patient preference':ab,ti OR 'self-reported':ab,ti OR 'outcome assessment':ab,ti)	1014043

Database	Search		Number of abstracts (16/01/2020)
	5	('economic evaluation'/exp OR 'economic evaluation' OR 'cost of illness'/exp OR 'cost of illness' OR cost*:ab,ti OR budget*:ab,ti OR finance*:ab,ti OR resource*:ab,ti OR 'resource use':ab,ti OR 'length of stay':ab,ti OR admission*:ab,ti OR economic*:ab,ti OR hospitali?ation:ab,ti OR absenteeism:ab,ti OR productivity:ab,ti OR ((value NEAR/1 (money OR monetary)):ab,ti))	2081894
	6	('pharmacoeconomics'/exp OR 'pharmacoeconomics' OR (((economic* OR cost* OR budget*) NEAR/1 model):ab,ti) OR ((cost NEAR/1 (efficacy OR effective* OR benefit OR utility*)):ab,ti) OR 'monte carlo':ab,ti OR markov:ab,ti OR 'discrete event simulation':ab,ti OR 'technology assessment':ab,ti)	476890
	7	4 OR 5 OR 6	3110512
	8	1 AND 7	14180
	9	('positive end expiratory pressure'/exp OR 'positive end expiratory pressure' OR 'cpap device'/exp OR 'cpap device' OR cpap:ab,ti OR 'continuous positive airway pressure':ab,ti)	58257
	10	8 AND 9	3809
	11	10 Limited to humans with abstracts	3221
	12	**3 OR 11 limited to humans, abstracts**	**2153**
Embase (via ProQuest)	1	('sleep disordered breathing'/exp OR 'sleep disordered breathing' OR 'sleep apnea':ab,ti OR osa:ab,ti OR 'sleep apnoea':ab,ti)	84217
	2	(pitolisant:ab,ti OR tiprosilant:ab,ti OR 'modafinil'/exp OR 'modafinil' OR modafinil:ab,ti OR 'dexamphetamine'/exp OR 'dexamphetamine' OR dexamphetamine:ab,ti OR 'methylphenidate'/exp OR 'methylphenidate' OR methylphenidate:ab,ti OR 'oxybate sodium'/exp OR 'oxybate sodium' OR 'sodium oxybate':ab,ti OR 'solriamfetol'/exp OR 'solriamfetol' OR solriamfetol:ab,ti OR 'pitolisant'/exp OR 'pitolisant' OR BF2.649 OR JZP-110)	37638
	3	1 AND 2	1099

Database	Search		Number of abstracts (16/01/2020)
	4	('quality of life'/exp OR 'quality of life' OR 'quality of life':ab,ti OR qol:ab,ti OR hqol:ab,ti OR hrqol:ab,ti OR hql:ab,ti OR hrql:ab,ti OR utilit*:ab,ti OR 'patient reported':ab,ti OR 'patient-reported':ab,ti OR euroqol:ab,ti OR 'eq 5d':ab,ti OR eq5d:ab,ti OR 'eq vas':ab,ti OR "health utilit* index":ab,ti OR hui:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR 'hui 2':ab,ti OR 'hui 3':ab,ti OR (('short form':ab,ti OR 'short-form':ab,ti OR shortform:ab,ti OR sf:ab,ti) AND (6:ab,ti OR 12:ab,ti OR 36:ab,ti)) OR 'time trade off':ab,ti OR 'time trade-off':ab,ti OR tto:ab,ti OR 'standard gamble':ab,ti OR 'patient preference':ab,ti OR 'self-reported':ab,ti OR 'outcome assessment':ab,ti)	1014043
	5	('economic evaluation'/exp OR 'economic evaluation' OR 'cost of illness'/exp OR 'cost of illness' OR cost*:ab,ti OR budget*:ab,ti OR finance*:ab,ti OR resource*:ab,ti OR 'resource use':ab,ti OR 'length of stay':ab,ti OR admission*:ab,ti OR economic*:ab,ti OR hospitali?ation:ab,ti OR absenteeism:ab,ti OR productivity:ab,ti OR ((value NEAR/1 (money OR monetary)):ab,ti))	2081894
	6	('pharmacoeconomics'/exp OR 'pharmacoeconomics' OR (((economic* OR cost* OR budget*) NEAR/1 model):ab,ti) OR ((cost NEAR/1 (efficacy OR effective* OR benefit OR utility*)):ab,ti) OR 'monte carlo':ab,ti OR markov:ab,ti OR 'discrete event simulation':ab,ti OR 'technology assessment':ab,ti)	476890
	7	4 OR 5 OR 6	3110512
	8	1 AND 7	14180
	9	('positive end expiratory pressure'/exp OR 'positive end expiratory pressure' OR 'cpap device'/exp OR 'cpap device' OR cpap:ab,ti OR 'continuous positive airway pressure':ab,ti)	58257
	10	8 AND 9	3809
	11	10 Limited to humans with abstracts	3221
	12	**3 OR 11 limited humans abstracts**	3738
	1	MeSH descriptor: [Sleep Apnea, Obstructive] explode all trees	1673

Database	Search		Number of abstracts (16/01/2020)
Cochrane library	2	sleep apnea OR "sleep apnoea"	6654
	3	1 OR 2	6679
	4	pitolisant OR tiprosilant OR modafinil OR dexamphetamine OR methylphenidate OR "oxybate sodium" OR "sodium oxybate" OR solriamfetol	3919
	5	**3 AND 4**	145
	6	Remove protocols	143
Heoro.com	Disease: Sleep apnea syndromes		561
	Study types: Cost and resource OR economic model OR PRO study		
ISPOR	Sleep Apnea OR Sleep Apnoea OR Solriamfetol OR Pitolisant		77
World sleep congress	Downloaded 2017 and 2019 abstract books (hand searched for sleep apnea and apnoea and pitolisant and solriamfetol)		379
Sleep meeting	Supplement booklets for 2019 and 2018 were downloaded and had searched for apnea and apnoea and pitolisant and solriamfetol		369
Sleep and breathing conference	Supplement booklets for 2019 and 2017 were downloaded and had searched for apnea and apnoea and pitolisant and solriamfetol		177
European respiratory society international congress	Supplement booklets for 2017, 2018 and 2019 were downloaded and had searched for apnea and apnoea and pitolisant and solriamfetol		473
British Thoracic society	Supplement issues were searched by hand		24
American thoracic society	Respiratory and critical care medicine abstract issue search by hand for 2019 and 2018		39
Clinicaltrials.gov	Disease: obstructive sleep apnea AND “Excessive daytime sleepiness”		70

Database	Search	Number of abstracts (16/01/2020)
Call for evidence from manufacturer		3
	Combined, after deduplication	5546

A2. Priority question: In Table 1 (Appendix D) the first strategy reports a search of Medline via Embase.

a. Please confirm that by this you are referring to a search of Embase conducted on the understanding that it now contains all records from Medline and conducted at the same time as the Embase search? If not was this a separate search of the Medline database?
b. If the Medline search is a separate search please clarify the impact of including Emtree rather than MeSH in the search?

Answer: We confirm that we searched Medline and Embase at the same time via the embase.com platform and not via a separate search of the Medline database.

A3. Please provide the date range for both the Medline and Embase searches.

Answer: No date limit was applied to the searches, so the date range was from the inception date of the databases (1946–1947) to 16 January 2020.

A4. In the final line both the Medline and Embase searches appear to contain a limit to only those records that contain abstracts. Please confirm that this is the case and explain what impact this may have had on your results and the rationale behind it.

Answer: We confirm that the final search was limited to studies conducted in humans that had abstracts. As studies without abstracts are mainly those that do not report primary research, such as editorials and opinion-piece publications, and as we hand-searched the citations of all identified systematic reviews to identify any additional studies that had been missed by our search, we do not believe that applying this limit to the search meant that any relevant publications were missed.

A5. Please provide the date range for the hand searches of supplements for the British Thoracic Society.

Answer: The British Thoracic Society supplements for 2017, 2018 and 2019 were hand searched.

A6. With regard to the additional search of Medline for MADs, please confirm the database host, date span and date of search.

Answer: The host was Dialog Proquest, accessed via the Royal Society of Medicine. The date span of the search was unrestricted, including any qualifying paper up to April 2020. The search was carried out on 30th April 2020.

Decision Problem

A7. Priority question: The scope states that the comparator is: 'Established clinical management without pitolisant'. It also refers to the NHS website with regards to recommended treatments (NHS (2016) Obstructive sleep apnoea: treatment. Accessed March 2020.), which in turn cites the British Lung Foundation website (https://www.blf.org.uk/support-for-you/obstructive-sleep-apnoea-osa/treatment), which states: 'You're likely to need another treatment as well as making lifestyle changes. Mandibular advancement devices (MADs) and continuous positive airway pressure (CPAP) machines are common.' No mention is made of whether patients have refused CPAP before being offered a MAD. It is also possible that MAD might be prescribed instead of CPAP even if CPAP might be acceptable.

a. Could the company please explain why MAD is not a comparator in the base case indirect treatment comparison and why it is not a comparator for those who have not refused CPAP?
b. Could the company please include MAD as a comparator, including in the subgroup of those who have not refused CPAP?

Answer:

a. CPAP is the gold standard treatment for OSA as recommended in NICE Technology Appraisal 139[1]. In the guidelines, CPAP is recommended as a treatment option for adults with moderate or severe symptomatic obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and in adults with mild disease if it impacts

on their quality of life (QOL) and ability to go about their daily activities and lifestyle advice and any other relevant treatment options have been unsuccessful or are considered inappropriate.

The licence for pitolisant is for EDS in patients with OSA either treated by CPAP but still complaining of EDS, or in patients with OSA refusing/not tolerating CPAP[2].

MADs are not an appropriate comparator in people who are eligible for CPAP and who are happy to use it. Pitolisant can only be used in this patient group if patients do not achieve adequate relief from EDS whilst using CPAP. Furthermore, MADs cannot be used at the same time as CPAP, rendering them an inappropriate comparator.

With regard to MADs (also known as dental devices), the guidance in NICE Technology Appraisal 139 states that *Dental devices are designed to keep the upper airway open during sleep. The efficacy of dental devices has been established in clinical trials, but these devices are traditionally viewed as a treatment option only for mild and moderate OSAHS.* Given this statement and our understanding from clinical advisors, we believe that patients who are eligible for CPAP and who are happy to use it will not be offered MADs and will proceed directly to CPAP. However, if patients do try a MAD prior to initiating CPAP, pitolisant is not licensed for use with a MAD.

b. As discussed in our call with the ERG on 16th June, the comparison versus MAD in CPAP refusers was included as a scenario analysis in our submission. It was therefore agreed by the ERG that no further action was required regarding this question.

Technology

A8. Priority question: Please clarify whether there are any stopping rules for pitolisant, and how long patients are expected to use pitolisant.

Answer: Patients take pitolisant for as long as they achieve a clinical benefit (reduction in EDS). There are no formal stopping rules, however, patients are likely to stop treatment with pitolisant if they no longer achieve a clinical benefit or if adverse events (AE) make continuation with treatment difficult. Over the course of 1

year, discontinuations due to AE were 5.3% in HAROSA I (patients using CPAP)[3] and 2.2% in HAROSA II (patients refusing CPAP)[4].

A9. Please provide more information about the expected time of marketing authorisation from EMA and an un-embedded version of the SmPC.

CHMP opinion is expected November 2020 (the company are currently responding to questions) with final approval expected at the end of 2020/early 2021.

Answer: The latest version of the SmPC is included with this document.

Pitolisant Trials

A10. While the company has provided short, draft versions of the CSRs, please provide full, final CSRs for HAROSA I and II, including all tables, figures and graphs (Section 14) and Appendices (Section 16).

Answer: The latest CSR are provided as PDF files with this document, together with Section 14 and 16 for each study.

The documents are provided as eight files

1. Final CSR for HAROSA I
2. Final CSR for HAROSA II
3. Appendices (section 16) for HAROSA I
4. Appendices (section 16) for HAROSA II
5. Section 14 for HAROSA I (double blind)
6. Section 14 for HAROSA I (open label)
7. Section 14 for HAROSA II (double blind)
8. Section 14 for HAROSA II (open label)

A11. Both HAROSA I and II include patients who are 'still complaining of EDS'.

a. Please provide a complete breakdown of which primary obstructive sleep apnoea therapies patients in HAROSA I and II have already experienced, including the number of patients who had tried MADs.
b. Please provide a complete breakdown of smoking status, including the number of patients who have already quit since diagnosis with OSA.
c. Please provide a complete breakdown of patient weight, including number classified as obese and the number who had tried weight loss since diagnosis of OSA.

Answer:

a. At the first screening visit (2 weeks before randomisation) a medical questionnaire was completed which included participant's medical history (specifically OSA and EDS). This questionnaire included information on current and previous treatment for EDS. However, the questionnaire and data elicited by the questionnaire are not available in the CSR.

b. This data is not available in the CSR.

c. Severely obese patients (body mass index [BMI] > 40 kg/m^2) were excluded from the HAROSA studies[3,5]. Data available on weight and BMI from the CSR are shown below in Table 2.

The CSR also provide data on minimum and maximum BMI, quartiles and median, which give us an indication of the BMI profile, but does not provide information on the number of patients who were obese (30 mg/kg^2 or over).

For HAROSA I, the first quartile BMI was 28.6 in the pitolisant arm and 29.0 in the placebo arm and median BMI was 33.5 and 31.6 respectively, indicating that between one-half and three-quarters of people in the study were obese.

For HAROSA II, the data is clearer, since the first quartile BMI was 30 in both arms, indicating that three-quarters of people in the study were obese.

Data is not available on the number of patients who had tried weight loss since diagnosis of OSA, since it was not collected in the studies.

Table 2: Weight and BMI in the HAROSA studies

	HAROSA I		HAROSA II	
	Pitolisant (n=183)	**Placebo (n=61)**	**Pitolisant (n=200)**	**Placebo (n=67)**
Weight (Mean, SD), Kg				
Baseline	98.2 (18.9)	97.7 (14.8)	97.7 (15.7)	99.9 (16.1)
End of double-blind period	97.9 (18.2)	98.0 (14.1)	96.6 (15.6)	98.9 (15.4)
Body mass index (Mean, SD), Kg/m^2				
Baseline	32.64 (5.26)	32.11 (4.31)	32.8 (4.6)	33 (4.3)
End of double-blind period	32.57 (4.97)	32.08 (4.18)	32.4 (4.4)	32.7 (4.4)
First quartile at baseline	28.6	29.0	30	30
Median at baseline	33.5	31.6	33	33
Third quartile at baseline	37.4	36.4	37	37

A12. Please explain what would be classified as a clinically significant benefit in terms of ESS? In the EMA assessment of modafinil, the EMA concluded that modafinil had a “consistent short-term effect of in all variables measured. However, the effect size is small and does not necessarily reflect a clinically significant benefit”. The change in ESS at 12 weeks for modafinil 200mg was -4.5 versus -1.8 for placebo. Please explain how that compares to pitolisant, and how that compares to the statement in the company submission (CS, page 25) that the “minimal important difference (MID) for the ESS is estimated at 2 points in patients with OSA and EDS”.

Answer: At 12 weeks the reduction in ESS with pitolisant was -5.52 in HAROSA I and -6.30 in HAROSA II, the corresponding reductions in ESS with placebo were -2.75 and -3.6. The mean treatment difference was 2.77 in HAROSA I and -2.7 in HAROSA II.

The primary end-point last observation carried forward (LOCF) was analysed using an ANCOVA model adjusting for ESS and BMI at visit 2 and study site as a random effect, resulting in a treatment effect of -2.6 and -2.8 respectively.

These are consistent with the benefit seen with modafinil, placebo-controlled difference -2.7.

A paper published in 2019, by Crook et al[6] used data from three randomised controlled trials (RCT) of CPAP (two studies) and Provent, an expiratory nasal resistance valve used to prevent the recurrence of OSA following withdrawal of CPAP therapy to determine the MID change in ESS that reflects a clinically relevant change in sleepiness. The three studies included 574 patients overall, with similar baseline demographics to the HAROSA studies. Changes in domains of the Functional Outcomes of Sleep Questionnaire (FOSQ) and energy/vitality domain and physical component of 36-item Short Form Health Survey (SF-36) were used as anchors. Change score correlations were lower with the SF-36 domains, since SF-36 measures general QOL rather than sleep-specific QOL. The study also used distribution-based estimates of the MID. Triangulation of all estimates let to a MID of 2 points on the ESS.

The reduction in sleepiness with pitolisant treatment was greater than 2 points in both studies, suggesting that the benefits of pitolisant to the patient are clinically relevant.

A13. The 'Trial methodology' section for the HAROSA trials (CS, page 22) states that the wash-out phase lasted 1 week. Please provide justification that this period of time is sufficient enough for this group of patients.

Answer: On rechecking the CSR, we note that the wash-out period was in fact 2 weeks (from the screening visit to the baseline visit at which point patients were randomised to pitolisant or placebo). Contact by telephone was made 1 week after the screening visit to ensure that the participant had discontinued previous treatment for EDS and other prohibited treatments.

Treatments for EDS must be taken every day due to their short half-life. For example, modafinil has a half-life of 15 hours, dextroamphetamine has a half-life of 10 to 12 hours and methylphenidate has a half-life of 2-3 hours. Therefore, a wash-out period of 1 week would be adequate to eliminate active treatment from the body and 2 weeks would be more than adequate.

A14. In Table 4 of the company submission (CS, page 22) it is stated that "A score of 0-10 is normal, 11-12 mild EDS, 13-15 moderate and 16-24 severe". However, the inclusion criteria for the HAROSA trials are 'ESS ≥ 12'. Please explain how many

patients were included in each trial with a baseline ESS of 12, and why these patients with mild EDS were included.

Answer: The licence for pitolisant is for EDS in patients with OSA either treated by CPAP but still complaining of EDS, or in patients with OSA refusing/not tolerating CPAP[2].

People with OSA with a score of 12 on the ESS are at the upper end of mild EDS. The impact of the fragmented night-time sleep in people with OSA on daytime wakefulness is subjective and an ESS score of 12 may have a considerable impact on QOL and the ability to undergo activities of daily living. Patients were only enrolled in the studies if EDS was impacting on their lives.

Data is not available on the number of patients with ESS of 12 however, other statistical measures give us an indication of the proportion of patients at the lower end of the range.

The mean (standard deviation) baseline ESS scores in HAROSA I were 14.9 (2.7) in the pitolisant arm and 14.6 (2.8) in the placebo arm. Baseline scores in HAROSA II were 15.7 (3.1) and 15.7 (3.6) respectively.

The first quartile ESS score at baseline was 13 in both arms of both HAROSA studies, which tells us that one-quarter of patients had an ESS of 12 or 13.

Table 3: ESS scores in the HAROSA studies

	HAROSA I		**HAROSA II**	
	Pitolisant (n=183)	**Placebo (n=61)**	**Pitolisant (n=200)**	**Placebo (n=67)**
Weight (Mean, SD), Kg				
Baseline	14.9 (2.7)	14.6 (2.8)	15.7 (3.1)	15.7 (3.6)
First quartile at baseline	13	13	13	13
Median at baseline	15	14	15	14
Third quartile at baseline	16	15	18	18

A15. The company state that the HAROSA studies compare ‘treatment with pitolisant plus BSC versus placebo plus BSC’ (CS, page 34). Please clarify what the

company means by BSC in both of those trials and provide the evidence that BSC was monitored in the trials. Please also comment how BSC in the trials compares to BSC in UK practice.

Answer: BSC is standard medical practice, this includes lifestyle changes (weight loss, smoking cessation, limiting alcohol intake) as first-line treatment, followed by CPAP in patients with moderate to severe OSAHS or mild OSAHS with symptoms that impact on QOL.

The standard of care for residual EDS in OSA is optimisation of CPAP, which includes patient education, sleep hygiene, appropriate CPAP mask selection and use, and use of humidification, as well as assessment of whether residual CPAP is due to other co-morbidities (obesity, depression, diabetes, hypothyroidism) or other sleep disorders (behaviourally induced insufficient sleep, restless legs syndrome/periodic limb movement in sleep, or narcolepsy) and management of co-morbidities if present.

The HAROSA studies were carried out at major sleep centres across Europe and led by leaders in the field, therefore patients would have received the most appropriate treatment for their condition.

Patients entering HAROSA I had to have tried CPAP for at least 3 months and be still complaining of EDS, despite efforts made beforehand to optimise CPAP. Therefore, lifestyle changes and optimisation of CPAP would have been carried out prior to study entry. Patients were forbidden to take any other wakefulness agents during the duration of the study.

During the study adherence to nightly CPAP was monitored at visit 3 (week 3 adjustment visit), visit 4 (week 4 to week 7, dose confirmation visit), visit 5 (week 8 to week 12, control visit) and visit 6 (week 13 to week 14, end of the double-blind period). At each of these visits there would be the opportunity to further optimise CPAP, although this was not formally monitored.

Patients entering HAROSA II were experiencing EDS and had refused CPAP treatment. Patients were forbidden to take any other wakefulness agents during the duration of the study. Treatment options in this patient group were limited.

A16. Please clarify the number and percentage of patients in both treatment groups (Pitolisant and placebo) in the HAROSA I trial as there are discrepancies between the submission and CSR provided (Document B Table 16 and page 314 of HAROSA I CSR 'TEAEs leading to study drug withdrawal').

Answer: Apologies, I have corrected the table below (1.1% in Document B corrected to 2.2%)

Table 4: Treatment emergent AE (TEAE) leading to discontinuation in the double-blind period (safety population)[3,5]

	Pitolisant (n=183)	Placebo (n=61)	Absolute risk (95% CI)	Relative risk (95% CI)
HAROSA I	4 ~~(1.1%)~~ (2.2%)	2 (3.3%)		0.67 (0.13-3.55), NS
	Pitolisant (n=200)	Placebo (n=67)	Absolute risk (95% CI)	Relative risk (95% CI)
HAROSA II	3 (1.5%)	2 (3.0%)		0.50 (0.09-2.94), NS

A17. The CS notes that OSA with EDS can have a cognitive impact, why were cognitive-related outcomes not reported?

Answer: It is well established that OSA can impact on cognition – as one might expect people who have experienced interrupted, fragmented sleep with resultant EDS will find it hard to concentrate and focus during the day[7,8].

Patients were excluded from the HAROSA studies if they had cognitive impairment as measured on the Minimal Mental State Examination (MMSE). Patients with a score of <28 were excluded. For context, a score of 24 points (out of 30) indicates normal cognition, 19-23 points mild cognitive impairment, 10-18 points moderate cognitive impairment and ≤9 points severe cognitive impairment.

The HAROSA studies considered the Trail Making Test (TMT) Parts A&B as a secondary end-point to measure cognition. This test consists of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient is asked to draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient is asked to draw lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the

pen or pencil from the paper. Time the patient as he or she connects the "trail." If the patient makes an error, point it out immediately and allow the patient to correct it. Errors affect the patient's score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the patient has not completed both parts after five minutes have elapsed. A higher score indicates greater cognitive impairment, for Trial A the average time is 29 seconds, a score of >78 seconds indicates cognitive impairment and for Trial B the average time is 75 seconds, with a score of >273 seconds indicating cognitive impairment.

In the HAROSA studies baseline TMT A and TMT B scores were above average at baseline (HAROSA I: TMT A 49 for pitolisant arm, 48.1 for placebo arm and TMT B 101.6 for pitolisant arm and 98.5 for placebo arm and HAROSA II 51.9/50.6 and 114.9/106.2, see Table 5).

There was a reduction in both the pitolisant and placebo arms during the double-blind period, although this was not significant, TMT scores reduced further during the open label phase but remained above normal.

Table 5: Trail making test parts A and B

	HAROSA I				**HAROSA II**			
	Pitolisant		Placebo		Pitolisant		Placebo	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
TMT A Mean (SD) Range N	49.0(20.4) 14 to 134 181	42.8 (17.9) 12 to 115 174	48.1(24.0) 12 to 126 61	42.6(19.9) 15 to 118 57	51.9(21.7)20 to 142 200	43.3 (16.4) 16 to 96 189	50.6(22.7) 18 to 120 67	43.9 (19.0) 19 to 110 64
Mean change	-5.9 (13.0)		6.2(13.3		-8.9 (12.7)		-7.3 (13.7)	
TMT B Mean (SD) Range N	101.6(45.5) 35 to 289 180	90.0(46.2) 30 to 381 174	98.5(50.6) 32 to 259 61	84.9(41.9) 32 to 218 57	114.9(51.3) 44 to 305 200	93.0 (46.1) 22 to 492 189	106.2(45.5) 44 to 242 67	88.9 (37.9) 10 to 192 64
Mean change	-11.7 (37.0)		-15.3(34.4)		-22.5 (40.0)		-16.3 (33.8)	

However, given that patients with cognitive impairment were excluded from the studies and that sleepiness is subjective rather than objective, it is probably more helpful to look at the benefit in wakefulness and relief of daytime sleepiness as reflected by Physicians Global Impression of Change (PGIC) and Patient's Global Opinion of the Effect (PGOE) of treatment. During the double-blind period there was a statistically significant difference in the proportion of Physicians and Patients who

rated the treatment effect as improved, see Table 13 of our original submission (reproduced below).

By the end of the open-label period both physicians and patients rated the treatment effect as further improved over the double-blind period. In HAROSA I, 90.8% of physicians with patients originally randomised to pitolisant and 90.2% originally randomised to placebo rated the treatment effect as improved (67.7% and 58.5% as very much or much improved).

Table 6: Physicians Global Impression and PGOE of treatment (ITT population)

	Physicians Global Impression of Change			**Patient's Global Opinion of the Effect**		
	Pitolisant	**Placebo**		**Pitolisant**	**Placebo**	
HAROSA I	78.0% assessed as improved (11.0% very much improved, 42.2% much improved, and 24.9% minimally improved)	53.4% assessed as improved (6.9% very much improved, 27.6% much improved, and 19.0% minimally improved)	p<0.001	76.4% assessed as improved (marked effect 33.3%, moderate effect 27.6%, minimal effect 15.5%)	56.9% assessed as improved (marked effect 25.9%, moderate effect 10.3%, minimal effect 20.7%)	p=0.005
HAROSA II	84.2% assessed as improved (11.1% very much improved, 44.2% much improved, and 28.9% minimally improved)	56.3% assessed as improved (4.7% very much improved, 29.7% much improved, and 21.9% minimally improved)	p<0.001	86.3% assessed as improved (marked effect 30.0%, moderate effect 33.7%, minimal effect 22.6%)	60.9% assessed as improved (marked effect 21.9%, moderate effect 18.8%, minimal effect 20.3%)	p<0.001

A18. The concerns regarding Modafinil included psychiatric disorders, CV symptoms, and serious skin/ multi-organ hypersensitivity. Why were only CV symptoms addressed in the submission?

Answer: The EMA[9] noted that

….modafinil is associated to a rare risk of serious, life-threatening skin reactions. This risk appears to be higher in children.

Serious nervous system and psychiatric related events such as suicidal ideation, psychotic episodes, and depression have also been identified in association to modafinil.

Cardiovascular adverse events such as hypertension and arrhythmias are documented in association with modafinil. The cardiovascular profile of modafinil is of particular concern in the OSA population given the already elevated baseline risk.

The clinical studies for pitolisant looked at psychiatric disorders, CV symptoms, and serious skin/ multi-organ hypersensitivity as AE.

The only psychiatric disorders reported in more than 2% of the population were insomnia, skin and subcutaneous tissue disorders were reported in around 3.5% of all patients in HAROSA I and not at all in HAROSA II (see Table 17 in our original submission). Importantly, rates were similar in patients randomised to placebo and those randomised to pitolisant, with no excess risk associated with pitolisant treatment.

Anxiety was reported as a treatment emergent AE (TEAE) of special interest in 1.1% of pitolisant patients in HAROSA I, in 1.0% of pitolisant patients in HAROSA II and in 0% of placebo patients.

The Summary of Product Characteristics[2] states that *Pitolisant should be administered with caution in patients with history of psychiatric disorders such as severe anxiety or severe depression with suicidal ideation risk.* There is no warning for skin disorders.

Table 7: TEAE in the double-blind period (safety population), n=244 for HAROSA I and n=267 for HAROSA II[3,5]

	HAROSA I				HAROSA II			
	Pitolisant (n=183)	**Placebo (n=61)**	**Absolute risk reduction (95% CI)**	**Relative risk (95% CI)**	**Pitolisant (n=200)**	**Placebo (n=67)**	**Absolute risk reduction (95% CI)**	**Relative risk (95% CI)**
TEAE by system organ class and preferred term reported by ≥2% of patients in any arm								
Psychiatric disorders	23 (12.6%)	3 (4.9%)	-0.08 (-0.15-0.00)	2.56 (0.79-8.22)	19 (9.5%)	3 (4.5%)	-0.05 (-0.11-0.01)	2.12 (0.65-6.95)
Insomnia	17 (9.3%)	2 (3.3%)	-0.06 (-0.12-0.00)	2.83 (0.67-11.91)	11 (5.5%)	2 (3.0%)	-0.03 (-0.08-0.03)	1.84 (0.42-8.10)
Skin and subcutaneous tissue disorders	7 (3.8%)	2 (3.3%)	-0.01 (-0.06-0.06)	1.17 (0.25-5.47)				
TEAE of special interest								
Insomnia	17 (9.3%)	2 (3.3%)	-0.06 (-0.12-0.00)	2.83 (0.67-11.91)	11 (5.5%)	2 (3.0%)	-0.03 (-0.08-0.03)	1.84 (0.42-8.10)
Initial insomnia					1 (0.5%)	0 (0.0%)	-	-
Abdominal pain upper	2 (1.1%)	1 (1.6%)	0.01 (-0.03-0.004)	0.67 (0.06-7.22)	1 (0.5%)	0 (0.0%)		
Abdominal discomfort	2 (1.1%)	0 (0.0%)	-	-				
Gastroesophageal reflux disease	2 (1.1%)	0 (0.0%)	-	-	1 (0.5%)	0 (0.0%)	-	-
Dyspepsia					0 (0.0%)	1 (1.5%)	-	-
Anxiety	2 (1.1%)	0 (0.0%)	-	-	2 (1.0%)	0 (0.0%)	-	-
Depression					0 (0.0%)	1 (1.5%)	-	-
Electrocardiogram QT prolonged	0 (0.0%)	1 (1.6%)	-	-	2 (1.0%)	0 (0.0%)	-	-
Weight increased	1 (0.5%)	0 (0.0%)	-	-				

The Clinical Overview[10] document which contains pooled data on five studies using pitolisant in adult patients with OSA. Overall, 603 patients received pitolisant and 151 received placebo. The mean (SD) duration of pitolisant treatment (all doses) in double-blind, placebo-controlled studies in OSA was 10.0 (4.1) weeks as compared with 33.5 (14.0) weeks in single-blind and open-label studies of pitolisant in OSA.

Approximately two-thirds of all patients (74.8%) received a maximal pitolisant dose of 18 mg once daily, and a comparable proportion of patients (63.5%) received a maintenance dose of 18 mg once daily.

In total, 284 (47.1%) patients were exposed to a maximal dose for 6 months to 1 year, and 108 (17.9%) were exposed for 1 year or more.

Table 8 shows the TEAE reported in at least 1% of patients in the pitolisant group the double-blind placebo-controlled studies. Insomnia and anxiety are the only psychiatric disorders reported. For insomnia, the relative reduction is 1.83 (95% CI 0.78-4.27, p=0.09) indicating a non-significant difference. The final column in the table below shows the incidence for all patients exposed to pitolisant, including patients receiving pitolisant in the open label extension studies. Rates of insomnia and anxiety are 8.9% and 2.2% respectively.

Table 8 : TEAE reported in at least 1% of patients in the pitolisant group in the double-blind placebo-controlled studies

MedDRA Preferred Term	**Double-blind placebo-controlled**		**TOTAL Pitolisant (N=603) n (%)**
	Placebo (N=151) n (%)	**Pitolisant (N=468) n (%)**	
Any Study Treatment-Related AE	32 (21.2%)	127 (27.1%)	208 (34.5%)
Headache	16 (10.6%)	45 (9.6%)	75 (12.4%)
Insomnia	**6 (4.0%)**	**34 (7.3%)**	**54 (8.9%)**
Nausea	2 (1.3%)	15 (3.2%)	20 (3.3%)
Abdominal pain	1 (07%)	11 (2.3%)	17 (2.8%)
Vertigo	2 (1.3%)	7 (1.5%)	10 (1.7%)
Anxiety	**0**	**6 (1.3%)**	**13 (2.2%)**
Diarrhoea	1 (0.7%)	6 (1.3%)	6 (1.0%)

Adverse Events

A19. Is there any information on adverse events outside the HAROSA trials?

Answer: The Clinical Overview mentioned in A18 above[10] included data from five studies which looked at pitolisant for the treatment of EDS in patients with OSA. A total of 659 patients were enrolled. Overall, 609 patients were exposed to pitolisant and 152 to placebo alone (Table 9). The safety population included 603 patients who had received pitolisant and 151 who had received placebo.

Table 9: Number of patients treated in pitolisant efficacy studies

			Double-blind placebo-controlled		Single-blind and open-label pitolisant	TOTAL Pitolisant
Study ID			Placebo arm	Pitolisant arm	Exposed to pitolisant	Total exposed to pitolisant
P04-01		Pilot	-	-	12	12
P05-01		Pilot	-	-	20	20
P09-16		Pilot	24	91	-	91
P09-08	HAROSA I	Pivotal	61	183	199	231
P09-09	HAROSA II	Pivotal	67	201	236	255
Total			**152**	**475**	**467**	**609**

Note: the total number of patients does not take into account the notion of unique patients. Some patients participated into two studies (P09-08/P09-16 or P09-09/P09-16).

Studies P04-01 and P05-01 were early pilot single-blind placebo-controlled studies. Their objectives were mainly to identify possible clinical efficacy of pitolisant in this indication and to derive preliminary safety data. In these studies, the 40 mg once daily fixed dose significantly decreased ESS score and increased sleep onset latency (Osler test).

Study P09-16 was designed to evaluate the minimum effective dose of pitolisant in reducing EDS in patients with OSA.

When looking at safety, the narcolepsy studies were also considered and showed that AE profiles were consistent across all indications. AEs were consistent in type and severity even at different daily doses and varying lengths of exposure, including treatment out to 5 years (see Table 10).

Table 10: Overview of AE: OSA and all indications (nacrolepsy and OSA) – safety population

	OSA				All indications (OSA and narcolepsy)			
	Double-blind placebo-controlled		Single-blind and open-label pitolisant (N=468)	TOTAL Pitolisant [a] (N=603)	Double-blind placebo-controlled		Single-blind and open-label pitolisant (N=1,021)	TOTAL Pitolisant (N=1,513)[b]
Event	Placebo (N=151)	Pitolisant (N=468)			Placebo (N=475)	Pitolisant (N=1043)		
	n (%) of patients				n (%) of patients			
At least 1 TEAE	47 (31.1)	184 (39.3)	188 (40.2)	282 (46.8)	222 (46.7)	525 (50.3)	554 (54.3)	901 (59.6)
At least 1 severe TEAE	5 (3.3)	24 (5.1)	29 (6.2)	46 (7.6)	23 (4.8)	71 (6.8)	113 (11.1)	173 (11.4)
At least 1 SAE	0	4 (0.9)	11 (2.4)	14 (2.3)	15 (3.2)	27 (2.6)	62 (6.1)	87 (5.8)
At least 1 related TEAE	32 (21.2)	127 (27.1)	119 (25.4)	208 (34.5)	115 (24.2)	329 (31.5)	332 (32.5)	604 (39.9)
At Least 1 related severe TEAE	3 (2.0)	13 (2.8)	8 (1.7)	20 (3.3)	12 (2.5)	33 (3.2)	49 (4.8)	81 (5.4)
At least 1 related SAE	0	0	1 (0.2)	1 (0.2)	7 (1.5)	5 (0.5)	3 (0.3)	8 (0.5)
TEAE resulting in discontinuation	4 (2.6)	12 (2.6)	16 (3.4)	27 (4.5)	25 (5.3)	63 (6.0)	70 (6.9)	132 (8.7)

n = number of patients; SAE=serious adverse event; TEAE=treatment-emergent adverse event

[a] Includes double-blind, placebo-controlled studies; and single-blind and open-label studies in the All OSA pool.

[b] Includes double-blind, placebo-controlled studies; and single-blind and open-label studies in the All Indications pool.

Note: Patients with multiple occurrences of a preferred term are counted only once for that term in each column.

Patient with an AE resulting in discontinuation in more than 1 study is counted for each corresponding discontinuation reason from those studies in which the events occurred.

If more than 1 study had the same reasons for discontinuation for a patient, the patient was counted only once in the table for that row.

Incidence of specific AE were similar in the pitolisant and placebo arms of double-blind placebo-controlled studies. If we consider the 1,513 patients exposed to pitolisant with OSA or narcolepsy, the AE profile in the overall population was similar to that seen in the OSA population, and no new safety signals were identified.

Table 8 in the answer to Q18 details the most common AE in patients enrolled in the OSA studies, AE are consistent with the HAROSA studies.

Severity of AE

The majority of TEAEs in patients who received pitolisant in double-blind, placebo-controlled OSA studies were mild (25.4%, 119/468) or moderate (21.4%, 100/468) in severity. Severe TEAEs were reported in a slightly higher proportion of pitolisant-treated patients (5.1%, 24/468) compared with placebo-treated patients (3.3%, 5/151). Similar results were observed in pooled data (all OSA studies) with 29.4% (177/603) mild TEAEs, 30.0% (181/603) moderate TEAEs and 7.6% (46/603) severe TEAEs.

Headache was the most frequently reported TEAE in the OSA clinical trials. It was mostly of mild to moderate intensity in all groups with the same frequency for both pitolisant and placebo in the double-blind studies (12.6% for both), 16.0% in the total pooled data (all OSA studies).

The only severe TEAE reported in >1% of pitolisant-treated patient in double-blind, placebo-controlled studies was headache, which was comparable with the incidence in patients receiving placebo (1.1% vs. 1.3% placebo).

Serious AE

The incidence serious TEAEs in double-blind, placebo-controlled studies in OSA patients was low and similar between the pitolisant (0.9% [4/468patients]) and placebo (0%) treatment groups. The serious AEs reported in the four patients who received pitolisant in the double-blind, placebo-controlled group were: cardiopulmonary failure, irritable bowel syndrome, QT prolonged on ECG and musculoskeletal pain. None of which was considered treatment-related.

In single-blind and open-label OSA studies of pitolisant (which had a longer mean treatment duration than double-blind placebo-controlled studies), 11/468 patients

(2.4%) experienced at least one treatment-emergent serious AE. Each serious AE was only reported by one patient and only one case of hypertension was considered treatment-related by the investigator.

Discontinuations due to AE

Few patients with OSA who received pitolisant discontinued treatment due to a TEAE (4.5%, 27/603 patients). Incidence of discontinuation was comparable between the pitolisant and placebo groups.

AE leading to discontinuation included

- Nervous system disorders (9/603, 1.5%): headache (n=5), dizziness (n=2), circadian rhythm sleep disorder (n=1), somnolence (n=1) and tremor (n=1)
- Psychiatric disorders (9/603, 1.5%): insomnia (n=5), depression (n=2), depressed mood (n=1), anxiety (n=1), irritability (n=1), mood altered (n=1) and libido decreased (n=1)
- Gastrointestinal disorders (6/603, 1.0%): nausea (n=3), enterocolitis (n=1), dry mouth (n=1) and breath odour (n=1).

Long-term safety

In patients treated for OSA, 284 out of 603 patients (47.1%) were treated with pitolisant for 6 months to <1 year and 108 out of 603 patients (17.9%) were treated for 1 year or more. TEAEs reported with a late onset (6 months to >1 year or ≥1 year) following the initiation of pitolisant treatment were generally consistent with the overall AE profile of pitolisant. Influenza (n=7, 1.1%), back pain (n=6, 1%) and anxiety (n=6, 1%) were the most frequent new AE reported after 6-12 months and headache was the most frequent new AE reported after 1 year

Deaths

There were few deaths in patients who received pitolisant across the whole clinical development programme (OSA and narcolepsy). Overall, there were six deaths within 30 days of the last dose of pitolisant. All six deaths were considered unrelated to pitolisant.

One of the six deaths was excluded from the pooling of Safety Population because it occurred in study P04-08 in a schizophrenic patient belonging to the excluded arm where patients received pitolisant in combination with olanzapine that could jeopardise the assessment of AE causality due to this combination.

Of the five remaining deaths, all occurred in pitolisant-treated patients, including two deaths that occurred in a OSA study (P09-09 HAROSA II), one death in a patient with narcolepsy (study P09-10 HARMONY III) and two deaths in patients with Parkinson's disease in study P06-11.

Post-marketing data

The post-marketing safety information includes cumulative events from the international birth date (IBD) of pitolisant (31 March 2016) through a data cut-off date of 31 March 2019.

The most frequent adverse drug reactions reported during the post-marketing period 31 March 2016 through 31 March 2019 were headache (6.2%), insomnia (4.8%), depression (3.4%) and nausea (3.4%). CV AE such as arrhythmia and hypertension were rare.

A20. What is the total number of patient treatment-years on which the adverse events profile of pitolisant is based?

Answer: The post-marketing safety information includes cumulative events from the international birth date (IBD) of pitolisant (31 March 2016) through a data cut-off date of 31 March 2019.

In the Clinical Overview[10], the estimated cumulative patient-years of treatment with pitolisant for narcolepsy and OSA from March 2016 to March 2019 is estimated at 4,931 patient-years.

Data are not available on the total number of patient treatment-years on which the AE profile for patients receiving pitolisant for EDS due to OSA.

Indirect Comparisons

A21. Please provide the full WinBUGS code including datasets for the indirect comparison of pitolisant with mandibular advancement devices (MAD).

Answer: The WinBUGs code along with the datasets used to perform the indirect treatment comparison of pitolisant with MAD is presented below:

```
# Fixed effects model for two-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns2) { # LOOP THROUGH 2-ARM STUDIES
y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
var[i,2] <- pow(se[i,2],2) # calculate variances
prec[i,2] <- 1/var[i,2] # set precisions
dev[i,2] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2] #Deviance contribution
delta[i,2] <- d[t[i,2]] - d[t[i,1]] # trial-specific treat effects distributions
}
totresdev <- sum(dev[,2]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects
for (c in 1:(nt-1)) {
 for (k in (c+1):nt) {
 diff[c,k] <- (d[k]-d[c])
      }
   }
} # *** PROGRAM ENDS

# Data (OSA data from Linda D. Sharples et al.  – trial-level data: treatment differences)
list(ns2 = 7, nt=3) # ns2: Number of studies, nt: Number of treatments
t[,1]      t[,2]      y[,2]      se[,2]      # Study
1          2           1.6         1.76       # Arab 2011
1          2          -1           0.57       # Barnes 2004
1          2          -2           0.51       # Gotsopoulos 2002
1          2          -1           1.41       # Lam 2007
1          2          -0.94        1.1         # Jhonston 2002
1          2          -1.2         1.19       # Petri 2008
1          3          -2.8         0.638      # HAROSA II
END

# Initial Values
#chain 1
list(d=c( NA, 0,0))
#chain 2
list(d=c( NA, -1,-3),)
#chain 3
list(d=c( NA, 2,2))
```

Section B: Clarification on cost-effectiveness data

Decision Problem

B1. Priority question: The scope states that the comparator is: 'Established clinical management without pitolisant'. It also refers to the NHS website with regards to recommended treatments (NHS (2016) Obstructive sleep apnoea: treatment. Accessed March 2020.), which in turn cites the British Lung Foundation website (https://www.blf.org.uk/support-for-you/obstructive-sleep-apnoea-osa/treatment), which states: 'You're likely to need another treatment as well as making lifestyle changes. Mandibular advancement devices (MADs) and continuous positive airway pressure (CPAP) machines are common.'

Could the company please include MADs as a comparator, at least in the subgroup of those who refuse CPAP?

Answer: As discussed in our call with the ERG on 16th June, the comparison versus MAD in CPAP refusers was included as a scenario analysis in our submission. It was therefore agreed by the ERG that no further action was required regarding this question.

Model structure

B2. The model has a 25-year horizon, which is deemed appropriate as the life expectancy at birth for men in the UK is around 80 years. The life expectancy at 52 years (mean age of trial cohorts), however, is 84 years and expected median survival in a general population cohort of 52 year old UK men is around 34 years. Therefore, it could be that a substantial part of the modelled cohort lives beyond the model horizon of 25 years, even though the mortality is higher in the modelled patient population compared to the general population. Please adjust the time horizon of the model to reflect a true life-time time horizon.

Answer: The model has been updated to reflect the true life-time horizon of the cohort of patients included in the model. It has now been assumed that patients could live for up to 100 years.

Clinical parameters and variables

B3. Priority question: In previous applications of the model (i.e. references 80 and 81 in the company submission) and NICE TA139, the effect of interventions such as CPAP on CV events was based on the observed effect of such interventions on blood pressure and translating this change in blood pressure to a change in CV risk through a risk equation (such as Framingham). The HAROSA trials indicate that pitolisant does not have an effect on blood pressure. Could you please substantiate your assumption that pitolisant has an effect on the risk for CV events, in particular by describing the biological mechanism through which a reduction in CV risk is to be expected from the use of pitolisant?

Answer: A number of studies have shown an association between OSA and increased CV risk, particularly in patients with EDS[11-17].

Hypertension is an easily identifiable CV risk factor that has been shown to be more frequent in people with OSA and EDS[18,19].

The use of CPAP has been shown to exert a modest beneficial effect on blood pressure[20]. It is proposed that this effect underlies the observed improvement in CV events, at least in those patients with hypertension[21].

However, two studies have shown that CPAP only exerts a lowering effect on blood pressure in the presence of EDS, non-sleepy patients showing no change in blood pressure, even in the presence of hypertension[22,23]. This suggest that EDS either has a direct causative role in raising blood pressure or is a marker of a third unknown factor, that may mediate the CV changes in a more subtle way than simply elevating blood pressure.

This not an unreasonable hypothesis, given that OSA appears to exert its CV effect via a range of different neurohumoral mechanisms, with the effect on blood pressure being one component of a complex autonomic interaction[24,25].

Additionally, the presence of EDS has been shown to be strongly associated with the risk of myocardial infarction, heart failure and stroke, even after correction for the effect of a wide range of known CV risk factors, including hypertension[26-28].

There is therefore reason to believe that the interaction between OSA with EDS is considerably more complex than a simple blood pressure effect. Although it is difficult to demonstrate a causal association between EDS and CV risk, there is sufficient evidence to justify modelling CV outcomes based on the surrogate measure of ESS score. Even in the absence of an impact of pitolisant on blood pressure, this is consequently a plausible strategy.

B4. Priority question: On page 62 is it stated that: "We assumed that the increased risk of CV events reported by Loke et al[88]. was matched by the risk reduction observed in patients treated with CPAP, as previously assumed in NICE guidance (TA139)[28] We also assumed that this reduction was uniquely and independently explained by the difference in terms of ESS score between CPAP and its comparators (BSC and MAD)."

a. Regarding the first sentence, please explain where we can find in TA139 that such an assumption was made.

b. Please substantiate the assumption made in the last sentence.

c. Can you provide substantiation why the observed relation between ESS and CV risk observed in patients treated with CPAP can be applied to other interventions that do not apparently change cardiovascular risk factors?

Answer:

a. Our apologies – this is untrue, the York model (McDaid, 2009)[29] used changes in blood pressure to calculate changes in CV risk.

b. Please see answer to B3 above. We believe that the evidence cited in this answer provides support for the independent CV predictive role of reduction in ESS. Whether this effect is the unique predictor of the change in risk is more difficult to prove. However, in the absence of evidence to the contrary, we believe this was a reasonable assumption to make.

c. Please see answer to B3 above. As discussed in the answer to question B3, there is evidence that the presence of EDS is an independent determinant of CV risk, even after the role of known CV risk factors has been taken into account[26-28]. In all three of

these studies, the ESS score was used as the determinant of EDS. We consequently believe that our strategy of mapping change in ESS score to change in CV risk has a basis in objective evidence.

B5. Priority question: At various places in the model, odds ratios have been multiplied with risks as if they were the same as risk ratios, for example in the calculation of “Risk of CHD for patients in CPAP + BSC group”. Please provide an updated model where this has been corrected.

Answer: When events rates are low, as is the case for road traffic accidents (RTA) and CV outcomes in these patients, there is negligible difference between the application of an odds ratio and a risk ratio in this fashion. For computational simplicity we therefore elected to assume the two measures were interchangeable in the original model. We acknowledge that this is technically incorrect and have reformulated the calculations throughout the revised model to reflect this.

B6. The risk of CV events is based on existing risk equations (Framingham, QRISK 3 and QStroke). In these risk equations, the relation between risk factors and estimated risk is not linear. This means that when the risk for the ‘average patient’ from a certain cohort (i.e. the mean value in that cohort for every risk factor) is estimated, this does not represent the mean risk in that cohort.

a. Was the CV risk estimated using the average value in the pitolisant arm for each of the required risk factors in the risk equations, or was CV risk estimated per individual in the pitolisant arm?

b. In case risk was estimated using average values as input into the risk equation, what is the difference in estimated baseline CV risk when risk is predicted per individual?

Answer:

a. The CV risk was estimated using the average values for each of the required risk factors in the equations in the Pitolisant arm.

b. McDaid et al.[29] explored this issue by testing whether or not the use of mean blood pressure would bias the results using a set of individual patient data. The risk of CV events and stroke were predicted using blood pressure for each patient and

the mean taken. This was compared with the risk calculated based on the mean of group blood pressure. The risk calculated by the two different methods was the same to two decimal places.

We used the same approach as that used in McDaid et al.[29] to explore whether the use of mean age, systolic blood pressure, weight and BMI would bias the results. A population of 1,000 patients was randomly generated, and mean age, systolic blood pressure, weight and BMI were all assumed to follow a normal distribution with the mean and standard deviation observed in male patients treated with pitolisant in HAROSA I study.

The risk of a CV event at 10 years was then predicted for each of the 1,000 patients using the QRISK3 predictive model, and the mean risk (12.61%) obtained from the simulated population was compared with the risk calculated based on the mean values of the above-mentioned variables (12.7%). The similarity observed clearly shows that the use of aggregate-level data did not significantly bias the result.

R software version along with the QRISK3 package were used to perform the above analysis. The R code for this analysis is reported below:

```
## Importing QRisk 3 package
library(QRISK3)

## Vector with variables names
data(QRISK3_2019_test)
test_all <- QRISK3_2019_test

Var_names <- names(test_all)[2:27]

## Create a vector to store the CHD risk score
Results <- vector("numeric", 100)

## Code to simulate IPD and compute the CHD risk score
for(j in 1:100) {

## Code to simulate the patients height


Poids <- rnorm(1000, 97.9, 18.2) # Weight

BMI <- rnorm(1000, 32.57, 4.91) # BMI

Height <- vector("numeric", 1000)
```

```
for (i in 1:1000){
  Height[i] <- round(sqrt(Poids[i]/BMI[i])*100, 0)
}
# Simulation of patients baseline Characteristics.
Age <- rnorm(1000, 53.8, 0.77) # Age
Gender <- rep(0, 1000) # Gender
AF <- rep(0, 1000) # Atrial fibrillation
AA <- rep(0, 1000) # Atypical antisepsy
RST <- rep(0, 1000) # Regular steriod tablet
ED <- rep(0, 1000) # Erectile disfunction
Migraine <- rep(0, 1000) # Migraine
RA <- rep(0, 1000) # Rheumatoid arthritis
CKD <- rep(0, 1000) # Chronic kidney disease
SMI <- rep(0, 1000) # Severe mental illness
SLE <- rep(0, 1000) # Systemic lupus erythematosis
BPT <- rep(0, 1000) # Blood pressure treatment
D1 <- rep(0, 1000) # Type 1 diabetes
D2 <- rep(0, 1000) # Type 2 diabetes
Poids <- Poids # Weight
Height <- Height # Height
Eth <- rep(1, 1000) # Ethnicity
HAR <- rep(0, 1000) # Heart attack relative
CHDL <- rep(5, 1000) # cholesterol HDL ratio
SBP <- rnorm(1000, 128.7, 12) # Systolic Blood pressure
SDSBP <- rep(12, 1000) # std systolic blood pressure
```

```
Smoke <- rep(4, 1000) # Smoking status

Surv <- rep(10, 1000) # Survival

town <- rep(0, 1000) # Townsend

BMI <- BMI # BMI

Pat_ID <- 1:1000 # Patients ID


Data <- data.frame(Age = Age, Gender = Gender, AF = AF, AA = AA, RST = RST,
ED = ED,
                   Migraine = Migraine, RA = RA, CKD = CKD, SMI = SMI, SLE = SLE,
                   BPT = BPT, D1 = D1, D2 = D2, Poids = Poids, Height = Height,
                   Eth = Eth, HAR = HAR, CHDL = CHDL, SBP = SBP, SDSBP = SDSBP,
                   Smoke = Smoke, Surv = Surv, town = town, BMI = BMI, Pat_ID =
Pat_ID)


names(Data) <- names(test_all)[2:27]


test_all_rst <- QRISK3_2017(data=Data, patid="ID", gender="gender", age="age",
                            atrial_fibrillation="b_AF", atypical_antipsy="b_atypicalantipsy",
                            regular_steroid_tablets="b_corticosteroids",
erectile_disfunction="b_impotence2",
                            migraine="b_migraine", rheumatoid_arthritis="b_ra",
                            chronic_kidney_disease="b_renal",
severe_mental_illness="b_semi",
                            systemic_lupus_erythematosis="b_sle",
                            blood_pressure_treatment="b_treatedhyp", diabetes1="b_type1",
                            diabetes2="b_type2", weight="weight", height="height",
                            ethiniciy="ethrisk", heart_attack_relative="fh_cvd",
                            cholesterol_HDL_ratio="rati", systolic_blood_pressure="sbp",
                            std_systolic_blood_pressure="sbps5", smoke="smoke_cat",
townsend="town")


Results[j] <- mean(test_all_rst$QRISK3_2017_1digit)

}

## Print the CHD risk score
mean(Results)
```

B7. Please provide a journal reference for the UK-based Framingham risk score.

Answer: The use of the term “UK-based” Framingham risk score was derived from a web-based calculator that we used to generate these estimates. On closer inspection, it emerges that the “UK-based” component actually only reflects the guidelines-driven recommendations that flow from the risk calculation, which are based on the original US formula. We apologise for this error and have consequently made the decision to use the QRisk/QStroke formulas in our base case.

B8. Please explain why the Framingham risk score was used in the base case analysis, rather than the QRISK 3 and QStroke.

Answer: We used the Framingham risk score since it was consistent with the earlier York model[29]. QRISK 3 and QStroke were included in our original modelling as a scenario analysis.

As explained in the answer to B7 above, we incorrectly believed that the version of the Framingham risk formula that we were using had been remapped to UK risk profiles. As this turns out not to be the case, we have adopted QRisk/QStroke for the base case and relegated the US Framingham-based estimate to a scenario analysis.

B9. Please explain why the risk of CHD and stroke is constant over time, given that age is one of the independent variables in the risk equations.

Answer: Apologies, the model will be updated to incorporate age CV risk dependency.

B10. On page 60 of the CS, 3 lines above Table 25, it states **“***When data were not available, plausible assumptions were used.”* Please explain which data was not available and which assumptions were made.

Answer: The new base case uses the QRisk and QStroke formulas. These include a range of biovariables and clinical criteria. Limited baseline information was available for the recruited populations in the HAROSA studies. Of the required inputs we were able to obtain accurate information from the HAROSA studies for:

- Age
- Gender

- Total cholesterol
- HDL-cholesterol
- Blood pressure

For all other inputs to the formulas we assumed the absence of the risk factor. The consequence of this is that we almost certainly under-estimated the baseline CV risk of the population. However, as there is no reason to expect anything other than random differences between treatment groups for these undocumented risk factors, it is unlikely that this assumption will have introduced a between-groups bias.

B11. Priority question: In the model, the odds of a CHD in pitolisant vs CPAP is calculated by =EXP(($C$21/$C$16)*LN(D28)), which can be expressed as
=EXP((ESS_pito_CPAP/ESS_CPAP_BSC)*LN(odds(CPAP vs BSC)))
which is mathematically the same as
Odds(pito vs CPAP) = odds(CPAP vs BSC)^(ESS_pito_CPAP/ESS_CPAP_BSC).
Please explain why this equality holds or why it might be reasonable to assume that this equality holds.
Answer: The calculation above is related to the odds ratio (OR) of a CHD event in people receiving pitolisant vs people receiving BSC. The cell $C$21 in the model reports the ESS score difference between the pitolisant and BSC groups. This implies that the mathematical formulation of the OR between pitolisant and BSC should be expressed as follows: OR(Pito vs BSC) = EXP(ESS_Pito_BSC/ESS_CPAP_BSC)*LN(OR(CPAP vs BSC).

This equality was made possible by assuming that the OR of a CHD event between pitolisant and BSC arms was exclusively explained by the ESS score difference between the two treatment arms [e.g. OR(Pito vs BSC) = EXP(ESS_Pito_BSC)]. Additionally, given that the LN(OR) of a CHD and the ESS score difference were available for CPAP versus BSC, it was then reasonable to derive the LN(OR) of a CHD between pitolisant and BSC using the following approach:
If the assumption made above holds and the OR of a CHD event along with the ESS score difference between CPAP and BSC are available, we can reasonably apply the direct rule of three to derived the OR of a CHD between pitolisant and BSC given

that the ESS score difference between pitolisant and BSC was made available from HAROSA studies.

B12. The two prior iterations of the model used age and sex specific mortality rates from UK life tables in the OSAHS state and use relative risk estimates to increase mortality risk in the OSAHS post CHD and OSAHS post stroke health states. The current model uses non-age-and-sex-specific annual probabilities for death in these health states.

a. Could you please clarify the decision to adapt the model in this aspect (i.e. to use a single estimated annual probability to die, rather than apply a relative risk to the age and sex specific mortality from the OSAHS health state)?

b. Please provide more detail on the method by which the data published in references 92 through 95 was used to compute the figures presented in table 29 of the submission, in particular which data from the referred publications were used as inputs.

Answer:

a. Given that the model uses age-and-sex-specific all cause annual probability of death, we believed that applying this to OSAHS post-CHD and OSAHS post-stroke health state would have no significant effect on the final ICER.

b. In Smolina et al. 2012 (reference 92 in the original submission)[30], the 7-year risk of death post CHD in men was reported (13.9%; 95% CI, 13.7–14.1); we assumed that the risk of death followed an exponential distribution, and derived the annual risk of death post-CHD from this assumption.

Crichton et al. 2016 (reference 93 in the original submission)[31] reports the Kaplan Meier survival estimate at 15 years in Figure 1. We were able to obtain the risk of death post-stroke along with the confidence interval by using digitilizer software (DigitizeIt version 2.3.3) to extract the values. The annual risk of death post-stroke was computed using the same approach as described above.

For the risk of fatal CHD and stroke, the fatality rates at 30 day were reported in Read et al, 2019 (reference 94 in the original submission)[32] and Seminog et al. 2019 (reference 95 in the original submission)[33].

B13. In the two prior iterations of the model, the risk for both fatal and non-fatal CV-events was based on the CV risk equations (e.g. Framingham). The current model uses the CV risk equations to estimate the effect of non-fatal CV-events only, while using other published data to estimate the annual probability to estimate fatal CV-events.

a. Please clarify the decision to adapt the model in this aspect.

b. Please clarify how the currently used annual probabilities for non-fatal CHD and stroke compare to those based on the risk equations to predict non-fatal CV-events.

c. Please provide an updated version of the model that incorporates fatal CV-events based on the Framingham risk score.

Answer: Our understanding is that neither McDaid et al[29] nor Sharples et al[34] used the Framingham risk formula to estimate fatal events, as it does not allow disaggregation of fatal and non-fatal occurrences. A similar limitation applies to the QRisk3/QStroke formulas that we have now adopted for the base case.

McDaid et al[29] state:

"…The mortality rate for individuals who have not experienced CHD or stroke (by age and sex) was taken from the UK life tables of the Government Actuary Department (www.gad.gov.uk). For each age band, the all-cause hazard was reduced by the proportion of people dying of cardiovascular disease (CVD) or Ischaemic heart disease (IHD) causes to get the hazard of death for non-CVD or non-IHD causes using methods developed by Chiang.[168] For patients who experienced CHD or stroke, an elevated mortality rate was used based on relative risks from the literature. For patients who experienced CHD and stroke, relative risks of death of 3.2 and 2.3, respectively, were employed. These relative risks were applied to the non-cardiovasular/ischaemic heart disease mortality rates in the UK population (by age and sex)..."

Sharples et al[34] state:

"…The equation was used to calculate the 4-year probability of an event, with a piece-wise exponential used to convert this into a yearly probability to correspond to the cycle length. Long-term observational studies were consulted for estimates of the increased risk of mortality following events relating to stroke and CHD once an initial event had occurred…"

"…Non-cardiovascular disease mortality, originally based on data from 2004 in McDaid et al.,[8] was updated using interim life tables (2009–11) and mortality statistics for 2010 from the Office for National Statistics. The interim life tables gave age- and gender-specific mortality rates, from which the all-cause hazard was reduced according to the proportion of people who died of CHD and ischaemic heart disease. Underlying mortality rates for patients who have suffered a stroke or CVE were adjusted based on data from two long-term follow-up studies…"

We therefore believe that our approach is reasonable and in line with the previous iterations of the model.

B14. The probability of a patient to be involved in a traffic accident (fatal or non-fatal) is assumed to be the same as that in the general population. However, the adverse effects of pitolisant include effects that might affect driving ability (e.g. anxiety, irritability, vertigo). Could you please provide evidence to substantiate the plausibility of the aforementioned assumption?

Answer: The HAROSA studies did not assess RTA within the study design. As you note, we have assumed that the probability of RTA in patients receiving pitolisant is equivalent to that of the general public. We believe that this is appropriate since the most common AE with pitolisant is headache, with similar incidence in both pitolisant and placebo arms. The AE noted in B14 (anxiety, irritability, vertigo) are rare. In the pooled dataset described in the Clinical Overview[10] anxiety was reported by 2.2% of patients, vertigo by 1.7% and irritability by 0% (see Table 8).

B15. The effect of pitolisant on the probability to be involved in a traffic accident is assumed to be proportional to the effect on ESS. Could you please provide evidence to substantiate this assumption?

Answer: As described in question **B11**, it was assumed that the odds ratio of being involved in an RTA between people taking pitolisant and BSC was exclusively explained by the ESS score difference between the two treatment arms. This approach was also been used in Sharples et al. 2014[34].

B16. Tables 25 and 38 both show the annual probability of a CVD and stroke event in the pitolisant arm. However, the figures presented differ between these tables. Could you please clarify which table presents the actual base case parameter values?

Answer: The correct annual probability of a CHD and stroke event are reported in Table 25, the values reported in Table 38 were mistakenly inserted.

A revised version of Table 38 with all the new parameters is inserted below for clarity.

Table 11: Summary of variables applied in the economic model (Table 38 in our original submission)

Parameter	Value	Measurement of uncertainty and distribution used in the OWSA: CI (distribution)	Distribution
Discount rate - Cost	0.035	0.028 – 0.042 (20% variation)	BETA
Discount rate - Utility	0.035	0.028 – 0.042 (20% variation)	BETA
Clinical Inputs			
Baseline ESS - HAROSA I	11.87	95% CI: 10.4392 - 13.3008	NORMAL
Baseline ESS - HAROSA II	12.1	95% CI: 10.6437 to 13.5563	NORMAL
CPAP + Pitolisant vs CPAP + BSC (HAROSA I): ESS Effect Size	-2.6	95% CI: -3.9 to -1.4	NORMAL
Pitolisant vs BSC (HAROSA II): ESS Effect Size	-2.8	95% CI: -4 to -1.5	NORMAL
Pitolisant vs MAD (HAROSA II): ESS Effect Size	-1.466	25% CI: -2.866 to -0.063	NORMAL
Transition Probabilities RTA and FRTA Pitolisant - Baseline			
CPAP + Pitolisant: TP from OSAHS to RTA	0.0037	0.003 to 0.0044 (20% variation)	BETA
CPAP + Pitolisant: TP from OSAHS to FRTA	0.0001	0.0000 to 0.0001 (20% variation)	BETA
Transition Probabilities Pitolisant (HAROSA I)			
CPAP+Pitolisant (HAROSA I): TP from OSAHS to Acute CHD	0.0100	0.008 to 0.012 (20% variation)	BETA
CPAP+Pitolisant (HAROSA I): TP from OSAHS to Acute Stroke	0.0028	0.0022 to 0.0033 (20% variation)	BETA
Transition Probabilities BSC (HAROSA I)			
CPAP+BSC (HAROSA I): TP from OSAHS to Acute CHD	0.0167	95% CI: 0.0080 to 0.0346	BETA
CPAP+BSC (HAROSA I): TP from OSAHS to Acute Stroke	0.0071	95% CI: 0.0047 to 0.0107	BETA
CPAP+BSC (HAROSA I): TP from OSAHS to RTA	0.0296	95% CI: 0.0198 to 0.0556	BETA
CPAP+BSC (HAROSA I): TP from OSAHS to FRTA	0.0005	95% CI: 0.0004 to 0.0006	BETA
Transition Probabilities Pitolisant (HAROSA II)			
Pitolisant (HAROSA II): TP from OSAHS to Acute CHD	0.0087	0.0069 to 0.0104 (20% variation)	BETA
Pitolisant (HAROSA II): TP from OSAHS to Acute Stroke	0.0020	0.0016 to 0.0024 (20% variation)	BETA
Transition Probabilities BSC (HAROSA II)			
BSC (HAROSA II): TP from OSAHS to Acute CHD	0.0152	95% CI: 0.0069 to 0.0332	BETA
BSC (HAROSA II): TP from OSAHS to Acute Stroke	0.0055	95% CI: 0.0035 to 0.0086	BETA
BSC (HAROSA II): TP from OSAHS to RTA	0.0340	95% CI: 0.0221 to 0.0672	BETA
BSC (HAROSA II): TP from OSAHS to FRTA	0.0005	0.0004 to 0.0006 (20% variation)	BETA
Transition Probabilities MAD (HAROSA II)			
MAD (HAROSA II): TP from OSAHS to Acute CHD	0.0116	95% CI: 0.0077 to 0.0175	BETA
MAD (HAROSA II): TP from OSAHS to Acute Stroke	0.0034	95% CI: 0.0027 to 0.0043	BETA
MAD (HAROSA II): TP from OSAHS to RTA	0.0117	95% CI: 0.0093 to 0.0167	BETA
MAD (HAROSA II): TP from OSAHS to FRTA	0.0002	0.0001 to 0.0002 (20% variation)	BETA
Transition Probability - Fatal CVEs and Death			
TP from Acute CHD to Fatal CHD	0.1020	0.0816 to 0.1224 (20% variation)	BETA
TP from Acute Stroke to Fatal Stroke	0.2640	0.2112 to 0.3168 (20% variation)	BETA

TP from Post CHD to Death	0.0212	95% CI: 0.0208 to 0.0215	BETA
TP from Post stroke to Death	0.0491	95% CI: 0.0467 to 0.0513	BETA
Absolute Utility			
Utility RTA	0.6200	0.4960 to 0.7440 (20% variation)	BETA
Costs			
Cost of fatal CVE	£3,813	£3,050 to £4,576 (20% variation)	GAMMA
Treatment cost of CHD	£12,619	£10,095 to £15,143 (20% variation)	GAMMA
Management cost of CHD	£933	£746 £1,120 (20% variation)	GAMMA
Treatment cost of stroke	£13,452	95% CI: £4,391 to £26,902	GAMMA
Management cost of stroke	£1,128	95% CI: £468 £2,630	GAMMA
HAROSA I: Cost of RTA	£4,815	£3,852 to £5,778 (20% variation)	GAMMA
HAROSA II: Cost of RTA	£4,745	£3,796 to £5,694 (20% variation)	GAMMA
Cost Fatal RTA	£6,289	£5,031 to £7,546 (20% variation)	GAMMA
Year 1 social care cost of CHD	£2,240	£1,792 to £2,688 (20% variation)	GAMMA
Year 2-5 social care cost of CHD	£5,350	£4,280 to £6,420 (20% variation)	GAMMA
Year 1 social care cost of stroke	£9,731	95% CI: £3,178 to £19,467	GAMMA
Year 2-5 social care cost of stroke	£5,176	95% CI: £2,147 to £12,067	GAMMA
Regression parameters for mapping ESS score to utility (EQ-5D-3L)			
Utility: Constant parameter (EQ-5D-3L / McDaid et al. 2009)	0.8925	95% CI: 0.8357 to 0.9493	NORMAL
Utility: Slope parameter for ESS (EQ-5D-3L / McDaid et al. 2009)	-0.0095	95% CI: -0.0123 to -0.0068	NORMAL
Utility: Constant parameter (EQ-5D-3L / Sharples et al. 2014)	0.8925	95% CI: 0.8664 to 0.9525	NORMAL
Utility: Slope parameter for ESS (EQ-5D-3L / Sharples et al. 2014)	-0.0061	95% CI: -0.0101 to -0.0020	NORMAL
Regression parameters for mapping ESS score to utility (SF-6D)			
Utility: Constant parameter (SF-6D / McDaid et al. 2009)	0.8068	95% CI: 0.7841 to 0.8294	NORMAL
Utility: Slope parameter for ESS (SF-6D / McDaid et al. 2009)	-0.0095	95% CI: -0.0123 to -0.0068	NORMAL
Utility: Constant parameter (SF-6D / Sharples et al. 2014)	0.7529	95% CI: 0.7302 to 0.7756	NORMAL
Utility: Slope parameter for ESS (SF-6D / Sharples et al. 2014)	-0.0067	95% CI: -0.0087 to -0.0046	NORMAL
Disutility			
Utility decrement-based stroke	-0.0524	95% CI: -0.0526 to -0.0522	NORMAL
Utility decrement-based CHD- Weighted average disutility	-0.0411	95% CI: -0.0417 to -0.0405	NORMAL

HRQoL

B17. Priority question: EQ-5D assessments were carried out as part of the HAROSA I and HAROSA II studies. Results are reported in Table 26 and 27 of both clinical study reports for protocol for HAROSA I and HAROSA II. However, these results were not converted to utilities using the UK tariff. Please provide the mean utilities using the UK tariff for the EQ-5D-3L for both trial arms from the HAROSA I and HAROSA II studies and a scenario analysis that uses these utilities instead of the utilities based on the mapping algorithm.

Answer: Clinical opinion, systematic reviews and work carried out by the Assessment Group for the NICE CPAP HTA indicate that generic instruments to measure QOL, including EQ-5D, do not capture benefit in QOL in patients with EDS[35-37]. These instruments have not been specifically designed to assess aspects of QOL in patients with OSA or EDS and sleep is not included as a specific dimension. Therefore, the true benefits of treatment are unlikely to be captured by the modelling.

With this in mind, earlier economic modelling in OSA has used techniques to map mean change in ESS score to utility change[29,34]. This approach was used by NICE in the assessment of the cost effectiveness of CPAP (NICE TA139)[1].

Given that our model was based on the earlier York model[29] used in NICE TA139 we believe that using mapping in our model was the most appropriate approach.

The CSR do not contain adequate data to perform the edits to the model requested within B17. Although Table 26 and 27 of the clinical study reports for HAROSA I and HAROSA II do indeed report on the total EQ-5D descriptive score and the EQ-5D VAS, the study analysis plan does not appear to have included a mapping of the individual patient descriptive scores to utility estimates. As the dataset with the original EQ-5D questionnaire responses was not available to us, we were unable to carry out this mapping ourselves.

Although mean VAS scores were present in the CSR, this is an individual patient-based metric and is not referable to a general population preference score. For this

reason, NICE do not recommend using EQ VAS scores (see paragraph 3.3.2 of DSU 11[38]) to produce utilities.

B18. The company submission used the algorithm from the York model (McDaid et al. 2009) to map mean changes in ESS score to utility change because the population in the York model was the best match for those eligible for treatment with pitolisant. Please provide a sensitivity analysis where the algorithm from Sharples et al. (2014) is used to show the impact of the chosen algorithm on the cost-effectiveness outcomes.

Answer: A scenario analysis using the algorithm from Sharples et al. (2014) is now incorporated into the economic model.

B19. Priority question: The utility decrement for coronary heart disease (CHD; -0.064) is derived from the disutility of heart failure estimated in Sullivan et al. (2009). This utility decrement is in line with the approach used by McDaid et al in the York model for CHD. However, heart failure is not the only condition included in CHD. According to the Framingham risk score (which is used to determine risk of CHD in the model), non-fatal CHD includes angina pectoris, coronary insufficiency, and myocardial infarction. Sullivan et al. (2009) also provided utility decrements for these events which are smaller than for heart failure (i.e. angina pectoris: −0.0412 and acute myocardial infarction: −0.0409).

Please provide a disutility of CHD that reflects all the non-fatal CHD (angina pectoris, coronary insufficiency, and myocardial infarction) included in the Framingham risk score using the disutilties reported by Sullivan et al. (2009), and use this as the utility decrement for CHD in a sensitivity analysis.

Answer: As we have now made the decision to use the QRISK3 and QStroke predictive algorithms in our base case, in response to question B8, this is the relevant reference for this question. In the supporting publication for the QRisk 3 score[39], the number of events on which the predictive score is based are:

- Myocardial infarction: 78,327
- Angina: 152,141
- TIA: 49,504

- Ischaemic stroke: 83,593

As the QRisk3 tool does not allow disaggregation of CHD events, we used the QStroke tool to estimate stroke/TIA risk and subtracted this from the QRisk3 result to arrive at an estimate for CHD. Looking at CHD alone, the events are distributed as: 34% MI; 66% angina.

Applying these proportions to the diagnosis-specific disutilites quoted in Sullivan et al[40] yields a **composite decrement of -0.0410.** This has been applied to the model.

B20. Please explain why the coefficient for Baseline ESS is not used in the calculation of the utilities? For example, in cell O21 on 'Clinical Inputs', the utility is calculated as the constant + baseline ESS * Coefficient for change ESS (O12), where we would have expected baseline ESS * Coefficient for baseline ESS (O13),

Answer: As described in the algorithm used in the York model (McDaid et al. 2009[29]), the baseline ESS coefficient in the predictive utility equation represents the change in the slope of the regression line for a particular cut-off value of ESS. However, there was no evidence to support such a subgroup effect and was not considered when mapping the ESS score at baseline in BSC treatment arm to utility based on EQ-5D and SF-6D.

B21. In the company submission, the 95% confidence interval of the utility scores in the 'Clinical inputs' tab only includes the uncertainty of the regression coefficients of the mapping algorithm. Please also include the uncertainty of baseline ESS and ESS effect size in the HAROSA I and HAROSA II studies and the uncertainty of the utility decrements of stroke and CHD (reported by Sullivan et al. 2009).

Answer: The baseline ESS and ESS effect size are used as input in the computation of utility for BSC and pitolisant arms, respectively. The uncertainty surrounding these parameters is now captured in the PSA and DSA in the model.

Costs

B22. Priority question: The CS states on page 68 that the cost of pitolisant is [redacted]. However, it is not explained whether these costs are the same for all dosages. This is particularly relevant given that there exists variation in dosage per day both within and between patients, and most patients in the HAROSA trials

received the maximum dosage. Also, the switching in dosage may lead to wastage costs.

a. Please explain whether the same price per tablet applies regardless of dosage or provide the different prices per dosage.

b. Please use data from the HAROSA trials on the individual dosages per patient to inform calculations of drug acquisition costs.

c. Please explain why wastage costs are not included in the model.

d. Please amend the analysis to include these wastage costs based on conservative assumptions (i.e. by assuming wastage, when applicable, is maximal), preferable by providing the option the run the model with and without wastage.

Answer:

a + b. The price of 30 tablets of 4.5 mg or 18 mg pitolisant are identical. However, on reviewing this issue for the purposes of answering the query, it emerged that some patients in the studies also received 9 mg daily (see Table 11 below). As there is no 9 mg tablet available, this requires the use of 2 x 4.5 mg tablets daily, at double the cost of the single tablet doses. We have therefore adjusted the model to take this into account.

Table 11: Stable dosage use in HAROSA studies, following titration

	HAROSA I		HAROSA II	
	Weeks 1-12	**Week 12+**	**Weeks 1-12**	**Week 12+**
18 mg	70.3%	77.4%	75.4%	76.3%
9 mg	21.1%	17.3%	15.7%	12.2%
4.5 mg	8.6%	5.3%	8.9%	11.5%

c. During dose titration, an increase in dose will not result in wastage, as the lower strength tablets can be used to make up the higher dose. If a patient is down-titrated from the 18 mg dose to either 9 mg or 4.5 mg, however, there is a risk of wastage of the higher strength tablets.

Data from both the 12-week double-blind phase and the open label phase out to 1 year, allow us to estimate how many patients this applies to (see Table 12). In order to estimate the impact that this will have on the mean cost of treatment, we have assumed that the difference between the proportion of patients with a maximum dose of 18 mg and a stable dose of 18 mg represents the group that will potentially incur wastage.

Table 12: Data to identify potential wastage in down-titration from 18mg

	% with maximum dose = 18 mg	% with stable dose = 18 mg	Difference
HAROSA I			
1 - 12 weeks	79.8%	70.3%	9.6%
12 - 52 weeks	87.4%	77.4%	10.0%
HAROSA II			
1 - 12 weeks	82.5%	75.4%	7.1%
12 - 52 weeks	81.8%	76.3%	5.5%

Using a conservative assumption that the down-titration is equally likely to occur at any stage in pack usage, we have estimated that the mean quantity of wastage is 15 tablets.

The cost of this has therefore been applied to the down-titrating population once in the first 12 weeks and once in the period 12-52 weeks. We have assumed that there will be no further wastage in subsequent years.

d. The model has been adjusted to reflect the altered costs, taking into account both the cohort with a dosage of 9 mg and the potential for wastage. As requested, a facility has been introduced to allow the ERG to vary the wastage estimates.

Table 13: Revised annual cost for pitolisant taking into account wastage and cost of 9 mg dose based on price of [redacted] for 30 tablets

	HAROSA I	HAROSA II
Net cost in year 1	[redacted]	[redacted]
Equivalent cost per 30 days	[redacted]	[redacted]
Net cost per year from year 2	[redacted]	[redacted]
Equivalent cost per 30 days	[redacted]	[redacted]

B23. Please explain how the cost of fatal CV events, the first year cost of CHD, and the ongoing cost of CHD (years 2-5) (Table 34 of the CS) were derived from the regression equation as published in Briggs et al. (2007). In the explanation, please also clarify how the costs for CHD (angina pectoris, coronary insufficiency, and myocardial infarction) in the model relate to the costs of an event (stroke, transient ischaemic attack or peripheral vascular disease) as estimated by Briggs et al. (2007).

Answer: In researching the answer to this question, we reconsidered the use of the Briggs-based estimate. We originally used this to be consistent with previously published versions of the York model[29,34]. However, the clinical practice data on which it is based are now severely out of date (the EUROPA study ran from 1997-2003) and only 15% of the recruited patients were from the UK[41].

We were satisfied with using data from the Sentinel Stroke National Audit Project for stroke costs. For the CHD costs we have now chosen to use the data from the analysis by Walker et al[42], which draws on uniquely UK data from the Myocardial Infarction National Audit Project, Hospital Episode Statistics, the Clinical Practice Research Database and the Office for National Statistics. The period covered is 2001-2010, which brings it more into line with current clinical practice.

The data for CHD-related medical costs are drawn from supplementary Table A6 in the publication by Walker et al[42], updated to 2018-19 values in the table below. We have split costs according to the ratio described in question B19 (64% stable angina + 36% myocardial infarction) and have taken a conservative approach by ignoring the incremental costs incurred by patients with concomitant morbidities.

Thus, for each patient experiencing a CHD event (myocardial infarction or angina):

- In year 1, costs will be: (64% x 800) + (36% x £7,866) = £3,344
- In year 2+ costs will be: (64% x 800) + (36% x £2,116) = £1,274

Table 14: CHD-related costs updated to 2018-19 values (adapted from Walker et al[42])

Element	2011-12 cost per 90 days	2018-19 cost per 90 days
Stable angina	£179	£200
Cost per year		**£800**
Acute myocardial infarction		
First 90 days	£4,658	£5,192
Second 90 days	£1,166	£1,300
Third 90 days	£590	£658
Fourth 90 days	£642	£716
Cost per year		**£7,866**
Subsequent 90 days	£475	£529
Cost per year		**£2,116**

We have been unable to identify a costing study in CHD that assess the impact of personal social care. In Xu et al[43], which we have used as the primary costing paper for our stroke estimates, community-delivered social care costs are assessed, although residential care costs are not included. In this analysis, the social care costs in year 1 represent 67% of total medical costs, whilst in years 2-5, social care incurs 4.2 x the costs of medical care.

We have applied the same factors to the CHD costs above, although a degree of caution is required in the interpretation of the consequent results. Thus, for each patient experiencing a CHD event (myocardial infarction or angina):

- In year 1, social care costs will be: [(64% x 800) + (36% x £7,866)] x 67% = £2,240
- In year 2+ costs will be: [(64% x 800) + (36% x £2,116)] x 4.2 = £5,351.

B24. The costs of stroke, which were sourced from Xu et al. (2017) have not been updated to 2018 / 2019 values. Furthermore, it is not clear how data on the uncertainty surrounding these cost estimates were obtained (i.e. a 95% CI is reported in the CS, but these data are not available from the paper by Xu et al.

(2017). Lastly, Xu et al. (2017) also report substantial costs due to social care in addition to health care costs.

a. Please update the stroke costs to 2018 / 2019 using the NHS Cost Inflation Index.

b. Please explain how data on uncertainty of stroke costs were obtained.

c. Please explain why costs related to social care have not been included.

d. Please update the model analysis with the option (i.e. via a drop-down selection) to include these costs.

Answer:

a. Xu et al[43] calculated values based on 2013-14 prices. We have updated these using NHS inflators to 2018-19 prices (the latest for which an inflator is available[44]). We have assumed that the same inflators apply to both health and social care costs.

Table 15: Cost estimates from Xu et al, inflated to 2018/19 values

	Original costs (2013-14)		Inflated costs (2018-19)	
	Year 1	**Year 2-5**	**Year 1**	**Year 2-5**
Health care costs	£13,452	£17,963	£14,573	£19,472
Social care costs	£8,977	£28,076	£9,731	£30,435

b. Xu et al. (2017)[43] reports health care costs for stroke at year 1 (£13,452) and year 2-5 (£17,963). In addition, the total cost of health and social care for stroke along with the confidence interval (95% CI) at year 1 (£22,429, 95%CI: £7,322 - £44,854) and year 2-5 (£46,039, 95%CI: £19,101 - £107,336) were reported.

In order to derive the 95% CI of the health care cost for stroke in year 1, we first computed the proportion of heath care cost incurred by the health care cost relative to the total cost (£13,452/£22,429 = 0.599), and this proportion was subsequently applied to the lower CI of the total cost (£7,322 x 0.599 = £4,391) and the upper CI of the total cost (£44,854 x 0.599 = £26,902) to derive the confidence interval for health care cost. The same approach was applied to the cost of management care for stroke.

c. + d. We initially included social care costs in our model, but subsequently excluded these as, although nominally of interest to NICE, our experience has been that committee decisions tend to hinge on health care costs alone. We have happily re-introduced these, as requested

Table 16: Health care costs and social care costs

	Original costs (2013-14)	
	Year 1	**Year 2-5**
Health care costs	£14,573	£1,225 per year
Social care costs	£9,731	£5,365 per year

B25. The cost estimate of a mandibular advancement device is based on NHS Tariffs, but the preferred NHS Reference costs are also available: WF01A / WFO1B, Service Code 144. Please confirm that these should be used in the model instead, and change this in the model.

Answer: As discussed in the checkpoint call on 16th June, the NHS reference costs for a new Maxillo-facial consultation is based on a single patient (see below).

Table 17: NHS reference costs for a new Maxillo-facial consultation

National Schedule of NHS Costs - Year 2018-19 - NHS trusts and NHS foundation trusts
OUTPATIENT PROCEDURES

Service code	Service Description	Currency Code	Currency Description	Procedures	National Average Unit Cost	Total Cost	No. Data Submissions
144	Maxillo-Facial Surgery	WF01A	Non-Admitted Face-to-Face Attendance, Follow-up	2,544	£190	£482,883	2
144	Maxillo-Facial Surgery	WF01B	Non-Admitted Face-to-Face Attendance, First	1	£97	£97	1

Additionally, with the introduction of blended tariffs for non-admitted contacts in 2020-21, the use and costing basis of the WF01A and WF01B currency codes has changed.

According to guidance issued by NHS England[45], blended payments using these codes should, where available, use locally agreed prices. Where these do not exist, the appropriate National Tariff should be applied.

When we carried out the initial modelling, the current Tariff related to 2019-20, which we therefore used. This listed a tariff of £147 for currency code WF01B and service code 144. The now current Tariff for 2020-21 has increased this price to £149. We have therefore updated our MAD costing accordingly, yielding a marginally increased figure of **£688** per year.

Section C: Textual clarification and additional points

Typographical error

C1. Table 34 of the CS lists the cost of a non-fatal road traffic accident (RTA) per patient in HAROSA I as £4,745 (same as in HAROSA II), whereas both the electronic model as well as Table 37 in the CS list this as £4,815. Please confirm this is a typo, and that the cost of a non-fatal RTA per patient in HAROSA I is £4,815.

Answer: Thank you for pointing this typo out, we confirm that the cost of a non-fatal RTA is £4,815 in HAROSA I and £4,745 in HAROSA II.

Appendix 1

Results from original modelling in our submission

Table 18: Discounted costs and effects – patients with residual EDS despite CPAP (HAROSA I) (Table 40 in our submission)

Base case result: Discounted costs and effects (HAROSA I)			
	Costs	**QALYs**	**ICER (Cost/QALY)**
Pitolisant + CPAP + BSC	£33,266	11.77	
CPAP + BSC	£9,743	10.80	
Increment	£23,523	0.97	£24,237

Table 19: Discounted costs and effects – patients with EDS due to OSA who refuse CPAP (HAROSA II) (Table 42 in our submission)

Base-case result: Discounted costs and effects - Pitolisant vs BSC (HAROSA II)			
	Costs	**QALYs**	**ICER (Cost/QALY)**
Pitolisant + BSC	£33,426	11.86	
BSC alone	£9,535	10.85	
Increment	£23,891	1.01	£23,538

Table 20: Scenario A – comparison of pitolisant versus MAD in patients with EDS due to OSA who refuse CPAP (HAROSA II), discounted costs and effects (Table 47 in our submission)

Scenario A			
	Costs	**QALYs**	**ICER (Cost/QALY)**
Pitolisant + BSC	£33,426	11.86	
MAD + BSC	£14,984	11.40	
Increment	£18,441	0.46	£40,257

Results using updated modelling

Table 21: Discounted costs and effects – patients with residual EDS despite CPAP (HAROSA I) (updated model)

Base case result: Discounted costs and effects (HAROSA I)			
	Costs	**QALYs**	**ICER (Cost/QALY)**
Pitolisant + CPAP + BSC	£40,261	12.48	
CPAP + BSC	£11,121	11.77	
Increment	£29,140	0.71	£41,090

Table 22: Discounted costs and effects – patients with EDS due to OSA who refuse CPAP (HAROSA II) (updated model)

Base-case result: Discounted costs and effects - Pitolisant vs BSC (HAROSA II)			
	Costs	**QALYs**	**ICER (Cost/QALY)**
Pitolisant + BSC	£38,828	12.57	
BSC alone	£10,322	11.87	
Increment	£28,506	0.69	£41,238

Table 23: Scenario A – comparison of pitolisant versus MAD in patients with EDS due to OSA who refuse CPAP (HAROSA II), discounted costs and effects (updated model)

Scenario A			
	Costs	**QALYs**	**ICER (Cost/QALY)**
Pitolisant + BSC	£38,828	12.57	
MAD + BSC	£15,946	12.28	
Increment	£22,882	0.29	£79,356

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Pitolisant hydrochloride for treating excessive daytime sleepiness caused by obstructive sleep apnoea [ID1065]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Sleep Apnoea Trust Association (SATA)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	SATA is a patient charity which works to improve the lives of sleep apnoea patients, their partners and their families. It is run by a small group of volunteers, almost entirely unpaid, all of whom are sleep apnoea patients. SATA is funded by subscriptions from about 1400 members.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	SATA has held an annual conference (SATAday) since its inception in 1993. The SATA Committee has always regarded SATAday as an opportunity to meet members, and discuss issues, and the conferences include opportunities for members to ask questions, provide feedback, information etc. For many years SATA ran a telephone helpline, now conducted mainly by e-mails with telephone support where essential, and we occasionally survey members or invite them to participate in surveys conducted by medical professionals. SATA is therefore confident that we have a good knowledge of the issues of concern to our members. Since this is a new technology, none of our members will have been prescribed for EDS associated with OSA, so SATA does not consider that consulting our members directly would be required.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	If CPAP treatment is effective, living with the condition is a matter of coping with the minor discomfort and restriction of having to sleep wearing a face mask connected by tube to a small machine, though CPAP machines are now much smaller and quieter than they were a few years ago. CPAP treatment imposes further difficulties when travelling for work or leisure in that it involves carrying additional weight, a particular problem when travelling by air. Some airlines are reluctant to allow CPAP to be included in cabin baggage – which SATA regards as essential – and do not allow their use on board during long flights. Even within the UK problems arise in hotel rooms where plug sockets are rarely within easy reach of the bed, so patients have to pack extension leads as well as their CPAP. There are minor housekeeping obligations, for example regular cleaning of masks and tubes, daily cleaning of humidifiers if used, and regular changing of filters.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Over the past year NHS staff, and in particular staff in Respiratory departments, have been desperately fighting the effects of the Covid pandemic, and as a result many sleep clinics have been able to offer only a basic sleep service during that period. Before the pandemic took hold the majority of SATA members were very satisfied with their treatment for OSA, and the care they received from sleep clinics. Many would describe their CPAP treatment as life-changing, in terms of the dramatic improvement of their day-to-day health and sense of well-being by comparison with their condition before diagnosis and treatment. That is not to say the treatment is trouble-free. Some patients have difficulty adapting to wearing a mask; some mouth-breathers cannot easily use a nasal mask, having to resort to a full-face mask or chin strap; some suffer severe panic attacks or claustrophobia. Patient access to diagnosis and treatment of OSA is erratic. SATA has monitored NHS Sleep Clinic performance for many years, and though a number of excellent sleep clinics were able to diagnose and treat patients within reasonably short wait times, many had excessive waiting times for diagnosis, and an unreasonably long interval between diagnosis and setting patients up on CPAP treatment. In some cases this was due to CCGs failing to fully understand their legal obligation under NICE TA139 to provide adequate funding for clinics in their area of responsibility. In addition SATA considers that many GPs do not fully understand OSA, and therefore the need to refer a patient to a sleep clinic is not necessarily their first consideration when presented with a patient's description of symptoms. In conversations with GPs at, for example, RCGP Annual Conferences, it seems that in most 5-year medical degree courses the time allocated to learning about OSA varies between 15 minutes and an hour. SATA's impression is that some GPs are slow to recognise symptoms in children which might be caused by sleep disturbance arising from OSA, and instead focus on ADHD and other similar disorders.

8. Is there an unmet need for patients with this condition?	Yes. The Company Submission uses a 2015 British Lung Foundation estimate of 1.5 million people in the UK with OSA, of whom 85% (1.27m) are undiagnosed. SATA believes the true figures are much higher, and our estimate is that there are 4 million adults in the UK who may have OSAHS, with only about 1 million diagnosed and under treatment. SATA believes that the key to getting these 3 million OSA sufferers on to a diagnosis and treatment pathway is greater understanding of OSA by the primary care sector, and also greater GP involvement in the initial assessment process, for example use by GPs of home sleep apnoea testing, eg overnight oximetry, peripheral arterial signal etc.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The main technology, Continuous Positive Airway Pressure (CPAP), is recommended by NICE TA139 for treatment of patients with moderate to severe OSAHS and for mild OSAHS where symptom affect quality of life or daily activities and lifestyle changes or other treatments are unsuccessful or inappropriate. If successful it effectively eliminates or mitigates the symptoms of OSA for most patients. SATA has no data or information on the proportion of patients with OSA who may still experience EDS, and the lack of even anecdotal evidence suggests that only a relatively small proportion may be affected.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	In terms of CPAP treatment the need to wear a nasal or full-face mask whilst asleep can be restrictive and uncomfortable, and may cause panic attacks and claustrophobia, and the mask can cause irritation. **Compliance**. SATA is concerned that there is no reference in the Company Submission to the possibility that the use of this technology might lead to reduced compliance with CPAP therapy. The CS acknowledges that around one third of diagnosed patients are non-compliant with CPAP therapy. For those patients with OSAHS, EDS is the most obvious and visible symptom of the condition. If EDS persists despite CPAP therapy, the temptation to stop using CPAP if this technology successfully

	eliminates EDS could increase non-compliance, particularly with patients who travel a lot (see above). To the extent that reducing or eliminating EDS by means of Pitolisant leads to non-compliance with CPAP treatment it would not only have an impact on the overall health of patients but could undermine the cost-effectiveness case for Pitolisant. Increased non-compliance with CPAP as a direct result of use of this technology could increase overall NHS costs for patients with OSA who would be effectively untreated and whose previous OSA symptoms may return as a result, or alternatively would require additional follow-ups to monitor compliance. Current DVLA driving regulations for patients with moderate to severe OSA require them not to drive until their OSA is under control, their sleepiness is no longer excessive, *and they are complying with CPAP treatment* (our italics). Furthermore, the DVLA guidelines require patients to confirm that a review of their condition has been undertaken by a sleep clinic at least every three years for a Group 1 driver and at least annually for Group 2 drivers (bus, truck, taxi drivers etc). Though the DVLA is primarily concerned about excessive sleepiness, the guidelines nevertheless include the requirement of compliance with CPAP treatment. SATA's experience of dealings with DVLA over the past few years suggests that it would take months, if not years, to secure an amendment to the DVLA guidelines to reflect the benefits of this technology on EDS. Meanwhile, the burden on sleep clinics to undertake the annual or triennial reviews, in terms of both time and cost, would increase to the extent that use of this technology increased non-compliance with CPAP treatment, therefore requiring a more detailed sleep clinic review, which would further erode the business case for this treatment. In B.2.5.2 the CS states that the demographic is "predominantly middle aged, obese men". The BLF Toolkit referenced in this comment states "OSA can affect anyone, but is more common in some people, eg those who are male, middle aged, elderly and overweight". Of a current SATA membership of 1400, 68% of members are male. The statement in the CS is not an accurate representation of the BLF Toolkit comment. In B.2.13 the CS states "Two well conducted, placebo-controlled clinical studies ….. have shown that pitolisant acts quickly to increase wakefulness and reduce daytime sleepiness….". Elsewhere the CS states "Pitolisant works within 5 weeks to increase wakefulness and reduce daytime sleepiness, by week 5 of treatment mean ESS was in the normal range..". Though these statements are not incompatible it could be argued that a 5-week period before full effectiveness is at odds with "quickly".

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The only patients who might benefit from the technology are those whose symptoms of EDS have not been controlled by CPAP.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Many GPs, to the extent that they are fully aware of the condition, regard OSA as essentially a condition which affects middle aged and older, overweight, males. This view is reinforced in the CS (B.2.5.2), though the CS reference does not accurately represent the BLF comments from where it was derived. It is increasingly being recognised that OSA is a condition affecting women, children, and in younger males. The increasing levels of obesity in the UK population, including in children, are likely to increase the prevalence of OSA in both sexes and in all age groups. The CS does not reflect this.

Other issues	
13. Are there any other issues that you would like the committee to consider?	SATA hopes that if this technology is approved by NICE it would be subject to an expectation that sleep clinics would fully explore adjustment to standard CPAP treatment to control EDS before resorting to this technology, and that increased follow-up support would be provided to ensure continuing compliance with CPAP therapy.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- The CS fails to recognise that the successful use of Pitolisant may lead to non-compliance with primary CPAP therapy.
- The CS description of the demographic is a more sweeping generalisation than the BLF source document describes.
- There is a potential inconsistency between trial results which indicate effectiveness of Pitolisant after 5 weeks, and a statement in the CS that Pitolisant “acts quickly”
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Pim Wetzelaer, Simone Huygens, Gimon de Graaf and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Annette Chalker and Edyta Ryczek acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse events
AIC	Akaike Information Criterion
BI	Budget impact
BIC	Bayesian information criterion
BSC	Best supportive care
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHD	Coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPAP	Continuous Positive Airway Pressure
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CV	Cardiovascular
DCIS	Ductal carcinoma in situ
DSU	Decision Support Unit
EDS	Excessive daytime sleepiness
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence Review Group
ESS	Epworth Sleepiness Scale
EUR	Erasmus University Rotterdam
FAD	Final appraisal document
FDA	Food and Drug Administration
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IC	Indirect comparison
ICER	Incremental cost effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
KSR	Kleijnen Systematic Reviews
LOCF	Last observation carried forward
LYs	Life years
LYG	Life years gained
MAD	Mandibular advancement device
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
OS	Overall survival
OSA	Obstructive sleep apnoea
OSAHS	Obstructive sleep apnoea hypopnoea syndrome
PAS	Patient Access Scheme

PFS	Progression-free survival
PGIC	Physicians global impression of change
PGOE	Patient's global opinion of the effect
PRESS	Peer review of electronic search strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk; risk ratio
RTA	Road traffic accident
SAE	Serious adverse events
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
STA	Single technology appraisal
TA	Technology assessment
TEAE	Treatment emergent adverse events
TTO	Time trade-off
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
VAS	Visual analogue scale
WHO	World Health Organization
WTP	Willingness-to-pay

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population considered in the company submission (CS) is in line with the National Institute for Health and Care Excellence (NICE) scope and with the anticipated marketing authorisation for pitolisant: Pitolisant is indicated for the treatment of Excessive Daytime Sleepiness (EDS) in patients with Obstructive Sleep Apnoea (OSA) and treated by Continuous Positive Airway Pressure (CPAP) but still complaining of EDS, or in patients with OSA refusing/not tolerating CPAP. A European marketing authorisation application for pitolisant was submitted to the European Medicines Agency (EMA) in November 2019.

The description of the comparators in the NICE scope is as follows: "Established clinical management without pitolisant hydrochloride". The main comparison of the CS was a head-to-head comparison of pitolisant with best supportive care in the HAROSA trials. In addition, Mandibular advancement devices (MADs) could be regarded as a relevant comparator, yet they have been explicitly excluded from the systematic review for efficacy and safety studies by the company. The company did perform an additional search to identify studies evaluating MADs; however, this search used Medline only and searched for systematic reviews and meta-analyses only. Therefore, the search for MADs was considered poor and the results of the indirect comparison of pitolisant versus MADs are unreliable. It is unclear whether all relevant studies have been included for MADs.

1.2 Summary of the key issues in the clinical effectiveness evidence

A full summary of the clinical effectiveness evidence can be found in Section 4.6 of this report, the key effectiveness results can be found in Tables 4.8 and 4.9 (pages 32-33) and safety results can be found in Tables 4.12 to 4.14 (pages 34-37). The key issues in the clinical effectiveness evidence are as follows:

Trial results:

- Pitolisant significantly reduced daytime sleepiness (ESS score) after 12 weeks in both trials. However, no evidence of effects on CVD risk factors including blood pressure was observed in the pitolisant trials.

Comparators:

- Is best supportive care in the two HAROSA trials equivalent to the comparator in the NICE scope: "Established clinical management without pitolisant hydrochloride"
- Are MADs a relevant comparator, and if so, are the results of the indirect comparison of pitolisant versus MADs reliable?

Included trials:

- Is the follow-up period in the trials sufficient? According to the company no formal stopping rules for pitolisant exist and patients could take pitolisant as long as a clinical benefit is achieved. However, the trials only included 12-week comparisons between pitolisant and placebo.

1.3 Summary of the key issues in the cost effectiveness evidence

The two main critique points of the Evidence Review Group (ERG) are the insufficient substantiation of the impact of pitolisant on cardiovascular events and the use of a mapping algorithm for utilities instead of the direct utility measurement in the HAROSA I and II trials.

As pitolisant is primarily aimed at alleviating a specific symptom, daytime sleepiness, it cannot be assumed without evidence that it has broader effects such as the reduction of cardiovascular risk. Additionally, CPAP treatment has been shown to reduce known cardiovascular risk factors, predominantly blood pressure. Studies of pitolisant have shown no change in cardiovascular risk factors. The substantiation of the assumptions made by the company were deemed insufficient to warrant the inclusion of an effect of pitolisant on the incidence of coronary heart disease (CHD) and stroke. Therefore, the ERG base-case did not include such an effect.

The remaining benefits of pitolisant after removing the impact on cardiovascular events are the utility improvement associated with reduced excessive daytime sleepiness (EDS) and reduced occurrence of road traffic accidents (RTAs).

The ERG is concerned about the use of a mapping algorithm for utility values in the model instead of the EQ-5D measurements in the HAROSA I and II trials. According to the company, the true benefits of treatment are unlikely to be captured when using the EQ-5D results. However, the ERG argues that it is also possible that a modest decrease in excessive sleepiness truly does not impact the health-related quality of life importantly. But even if the ERG agreed to some extent that generic instruments may not capture the entire benefit of treatment in patients with EDS, they would have preferred the use EQ-5D utilities in the base-case or scenario analysis to be able to compare the cost effectiveness of pitolisant with treatments for other diseases and to assure adherence to the NICE reference case. Therefore, the ERG requested a scenario analysis with utility values based on the EQ-5D assessment in the clarification letter. This was not provided by the company in the clarification response because, as they stated, the underlying EQ-5D data was not available to them. However, given that EQ-5D descriptives are presented in the CSRs the ERG would argue that it should be possible to request the underlying individual patient data and convert the EQ-5D responses to utilities using the UK tariff.

There is no evidence of a direct effect of pitolisant on the probability of being involved in an RTA. Furthermore, the ERG had concerns about the indirect effect estimation, which was not well substantiated by the company. In addition, the ERG had concerns about the large utility impact of slight RTAs in the company base-case. According to the company, RTAs were associated with a utility of 0.62. This utility seems reasonable for severe RTAs, but the ERG has strong reservations about injuries caused by slight RTAs being associated with such a low utility, especially considering that in the model the utility for patients who have had a stroke is about 0.77. Therefore, this impact of slight RTAs on utility was reduced in the ERG base-case.

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG preferred changes to the company base-case are detailed in Section 7.1.2 of this report and summarised below:

1. Extending the time horizon from 25 years to 47 years to reflect a lifetime horizon.
2. Excluding the impact of pitolisant on cardiovascular events.
3. Reducing the disutility of RTAs to account for the large number of slight RTAs.
4. Correcting the application of a utility decrement for ageing and changing the constant utility decrement to an age dependent utility decrement for ageing.

Besides making these ERG preferred changes to the company base-case, various errors in the company base-case were corrected. These corrections increased the incremental costs and incremental Quality-Adjusted Life Years (QALYs) both to such extent that the Incremental Cost-Effectiveness Ratio (ICER)

remained close to the company base-case. Table 1.1 and 1.2 present the results of the ERG preferred base-case.

For the patient population with residual EDS whilst on CPAP we find an ICER of almost £70,000 for pitolisant treatment versus Best Supportive Care (BSC).

For the patient population with EDS who refuse CPAP the results are presented as a full incremental analysis. That is, pitolisant + BSC, MAD + BSC and BCS alone are sorted according to their accumulated QALYs. Subsequently first the ICER of the two treatments with the lowest estimated QALYs is determined, and then the ICER of the middle and the highest QALYs. This translates into an ICER of almost £37,000 per QALY gained for MAD + BSC versus BSC alone, and then an ICER of about £100,000 for pitolisant versus MAD.

Table 1.1: ERG base-case deterministic results: patients with residual EDS despite CPAP (based on HAROSA I)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + CPAP + BSC	£35,043	17.68	14.28	£32,626	0.09	0.48	£67,557
CPAP + BSC	£2,416	17.60	13.80				

BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; EDS = excessive daytime sleepiness; LYG = life years gained; QALYs = quality-adjusted life years

Table 1.2: ERG base-case deterministic results: patients with EDS due to OSA who refuse CPAP (based on HAROSA II), full incremental analysis

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + BSC	£34,752	18.33	14.76	£21,322	0.03	0.22	£97,483
MAD + BSC	£13,430	18.30	14.54	£10,603	0.08	0.29	£36,735
BSC	£2,827	18.23	14.26				

BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; LYG = life years gained; MAD = mandibular advancement device; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG performed a probabilistic sensitivity analysis (PSA) using their preferred base-case model. This analysis resulted in a probabilistic ICER of £66,462 per QALY gained (incremental costs were £32,561and incremental QALYs were 0.49) for patients with residual EDS despite CPAP (based on HAROSA I), which is in line with the ERG deterministic ICER of £67,557 per QALY gained for this subgroup. For the subgroup of patients with EDS due to OSA who refuse CPAP (based on HAROSA II), the PSA results for the comparison between MAD + BSC versus BSC only indicated a probabilistic ICER of £34,930 per QALY gained (incremental costs were £10,366 and incremental QALYs were

0.30), and a probabilistic ICER of £96,297 per QALY gained (incremental costs were £21,210 and incremental QALYs were 0.22) for the comparison between pitolisant + BSC versus MAD + BSC. The cost effectiveness acceptability curve shows that the probability of cost effectiveness for the addition of pitolisant to BSC was 2% (as opposed to 49% in the company's PSA) at a threshold ICER of £30,000 per QALY gained.

The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. These key uncertainties were related to the inclusion of costs and QALYs related to CHD and stroke, social care costs due to the same cardiovascular (CV) events, the use of the SF-6D as an alternative to the EQ-5D-3L, and using an alternative utility mapping algorithm The inclusion of CV events reduced the ICERs by more than half, and the inclusion of social care costs reduced the ICERs further. The use of the SF-6D only marginally increased the ICERs, and the use of the alternative mapping algorithm led to substantially higher ICERs.

2. BACKGROUND

2.1 Introduction

In this report, the ERG provides a review of the evidence submitted by Lincoln Medical Limited in support of pitolisant, trade name Ozawave®, for excessive daytime sleepiness (EDS) in patients with obstructive sleep apnoea (OSA). In this section, the ERG summarises and critiques the company's description of the underlying health problem and the company's overview of the current service provision. The information for this critique is taken from Document B of the company submission (CS).[1]

2.2 Critique of company's description of the underlying health problem

The health problem at the focus of this appraisal is EDS which is caused by OSA. OSA causes the walls of the upper airways to relax and narrow during sleep, resulting in interrupted breathing which leads to intermittent hypoxia, arousal from sleep and fragmented sleep. The interrupted, fragmented sleep in patients with OSA is poor in both quality and quantity, resulting in EDS.[2]

The CS states that EDS is characterised by persistent sleepiness, fatigue and lethargy during the day. People with EDS have uncontrollable daytime sleepiness that interferes with their daily life. Patients may doze off during their usual daily activities.[2, 3] The cognitive functions are impaired in around two-thirds of people with EDS[2, 4] and around one-half of people with severe EDS have co-existing depression.[5]

According to the CS, people with EDS and OSA have reduced quality of life (QoL), as well as poorer respiratory-specific health-related QoL,[6, 7] and reduced productivity at work.[8, 9] They are more likely to leave work due to ill health or be on long-term sick leave.[7] The company emphasise that EDS is associated with an increased risk of accidents (particularly road traffic accidents [RTAs]),[10] with estimated 40,000 RTAs/year in the UK due to untreated OSA,[11] and reference the advice from the Driver and Vehicle Licensing Agency (DVLA) that anyone with excessive sleepiness due to OSA must not drive and must notify the DVLA.[12] EDS has an impact on morbidity and mortality. People with EDS are at increased risk of hypertension, coronary heart disease (CHD), arrhythmia, heart failure, and stroke.[13-15]

The company provides the data from the British Lung Foundation which states that there are 1.5 million people in the UK with OSA, of whom 45% (675,000 people) have moderate and severe OSA. Up to 85% of these patients are undiagnosed and therefore untreated.[11] OSA is common in middle-aged and older people. Estimates of prevalence vary according to definition and diagnostic techniques but around 17% of men and 9% of women aged 50-70 years have clinically significant moderate/severe OSA.[16] The prevalence increases with increased body mass index (BMI).[16, 17] The ERG notes that no EDS-specific prevalence is reported in the CS.

The company highlights two UK studies - the UK Sleep Study, which surveyed people aged 18-100 years and found self-reported rates of sleep apnoea (defined as stopping breathing in the night) of 9% in men and 6% in women,[17] and another study which identified the rate of observed OSA in patients admitted to a UK hospital of 65%.[18] The co-existence of moderate/severe OSA and EDS, referred to as obstructive sleep apnoea/hypopnoea syndrome (OSAHS), is difficult to estimate; however, around 7% of men and 3% of women aged 50-70 years have OSAHS.[16]

ERG comment: No further clarification was required in relation to the company's description of the health problem and the cited references. The ERG considers the company's background section an adequate description of the underlying health problem for this appraisal.

2.3 Critique of company's overview of current service provision

The CS describes relevant sources that were used in the company's interpretation and justification of the positioning of pitolisant in the treatment pathway: NICE TA139 (Continuous positive airway pressure (CPAP) for the treatment of OSAHS),[19] Canadian Agency for Drugs and Technologies in Health (CADTH) Health Technology Appraisal (HTA) on CPAP,[20] NICE IPG241 (Soft-palate implants for OSA),[21] NICE IPG598 (Hypoglossal nerve stimulation for moderate to severe OSA)[22] and the European Medicines Agency's (EMA) assessment report on modafinil.[23]

The first-line treatment option for patients with OSAHS are lifestyle measures (weight loss, smoking cessation, limiting alcohol consumption). Furthermore, based on NICE TA139, CPAP is recommended for:

- people with moderate or severe symptomatic OSAHS
- for people with mild OSAHS with symptoms that impact on QOL and in whom lifestyle measures or other relevant treatment options have been unsuccessful or are considered inappropriate[19].

The company highlights that CPAP is the gold standard treatment for EDS due to OSA, however, this information is based only on TA139 and no additional references were provided in the response to ERG's Clarification letter.[24] CPAP involves wearing a mask attached to a CPAP machine during sleep with the aim to prevent the airway from narrowing and keeping the upper airway open during sleep.[25] The CADTH's HTA concluded that CPAP was more effective than lifestyle measures or mandibular advancement devices (MAD).[20] However, up to 55% of patients will have residual EDS despite CPAP[26] due to co-morbidities, such as narcolepsy or restless legs syndrome,[27] or other mechanisms.[28] Those patients will be offered CPAP optimisation which includes patient education, sleep hygiene, appropriate CPAP mask, use of humidification and assessment of whether residual CPAP is due to other sleep disorders or co-morbidities that needs additional management.[29] The company highlights that, at present, there are no licensed treatment options to reduce EDS in patients who adhere to CPAP with residual EDS.[1]

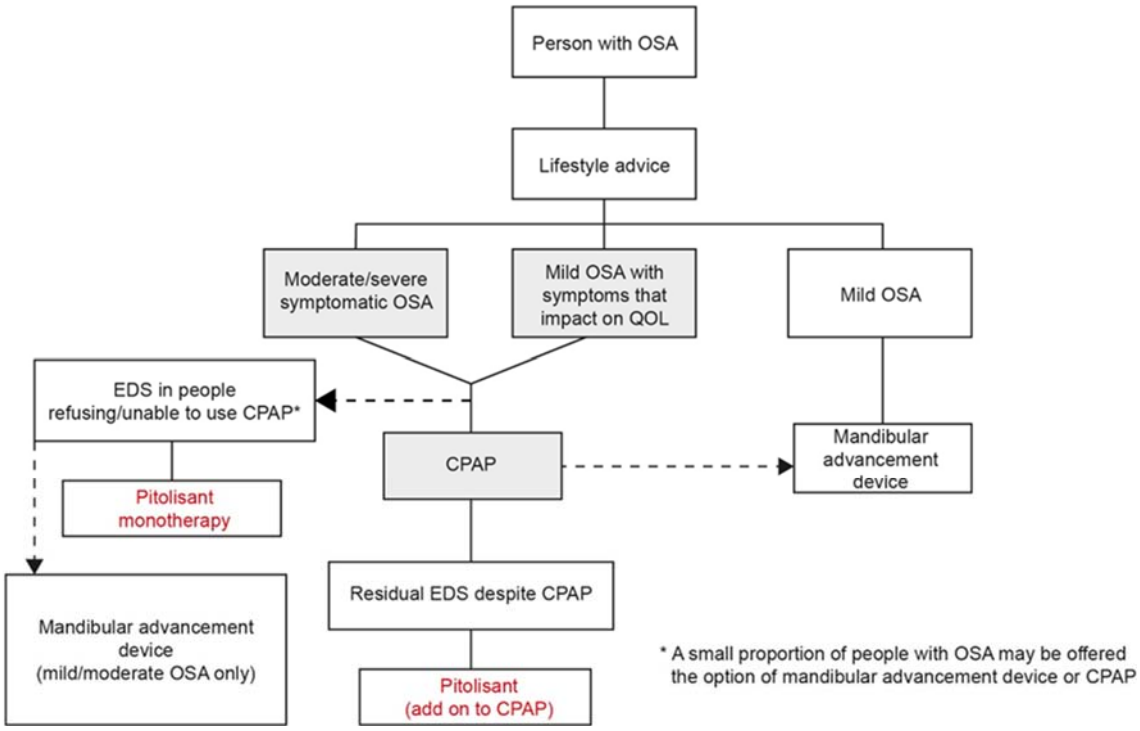
The CS states that approximately one-third of CPAP patients are not adherent or refuse CPAP, due to discomfort, inconvenience or claustrophobia, with MAD as the only alternative.[30] MADs, a gum-shield like device that holds the airway open during sleep, are an option for people with mild/moderate OSAHS unable to use CPAP or for those who snore or have mild OSAHS with normal daytime alertness.[31] The CS highlights that their use is limited and associated with a number of side-effects. Patients require a complete dental assessment as dental or gum diseases or wearing dentures will hinder fitting MAD.

Other treatment options are surgery and soft-palate implants; however, they are not routinely recommended by NICE.[19, 21, 22] The CS highlights that there are no licensed wakefulness promoting agents at present.[32] Modafinil was previously used, but it lost its marketing authorisation in 2011 as the EMA identified risks for the development of skin and hypersensitivity reactions, neuropsychiatric reactions and concerns about its cardiovascular (CV) risk profile.[23]

Figure 2.1 shows the proposed treatment pathway for patients with EDS caused by OSA. In the proposed pathway, pitolisant is considered in two locations within the pathway. Following first-line treatment consisting of lifestyle advice, patients with moderate/severe symptomatic OSA or mild OSA

with symptoms that impact on QoL will receive second-line treatment consisting of CPAP. The company proposes to add on pitolisant for patients with residual EDS despite CPAP or use pitolisant as monotherapy for patients with EDS who refuse/are unable to use CPAP.

Figure 2.1: Treatment pathway based on current NICE recommendations for patients with EDS caused by OSA as proposed by the company



Source: Section 1.3.2 of the CS[1]
CPAP = continuous positive airway pressure; EDS – excessive daytime sleepiness; OSA = obstructive sleep apnoea; QOL = Quality of Life

ERG comment: The company did not provide additional references to support the statement '(…) CPAP is the gold standard treatment for EDS due to OSA'.[1] No further clarification was required in relation to the company's overview of current service provision and the cited references. The ERG considers that the company has provided an adequate description of current practice. Placement of pitolisant in the pathway is supported by the current guidance.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	Adults with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such CPAP	As per scope. In line with the clinical study programme, two subgroups were considered: 1. Patients receiving CPAP with residual EDS (HAROSA I study)[33] 2. Patients refusing CPAP with EDS (HAROSA II study)[34]	Pitolisant was investigated in two patient populations in two separate studies: 1. Patients receiving CPAP who had residual EDS (HAROSA I study)[33] 2. Patients refusing CPAP with EDS (HAROSA II study)[34]	The population considered in the company submission is in line with the scope and the anticipated marketing authorisation for pitolisant.
Intervention	Pitolisant with or without primary OSA therapy	As per scope		The intervention is in line with the NICE scope
Comparator(s)	Established clinical management without pitolisant	As per scope Established clinical management includes optimised CPAP and lifestyle measures (losing weight, stopping smoking and limiting alcohol consumption). Mandibular advancement devices (MAD) are a potential treatment option for OSA and can be used in patients with mild or moderate disease.	The company have included MAD as a scenario analysis in their economic modelling of patients with EDS who refuse CPAP as some patients may be offered MAD in this situation, although only if their disease is mild or moderate.	The comparators are in line with the NICE scope.
Outcomes	• EDS • Fatigue • Length of life	As per scope The company will also consider Physicians Global	Physician and patient rating of treatment is helpful to understand how treatment impacts on the physician and patient.	The outcomes reported are in line with the NICE scope

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	• Adverse effects (AE) of treatment • Health-related quality of life (HRQoL)	Impression of Change (PGIC) and Patient's Global Opinion of the Effect (PGOE). The company will consider specific AE related to the cardiovascular (CV) system.	Length of life will be assessed by deaths during treatment. The HAROSA studies for pitolisant are over 1 year and therefore, longer term changes in mortality will not be apparent from the clinical study programme. Some treatments for EDS are associated with changes in CV risk factors, for example, modafinil which is no longer approved for EDS due to OSA. It is important to understand the CV risk profile of pitolisant, particularly as many people with EDS due to OSA have underlying CV risk factors and/or CV comorbidities.	
Economic analysis	Not addressed			The cost effectiveness analyses were conducted according to the NICE reference case.
Subgroups to be considered	• Mild, moderate and severe obstructive sleep apnoea • People who cannot have or have refused CPAP • People not continuing CPAP	OSA patients with EDS who cannot have CPAP, refuse CPAP or who are unable to continue with CPAP will be considered as one subgroup.	There is a lack of data to separate out patients according to severity of OSA. Pitolisant is likely to be used in people with moderate and severe OSA.	The cost effectiveness analysis does not take into account subgroups of patients based on the severity of OSA, due to a lack of data on this. A scenario analysis was performed on CPAP versus MAD, to address the single subgroup of patients

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
				who cannot have, have refused, or have discontinued CPAP, and who are assumed to be provided a MAD.
Special considerations including issues related to equity or equality	Not addressed			

Source: CS, Table 1, pages 10-12.

AE = Adverse effects; CPAP = Continuous positive airway pressure; CV = Cardiovascular; EDS = Excessive daytime sleepiness; HRQoL = Health-related quality of life; MAD = Mandibular advancement devices; OSA = Obstructive sleep apnoea; PGIC = Physicians Global Impression of Change; PGOE = Global Opinion of the Effect.

3.1 Population

The population defined in the scope is: Adults with obstructive sleep apnoea (OSA) whose excessive daytime sleepiness (EDS) has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure (CPAP).[35] In line with the scope and the available evidence, the company considered two subgroups:[1] 1) Patients receiving CPAP with residual EDS (HAROSA I study);[33] and 2) Patients refusing CPAP with EDS (HAROSA II study)[34, 36].

The population considered in the CS is in line with the anticipated marketing authorisation for pitolisant: Pitolisant is indicated for the treatment of EDS in patients with OSA and treated by CPAP but still complaining of EDS, or in patients with OSA refusing/not tolerating CPAP[37] (CS, Table 2, page 13).[1] A European marketing authorisation application for pitolisant was submitted to the European Medicines Agency (EMA) in November 2019.[1] This information was investigated further in the Clarification Letter (question A9); the company stated that the Committee for Medicinal Products for Human Use (CHMP) opinion is expected in November 2020 with final approval expected at the end of 2020/early 2021.[24]

3.2 Intervention

The intervention (pitolisant) is in line with the scope.

According to the company, pitolisant is a potent wakefulness promoting agent. Levels of histamine and other wake-promoting neurotransmitters are increased in the brain, resulting in improved wakefulness.[38] Pitolisant is an orally active histamine H3-receptor antagonist/inverse agonist which, via its blockade of histamine auto-receptors, enhances the activity of brain histaminergic neurones. Pitolisant also modulates various neurotransmitter systems, increasing acetylcholine, noradrenaline, and dopamine release in the brain. It should be noted that there is no increase in dopamine release in the reward centre of the brain (striatal complex including nucleus accumbens) with pitolisant.[38]

Pitolisant should be administered with caution in patients with:

- History of psychiatric disorders such as severe anxiety or severe depression with suicidal ideation risk
- Renal impairment or moderate hepatic impairment (Child-Pugh B)
- Acid-related gastric disorders or when co-administered with gastric irritants such as corticosteroids or NSAIDs
- Severe obesity or severe anorexia
- Severe epilepsy[37]

Treatment should be carefully monitored in patients with:

- Cardiac disease co-medicated with other QT-prolonging medicinal products or known to increase the risk of repolarisation disorders, or co-medicated with medicinal products that significantly increase pitolisant Cmax and area under the curve (AUC) ratio
- Severe renal or moderate hepatic impairment[37]

Women of childbearing potential should 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[37] (CS, Table 2 page 13).[1]

The presence of EDS should be confirmed by the Epworth Sleepiness Scale (ESS), a simple questionnaire-based scale scored out of 24. Scores of 11-12 indicate mild EDS, 13-15 moderate EDS and 16-24 severe EDS. There is no need for CV monitoring e.g. ECG monitoring.[1]

3.3 Comparators

The description of the comparators in the NICE scope is as follows: "Established clinical management without pitolisant hydrochloride".[35]

The company included mandibular advancement devices (MAD) as a scenario analysis in their economic modelling of patients with EDS who refuse CPAP as some patients may be offered MAD in this situation, although only if their disease is mild or moderate. The ERG proposed that it is also possible that MAD might be prescribed instead of CPAP even if CPAP might be acceptable and asked the company to include MAD as a comparator, including in the subgroup of those who have not refused CPAP.[24] The company responded that CPAP is the gold standard treatment for OSA because it was recommended by NICE Technology Appraisal 139.[19] In addition, the company stated that MADs are not an appropriate comparator in people who are eligible for CPAP and who are happy to use it because pitolisant can only be used in this patient group if patients do not achieve adequate relief from EDS whilst using CPAP; and MADs cannot be used at the same time as CPAP, rendering them an inappropriate comparator.

The ERG disagrees with this reasoning. Firstly because, even if CPAP is considered the gold standard treatment for OSA, this does not mean that other comparators cannot be considered. Secondly, the fact that pitolisant is always used in combination with CPAP, does not mean that all comparators should also be used in combination with CPAP. Therefore, the ERG still beliefs MADs could be regarded as a relevant comparator.

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- EDS
- Fatigue
- Length of life
- Adverse effects (AE) of treatment
- Health-related quality of life (HRQoL)

These were all assessed in the HAROSA trials. In addition, Physicians Global Impression of Change (PGIC) and Patient's Global Opinion of the Effect (PGOE) were included as outcome measures. And the company considered specific AEs related to the cardiovascular (CV) system.

3.5 Other relevant factors

According to the company, pitolisant has substantial health-related benefits that the ERG finds challenging to include in economic modelling (CS, Section B.2.12).[1]

There is no patient access scheme (PAS) in place. Pitolisant costs are based on the manufacturer's proposed list price (CS, Section 3.5.1, page 68).[1]

This appraisal does not fulfil the end-of-life criteria as specified by NICE because the life expectancy of patients eligible for pitolisant is well beyond 24 months. Therefore, treatment is not indicated for patients with a short life expectancy (normally less than 24 months).

According to the company, no equality issues related to the use of pitolisant for the treatment of adults with excessive daytime sleepiness caused by obstructive sleep apnoea exist (CS, Section B.1.4).[1]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D (Identification, selection and synthesis of clinical evidence), reported search methods for a single set of searches run in January 2020 used to inform all sections of the submission. Searches were intended to retrieve relevant papers on the treatment of excessive daytime sleepiness (EDS) in obstructive sleep apnoea (OSA) and also to identify relevant papers on model parameters relating to the quality of life (QoL) and utility values of adult patients with OSA being treated for EDS, costs and resource use associated with the conditions, and existing economic models in the treatment of OSA. A summary of the sources searched is provided in Table 4.1 below:

Table 4.1: Data sources for the identification, selection and synthesis of clinical evidence

Search strategy element	Resource	Host/source	Date range	Date searched
Electronic databases	MEDLINE	Proquest	1946-2020/01/16	16/1/20
	Embase			
	Cochrane Library	https://www.cochranelibrary.com/ (Wiley)		
	Heoro	www.heoro.com		
Conference proceedings	ISPOR	www.ispor.org	(2017-2019)	
	World sleep congress	www.worldsleepcongress.com	2017 & 2019	
	Sleep meeting	www.sleepmeeting.org	2018-2019	
	Sleep and breathing conference	Accessed via the ERJ: www.openres.ersjournals.com	2017 & 2019	
	European respiratory society international congress	Accessed via the ERJ: www.erj.ersjournals.com	2017-2019	
	British Thoracic society	Accessed via thorax journal: www.thorax.bmj.com	2017-2019	
	American thoracic society	www.atsjournals.org	2018-2019	
Trials registries	ClinicalTrials.gov	www.clinicaltrials.gov		
Additional methods	Call for evidence from manufacturer			
	Checking of reference lists			

ERG comments:

- Question A1 in the ERG request for clarification stated that "The ERG is currently unable to fully critique these searches due to the lack of hits per line for each strategy. Please provide full search strategies in their original format including hits per line".[24] Whilst hits per line were provided by the company, the strategies do not appear to be in their original format. There appears to be a reporting error in the line combinations in the Cochrane search. Whilst the combinations are correct, they are missing a # symbol before each line number, which in the Wiley interface would interfere with the rerunning of this search. The Cochrane handbook recommends that: "…the bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors."[39]
- This lack of clarity in reporting also appears to have affected the MEDLINE strategy where the final total in line #12 is lower than line #11 despite being OR'd with an earlier set of results from line #3 (see excerpt below). It is unclear if this was as a result of the MEDLINE records being separated from the joint MEDLINE/Embase results. Unfortunately, the ERG does not have access to MEDLINE/Embase via Proquest so is unable to rerun these searches to verify that this was the case or to check that no further errors were introduced in the formatting of these searches.

11	10 Limited to humans with abstracts	3221
12	**3 OR 11 limited to humans, abstracts**	**2153**

- In Table 1 (Appendix D of the CS) the first strategy reports a search of MEDLINE via Embase. In the request for clarification the ERG asked the company to clarify if by this they were referring to a search of Embase conducted on the understanding that it now contains all records from Medline and conducted at the same time as the Embase search, or if it was a separate search of the MEDLINE database. The company responded, "We confirm that we searched Medline and Embase at the same time via the embase.com platform and not via a separate search of the Medline database."[24] The ERG is concerned that this approach has limitations when using subject heading terms which could affect recall of results. Embase subject heading terms (Emtree) were used in the search strategy, and although simultaneous searching of Embase should automatically identify and search for equivalent MEDLINE subject heading terms (MeSH), it is not clear if this is the case for all potentially useful MeSH terms. Given the possible limitations of this approach, the ERG considered it preferable to search each database separately, or at least to ensure inclusion of both Emtree and MeSH terms in the search strategy. A separate companion MEDLINE search also allows the searcher to fully utilise the power of database specific study design filters developed to make the most of an individual database's subject headings. Whilst no filters were used for the clinical effectiveness element of the searches, filters for economic evaluations, HRQoL, costs and resource use were included. However, given the searches of additional bibliographic databases and grey literature resources reported by the company, it is unlikely that this omission would have impacted on the overall recall of results.
- The ERG noted that in the response to the previous point the company referred to the Embase.com platform, however all other reporting in both the original submission and response to clarification of both Embase and MEDLINE have referred to the databases being searched via the Proquest interface.

- It is unclear whether the MEDLINE/Embase search also included MEDLINE in Process, EPubs ahead of print and Daily updates, which may have affected the recall of more recently published papers.
- In Table 1 (Appendix D of the CS) the final line of both the MEDLINE and Embase searches contained a limit to only those records that contained abstracts. When asked to confirm if this was the case the company responded, "We confirm that the final search was limited to studies conducted in humans that had abstracts. As studies without abstracts are mainly those that do not report primary research, such as editorials and opinion-piece publications, and as we hand-searched the citations of all identified systematic reviews to identify any additional studies that had been missed by our search, we do not believe that applying this limit to the search meant that any relevant publications were missed."[24] The Ovid search notes for Embase indicate that only about 60% of the documents in Embase contain abstracts.[40] Therefore, a more cautious approach might have been to remove unwanted publication types rather than limiting to abstracts.
- The ERG noted the use of synonyms, alternative drug trade names (i.e. Wakix, Provigil, Dexedrine, Sunos, Ritalin etc.) and truncation was limited for all searches. Whilst this would have been mitigated to some extent by the use of Emtree, without rerunning the searches the ERG is unable to say what impact this may have had on the overall recall of results.
- Whilst not formally included in the request for clarification, the ERG queried the disparity between the number reported for screening after the removal of duplicates in Table 1 (Appendix D of the CS) and the search flow during the clarification TC with NICE on 16 June 2020. The search flow (Figure 1, Appendix D of the CS) reported 6,078 papers after the removal of duplicates, whilst Table 1 (Appendix D of the CS) reported 5,546. The company agreed to address this as part of their response to question A1 in the clarification letter, but this was not included in the final response. Therefore, the ERG remains unclear as to the cause of this disparity and whether the 528 additional records are due to a reporting error or a more consequential mistake.

4.1.1.1 Health-related quality of life

- The addition of the CPAP facet in the HRQoL facet of the MEDLINE and Embase searches may have been unnecessarily restrictive but is unlikely to have greatly affected the overall recall of results.

Table 4.2: Data sources for the systematic review of efficacy and safety of MADs

Search strategy element	Resource	Host/source	Date range	Date searched
Electronic databases	MEDLINE	Proquest	1946-2020/04/30	30/4/20

ERG comments:

- The CS reported that due to time constraints this search was only conducted on a single database supplemented by the hand searching of reference lists. It was intended to identify high quality SRs reporting on the efficacy of MADs in adult OSAHS. The ERG was concerned by the restrictions of this approach and by the lack of both truncation, MeSH and the limited use synonyms within the reported strategy. It is also unclear whether these searches included MEDLINE in Process, EPubs ahead of print and Daily updates which may have affected the recall of more recent papers particularly EPubs ahead of print. With the limitations discussed the ERG is concerned that relevant papers may have been missed.

4.1.1.2 Summary of searching

The company submission (CS) and response to clarification provided sufficient details for the ERG to appraise the searches for eligible studies. A good range of resources were searched and the structure appeared appropriate. Searches were conducted between January and April 2020. Database searches were not limited by date or language and the submission reported supplementary searching of a clinical trials registry and conference proceedings from the last three years. Further relevant papers were provided by the manufacturer and the checking of reference lists was confirmed at clarification. However, search strategies contained some limitations, with the search for MADs being of particular concern and there were issues in reporting that may affect the reproducibility of some searches. There was also an unexplained disparity in Appendix D of the CS between the number of records screened after deduplication between Table 1 and the search flow.

4.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for randomised controlled trials (RCTs) and non-RCTs is presented in Table 4.3.

Table 4.3: Eligibility criteria used in the efficacy and safety studies.

	Inclusion criteria	Exclusion criteria
Population	• Adults with excessive daytime sleepiness due to OSA	• Children with OSA or other sleep disorders. • Adults with other sleep disorders
Interventions	• Pitolisant • Modafinil • Dexamphetamine • Sodium oxybate • Solriamfetol • CPAP	• Studies comparing different regimens of one active intervention with no other comparator
Comparators	• Placebo • No treatment/ usual care • Any other relevant intervention as monotherapy or in combination	• Studies comparing a relevant intervention with an unlisted intervention e.g. mandibular advancement or other devices
Outcomes	• Daytime sleepiness • Other measures of sleep amount, quality or latency • Mortality • Adverse events (AEs)	
Study design	• Randomised controlled trials • Systematic reviews of randomised controlled trials (RCTs)	• Conference abstracts that report no additional data from the primary publication • RCT protocols with no results • Narrative reviews, opinion pieces, editorials, other publications that do not report primary research
Language restrictions	• No restrictions	

	Inclusion criteria	Exclusion criteria
Source: Table 2 of the Company Submission Appendices AE = adverse event; CPAP = continuous positive airway pressure; CS = company submission; OSA = obstructive sleep apnoea; RCT = randomised controlled trial;		

ERG comments: As explained in Section 3.3 in this report, the ERG believes that MADs could be regarded as a relevant comparator, yet they have been explicitly excluded from the systematic review for efficacy and safety studies by the company. The company did perform an additional search to identify studies evaluating MADs; however, this search used Medline only and searched for systematic reviews and meta-analyses only. Therefore, the search for MADs was considered poor. It is unclear whether all relevant studies have been included for MADs.

4.1.3 Critique of data extraction

The authors did not perform data extraction in duplicate. There was no mention of data extraction being checked by a second author.

ERG comment: The ERG notes that it is normally recommended that two reviewers are involved in data extraction to avoid bias and error.

4.1.4 Quality assessment

The quality assessment of the reviews was completed by two reviewers using the AMSTAR2 quality assessment tool. Any disagreements regarding scoring were resolved by the project leader. The quality of the trials was assessed using the Cochrane Risk of Bias tool-2. This tool uses six categories: 'randomisation process', 'deviations from intended interventions', 'missing outcome data', 'measurement of the outcome', 'selection of the reported result', and 'overall'. All categories were marked as low risk of bias by the company for both HAROSA trials.

ERG Comment: The ERG has no further comment regarding quality assessment.

4.1.5 Evidence synthesis

The company notes a meta-analysis was not possible for the HAROSA I and HAROSA II trials due to the trials focusing on different populations.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Included studies

Two RCTs were identified to provide evidence for pitolisant, which were both followed by open-label extensions (OLE). The CS noted a wash-out period was included in the trials and lasted one week. The ERG requested justification if this was a sufficient amount of time. The company responded that they had made a mistake in the CS and that on rechecking the CSR, the wash-out period was in fact two weeks (from the screening visit to the baseline visit at which point patients were randomised to pitolisant or placebo). In addition, the company stated that "treatments for EDS must be taken every day due to their short half-life. For example, modafinil has a half-life of 15 hours, dextroamphetamine has a half-life of 10 to 12 hours and methylphenidate has a half-life of 2-3 hours. Therefore, a wash-out period of 1 week would be adequate to eliminate active treatment from the body and 2 weeks would be more than adequate".[24] However, the company did not provide the half-life time for pitolisant.

Table 4.4: Pitolisant studies included in the company submission

Study	HAROSA I[33]	HAROSA II[34, 36]
Design (N)	Prospective, multicentre, randomised, double-blind placebo-controlled study followed by open-label extension (N=244).	Prospective, multicentre, randomised, double-blind placebo-controlled study followed by open-label extension (N=268).
Intervention	Pitolisant (starting dose 5 mg, titrated up to 20 mg maximum dose as needed)	Pitolisant (starting dose 5 mg, titrated up to 20 mg maximum dose as needed)
Comparator	Placebo	Placebo
Treatment duration	4-26 weeks	4-26 weeks
Trial conduct period	2011-2014	2011-2014
Countries	Belgium, Bulgaria, Denmark, Finland, France, Germany, Macedonia, Spain, and Sweden	Belgium, Bulgaria, Denmark, Finland, France, Germany, Macedonia, Serbia, Spain, and Sweden
Sources: CS Table 3, Table 4, and page 35; HAROSA I CSR[33]; HAROSA II CSR[36].		

4.2.2 Methodology of the included studies

4.2.2.1 HAROSA I (P09-08)[33] and HAROSA II (P09-09)[34, 36]

The HAROSA I and HAROSA II studies were prospective, multicentre, randomised, double-blind, placebo-controlled trials, which focused on patients who experienced EDS due to OSA. The populations of the two trials differed in that HAROSA I patients had previous nasal CPAP (nCPAP) therapy for at least three months and continued to experience EDS, whereas patients in the HAROSA II trial had refused nCPAP therapy and were experiencing EDS. Due to all patients in both trials having experienced EDS, the ERG asked for clarification regarding a complete breakdown of all treatments used for primary obstructive sleep apnoea, including those who used mandibular advancement devices (MADs) and a breakdown regarding patient weight and smoking status.[24] In the response to clarification, the company noted that prior to randomisation, a medical questionnaire was completed to identify information regarding EDS and OSA. However, this information was not made available in the clinical study reports (CSR) and could therefore not be presented.[24] The company stated that while information regarding smoking status was not available in the CSR, information regarding weight and body mass index (BMI) was available, and is reproduced below in Table 4.5.[24] It was noted that data was not available regarding patients who attempted weight loss since OSA diagnosis.[24]

Table 4.5: Weight and BMI in the HAROSA studies

	HAROSA I		HAROSA II	
	Pitolisant (n=183)	**Placebo (n=61)**	**Pitolisant (n=200)**	**Placebo (n=67)**
Weight (Mean, SD), Kg				
Baseline	98.2 (18.9)	97.7 (14.8)	97.7 (15.7)	99.9 (16.1)
End of double-blind period	97.9 (18.2)	98.0 (14.1)	96.6 (15.6)	98.9 (15.4)
Body mass index (Mean, SD), Kg/m^2				
Baseline	32.64 (5.26)	32.11 (4.31)	32.8 (4.6)	33 (4.3)
End of double-blind period	32.57 (4.97)	32.08 (4.18)	32.4 (4.4)	32.7 (4.4)
First quartile at baseline	28.6	29.0	30	30
Median at baseline	33.5	31.6	33	33
Third quartile at baseline	37.4	36.4	37	37
Source: Table 2 in response to clarification letter[24]				

The key inclusion criteria for both studies were: Male and/or female outpatients of at least 18 years of age; Minimal Mental State Examination (MMSE) ≥ 28; Beck Depression Inventory 13 items (BDI-13 items): score < 16 and item G=0; ESS ≥ 12; BMI ≤ 40kg/m^2; Female patients of child-bearing potential using a medically accepted method of birth control; Patients had to be willing not to operate a car (if sleepy at the wheel) or heavy machinery; Maintenance of behaviours which could affect diurnal sleepiness (e.g. caffeine consumption, nocturnal sleep duration). Patients were excluded from both trials if they had insomnia; co-existing narcolepsy; sleep debt not due to OSA (according to physician's judgment); non-respiratory sleep fragmentation (restless legs syndrome); shift workers/professional drivers; refusal from the patient to stop any current therapy for EDS, or predictable risks for the patient to stop the therapy; psychiatric illness; acute or chronic disease preventing the improvement assessment [for example, severe Chronic Obstructive Pulmonary disease (COPD)]; current or recent (within one year) history of drugs, alcohol, narcotic, or other substance abuse or dependence, any significant serios abnormality of the CV system (e.g. recent myocardial infarction, angina, hypertension or dysrhythmias within the previous six months, Electrocardiogram Bazett's corrected QT interval longer than 450 milliseconds, history of left ventricular hypertrophy or mitral valve prolapse), severe co-morbid medical or biological condition that could jeopardise the study participation (at the discretion of the investigator when regarding CV system and instable diabetes), positive serology tests (hepatitis, hepatitis B surface antigen and human immunodeficiency virus), pregnant or breast-feeding women, women with child-bearing potential and no efficient birth-control method, patients with a dominant arm deficiency impeding the achievement of the tests, patient using prohibited treatments, congenital galactose poisoning, glucose and galactose malabsorption, deficit in lactase (lactose in placebo), and participation in another study or follow-up period in another study.

Additional key inclusion criteria of the HAROSA I study were: Patients using CPAP therapy for a minimum period of three months and still complaining of EDS; Polysomnography performed between visit 1 and visit 2 or during the last 12 months with Apnoea-Hypopnea Index (AHI) ≤ 10 and Periodic Limb Movement Disorders (PLM) as defined by a PLM arousal index (PLMAI) ≤ 10 per hour.

Additional key inclusion criteria for the HAROSA II trial were: Patients refusing to be treated by nCPAP therapy, and still complaining of EDS; Polysomnography performed between visit 1 and visit 2 or during the last 12 months with AHI ≥ 15 and PLM as defined by PLMAI ≤ 10 per hour.

After identifying patients who met the selection criteria, patients in either study were randomised to either the placebo arm or the pitolisant treatment arm. Both studies commenced with a 12-week double-blind component, which started with an escalating dose period followed by treatment with the selected dose. The starting dose was 5 mg from days 1-7. From days 8-14, the 10 mg dose was introduced. The 15 mg dose was maintained or reduced at day 21 based on tolerability and dose stability. After the 12-week period, patients then had the option to complete a 40-week open label period, in which all patients were switched to pitolisant. The ERG questioned the use of treatment stopping rules in either trial.[24] The company noted in their response to clarification that there were no formal stopping rules and patients could take pitolisant as long as a clinical benefit was achieved.[24]

For both the HAROSA I and HAROSA II trials the primary outcome was the change from baseline in the Epworth Sleepiness Scale (ESS) score to the end of the 12-week double-blind. Patients were required to assess the likelihood of sleepiness or dozing in a variety of given situations on a scale of 0, meaning no daytime sleepiness, to 3, meaning a high likelihood of dozing. The ESS scores can range from 0 to 24. ESS was measured at all study visits, except during visit 7, during which was a dose adjustment prior to the start of the double-blind period. The secondary outcomes reported for both trials include fatigue, adverse events, and quality of life.

ERG comment: Components of the methodologies of the included trials had to be clarified for appropriate understanding; particularly when regarding prior treatment usage and treatment stopping rules. According to the company no formal stopping rules for pitolisant exists and patients could take pitolisant as long as a clinical benefit is achieved. However, the trials only included 12-week comparisons between pitolisant and placebo. After the 12-week period all patients who wanted to continue received pitolisant.

4.2.3 Baseline characteristics of the included studies

The baseline characteristics of the included studies are presented in Table 4.6. Both trials reported a randomisation process on a 3:1 basis. The participants in both trials were middle aged, obese, largely male, with most reporting full-time employment. The HAROSA I trial included patients who had an OSA diagnosis for four years and had an ESS score indicating moderate EDS. Whereas, the HARSOA II study included patients who had an OSA diagnosis for one year and had an ESS score indicating between moderate to severe EDS.

Table 4.6: Baseline characteristics: double-blind period

	HAROSA I[33]		HAROSA II[34, 36]	
	Pitolisant (n=183)	**Placebo (n=61)**	**Pitolisant (n=201)**	**Placebo (n=67)**
Age (years), Mean (SD)	53.8 (10.5)	51.0 (10.6)	51.9 (10.6)	52.1 (11.0)
Gender – Male, n (%) Female, n (%)	149 (81.4%) 34 (18.6%)	53 (86.9%) 8 (13.1%)	151 (75.1%) 50 (24.9%)	51 (76.1%) 16 (23.9%)
BMI, Mean (SD)	32.66 (5.22)	32.17 (4.28)	32.8 (4.6)	33.0 (4.3)
Professional activity-Yes, n (%) No, n (%)	117 (63.9%) 66 (36.1%)	50 (82.0%) 11 (18.0%)	139 (69.2%) 62 (30.8%)	49 (73.1%) 18 (26.9%)

	HAROSA I[33]		HAROSA II[34, 36]	
	Pitolisant (n=183)	**Placebo (n=61)**	**Pitolisant (n=201)**	**Placebo (n=67)**
Days of work per week Mean (SD)	5.1 (0.5)	5.0 (0.6)	5.0 (0.5)	5.1 (0.2)
Medical history Any significant CV	 152 (83.1%) 111 (60.7%)	 46 (75.4%) 27 (44.3%)	 142 (70.6%) 110 (54.7%)	 47 (70.1%) 35 (52.2%)
Time since OSA diagnosis (months), Mean (SD)	44.84 (44.07)	48.99 (57.08)	12.1 (25.0)	11.5 (23.2)
ESS, Mean (SD)	14.9 (2.7)	14.6 (2.8)	15.7 (3.1)	15.7 (3.6)
Baseline Pichot Fatigue Scale score, Mean (SD)	13.2 (7.2)	11.4 (7.2)	13 (6.5)	11.1 (5.9)
Source: Table 5 of CS SD = standard deviation				

ERG comment: Baseline characteristics were generally evenly matched in both trials. However, there were slightly more people without professional activity in the pitolisant group and slightly more people with a CV history in the pitolisant group in HAROSA I.

4.2.4 Statistical analyses of the included studies

HAROSA I and HAROSA II used identical statistical analysis methods for the primary analysis, as detailed in Table 4.7**Error! Reference source not found.**. The primary analyses were based on the intention to treat (ITT) population which was defined as all randomised patients. There were no additional planned subgroup analyses. Missing data was imputed using last observation carried forward (LOCF).

Efficacy analysis were also carried out on the per protocol (PP) population, which was defined as all patients in the ITT population without protocol violations or premature discontinuation of the double-blind period.

Table 4.7: Statistical analysis for the HAROSA studies

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
The primary efficacy end-point, change in ESS score between beginning of treatment (visit 2) and end of the double-blind period (Last Observation Carried Forward [LOCF])	Analysis was carried out on the ITT population, which was defined as all randomised patients. ANCOVA methodology was used to perform statistical analysis and all statistical tests were performed two-sided, at the 5% level of significance. The final LOCF ESS score was primarily analysed using an	The sample size was calculated after considering results from exploratory studies on pitolisant, which provided an estimate of the ESS residual variability to standard deviation (SD) of 6. The MID was fixed to ESS = 3, corresponding to an effect size of 0.5. The correlation between final and baseline ESS was conservatively estimated to r = 0.4 By assuming	During the double-blind period missing data for the primary efficacy variable and for response were allocated following the LOCF, defined as the last available assessment at V2, V3, and V4.

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	ANCOVA model adjusting for ESS and BMI at visit 2 (randomisation visit) and study site as random effect.	ANCOVA at 0.95 confidence level as the main confirmatory test, a difference of at least Delta = 3 should have been detected with a power of 90% in using at least 60 patients in the placebo group and 180 patients in the pitolisant treatment group.	
Source: Table 6 of the CS			

ERG comment: The statistical analysis of the change in ESS score used appropriate methods (ANCOVA adjusting for the baseline value and BMI). However, these results may be affected by the method used for imputing missing data (LOCF) depending on the proportion of missing data as other more robust methods such as multiple imputation are available.

4.2.5 Results of the included studies

The CS reported results regarding daytime sleepiness, fatigue, physician, and patient rating of treatment, death, and health-related quality of life (HRQoL).

The changes in daytime sleepiness are presented in Table 4.8. Pitolisant was noted to significantly reduce daytime sleepiness after 12 weeks in both trials. The reduction in ESS score was greater with pitolisant compared to placebo in HAROSA I (mean difference (MD) -2.6, 95% CI -3.9 to -1.4, p<0.001) and in HAROSA II patients, who refused CPAP, (MD -2.8, 95% CI -4.0 to -1.5, p <0.002). According to the company, the minimal important difference (MID) for ESS is two points in patients with OSA and EDS, which indicated that the difference was clinically and statistically significant.[41] ESS scores were further reduced in both trials after the open-label period, as seen in Table 4.9.

Table 4.8: Reduction in ESS, mean (SD), during the 12-week double-blind period (ITT population)

	Baseline	12 weeks (LOCF)	Baseline	12 weeks (LOCF)	Difference
HAROSA I[33]	Pitolisant (n=183)		Placebo (n=61)		-5.52 (4.41) vs -2.75 (5.90)
	14.9 (2.7)	9.42 (4.66)	14.6 (2.8)	11.87 (5.70)	Mean difference: 2.77 p<0.001 **Treatment effect of -2.6 (95% CI: [-3.9; -1.4]) (p<0.001)**
HAROSA II[34, 36]	Pitolisant (n=201)		Placebo (n=67)		-6.3 (4.5) vs -3.6 (5.5)
	15.7 (3.1)	9.4 (4.6)	15.7 (3.6)	12.1 (5.8)	Mean difference: 2.7 p<0.001 **Treatment effect of -2.8 (95% CI: [-4.0; -1,5]) (p<0.001)**
Source: Table 9 of the CS					

Table 4.9: Reduction in ESS, mean (SD), during the 40-week open-label period (ITT population)

	Entry into open-label	40 weeks (LOCF)	Difference	Entry into open-label	40 weeks (LOCF)	Difference
HAROSA I[33]	Pitolisant then pitolisant (n=151)			Placebo then pitolisant (n=48)		
	9.4 (4.8)	8.1 (4.7)	-1.21 (3.12)	12.0 (6.0)	7.9 (5.1)	-4.07 (5.29)
HAROSA II[34, 36]	Pitolisant then pitolisant (n=181)			Placebo then pitolisant (n=55)		
	9.3 (4.6)	7.7 (4.5)	-1.6 (3.4)	12.2 (5.6)	7.0 (4.0)	-5.2 (5.4)
Source: Table 10 of the CS						

In both the HAROSA I and HAROSA II trials, there was a greater reduction in reported fatigue-related scores with pitolisant compared to placebo, as presented in Table 4.10. The mean difference between groups was 0.9 (95% CI not reported) for the Pichot fatigue scale in HAROSA I which was not statistically significant. However, in the HAROSA II trial, the difference between groups was 2.6 (95% CI not reported) which was significant (p=0.005). Pichot fatigue scale scores were further reduced in both trials after the open-label period, as seen in Table 4.11.

Table 4.10: Reduction in Pichot Fatigue Score, mean (SD), during the 12-week double-blind period (ITT population)

	Baseline	12 weeks (LOCF)	Baseline	12 weeks (LOCF)	Difference
HAROSA I[33]	Pitolisant (n=183)		Placebo (n=61)		
	13.2 (7.2)	9.4 (6.9)	11.4 (7.2)	8.6 (6)	-3.8 (5.6) vs -2.9 (5.9) Treatment difference 0.9, NS
HAROSA II[34, 36]	Pitolisant (n=201)		Placebo (n=67)		
	13 (6.5)	9.2 (6.6)	11.1 (5.9)	10.5 (6.1)	-3.6 (5.6) vs -1 (6.3) Treatment difference 2.6, p=0.005
Source: Table 11 of the CS					

Table 4.11: Reduction in Pichot Fatigue Score, mean (SD), during the 40-week open-label period (ITT population)

	Entry into open-label	40 weeks (LOCF)	Difference	Entry into open-label	40 weeks (LOCF)	Difference
HAROSA I[33]	Pitolisant then pitolisant (n=151)			Placebo then pitolisant (n=48)		
	9.7 (7.1)	7.4 (6.2)	-1.6 (5.8)	8.9 (6.2)	7.0 (6.2)	-1.2 (5.8)
HAROSA II[34, 36]	Pitolisant then pitolisant (n=181)			Placebo then pitolisant (n=55)		
	9.2 (6.7)	7.6 (5.5)	-1.4 (5.9)	10.6 (6.1)	7.4 (4.7)	-2.9 (6.2)
Source: Table 12 of the CS						

The CS presented the benefit of wakefulness and relief from daytime sleepiness results using the Physician's Global Impression of Change (PGIC) and the Patient's Global Opinion of Effect (PGOE) of treatment. There was a noted significant difference in the proportion of physicians and patients who rated the treatment effect as improved.

The HAROSA I trial reported no differences in EQ-5D or Visual Analogue Scale (VAS) during the initial 12 weeks when evaluating HRQoL. In the HAROSA II trial, however, there was a noted significant improvement in the domain regarding pain and discomfort. However, the CS did not present the results for the other domains.

4.2.6 Adverse events

There were no reported deaths in the HAROSA I trial. However, there were two deaths reported in the HAROSA II trial, which the company stated were unlikely to be related to pitolisant.

Over the course of one year, discontinuations due to AE were 5.3% in HAROSA I (patients using CPAP) and 2.2% in HAROSA II (patients refusing CPAP). The Patient's Overall Evaluation of Tolerance, which was measured at the end of the double-blind period showed that in HAROSA I, 88.9% of patients randomised to pitolisant and 91.7% of patients randomised to placebo rated the tolerability of treatment as good. In HAROSA II, 100% of patients in both arms rated the tolerability of treatment as good.

The CS noted there were no significant difference regarding the incidence of treatment-emergent adverse events (TEAE) experienced in the HAROSA trials. However, the most frequently reported TEAE was headache experienced in the pitolisant arm in the HAROSA I trial (14.8%). The ERG requested more information regarding adverse events that were experienced outside the HAROSA trials.[24] The company provided information from a clinical overview including data from five studies (n=659) which looked at pitolisant for the treatment of EDS in patients with OSA.[24] Overall, 609 patients were exposed to pitolisant and 152 to placebo alone (some patients received placebo in the 12-week randomised period, followed by pitolisant in the open label period or participated in more than one study). The safety population included 603 patients who had received pitolisant and 151 who had received placebo. The mean (SD) duration of pitolisant treatment (all doses) in double-blind, placebo-controlled studies in OSA was 10.0 (4.1) weeks as compared with 33.5 (14.0) weeks in single-blind and open-label studies of pitolisant in OSA. Approximately two-thirds of all patients (74.8%) received a maximal pitolisant dose of 18 mg once daily, and a comparable proportion of patients (63.5%) received a maintenance dose of 18 mg once daily. In total, 284 (47.1%) patients were exposed to a maximal dose for six months to one year, and 108 (17.9%) were exposed for one year or more.

Table 4.12 shows the TEAEs reported in at least 1% of patients in the pitolisant group the double-blind placebo-controlled studies. Insomnia and anxiety are the only psychiatric disorders reported. For insomnia, the relative reduction is 1.83 (95% CI 0.78-4.27, p=0.09) indicating a non-significant difference. The final column in Table 4.12 below shows the incidence for all patients exposed to pitolisant, including patients receiving pitolisant in the open label extension studies. Rates of insomnia and anxiety are 8.9% and 2.2% respectively.

Table 4.12: TEAEs reported in at least 1% of patients in the pitolisant group in the double-blind placebo-controlled studies

MedDRA Preferred Term	Double-blind placebo-controlled		TOTAL Pitolisant (n=603), n (%)
	Placebo, (n=151), n (%)	Pitolisant (n=468), n (%)	
Any Study Treatment-Related AE	32 (21.2%)	127 (27.1%)	208 (34.5%)
Headache	16 (10.6%)	45 (9.6%)	75 (12.4%)
Insomnia	6 (4.0%)	34 (7.3%)	54 (8.9%)
Nausea	2 (1.3%)	15 (3.2%)	20 (3.3%)
Abdominal pain	1 (07%)	11 (2.3%)	17 (2.8%)
Vertigo	2 (1.3%)	7 (1.5%)	10 (1.7%)
Anxiety	0	6 (1.3%)	13 (2.2%)
Diarrhoea	1 (0.7%)	6 (1.3%)	6 (1.0%)
Source: Table 8 Response to clarification.			

The Summary of Product Characteristics states that pitolisant should be administered with caution in patients with history of psychiatric disorders such as severe anxiety or severe depression with suicidal ideation risk.[37] There is no warning for skin disorders.

Table 4.13 shows the treatment-emergent adverse events (TEAEs) by system organ class and preferred term reported by ≥2% of patients in any arm of the two HAROSA trials and the TEAEs of special interest.

The majority of TEAEs in patients who received pitolisant in double-blind, placebo-controlled OSA studies were mild (25.4%, 119/468) or moderate (21.4%, 100/468) in severity. Severe TEAEs were reported in a slightly higher proportion of pitolisant-treated patients (5.1%, 24/468) compared with placebo-treated patients (3.3%, 5/151). Similar results were observed in pooled data (all OSA studies) with 29.4% (177/603) mild TEAEs, 30.0% (181/603) moderate TEAEs and 7.6% (46/603) severe TEAEs.

In addition, safety data from narcolepsy studies were provided and showed that AE profiles were consistent across all indications (see Table 4.14).

Table 4.13: TEAEs in the double-blind period (safety population), n=244 for HAROSA I and n=267 for HAROSA II

	HAROSA I				HAROSA II			
	Pitolisant (n=183)	**Placebo (n=61)**	**Absolute risk reduction (95% CI)**	**Relative risk (95% CI)**	**Pitolisant (n=200)**	**Placebo (n=67)**	**Absolute risk reduction (95% CI)**	**Relative risk (95% CI)**
TEAE by system organ class and preferred term reported by ≥2% of patients in any arm								
Psychiatric disorders	23 (12.6%)	3 (4.9%)	-0.08 (-0.15-0.00)	2.56 (0.79-8.22)	19 (9.5%)	3 (4.5%)	-0.05 (-0.11-0.01)	2.12 (0.65-6.95)
Skin and subcutaneous tissue disorders	7 (3.8%)	2 (3.3%)	-0.01 (-0.06-0.06)	1.17 (0.25-5.47)				
TEAE of special interest								
Insomnia	17 (9.3%)	2 (3.3%)	-0.06 (-0.12-0.00)	2.83 (0.67-11.91)	11 (5.5%)	2 (3.0%)	-0.03 (-0.08-0.03)	1.84 (0.42-8.10)
Initial insomnia					1 (0.5%)	0 (0.0%)	-	-
Abdominal pain upper	2 (1.1%)	1 (1.6%)	0.01 (-0.03-0.004)	0.67 (0.06-7.22)	1 (0.5%)	0 (0.0%)		
Abdominal discomfort	2 (1.1%)	0 (0.0%)	-	-				
Gastroesophageal reflux disease	2 (1.1%)	0 (0.0%)	-	-	1 (0.5%)	0 (0.0%)	-	-
Dyspepsia					0 (0.0%)	1 (1.5%)	-	-
Anxiety	2 (1.1%)	0 (0.0%)	-	-	2 (1.0%)	0 (0.0%)	-	-
Depression					0 (0.0%)	1 (1.5%)	-	-
Electrocardiogram QT prolonged	0 (0.0%)	1 (1.6%)	-	-	2 (1.0%)	0 (0.0%)	-	-
Weight increased	1 (0.5%)	0 (0.0%)	-	-				

Source: Table 7, Response to clarification.
TEAE=treatment-emergent adverse event

Table 4.14: Overview of AE: OSA and all indications (narcolepsy and OSA) – safety population

	OSA				All indications (OSA and narcolepsy)			
	Double-blind placebo-controlled		Single-blind and open-label pitolisant (N=468)	TOTAL Pitolisant[a] (N=603)	Double-blind placebo-controlled		Single-blind and open-label pitolisant (N=1,021)	TOTAL Pitolisant (N=1,513)[b]
Event	Placebo (N=151)	Pitolisant (N=468)			Placebo (N=475)	Pitolisant (N=1043)		
	n (%) of patients				n (%) of patients			
At least 1 TEAE	47 (31.1)	184 (39.3)	188 (40.2)	282 (46.8)	222 (46.7)	525 (50.3)	554 (54.3)	901 (59.6)
At least 1 severe TEAE	5 (3.3)	24 (5.1)	29 (6.2)	46 (7.6)	23 (4.8)	71 (6.8)	113 (11.1)	173 (11.4)
At least 1 SAE	0	4 (0.9)	11 (2.4)	14 (2.3)	15 (3.2)	27 (2.6)	62 (6.1)	87 (5.8)
At least 1 related TEAE	32 (21.2)	127 (27.1)	119 (25.4)	208 (34.5)	115 (24.2)	329 (31.5)	332 (32.5)	604 (39.9)
At Least 1 related severe TEAE	3 (2.0)	13 (2.8)	8 (1.7)	20 (3.3)	12 (2.5)	33 (3.2)	49 (4.8)	81 (5.4)
At least 1 related SAE	0	0	1 (0.2)	1 (0.2)	7 (1.5)	5 (0.5)	3 (0.3)	8 (0.5)
TEAE resulting in discontinuation	4 (2.6)	12 (2.6)	16 (3.4)	27 (4.5)	25 (5.3)	63 (6.0)	70 (6.9)	132 (8.7)

Source: Table 10, Response to clarification.
n = number of patients; SAE=serious adverse event; TEAE=treatment-emergent adverse event
a) Includes double-blind, placebo-controlled studies; and single-blind and open-label studies in the All OSA pool.
b) Includes double-blind, placebo-controlled studies; and single-blind and open-label studies in the All Indications pool.
Notes: Patients with multiple occurrences of a preferred term are counted only once for that term in each column. Patient with an AE resulting in discontinuation in more than 1 study is counted for each corresponding discontinuation reason from those studies in which the events occurred. If more than 1 study had the same reasons for discontinuation for a patient, the patient was counted only once in the table for that row

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The main comparison in this appraisal is the head-to-head comparison of pitolisant with placebo (both with best supportive care) in the HAROSA trials. However, it can be argued that MADs are a relevant comparator according to the NICE scope as well. Therefore, the company performed an indirect comparison of pitolisant versus MADs to inform the economic model.

As explained in Section 4.1.2 of this ERG report, the company did perform an additional search to identify studies evaluating MADs; however, this search used Medline only and searched for systematic reviews and meta-analyses only. Therefore, the search for MADs was considered poor.

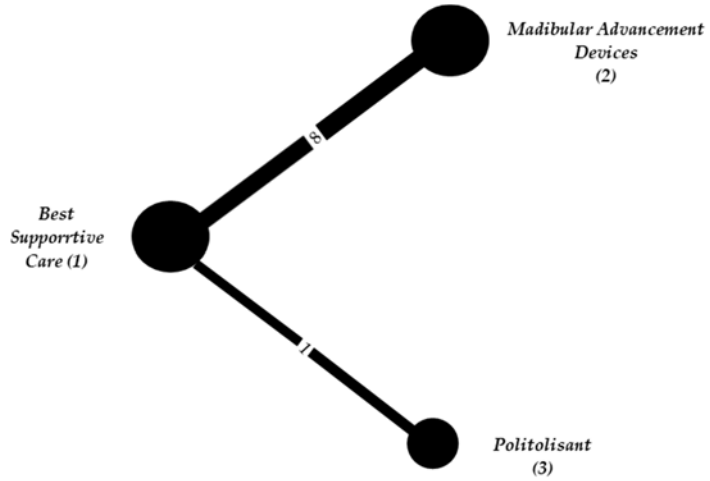
The company's systematic review of reviews identified 13 relevant systematic reviews. Based on a quality assessment of these 13 reviews, two were considered of highest quality, each having only one critical weakness (Sharples et al.[42] and Bratton et al.[43]) and a third review (Gao et al.[44]) had two areas of critical weakness. All other studies had three or more critical weaknesses.

The company compared the three systematic reviews in terms of date range and results. Based on this comparison it was decided to take the results from Sharples et al.[42] for the indirect comparison with pitolisant. However, the company only included a comparison of pitolisant versus MAD in patients with EDS due to OSA who refused CPAP (the HAROSA II population); therefore, only the HAROSA II trial was included for pitolisant.

The review by Sharples et al. identified 12 studies comparing MADs with best BSC which they used to carry out an ITC in people with moderate to severe OSAHS. Of these 12 studies, the company included eight studies in the indirect comparison (three were excluded due to lack of data, and one due to the inclusion of mild obstructive sleep apnoea/hypopnoea syndrome (OSAHS) patients).

The evidence network for ESS score is presented in Figure 4.1 below, each circle represents a treatment or group of treatments in the trials and connecting lines indicate pairs of treatments that have been directly compared in randomised trials. The numbers on the lines indicate the numbers of trials making that comparison, and the numbers by treatment names are the treatment codes used in the modelling. Line thickness is proportional to the number of trials making that comparison, and the width of the circles is proportional to the number of patients randomised to that treatment or group of treatments.

Figure 4.1: Network diagram for ITC comparing MAD and pitolisant via BSC for ESS



Source: Figure 7, Appendix D of the CS.

The model was coded in WinBUGS software version 1.4.3 (Medical Research Council Biostatistics Unit, Cambridge). The WinBUGS code for the ITC was adapted from the code developed by the NICE Decision Unit.[45] Fixed and random effect models were both assessed but the fixed effect models provided the better fit (lower deviance information criteria (DIC) and residual variance) and were used in the economic model. ITC results are shown below in Table 4.15

In addition, given the heterogeneity introduced by studies by Hans et al.[46] and Blanco et al.[47], due to both small patient numbers and outlying ESS results relative to the rest of the studies, an ITC excluding these studies was performed as a sensitivity analysis.

Table 4.15: Results of the ITC comparing pitolisant with MAD

Treatment	Median difference in change from baseline in ESS score	95% CrI	
MAD versus BSC	-1.334	-1.977	-0.6932
Pitolisant versus BSC*	-2.8	-4.046	-1.553
Pitolisant versus MAD	-1.466	-2.866	-0.06304

Source: CS, Table 15, page 36.
BSC = best supportive care, CrI = credible interval, ESS = Epworth Sleepiness Scale, MAD = Mandibular advancement device.
*Result from HAROSA II

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The company should have performed a full search for MAD studies, but were unable to do so due to time restrictions. It would have been better if the company had considered all systematic reviews and assessed all primary studies identified in the reviews for inclusion in the indirect comparison. However, even if they had done that, they would still have missed the most recent relevant studies comparing MAD with BSC. The eight studies used by the company for the comparison of MAD versus BSC were published between 1997 and 2011. This is also illustrated by a systematic review by Li et al. (2020) comparing MADs with CPAP.[48] They included 14 RCTs (six studies of these were published after 2011) and found no significant difference in ESS after therapy between the CPAP group and the MAD group (WMD=0.00, 95% CI: -0.08 to 0.08).[48] Although the review by Li et al. (2020) focusses on a comparison of MAD versus CPAP, it does suggest that MAD might be more effective in terms of ESS than estimated by the company. In addition, the company's search for systematic reviews was very basic and looked for MADs and patients with OSA, rather than patients with EDS due to OSA. From the information provided by the company it is not clear how many patients in the MAD studies had EDS due to OSA.

The ITC used the results of HAROSA II only, for patients who refused CPAP therapy, however it was not clear if this also applied to the MAD trials. As some of the MAD trials included a CPAP arm, it seems that patients in the MAD trials were eligible for CPAP and did not refuse CPAP. The included trials varied in duration of treatment from four to 26 weeks (HAROSA II was 12 weeks) and although the company stated that there was no correlation between ESS score and treatment duration they did not provide any supporting analysis for this statement. Some MAD trials were crossover designs and it was not clear whether only the results for the first period, or the whole trial had been included and whether the effect sizes were from appropriate analyses. There was no assessment of the clinical similarity of the studies included in the ITC nor of the statistical heterogeneity between the studies

evaluating MAD, so it was not possible to judge whether they were suitably similar to be pooled in the analysis.

The ERG believes that the results of the ITC are based on inadequate searches and a limited number of MAD studies. Therefore, due to the possibility of missing trials and between study heterogeneity, the results of the indirect comparison are unreliable.

It is not clear how the lack of more recent studies would have influenced the results of the ITC and how relevant the comparison with MADs is, given that there are head-to-head comparisons of pitolisant with BSC from the two HAROSA trials.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No further work was completed by the ERG.

4.6 Conclusions of the clinical effectiveness section

The considered population of OSA patients with residual EDS receiving CPAP and patients refusing CPAP are in line with the anticipated marketing authorisation for pitolisant. The intervention is also in line with the scope.

The scope notes the outcome measures as EDS, fatigue, length of life, adverse effects of treatment, and health-related quality of life. All of which were addressed in the included trials.

The company identified two randomised clinical trials which evaluated the use of pitolisant on patients who experienced EDS due to OSA.

- HAROSA I: a prospective, multicentre, RCT, which compared pitolisant, starting at a dose of 5 mg, titrated to a maximum dose of 20 mg if needed, to placebo with a duration of 4-26 weeks (n=244). This was followed by an open-label extension. This study was conducted in Belgium, Bulgaria, Denmark, Finland, France, Germany, Macedonia, Spain, and Sweden.
- HAROSA II: a prospective, multicentre, RCT, starting at 5 mg, titrated to a maximum dose of 20 mg if needed, to placebo with a duration of 4-26 weeks (n=268). This was followed by an open-label extension. This study was conducted in Belgium, Bulgaria, Denmark Finland, France, Germany, Macedonia, Serbia, Spain, and Sweden.

The ERG considered the trials to be good quality international trials with sufficient patients included. However, comparative evidence is only available for 12 weeks, after this period all patients received pitolisant.

Due to the HAROSA I and HAROSA II trials focusing on different populations, a meta-analysis of pitolisant trials was not possible.

While the HAROSA I trial included patients that had previous nCPAP therapy for at least three months and continued to experience EDS, the HAROSA II trial included patients that had refused previous nCPAP therapy. It was unclear what treatments had been previously utilised to address EDS due to the information captured by the medical questionnaire not being available according to the company. Information regarding smoking status and attempted weight loss by patients was also not available.

After the twelve-week double-blind period, patients were given the option to complete a 40-week open-label extension period, during which all patients could switch to pitolisant. The company noted that there were no formal stopping rules and pitolisant was meant to be continued as long as a clinical benefit was achieved.

Pitolisant was noted to reduce daytime sleepiness both the HAROSA I and HAROSA II trials. The mean treatment difference in terms of change in daytime sleepiness was: -2.77 in HAROSA I and -2.7 in HAROSA II, both favouring pitolisant. The company noted that the minimal important difference for ESS was two points, which indicated clinical and statistical significance. The HAROSA I and HAROSA II trials both reported a reduction in fatigue-related scores. However, this reduction was not considered significant in the HAROSA I trial.

The HAROSA I trial reported 5.3% of patients had discontinued the trial due to AEs, whereas in the HAROSA II trial 2.2% of patients had discontinued from the trial. While there were no significant differences regarding the incidence of TEAEs in either trial, the most frequently reported TEAE was headache, which was experienced in 14.8% of patients in the pitolisant arm of the HAROSA I trial. The majority of reported TEAEs in patients who received pitolisant were mild or moderate in severity.

The main comparison of the CS was a head-to-head comparison of pitolisant with best supportive care in the HAROSA trials. The ERG beliefs MADs could be regarded as a relevant comparator, yet they have been explicitly excluded from the systematic review for efficacy and safety studies by the company. The company did perform an additional search to identify studies evaluating MADs; however, this search used Medline only and searched for systematic reviews and meta-analyses only. Therefore, the search for MADs was considered poor. It is unclear whether all relevant studies have been included for MADs.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies.

5.1.1 Searches performed for cost effectiveness section

The searches used to identify relevant papers on model parameters relating to the quality of life (QoL) and utility values of adult patients with OSA being treated for EDS, costs and resource use associated with the conditions, and existing economic models in the treatment of OSA were conducted as part of a single set of searches designed to inform all elements of the submission. A critique of these searches can be found in Section 4.1.1 of this report.

5.1.2 Inclusion/exclusion criteria used in the study selection

Separate predefined inclusion/exclusion criteria were used to screen those records identified by the cost effectiveness, HRQoL and cost and resource use search strategies. The de-duplicated list of abstracts was screened independently according to agreed inclusion criteria by two researchers and any discrepancies agreed by discussion. All abstracts were screened independently by two researchers, with any disagreements resolved by the project leader. All abstracts that met the inclusion criteria were retrieved as full texts and screened for inclusion using the same criteria by two researchers working independently.

Inclusion/exclusion criteria for each of the three SLRs were based on the PICOS framework, relating to the population, interventions, comparators, outcomes and study design of interest.

Inclusion/exclusion criteria for the cost effectiveness, HRQoL and cost and resource use SLRs are shown in Tables 26, 31, and 39 of Appendices G, H and I, respectively, of the CS.[1] In each SLR, the population inclusion criterion was adults with excessive daytime sleepiness due to obstructive sleep apnoea. Inclusion was restricted to the following interventions or comparators in the cost effectiveness SLR: pitolisant, modafinil, dexamphetamine, sodium oxybate, solriamfetol, and CPAP. In the SLRs of HRQoL and cost and resource use, studies that did not describe a particular intervention or comparator were also included.

Outcomes of interest and accepted study designs varied by SLR. The cost effectiveness SLR included outcomes related to cost effectiveness, cost utility, cost benefit and cost minimisation analyses. Both trial-based and model-based economic evaluations, as well as systematic reviews were accepted study designs in the cost effectiveness SLR. In the HRQoL SLR, included outcomes were health utility values. In the cost and resource use SLR, included outcomes were healthcare costs, indirect costs and resource use. In the HRQoL and cost and resource use SLRs, accepted study designs were RCTs, economic evaluations, observational studies and systematic reviews.

Across all SLRs, studies conducted in children with OSA and children or adults with other sleep disorders were excluded.

ERG comment: The inclusion/exclusion criteria used in the SLRs were appropriate.

5.1.3 Identified studies

5.1.3.1 Economic SLR

A total of 11 model-based cost-utility studies were identified, of which four where applicable to a UK setting. A quality assessment of these 11 economic studies was conducted using the Drummond checklist for economic evaluations.[42, 49, 50] The results of this assessment are summarised in Table 27 of Appendix G of the CS. In general, the 11 economic evaluations are of good quality (i.e. most of the items on the Drummond checklist are present).[51]

All of the cost utilities studies identified studied the cost utility of CPAP or MADs. None assessed interventions for EDS in OSAHS patients. The four modelling studies conducted in a UK setting all took an NHS perspective, used utilities based on the EQ-5D and made use of ESS as a treatment effect variable to model treatment effects. Time horizon differed from four weeks to lifetime. Three out of the four UK-based models used similar health states, including states for stroke CHD (or CV event) and RTAs.

5.1.3.2 HRQoL SLR

A total of 24 relevant studies were found in populations with OSA. In 13 studies, patients also were specified to have EDS, usually defined as an ESS score of ≥9 or 10.

The most commonly used QOL tools were SF-36 and EQ-5D. Other tools used were EQ-VAS, SF-12, SF-6D, 15D and standard gamble interviews.

Nine of the studies were cost utility models, one of which was an economic evaluation that was based on data from one clinical trial that assessed utility values in participants with the 15D, three collected EQ-5D, EQ-VAS and/or SF-36 scores from RCT participants, the other five used utility values from other sources such as the published literature.

Most primary research studies reported QoL or utility values for a general population with OSA rather than for specific health states. Two studies of outpatients in Italy with suspected OSA found that SF-12 Physical Composite Scores (PSC) and Mental Health Composite Scores (MCS) scores were significantly lower for those with EDS compared with those with an ESS score ≤10. Four cost-utility model publications reported utility values for the health states in their model, which were based on CV and trauma events associated with OSA and EDS.

Twenty-one of the studies assessed how utilities altered as a result of treatments:

- Pitolisant
- Modafinil as adjunct to CPAP or alone
- Solriamfetol
- MADs
- CPAP or nasal CPAP
- Upper airway stimulation.

The relevant details of these studies are summarised in Appendix H in Table 33 to Table 38 of the CS.[1]

5.1.3.3 Cost and resource use SLR

Twenty studies were found to be relevant to costs and resource use associated with OSA. Three studies reported direct costs for the UK, from a clinical study of patients with mild to moderate OSA being

treated with MADs or as part of a cost-utility model of CPAP or CPAP and MADs. The other 17 studies covered a variety of countries, study designs and aims.

More information on these studies is reported in Appendix I of the CS, in Table 40 and Table 41.[1]

5.1.4 Interpretation of the review

Though the searches did not identify any cost effectiveness studies for pitolisant, several cost effectiveness studies were identified where interventions were assessed in OSA patients with EDS. These studies were used by the company as foundation for their own de novo cost effectiveness model,

It is interesting to see that in the search for health-related quality of life information the HAROSA I and II study were identified as of interest, as they administered EQ-5D during the clinical studies. However, in populating the model the company chose to forgo the EQ-5D data collected in the trials and opted instead to use a mapping approach to map scores on the ESS to utility values.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

A summary of the economic evaluation conducted by the company is presented in Table 5.1.

Table 5.1: Summary of the company submission economic evaluation

	Approach	Source/justification in the company submission	Signpost (location in ERG report)
Model	The company developed a cohort-level state transition model in Excel linking the ESS score of OSA patients to CHD, stroke and RTAs.	The model was based on the model developed by McDaid et al.[52] for the assessment of CPAP.	Section 5.2.2.
States and events	All patients start at the OSAHS state. If they experience a CHD event (myocardial infarction or angina), a stroke of a RTA, they will move to the health state Acute CHD, Acute Stroke, RTA-OSAHS or RTA-Post CHD if they survive the event, and to Fatal RTA or Fatal CVE if they die from the event. Patients who survive the event move the next year to Post CHD or Post Stroke if no new events occur. From all health states patients may die from non-CVS and non-RTA causes.	Consistent with the assumptions in McDaid et al.[52]	Section 5.2.2.
Comparators	The NICE scopes states that the comparator of interest is: "Established clinical management without pitolisant hydrochloride" The company looks at two specific subgroups of OSA patients: those treated by CPAP but still complaining of EDS, and those with EDS refusing/not tolerating CPAP. The comparator in the first subgroup is CPAP plus best supportive care (lifestyle changes e.g. weight loss and stopping smoking) and in the second subgroup just BSC or a mandibular advancement device (MAD)	Pitolisant is expected to be granted a licence for the treatment of EDS in patients with OSA and treated by CPAP but still complaining of EDS, or in patients with OSA refusing/not tolerating CPAP. The company included MAD as a scenario analysis in the economic modelling of patients with EDS who refuse CPAP as some patients may be offered MAD in this situation, although only if their disease is mild or moderate.	Section 5.2.4.
Natural history	OSAHS is the most common cause of EDS. In OSAHS patients, the walls of the upper airways relax and narrow during sleep, resulting in interrupted breathing which leads to intermittent hypoxia, arousal from sleep and fragmented sleep, ultimately resulting in EDS. People with EDS have uncontrollable daytime sleepiness that interferes with their usual daily activities, for example, whilst having a		Section 2.2

	Approach	Source/justification in the company submission	Signpost (location in ERG report)
	conversation, reading, watching television or driving. This has a significant impact on QoL. In addition, EDS in OSA patients may lead to cardiovascular events and road traffic accidents.		
Treatment effectiveness	Treatment effectiveness in terms of improvement of the ESS score was taken from the HAROSA I and II studies.[33],[34] It was then assumed that the difference in incidence of CHD and stroke between the pitolisant and non-pitolisant (i.e. best supportive care and best supportive care + MAD) treatment alternatives was proportional to the difference in change in ESS between these groups. The risks of CHD and stroke were estimated using the QRisk 3 and QStroke risk equations For the difference in risk of an RTA a similar approach was used; it was assumed that the ESS score was an independent predictor of the risk of RTAs. The same approach was applied to derive the relative risk of RTAs between pitolisant and MAD.	A similar approach was adopted by Sharples et al[42] in their economic model exploring the cost effectiveness of MADs.	Section 5.2.6
Adverse events	No adverse events from the use of pitolisant were included in the model.	There was no evidence of a specific AE signal associated with pitolisant versus placebo in the HAROSA pivotal trials. The use of pitolisant was not associated with any change in blood pressure or heart rate. Therefore, the company did not include an element of AE impact on either utilities or costs in our model.	Section 5.2.7
Health related QoL	A mapping algorithm was used that translates the mean change in ESS score to an EQ-5D utility change.	Though the EQ-5D was administered during the two pivotal RCTs, the company stated that they could not use this data for the health economic model, Hence,	Section 5.2.8

	Approach	Source/justification in the company submission	Signpost (location in ERG report)
		the mapping approach was adopted similar to the approach adopted in previous NICE submissions, specifically TA139.[52]	
Resource utilisation and costs	The economic analysis was performed from the NHS and PSS perspective. The following costs were included: the drug acquisition costs for pitolisant, and the health state costs relating to coronary heart disease, stroke, and road traffic accidents.	Dosage and wastage assumptions for pitolisant use were based on the HAROSA I and II studies.[33],[34] The costs inputs for the CHD event and post-CHD event health states were sourced from Walker et al.[53] The cost inputs for the stroke event and post-stroke event health states were based on the Sentinel Stroke National Audit Programme (SSNAP) in England, Wales and Northern Ireland in 2015 - 2016. The costs of fatal, serious and slight road traffic accidents (RTAs) were sourced from the Department of Transport report Reported Road Casualties Great Britain: 2018 Annual Report.[54]	Section 5.2.9
Discount rates	Cost and health outcomes discounted at 3.5%	As per NICE reference case	Section 5.2.5
Sensitivity analysis	Probabilistic, deterministic one-way sensitivity analysis and scenario analyses were conducted	As per NICE reference case	Section 6.2

Based on the CS[1]

AE = adverse event; CHD = coronary heart disease; CPAP = continuous positive airway pressure ; CVE = cardiovascular event; CS = company submission; EDS = excessive daytime sleepiness; ESS= Epworth Sleepiness Scale; EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health related quality of life; MAD = mandibular advancement device; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OSA = obstructive sleep apnoea; OSAHS = ;PSS = Personal Social Services; RCT = randomised clinical trial; RTA = road traffic accidents; TA = technology appraisal; UK = United Kingdom;

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.2: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	Direct health effects for patients included.
Perspective on costs	NHS and PSS.	NHS and PSS perspective taken.
Type of economic evaluation	Cost utility analysis with fully incremental analysis.	Cost utility analysis with pairwise analyses undertaken.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	Patients were modelled until death or an age of 100 years, reflecting a lifetime horizon.
Synthesis of evidence on health effects	Based on systematic review.	Systematic review conducted to identify additional evidence on health effects beyond trial data.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects were expressed in QALYs. ESS scores were mapped to EQ-5D utilities using a mapping algorithm.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	HRQoL was based on ESS scores mapped to utilities using a mapping algorithm. Therefore, HRQoL was not directly reported by patients and these values do not meet this element of the reference case.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	EQ-5D-3L data used to estimate the mapping algorithm were valued in a representative sample of the UK general population using the UK value set.[55]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No equity issues have been identified.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	The model includes the costs that relate to NHS and PSS resources, valued using the prices relevant to the NHS and PSS.

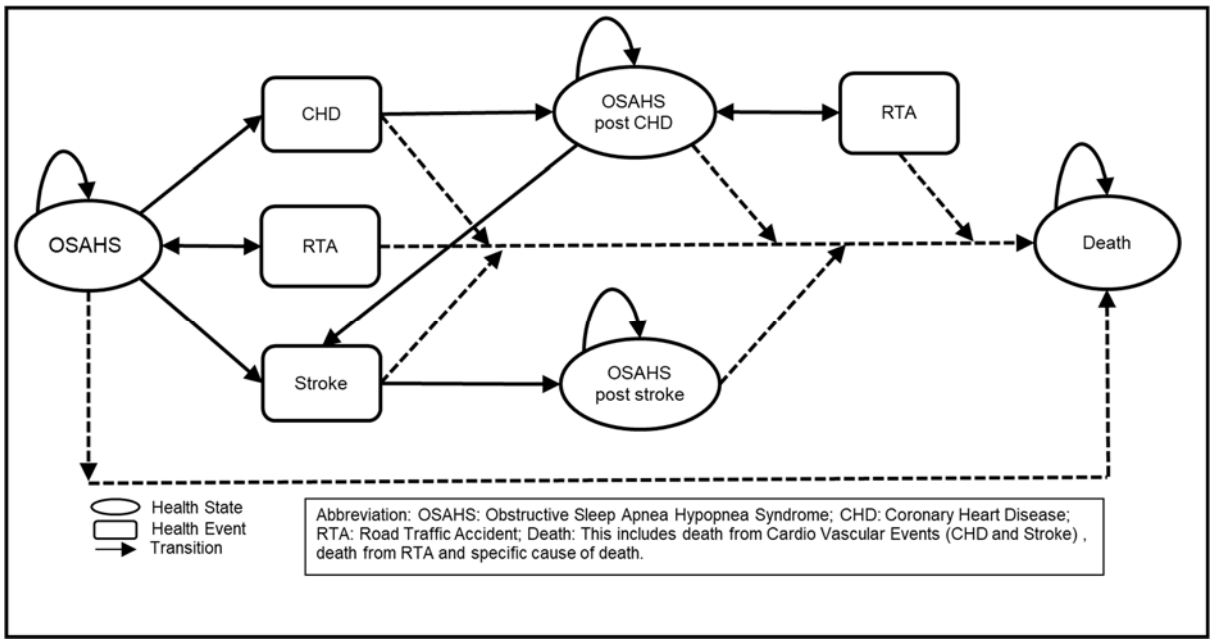
Element of health technology assessment	Reference case	ERG comment on company's submission
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	Costs and health effects are discounted at 3.5%.

EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality adjusted life year; UK = United Kingdom

5.2.2 Model structure

For the cost effectiveness analysis, the company made use of a previously developed cohort-level state transition model for the analysis of the use of CPAP in OAHSH.[52] This model has previously been adapted from its original form to include MADs.[42] Parameters of this model were updated where deemed appropriate. The model structure is depicted in Figure 5.1.

Figure 5.1: Model structure



Based on Figure 7, page 58 the CS

Patients can die at any time in the model and thus can transition from any health state to the death state. Patients enter the model in the OSAHS health state. They can experience one of three events: coronary heart disease (CHD), a road traffic accident (RTA), or a stroke. These events are modelled using transient states in which patients remain for one model cycle. In the case of CHD and stroke, patients' transition to the OSAHS post CHD and OSAHS post stroke health states, respectively, while in the case of an RTA patients return to the OSAHS health state. Patients in the OSAHS post CHD health state can experience RTAs (i.e. transition to the RTA health state for one cycle). Patients in OSAHS post stroke health state are assumed not to operate any vehicles and thus cannot experience an RTA. The software implementation of the model differs slightly from the schematic depiction in Figure 5.1, in that there are separate states for a fatal RTA and fatal cardiovascular event (which combines fatal CHD and fatal stroke) which are not depicted in Figure 5.1. These states are also absorbing states, meaning that they

serve as cause specific death states (patients in these states do not transit to other states). Patients can transition directly to both the non-fatal and fatal RTA states from the OSAHS and OSAHS post-CHD states. Only patients in the CHD and stroke states can transition to the fatal CVD state.

Cycle length in the model is one year. Half cycle correction is applied to costs and effect outcomes. The simulation is stopped when the age of the cohort reached 100 years.

The model was used in two different comparisons in the company submission. First, the cost effectiveness of pitolisant added to best supportive care compared to best supportive care only in OSAHS patients treated with CPAP with residual EDS. Second, the cost effectiveness of pitolisant added to best supportive care compared to best supportive care only or treatment with a MAD combined with best supportive care in OSAHS patients who refused treatment with CPAP. Transitions from the OSAHS state to the three event states (CHD, stroke, RTA) differ between treatment alternatives in both comparisons. Mortality (i.e. transitions from any model state to the death state) is the same for all treatment alternatives in both comparisons.

ERG comment: The model used in the cost effectiveness analysis was developed previously by the University of York.[52] The same model was also used in a previous NICE technology appraisal guidance (TA139).[19] The model was developed for the economic evaluation of CPAP versus dental devices and conservative management in OSAHS patients. The structure of the model and choice of model states was based on expert opinion on the mechanism of the disease and the available evidence on the effects of CPAP in OSAHS patients. Pitolisant and CPAP differ on aspects relevant to the model structure. Pitolisant is an intervention primarily aimed at relieving the burden of one particular symptom of OSAHS, namely the daytime sleepiness. On the other hand, CPAP aims to improve the sleep of patients with OSAHS, thereby potentially intervening at a more fundamental disease level, resulting in effects on a multitude of symptoms and complications of OSAHS. As such, using a model developed for the evaluation of CPAP is not necessarily an appropriate model for the evaluation of pitolisant. In particular, no evidence is provided for the rationale to include an effect of pitolisant on cardiovascular event. On the other hand, it is likely that all the relevant consequences of the comparisons currently in question can be adequately assessed using this model (i.e. the model structure is more elaborate than necessary for the current evaluation). The ERG thus concludes that the model structure is appropriate for the current evaluation.

5.2.3 Population

The population considered in the base-case cost effectiveness analyses was adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy (such as CPAP), which is in line with the final scope of this appraisal. This population was divided into two patient populations investigated in two separate studies on pitolisant: Patients receiving CPAP who had residual EDS (HAROSA I study)[33] and patients refusing CPAP with EDS (HAROSA II study).[34] The patients' baseline characteristics included in the economic model as input parameters are provided in

Table 5.3.

Table 5.3: Baseline characteristics

	HAROSA I		HAROSA II	
	Pitolisant (n=183)	Placebo (n=61)	Pitolisant (n=201)	Placebo (n=67)
Age (years), Mean (SD)	53.8 (10.5)	51.0 (10.6)	51.9 (10.6)	52.1 (11.0)
Gender, male, n (%)	149 (81.4%)	53 (86.9%)	151 (75.1%)	51 (76.1%)
BMI, Mean (SD)	32.66 (5.22)	32.17 (4.28)	32.8 (4.6)	33.0 (4.3)
Professional activity, n (%)	117 (63.9%)	50 (82.0%)	139 (69.2%)	49 (73.1%)
Days of work per week, Mean (SD)	5.1 (0.5)	5.0 (0.6)	5.0 (0.5)	5.1 (0.2)
Medical history **Any significant** **CV**	 152 (83.1%) 111 (60.7%)	 46 (75.4%) 27 (44.3%)	 142 (70.6%) 110 (54.7%)	 47 (70.1%) 35 (52.2%)
Time since OSA diagnosis (months), Mean (SD)	44.84 (44.07)	48.99 (57.08)	12.1 (25.0)	11.5 (23.2)
ESS, Mean (SD)	14.9 (2.7)	14.6 (2.8)	15.7 (3.1)	15.7 (3.6)
Baseline Pichot Fatigue Scale score, Mean (SD)	13.2 (7.2)	11.4 (7.2)	13 (6.5)	11.1 (5.9)

Based on Table 5 of the CS[1]
BMI = body mass index; CS = company submission; CV = cardiovascular; OSA = obstructive sleep apnoea; ESS = Epworth Sleepiness Scale; SD = standard deviation

ERG comment: It is not clear to the ERG to what extent the trial populations are representative of the UK population eligible for pitolisant. At the same time, it is also unclear to what extent the estimate of the primary outcome (ESS) would change if the UK OSA population differed substantially regarding the baseline characteristics.

5.2.4 Interventions and comparators

The intervention considered in this appraisal was pitolisant with or without primary OSA therapy. Pitolisant is an oral drug that is started at a dose of 5 mg per day and may be up titrated to a maximum of 20 mg per day.

Established clinical management without pitolisant was the only comparator listed in the NICE final scope and included in the cost effectiveness model. Established clinical management included optimised CPAP and lifestyle measures (losing weight, stopping smoking and limiting alcohol consumption). Mandibular advancement devices (MAD) are a potential treatment option for OSA and can be used in patients with mild or moderate disease. MAD were included as a scenario analysis in patients with EDS who refuse CPAP with mild or moderate OSA.

ERG comment: In the clarification letter, the ERG asked the company to explain why MAD was not a comparator in the base case analysis. The company responded that MAD was not included as a comparator in the subgroup of patients receiving CPAP who had residual EDS because CPAP was the golden standard and CPAP and MAD cannot be used at the same time. However, the company did not provide an answer to why MAD was only included in a scenario analysis and not included in the base-case analysis of patients who refused CPAP.

5.2.5 Perspective, time horizon and discounting

The economic analyses took the perspective of the NHS and Personal Social Services (PSS) and adopted a 25-year time horizon. Total costs and QALYs were discounted at a rate of 3.5% per annum, as is recommended in the NICE Reference Case.

ERG comment: The company model had a 25-year horizon, which was deemed appropriate as the life expectancy at birth for men in the UK is around 80 years with the patients being on average 52 years (in the clinical trials). However, the life expectancy at 52 years is 84 years and the expected median survival in a general population cohort of 52 year old UK men is around 34 years. Therefore, it could be that a substantial part of the modelled cohort lives beyond the model horizon of 25 years, even though the mortality is higher in the modelled patient population compared to the general population. The ERG, therefore, requested the company to adjust the time horizon of the model to reflect a true lifetime time horizon. In their clarification response, the company provided an updated model that allows patients to live up to an age of 100 years.

5.2.6 Treatment effectiveness and extrapolation

As explained in Section 5.2.2 of this report, the company presented the results of two different comparisons. The two comparisons are based on data from two different clinical studies. The HAROSA I trial[33] was the most important source to inform input parameters in the comparison of pitolisant added to best supportive care compared to best supportive care only in OSAHS patients treated with CPAP with residual EDS. The HAROSA II trial[34] was the most important source to inform input parameters in the comparison of pitolisant added to best supportive care compared to best supportive care only or treatment with a MAD combined with best supportive care in OSAHS patients who refused treatment with CPAP. In both comparisons the population enrolled in the trial that informed input parameters matched the modelled population. Table 5.4 presents an overview of all transition probabilities used; the way they were derived is discussed in the sections below.

Table 5.4 Overview transition probabilities

	Comparison 1: patients treated with CPAP experiencing residual EDS		**Comparison 2: patients who refused CPAP**			**Source**
Transition probability	Pitolisant + CPAP + BSC	CPAP + BSC	Pitolisant + BSC	BSC	MAD	
OSAHS to CHD*	0.010 (0.001)	0.017 (0.007)	0.009 (0.001)	0.015 (0.007)	0.012 (0.003)	QRisk 3,[56] assumption
OSAHS to Stroke*	0.003 ($2.8*10^{-4}$)	0.007 (0.002)	0.002 ($2.0*10^{-4}$)	0.006 (0.001)	0.003 ($4.1*10^{-4}$)	QStroke,[57] assumption
OSAHS to RTA	0.004 (0.004)	0.030 (0.009)	0.004 (0.004)	0.034 (0.012)	0.012 (0.002)	Department for Transport, 2019[54]
RTA to OSAHS	1.000 (0.000)	1.000 (0.000)	1.000 (0.000)	1.000 (0.000)	1.000 (0.000)	
OSAHS post CHD to RTA post CHD	0.004 (0.004)	0.030 (0.009)	0.004 (0.004)	0034 (0.012)	0.012 (0.002)	Department for Transport, 2019[54]

	Comparison 1: patients treated with CPAP experiencing residual EDS		Comparison 2: patients who refused CPAP			Source
Transition probability	Pitolisant + CPAP + BSC	CPAP + BSC	Pitolisant + BSC	BSC	MAD	
RTA post CHD to OSAHS post CHD	1.000 (0.000)	1.000 (0.000)	1.000 (0.000)	1.000 (0.000)	1.000 (0.000)	
OSAHS post CHD to Stroke*	0.003 ($2.8*10^{-4}$)	0.007 (0.002)	0.002 ($2.0*10^{-4}$)	0.006 (0.001)	0.003 ($4.1*10^{-4}$)	QStroke,[57] assumption
OSHAH to Death	Population mortality UK					
OSAHS to fatal RTA (death)	$5.8*10^{-5}$ ($5.9*10^{-6}$)	$4.6*10^{-4}$ ($4.7*10^{-5}$)	$5.8*10^{-5}$ ($5.9*10^{-6}$)	$5.2*10^{-4}$ ($5.3*10^{-5}$)	$1.8*10^{-4}$ ($1.8*10^{-5}$)	Department for Transport, 2019[54], Computed from baseline
CHD to Fatal CVE (death)	0.102 (0.010)	0.102 (0.010)	0.102 (0.010)	0.102 (0.010)	0.102 (0.010)	Read et al., 2019[58]
Stroke to Fatal CVE (death)	0.264 (0.027)	0.264 (0.027)	0.264 (0.027)	0.264 (0.027)	0.264 (0.027)	Seminog et al. 2019[59]
OSAHS post CHD to Death	0.021 ($1.7*10^{-4}$)	0.021 ($1.7*10^{-4}$)	0.021 ($1.7*10^{-4}$)	0.021 ($1.7*10^{-4}$)	0.021 ($1.7*10^{-4}$)	Smolina et al., 2012[60]
OSAHS post CHD to fatal RTA (death)	$5.8*10^{-5}$ ($5.9*10^{-6}$)	$4.6*10^{-4}$ ($4.7*10^{-5}$)	$5.8*10^{-5}$ ($5.9*10^{-6}$)	$5.2*10^{-4}$ ($5.3*10^{-5}$)	$1.8*10^{-4}$ ($1.8*10^{-5}$)	Department for Transport, 2019[54], Computed from baseline
OSAHS post Stroke to Death	0.049 (0.001)	0.049 (0.001)	0.049 (0.001)	0.049 (0.001)	0.049 (0.001)	Crichton et al., 2016[61]

Numbers in parentheses are standard errors.

* These transition probabilities are dependent on age. Transition probabilities shown are those for the first cycle of the model (i.e. corresponding to age 54 in comparison 1 and age 52 in comparison 2.

CPAP: continuous positive airway pressure, EDS: excessive daytime sleepiness, BSC: best supportive care, MAD: mandibular advancement device, OSAHS: obstructive sleep apnoea/ hypopnoea syndrome, CHD: coronary heart disease, RTA: road traffic accident, CVE: cardiovascular event.

5.2.6.1 Effect of treatment on incidence of coronary heart disease and stroke

The effect of treatment on the incidence of CHD and stroke was not observed in the HAROSA I and II trials. The primary endpoint in these trials was the change in ESS over the study period. In both comparisons, the incidence of CHD and stroke in the comparators that included pitolisant was based on

a risk prediction made using the QRISK 3 risk equation.[56] The QRISK 3 risk calculator estimates the 10-year combined risk of experiencing a myocardial infarction or stroke, based on a number of risk factors. This 10-year risk was converted in a one-year risk, using the assumption that survival followed an exponential distribution. As CHD events and stroke are modelled separately, the one-year risk for stroke or transient ischaemic attack is estimated using the QStroke risk equation.[57] The annual probability of experiencing a CHD event was subsequently obtained by subtracting the stroke risk (as estimated using the QStroke) from the combined stroke and myocardial infarction risk (as estimated using the QRISK 3). The patient characteristics of the patients in the pitolisant arms of the HAROSA I and HAROSA II studies were used as the input data for the risk equations. For this, the mean value of each of the relevant parameters was used. Assumptions were made for those parameters in the risk equations for which no data was available from the HAROSA I and HAROSA II studies.

It was assumed that the difference in incidence of CHD and stroke between the pitolisant and non-pitolisant (i.e. best supportive care and best supportive care + MAD) treatment alternatives was proportional to the difference in change in ESS between these groups. Therefore, the incidence of CHD and stroke in the non-pitolisant treatment alternatives was based on the estimate of these incidences in the pitolisant treatment alternative, to which an increment or decrement was applied depending on the direction and magnitude of the difference in ESS score. The magnitude of this increment or decrement was based on the ratio of the effects of the alternative treatments (defined as the change in ESS score), multiplied by the odds ratio for CHD and stroke. The ESS treatment effect of CPAP versus best supportive care and was based on a previously published meta-analysis.[42] The ESS treatment effect of the pitolisant treatment alternatives was based on the observed treatment effects in the HAROSA I and HAROSA II studies.

ERG comment: No direct evidence is available on the effect of pitolisant on the incidence of cardiovascular events. The pathological mechanisms linking OSAHS and cardiovascular events is complex and not well understood.[62, 63] As a result, it is difficult to determine the likely effects of a given intervention on this relation. There is substantial evidence that CPAP treatment reduces cardiovascular risk.[64] However, CPAP and pitolisant are markedly different interventions, with different modes of action. CPAP can be considered to address the symptoms and complications of OSAHS more fundamentally by improving ventilation during sleep, thereby resulting in a broad effect in alleviating OSAHS symptoms and reducing risk for (cardiovascular) complications. As pitolisant is primarily aimed at alleviating a specific symptom, daytime sleepiness, it cannot be assumed without evidence that it has broader effects such as the reduction of cardiovascular risk. Additionally, CPAP treatment has been shown to reduce known cardiovascular risk factors, predominantly blood pressure.[42, 52] The HAROSA I and II studies have shown no change in cardiovascular risk factors (Table 18 and Table 19 of the CS).[1]

In the clarification letter, the ERG questioned the decision to include a treatment effect of pitolisant on CHD events and stroke in the model. The answer to this question did not provide a strong rationale for the inclusion of an effect of pitolisant on CHD events and stroke. The company acknowledged that the pathological relation between OSAHS and cardiovascular risk is a complex one by stating that "OSA appears to exert its CV effect via a range of different neurohumoral mechanisms, with the effect on blood pressure being one component of a complex autonomic interaction".[24] The company argued that not all of the reduction in cardiovascular risk resulting from a treatment will be through the reduction in blood pressure. Additionally, in the response to the clarification letter the company argued that the presence of EDS is an independent determinant of CV risk, even after the role of known CV risk factors (e.g. blood pressure) have been taken into account.[24] To support this statement, a prospective study was

cited that concluded that EDS (as defined by an ESS score of 11 or higher) indeed was likely to be an independent prognostic factor for major cardiac events.[65]

The ERG concludes that there is neither direct nor indirect evidence that treatment with pitolisant has an effect on the incidence of CHD events and stroke. The company provided no evidence or rationale based on well understood biological mechanisms to substantiate the assumption that pitolisant has an effect on the incidence of CHD events and stroke. The company provided reasonable evidence that EDS is an independent prognostic factor for cardiovascular risk but did not provide any evidence or rationale that this is a causal relation and that the direction of causality is such that cardiovascular risk is reduced when EDS is treated. The substantiation of the assumptions made by the company are thus deemed insufficient to warrant the inclusion of an effect of pitolisant on the incidence of CHD events and stroke. Therefore, the ERG base-case will not include such an effect. Rather, these effects are explored in a scenario analysis.

The incidence of CHD events and stroke for patients treated with pitolisant was estimated using the QRISK 3 and QStroke risk equations. These risk equations do not include OSAHS as a risk factor. As such, it is implicitly assumed that OSAHS patients treated with pitolisant have the same cardiovascular risk as non-OSAHS patients with the same risk factor profile. Given the complex nature of the pathological relation between OSAHS and cardiovascular risk, the acceptance of this assumption would require further substantiation, which was not provided.

The first submission of the model made use of the Framingham risk score to estimate the risk of CHD events and stroke.[66] In that version of the model, the QRISK 3 and QStroke risk equations were used in a scenario analysis. As part of the changes made to the model by the company in response to the clarification letter, the QRISK 3 and QStroke equations were now used for the base-case, and the Framingham risk score is available as a scenario analysis. The reason for change by the company was that the Framingham risk score is based on data from the US, whereas the QRISK 3 and QStroke risk equations are based on UK data and therefore deemed more appropriate. The ERG concurs with this assessment. In addition, the company added the option to use age-dependent risks for CHD events and stroke. In the original version of the model, these risks were the same regardless of the age of the patient, despite age being one of the predictors in the risk equations. At the request of the ERG, the company adapted the model to account for increasing risk with age.

5.2.6.2 Treatment effect on the occurrence of road traffic accidents

The effect of pitolisant on the risk to be involved in a motor traffic accident was based on indirect evidence. In estimating this treatment effect, a distinction was made between non-fatal RTAs and fatal RTAs.

It was assumed that the probability for an individual treated with pitolisant to be involved in a fatal RTA or a non-fatal RTA is the same as for a member of the general public in Great Britain. These probabilities were based on an annual report from the Department of Transport of the UK, which presented data on the total number of slight, severe, and fatal RTAs, as well as the gender distribution in each category of RTA.[54] The gender specific probability of being involved in an RTA was based on the total number of RTAs divided by the number of active driving licence holders in Great Britain. The probability of being involved in an RTA in each of the two comparisons was then obtained by multiplying the weighted average of the gender specific probability of being involved in an RTA with gender distribution in the HAROSA I and HAROSA II studies.

To derive estimates for the probability of individuals not treated with pitolisant to be involved in a non-fatal RTA it was assumed that this probability would be independently predicted by the ESS score. The ratio between the treatment effect of CPAP versus best supportive care and pitolisant and CPAP versus CPAP was multiplied with the odds ratio of the effect of CPAP on the probability to be involved in an RTA. This was taken to be the effect size of pitolisant + CPAP versus CPAP (in the comparison of patients treated with CPAP). As the probability of patients treated with pitolisant and CPAP was assumed to be that of the general public, the inverse of this odds ratio was applied to the baseline probability of being involved in a RTA to obtain the estimate for patients treated with CPAP to be involved in an RTA. The same calculations were done for the treatment alternatives in the other comparison (i.e. those in the pitolisant treatment alternative were assumed to have the same probability of being involved in an RTA as the general population and this probability was increased by an odds ratio based on the difference in ESS score of the different treatment alternatives as observed in the HAROSA II study).

ERG comment: No direct effect of pitolisant on the probability to be involved in an RTA was available. An indirect effect estimation was conducted using two key assumptions: 1) that the change in probability to be involved in an RTA is proportional to the change in ESS score, and 2) that patients treated with pitolisant have the same probability of being involves in an RTA as the general public. Both assumptions were not well substantiated in the company submission. The ERG finds it intuitively plausible that the increased risk for RTAs in OSAHS patients is predominantly due to sleepiness/lack of attention while operating a vehicle. As such, the ERG accepted the assumption that the ESS sore is a satisfactory predictor of this probability. In both the HAROSA I and HAROSA II study, the mean ESS score in the pitolisant arms after 12 weeks was similar. It therefore made sense to assign the same probability to be involved in an RTA to the pitolisant treatment alternatives in both comparisons. However, the ESS score after 12 weeks was just below the upper end of the range defined as 'normal' (mean ESS pitolisant arm after 12 weeks, HAROSA I: 9.42, HAROSA II 9.4; ESS normal range: 0-10). As such, patients treated with pitolisant have a higher ESS than the general population, and presumably a higher probability to be involved in an accident. When the open label period is taken into account, the ESS of patients with pitolisant is reduced further to levels closer to what is expected in the general population. The approach taken by the company might result in an underestimation of the risk to be involved in an RTA for all treatment alternatives. However, as the treatment effects in the model are proportional, this will also result in an underestimation of treatment effect of pitolisant in absolute terms. The ERG thus considers this a conservative approach.

5.2.6.3 Duration of treatment effect

As described in the previous paragraphs, the treatment effect of pitolisant in the model was based on the difference in ESS score as observed at the end of the HAROSA I and HAROSA II studies. The follow-up period in both studies was 52 weeks (12 weeks double-blind and an additional 40 weeks open label). In the model, patients are expected to take pitolisant for the remainder of their lifetime. The treatment effect is also assumed to persist for as long as patients take the medication, i.e. until the end of their life.

ERG comment: As the model has a lifetime horizon (simulation ends when the cohort reaches 100 years), the treatment effects are assumed to persist for a maximum of 47 years. This is a considerable extrapolation from the one-year follow-up in the HRAOSA trials. No rationale was provided for the persistence of the treatment effect for this period. The trial results demonstrated that patients on pitolisant reported the lowest ESS at the end of the one-year follow-up. As such, the trial data does not

indicate that the treatment effect diminished over a short time horizon. Nonetheless, there was also no certainty that the treatment effect will remain over the patient's lifetime.

5.2.6.4 Mortality

The mortality for patients in the OSAHS state was based on all-cause mortality in the general population of the UK (2017-2018 UK lifetables).[67] This probability was reduced with the cause specific hazard of CHD and stroke.

The probability to transition from the CHD event state to the death state was taken from a publication reporting the case fatality of acute myocardial infarction and CHD death in Scotland.[58] The analysis was based on data from the Scottish Morbidity Records database and Scottish national death records. This publication provided the proportion of patients that died within 30 days after hospitalisation due to acute myocardial infarction (AMI). The probability to transition from the stroke event state to the death state was taken from a publication reporting the case fatality of stroke in England.[59] The analysis in this publication was based on data from the health episode statistics database (NHS Digital) and the National Mortality Statistics Database (Office for National Statistics). The reported figure represented the 30-day case fatality after stroke in England in 2010.

ERG comment: No direct evidence of the effect of pitolisant on mortality was available. No direct treatment effect of pitolisant on mortality was included in the analysis. Rather, pitolisant has an indirect effect on mortality by reducing the probability of experiencing events which are associated with excess mortality (i.e. CHD, stroke and RTA). Given the available evidence, the ERG agrees with this approach.

It was assumed that OSAHS patients that had not experienced a CHD event or stroke had a mortality risk equal to the general population. The model accounts for an increased cause-specific CHD and stroke mortality in OSHAHS patients. However, even when accounting for these specific causes, it is likely that there was an additional excess mortality in OSAHS patients compared to the general population. For example, the prevalence of obesity and type 2 diabetes is higher in OSAHS patients compared to the general population. These conditions are known to be associated with an increased mortality risk that is larger than only the increased mortality caused by a higher risk for CHD and stroke. As such, the mortality risk for OSAHS patients that had not experienced a CHD event or stroke was likely underestimated. As pitolisant has an impact on the survival of the modelled cohort by reducing the incidence of CHD and stroke, the underestimation of the mortality risk in the OSAHS state is likely to lead to an overestimation of the effect of pitolisant on survival.

The all-cause mortality for the OSAHS patients who refused treatment with CPAP appeared to have a two-year lag compared to the OSAHS patients treated with CPAP with residual EDS. As the ERG could not find a plausible explanation for this, this was corrected in the model.

The mortality in the CVD and stroke event states were both based on published figures for the 30-day mortalities of these events. As the cycle length of the model was one year, this led to the implicit assumption that those individuals that survive the first 30 days after experiencing the event have a probability of 0 to die the remainder of the year. This is unlikely to be realistic, as at least the background mortality (if not an increased mortality) is expected in the period from 30 days to one year after experiencing a CVD or stroke. The underestimation of the probability to die in the CHD and stroke event states will lead to an underestimation of the effect of pitolisant on survival.

5.2.7 Adverse events

No adverse events from the use of pitolisant were included in the model. This decision was made based on the lack of observed adverse events in the HAROSA I and HAROSA II trials.

The possibility of adverse events resulting from the use of MADs is acknowledged in the company submission. However, these were also not incorporated into the model due to a lack of evidence and the assumption that the cost and utility impact of these would be negligible.

ERG comment: Overview of the observed adverse events in the HAROSA I study shows that 47% of patients in the pitolisant arm and 20% of patients in the placebo arm experienced any treatment emergent adverse event. In the HAROSA II study this was 29.5% and 25.4%, respectively. Adverse events that are likely to be linked to the intervention (adverse events of special interest) were also observed. For example, in the HAROSA I study 9.3% of patients in the pitolisant arm reported insomnia, compared to 3.3% in the placebo arm. In the HAROSA II study this was 5.5% and 3.0%, respectively. The ERG does therefore not agree with the company that the reporting of adverse events in the HAROSA studies warranted the omission of adverse events in the model on the basis of the frequency of their occurrence. However, the ERG considers it likely that the costs and disutility associated with these adverse events are very small compared to all other costs and disutilities.

5.2.8 Health-related quality of life

5.2.8.1 Identification and selection of utility values

EQ-5D assessments were carried out as part of the HAROSA I and HAROSA II studies. However, the company claimed that they could not use the study-specific data to populate the economic model. Instead, the company used a mapping algorithm to populate the utility values of the health states in the model. This mapping approach reflects the approach adopted in previous NICE submissions, specifically TA139. In the mapping algorithm, the mean change in ESS score is mapped to utility change. There were two mapping algorithms available that were already used in published economic models (Table 5.5).[52] [42]

McDaid et al.[52] fitted an ordinary least squares (OLS) regression model to predict absolute utility scores from absolute ESS, controlling for baseline utility and baseline ESS in patients with CPAP for OSA. They used three data sets of individual patient data; two that measured ESS and SF-36 profile[52, 68] and one that measured ESS, SF-36 profile and EQ-5D.[69] Consequently, the OLS model for SF-6D was based on 294 patients, while the model for EQ-5D was based on 94 patients. The assumption of OLS regression that the error terms are normally distributed was assessed using residual plots. The assumption was reasonable for the SF-6D, but the residuals from the regression of the EQ-5D on ESS deviated somewhat from a normal distribution. However, a generalised linear model with an alternative error distribution did not improve the fit on the basis of the Akaike Information Criterion and so the OLS model was used for EQ-5D as well.

Sharples et al.[42] estimated a mapping algorithm with a linear mixed-effects regression model using data from the 'Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea' (TOMADO) trial including ESS, SF-36 and EQ-5D-3L measurements in people with mild to moderate obstructive sleep apnoea hypopnoea. The SF-36 model was based on 402 data points and the EQ-5D model on 404 data points (both including repeated measurements). Participants were included as a random effect. In line with the findings of McDaid et al.,[52] the residuals appeared to be reasonably close to normality for SF-6D, but less so for the EQ-5D-3L.

Table 5.5: Regression coefficient mapping algorithms McDaid et al. and Sharples et al.

EQ-5D-3L	**McDaid et al. (n=94)**	**Sharples et al. (n=404)**
Variable	**Coefficient (SE)**	**Coefficient (SE)**
ESS	-0.0097 (0.0039)	-0.0061 (0.0020)
Baseline ESS	0.0030 (0.0034)	0.0139 (0.0145)
Baseline utility	0.6288 (0.1346)	
Constant	0.8925 (0.0286)	0.9094 (0.0220)
SF-36	**McDaid et al. (n=294)**	**Sharples et al. (n=402)**
Variable	**Coefficient (SE)**	**Coefficient (SE)**
ESS	-0.0095 (0.0014)	-0.0067 (0.0011)
Baseline ESS	0.0050 (0.0012)	-0.0020 (0.0079)
Baseline utility	0.5589 (0.0535)	
Constant	0.8068 (0.0115)	0.7529 (0.0116)

ERG comment: The NICE reference case states that the source of data for the measurement of HRQoL should be obtained through direct reporting by patients and valued in a representative sample of the UK general population. Instead of using the data derived from the EQ-5D assessments that were carried out as part of the HAROSA I and HAROSA II studies to fulfil the requirements of the NICE reference case, the company used a mapping algorithm to populate the utility values of the health states in the model.

The reason that the company preferred the mapping algorithm over the EQ-5D data is that evidence showed that generic instruments to measure QoL (including EQ-5D) do not capture the true benefits of treatment in patients with EDS because they have not been specifically designed to assess aspects of QoL in patients with OSA or EDS and sleep is not included as a specific dimension.[29 70 71] The company concluded that the true benefits of treatment were unlikely to be captured when using the EQ-5D results. However, it is possible that a modest decrease in excessive sleepiness truly does not impact the health-related quality of life importantly. But even if the ERG agreed to some extent that generic instruments may not capture the entire benefit of treatment in patients with EDS, they would have preferred the use EQ-5D utilities in the base-case or scenario analysis to be able to compare the cost effectiveness of pitolisant with treatments for other diseases and to assure adherence to the NICE reference case. Therefore, the ERG requested a scenario analysis with utility values based on the EQ-5D assessment in the clarification letter. This was not provided by the company in the clarification response because, as they stated, the underlying EQ-5D data was not available to them. However, given the evidence presented in the CSR (i.e. EQ-5D Descriptive System Total Score, EQ-5D VAS and EQ-5D Z-score), the ERG would argue that it should be possible to request the underlying individual patient data and convert the EQ-5D responses to utilities using the UK tariff.

Disregarding the ERG's preference for using EQ-5D data assessments instead of a mapping algorithm, the ERG agrees with the choice of the mapping algorithm of McDaid et al.in the company model.[52] The population in McDaid et al. was the best match for those eligible for treatment with pitolisant who also received CPAP therapy in contrast to the population used to estimate the algorithm of Sharples et al. in which patients on CPAP were excluded.[42] Nevertheless, the ERG requested a scenario analysis using the mapping algorithm of Sharples et al., which was provided by the company in the clarification response.

5.2.8.2 Health event disutilities

The model included utility decrements associated with CHD, stroke, RTA, and age.

In their original submission, the company provided a utility decrement for CHD (-0.064) based on 284 patients with heart failure.[72] However, according to the Framingham risk score that was used for the clinical input of CHD in the original company base case, non-fatal CHD includes angina pectoris, coronary insufficiency and myocardial infarction, and is therefore broader than heart failure alone. For that reason, the ERG suggested in the clarification letter to use the utility decrements for angina pectoris (-0.0412) and acute myocardial infarction (-0.0409) that were also reported by Sullivan et al.[72] In the clarification response, the company decided to use the QRISK3 and QStroke predictive algorithms in the revised company base case as discussed earlier. The CHD events included in the QRisk3 score are myocardial infarction and angina. Based on the number of events on which the QRisk3 is based these events are distributed as 34% MI:66% angina. These proportions were applied to the diagnosis-specific disutilities quoted in Sullivan et al. yielding a composite decrement of -0.0411. This has been applied as the utility decrement for CHD in the revised company base case.

The utility decrement for stroke (-0.052) was based on 340 patients with CVA.[72]

For RTAs, the company assumed that patients would spend the year of the accident in a health state valued by 0.62. This value was based on EQ-5D measures from the Health Outcomes Data Repository (HODaR) [73], as reported by Jenkinson et al.[69]

In addition, a constant utility decrement of -0.0007 per year to adjust EQ-5D utility values for age based on Sullivan et al. was applied in a scenario analysis.[72]

ERG comment: The ERG agrees with the disutility of stroke and the adapted disutility for CHD after clarification.

The reference of the utility in the RTA health state is unclear. As stated, the EQ-5D measures from the Health Outcomes Data Repository (HODaR)[73] were used, as reported by Jenkinson et al.[69] It is unclear why the company referred to the study of Jenkinson et al. as this study was published years before the publication of HODaR EQ-5D outcomes and there was no reference to the Health Outcomes Data Repository. McDaid et al.[52] also based the utility associated with experiencing an RTA on EQ-5D measures from the HODaR. They explained that this utility was based on EQ-5D data for 56 individuals six weeks after their inpatient episode (at Cardiff Hospital, UK) for injuries experienced from an RTA (i.e. a traffic accident as a motorcycle rider, an occupant of a three-wheel motor vehicle, a car occupant or an occupant of a pick-up truck or a van (V20 to V59, ICD10 codes)).[52] However, this utility of 0.62 assumed for RTAs was not reported in the HODaR publication that was referenced by McDaid et al. and the company.

Based on the explanation provided in McDaid et al.[52] the utility of 0.62 seems reasonable for severe RTAs (including broken neck or back, severe head and chest injuries, fractured limbs etc.). However, in the model this utility is also applied to patients who experienced slight RTAs (i.e. shock, bruising, sprains and strains, shallow cuts, lacerations, abrasions, and whiplash or neck pain). The ERG has strong reservations about these slight injuries being associated with such a low utility, especially considering that in the model the utility for patients who have had a stroke is about 0.77. However, there is no data of the utility after slight RTAs. Therefore, in the ERG base-case, these patients are assumed to experience a disutility equal to the most severe other event in the model, namely stroke (i.e. disutility of -0.052).

It is standard practice within NICE appraisals to adjust utilities over the lifetime horizon of the model to account for the decline in utilities due to ageing. However, this was only included in a scenario analysis and not in the company base-case.

The study used by the company to estimate the yearly decline in utility was a US study that aimed to develop EQ-5D index scores for chronic diseases. The study also reported average utility scores per 10-year age bands. However, there is a good UK alternative for age-adjusted utilities, i.e. a study by Ara and Brazier 2010,[74] who developed an equation which estimates the mean utility of the UK general population, adjusted for age and gender. The equation obtained from Ara and Brazier is as follows:

*EQ-5D = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2*

When using the Ara and Brazier equation, the decline in utility due to ageing increases as people age.[74] For example, at the age of 55 years, the loss of utility from ageing one year is approximately 0.004, while at the age of 70 years it is 0.005 and at the age of 80 years it is 0.006. These disutilities are considerably larger than the annual disutility of -0.0007 applied in a scenario analysis provided by the company. However, the results of the US study,[72] showed a decline of around 0.03 per 10 years, so the ERG is not sure how the company arrived at a decrement of 0.007 per 10 years (0.0007*10). In the ERG base-case the equation of Ara and Brazier 2010 is used to account for the decline in utility due to ageing.

5.2.8.3 Utility values used in the model

Table 5.6 shows the utility values used in the company base case analysis.

Table 5.6: Utility scores used in the base case analysis

Utility	Mean	Source
OSAHS BSC – baseline (HAROSA I / HAROSA II)	Baseline ESS x -0.0097 + 0.8925 = 0.777 / 0.775	Estimated from prediction equation (Table 5.1)
OSAHS treated with pitolisant – change from BSC (HAROSA I / HAROSA II)	$\Delta ESS_{Pitolisant-BSC}$ x -0.0097 = 0.803 / 0.800	Estimated from prediction equation (Table 5.1)
OSAHS treated with MAD – change from pitolisant (HAROSA II), used in scenario analysis	$\Delta ESS_{Pitolisant-MAD}$ x -0.0097 = 0.789	Estimated from prediction equation (Table 5.1)
CHD (absolute decrement)	-0.041	Sullivan et al, 2006[72]
Stroke (absolute decrement)	-0.052	Sullivan et al, 2006[72]
Non-fatal RTA	0.62	Currie et al, 2005[73]
Age (annual decrement)	-0.0007	Sullivan et al, 2006[72]

The baseline utility for the OSAHS health state in the BSC arm of the economic model was estimated by converting the mean ESS score of patients in the BSC treatment group to utilities with the mapping algorithm of McDaid et al.[52] described above in Section 5.2.8.1 of this report. In their submission, the company calculated the baseline utility with the following formula:

Utility OSAHS BSC = Constant + Baseline ESS * ESS coefficient

The baseline utility for the OSAHS health state in the pitolisant arm of the economic model was estimated by adjusting the utility in the OSAHS health state in the BSC arm for the difference in ESS between BSC and pitolisant multiplied with the ESS coefficient.

Utility OSAHS pitolisant = Utility OSAHS BSC + Effect size pitolisant ESS * ESS coefficient

In both arms, the utility values for the post-CHD and post-stroke health states were calculated by subtracting the utility decrement from the OSAHS utility value.

In the company submission, the 95% confidence interval of the utility scores only included the uncertainty of the regression coefficients of the mapping algorithm. In the clarification letter, the ERG asked the company to also include the uncertainty of baseline ESS and ESS effect size in the HAROSA I and HAROSA II studies to correctly capture this uncertainty in the utility value parameters.

ERG comment: The ERG would have expected that the baseline ESS was multiplied with the coefficient for baseline ESS instead of the coefficient for change in ESS. In the clarification response, the company explained that this coefficient was not used as McDaid et al. reported that a test was performed to see if there was evidence for a change in relationship between different levels of baseline ESS (i.e. a change in the slope of the regression line for particular cut-off values of ESS) but there was no evidence to support such a sub-group effect.[52] It was not clear to which test the company refers, but possibly to the large p-value of the baseline ESS coefficient. Firstly, this would not be a reason to exclude the variable form the OLS. Secondly, it is not correct to exclude the coefficient from the mapping algorithm without estimating a new model excluding the baseline ESS as a variable. Furthermore, baseline utility is included as a variable in the OLS, but this coefficient is also not used in the mapping algorithm. Hence, it is not clear to the ERG if the mapping formula has been used as intended by the developers of the mapping algorithm.

5.2.9 Resources and costs

The costs included in the economic analysis consist of the drug acquisition costs for pitolisant, and the health state costs relating to coronary heart disease (CHD), stroke, road traffic accidents (RTAs), and death. Health state costs were sourced from relevant literature, and updated to 2018/2019 using the NHS cost inflation index (NHSCII) from the Personal Social Services Research Unit (PSSRU) 2019.[75]

5.2.9.1 Intervention and comparator costs

The intervention costs included in the economic analysis consist of the drug acquisition costs for pitolisant. All patients were assumed to receive best supportive care (BSC), in line with HAROSA I and HAROSA II where each patient received BSC in addition to their randomised treatment (i.e. in combination with CPAP in HAROSA I or as stand-alone treatment in HAROSA II). Hence, no incremental costs were assumed for BSC in the economic analysis.

Drug acquisition costs

The drug acquisition costs for pitolisant are based on the company's proposed list price of [redacted]. Pitolisant is available in tablets of 5 mg and 20 mg, to which the same price applies. Patients who receive pitolisant in a dose of 10 mg daily are assumed to use two tablets of 5 mg (this was amended by the company in response to clarification questions). Dosage assumptions were based on the proportions of patients receiving each dose in the HAROSA I and HAROSA II trials. In response to a request by the ERG during the clarification phase drug wastage costs were included by the company only for patients who were down-titrated from the maximal dose of 20 mg to a lower dose in HAROSA I and HAROSA II.

Down-titration could occur either in the first 12 weeks of treatment or between 12 and 52 weeks of treatment with pitolisant. The number of patients incurring wastage costs due to down-titration from the 20 mg dose was based on the difference between the proportions of patients receiving the maximal dose of 20 mg and patients receiving a stable dose of 20 mg. Based on the assumptions that down-titration is equally likely to occur at any stage of pack usage, the company assumed an average wastage of 15 tablets. The proportions of patients receiving pitolisant in a stable dosage following titration at treatment initiation in HAROSA I and HAROSA II are shown for each dose in Table 5.7, and the proportions of patients that were used to calculate potential wastage costs are shown in Table 5.8. Table 5.9 presents the resulting yearly costs separately for year 1 and subsequent years.

Table 5.7: Proportions of patients with stable dosage in HAROSA I and HAROSA II

Pitolisant dosage	HAROSA I		HAROSA II	
	Weeks 1 -12	Week 12+	Weeks 1 -12	Week 12+
20 mg	70.3%	77.4%	75.4%	76.3%
10 mg	21.1%	17.3%	15.7%	12.2%
5 mg	8.6%	5.3%	8.9%	11.5%

Based on Table 11 in the company's response to clarification questions.[24]
mg = milligram.

Table 5.8: Proportions of patients that incur potential wastage costs in HAROSA I and HAROSA II

	% with maximum dose = 20 mg	% with stable dose = 20 mg	Difference
HAROSA I			
1 - 12 weeks	79.8%	70.3%	9.6%
12 - 52 weeks	87.4%	77.4%	10.0%
HAROSA II			
1 - 12 weeks	82.5%	75.4%	7.1%
12 - 52 weeks	81.8%	76.3%	5.5%

Based on Table 12 in the company's response to clarification questions.[24]
mg = milligram.

Table 5.9: Annual and 30-day acquisition costs for pitolisant

	HAROSA I	HAROSA II
Year 1		
Annual cost	[redacted]	[redacted]
30-day cost	[redacted]	[redacted]
Year 2 and onwards		
Annual cost	[redacted]	[redacted]
30-day cost	[redacted]	[redacted]

Based on Table 14 in the company's response to clarification questions.[24]

Mandibular advancement device costs

Three types of mandibular advancement devices (MADs) exist: thermoplastic (i.e. self-fitted), semi-bespoke (i.e. patient-administered dental impression sent to manufacturer), and bespoke (i.e. in-clinic

dental assessment, followed by specialist manufacture) devices. The company assumed that patients treated in NHS Sleep Clinics are provided the bespoke type of MAD. Although the CS states that this was based on input from the company's clinical advisers, no reference was provided for this. The company followed the approach by Sharples et al.,[42] to estimate the cost of a MAD based on the assumption that it requires seven hours for a grade 6-8 technician in an NHS maxillofacial laboratory to manufacture a MAD from a patient's dental mould. These hours were costed using the lowest estimate for the cost per hour of a band 8d professional (£112) from the PSSRU 2019.[75] A lifespan of 18 months was assumed for a MAD. The total annual cost estimation for a bespoke MAD is detailed in Table 5.10. The results of the scenario analysis comparing pitolisant with MADs are provided in Section 6.2.3 of this report.

Table 5.10: Mandibular advancement device costs

Cost item	Unit cost	Total cost	Source
Assessment and measurement: Maxillofacial consultant – first appointment	£147	£147	NHS Tariff 2019 - 2020; Outpatient attendance prices [76]
Manufacturing cost 7 hours band 8d	£112	£784	PSSRU 2019[75]
Total device cost		£931	
Follow-up (x1 per year) Maxillofacial consultant – follow-up appointment	£66	£66	NHS Tariff 2019 - 2020; Outpatient attendance prices [76]
Annualised cost of MAD assuming an 18-month device lifespan		**£687**	Total device cost x 12/18 + Follow-up cost

Based on Table 36 in the CS.[1]
CS = company submission; MAD = mandibular advancement device; NHS = National Health Service; PSSRU = Personal Social Services Research Unit.

5.2.9.2 Health state costs

The model includes health states relating to coronary heart disease (CHD), stroke, road traffic accidents (RTAs), and death. The sources used to inform these health state costs are detailed below.

Coronary heart disease costs

The costs of a CHD event were included as the annual costs in the year that the CHD event occurred (i.e. in the CHD event health state), followed by the annual costs related to the event in subsequent years (i.e. in the post-CHD event health state). The costs inputs for the CHD event and post-CHD event health states were sourced from Walker et al.,[53] and are based on data from UK patients with CHD collected in 2001-2010. These costs pertain to the costs due to stable angina and myocardial infarction and are shown in Table 5.11.

Table 5.11: CHD-related costs due to stable angina and myocardial infarction

	Cost*
Stable angina	
Per 90 days	£200
Annual cost	£800
Myocardial infarction	
First 90 days	£5,192
Second 90 days	£1,300
Third 90 days	£658
Fourth 90 days	£716
Subsequent 90 days (Year 2 and onwards)	£529
Annual cost in first year	£7,866
Annual cost in subsequent years (Year 2 and onwards)	£2,116

*CHD-related costs were sourced from Walker et al.,[53] and updated to 2018/2019 using the NHSCII from PSSRU 2019.[75]
Based on Table 14 in the company's response to clarification questions.[24]
CHD = coronary heart disease; NHSCII = NHS cost inflation index; PSSRU = Personal Social Services Research Unit.

It is assumed that 64% of CHD-related costs is due to stable angina and 36% is due to myocardial infarction, based on the numbers of events that are reported in the supporting publication for the QRisk 3 score.[77] Therefore, the CHD-related medical costs (i.e. for stable angina and myocardial infarction combined) are £3,344 in the first year and £1,274 in the second year.

When reviewing the literature source used to inform the costs of stroke the ERG noted that in the article by Xu et al.,[78] in addition to medical costs, also the costs for social care were substantial. Therefore, the ERG requested during the clarification phase for the company to amend the model with an option to include the costs of social care in the economic analysis. In addition to this, the company also included the costs for social care in the CHD health states. In absence of direct evidence for social care costs due to CHD, the company calculated which proportion of social care costs is represented in the total of health and social care costs in stroke, and applied this to the health care costs of CHD to obtain an estimate of the social care costs of CHD. The ERG used these additional inputs for social care costs in a scenario analysis.

Stroke costs

The costs of a stroke event were included as the annual costs in the year that the stroke event occurred (i.e. in the stroke event health state), followed by the annual costs related to the event in subsequent years (i.e. in the post-stroke event health state). The cost inputs for the stroke event and post-stroke event health states were sourced from Xu et al.,[78] and are based on the Sentinel Stroke National Audit Programme (SSNAP) in England, Wales and Northern Ireland in 2015-2016.

Table 5.12: Cost estimates per health state or event

Parameters	Mean cost	Source
Cost of fatal CV events	£3,813	Briggs et al, 2007
Year 1 cost of CHD	£3,344	Walker[78]
Ongoing cost of CHD (years 2-5)	£1,274	Walker[78]
Year 1 social care cost of CHD	£2,240	Calculated
Year 2+ social care cost of CHD	£5,350	Calculated
Year 1 cost of stroke	£14,573	Xu et al, 2017[78]
Ongoing cost of stroke (years 2-5)	£1,225	Xu et al, 2017[78]
Year 1 social care cost of stroke	£9,731	Xu et al, 2017[78]
Year 2+ social care cost of stroke	£5,176	Xu et al, 2017[78]
Fatal RTA per patient	£6,289	Department of Transport[54]
Serious RTA	£17,323	Department of Transport[54]
Slight RTA	£1,494	Department of Transport[54]
Based on Table 37 of the CS[1] and the electronic model after the clarification letter RTA = road traffic accident; CHD = coronary heart disease; CV = cardiovascular		

Road traffic accidents costs

The costs of fatal, serious and slight road traffic accidents (RTAs) were sourced from the Department of Transport report Reported Road Casualties Great Britain: 2018 Annual Report.[54] Subsequently, data on the proportions of patients in both HAROSA I and HAROSA II who had severe and slight RTAs was combined with the costs of serious and slight RTAs to calculate a weighted average cost of a non-fatal RTA for each trial population.

5.2.9.3 Adverse events costs

No costs for adverse events (AEs) were included in the economic analysis.

ERG comment: In general, the ERG considers the assumptions regarding resource use and costs appropriate. During the clarification phase, the company updated the assumptions regarding the costs of CHD. Whereas in the original CS, these costs were based on a publication by Briggs et al.,[76], the company provided the costs as estimated by Walker et al.[53] in the updated version of the model. However, upon reviewing the updated model the ERG noted that the calculations in the model were still based on the CHD cost estimates from Briggs et al., instead of those from Walker et al. Furthermore, the company provided the option to include social care costs in the economic analysis at the request of the ERG during the clarification phase. Although the ERG only requested this to be done for the costs of stroke, the company chose to also implement the option to include social care costs for CHD (by applying the same relative proportion of social costs to total health care costs for CHD as for stroke). Also, the company chose to only include social care costs in the years subsequent to the year that a stroke or CHD event occurred. The social care costs that were incurred for patients in the same year that the stroke or CHD event occurred were therefore not included by the company. The ERG made use of the option to include social care costs for stroke and CHD in a scenario analysis, see Section 7.2.2.2 of this report.

6. COST EFFECTIVENESS RESULTS

6.1 Company's cost effectiveness results

The company's base-case cost effectiveness results from the original CS[1] are shown in Table 6.1 for patients with residual EDS despite CPAP (based on HAROSA I), and in Table 6.2 for patients with EDS due to OSA who refuse CPAP (based on HAROSA II). These results indicated that the addition of pitolisant to CPAP + BSC leads to higher costs as well as a higher number of QALYs gained, with an ICER of £17,446 per QALY gained for patients with residual EDS despite CPAP, and an ICER of £16,896 per QALY gained for patients with EDS due to OSA who refuse CPAP.

Table 6.1: Company's base-case cost effectiveness results from the original CS: patients with residual EDS despite CPAP (based on HAROSA I)

Technologies	Total costs	Total LYs	Total QALYs	Incr. costs	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Pitolisant + CPAP + BSC	£26,675	14.81	11.77	£16,932	0.62	0.97	£17,446
CPAP + BSC	£9,743	14.19	10.80				

Source: the electronic model from the original CS.[1]
BSC = best supportive care; CPAP = continuous positive airway pressure; CS = company submission; EDS = excessive daytime sleepiness; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYs = life years; QALYs = quality-adjusted life years.

Table 6.2: Company's base-case cost effectiveness results from the original CS: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)

Technologies	Total costs	Total LYs	Total QALYs	Incr. costs	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Pitolisant + CPAP + BSC	£26,684	14.92	11.86	£17,149	0.63	1.01	£16,896
CPAP + BSC	£9,535	14.29	10.85				

Source: the electronic model from the original CS.[1]
BSC = best supportive care; CPAP = continuous positive airway pressure; CS = company submission; EDS = excessive daytime sleepiness; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYs = life years; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years.

The company provided an updated version of the electronic model in response to the ERG's clarification questions. The results of this updated model are shown in Table 6.3 for patients with residual EDS despite CPAP (based on HAROSA I), and in Table 6.4 for patients with EDS due to OSA who refuse CPAP (based on HAROSA II). These results indicated that the addition of pitolisant to CPAP + BSC leads to higher costs as well as a higher number of QALYs gained, with an ICER of £29,698 per QALY gained for patients with residual EDS despite CPAP, and an ICER of £29,803 per QALY gained for patients with EDS due to OSA who refuse CPAP.

Table 6.3: Company's base-case cost effectiveness results from the updated CS: patients with residual EDS despite CPAP (based on HAROSA I)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pitolisant + CPAP + BSC	£32,182	12.48	£21,061	0.71	£29,698
CPAP + BSC	£11,121	11.77			

Source: Table 22 in the response to the clarification questions.[24]
BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.

Table 6.4: Company's base-case cost effectiveness results from the updated CS: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pitolisant + BSC	£30,923	12.57	£20,601	0.69	£29,803
BSC	£10,322	11.87			

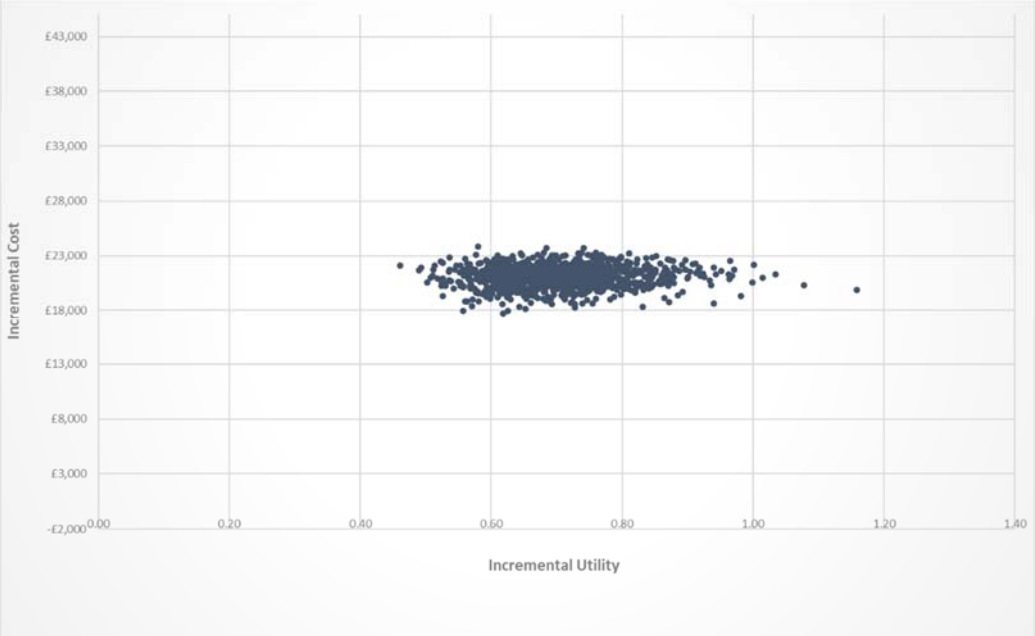
Source: Table 23 in the response to the clarification questions.[24]
BSC = best supportive care; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; ICER = incremental cost effectiveness ratio; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years.

6.2 Company's sensitivity analyses

6.2.1 Probabilistic sensitivity analysis

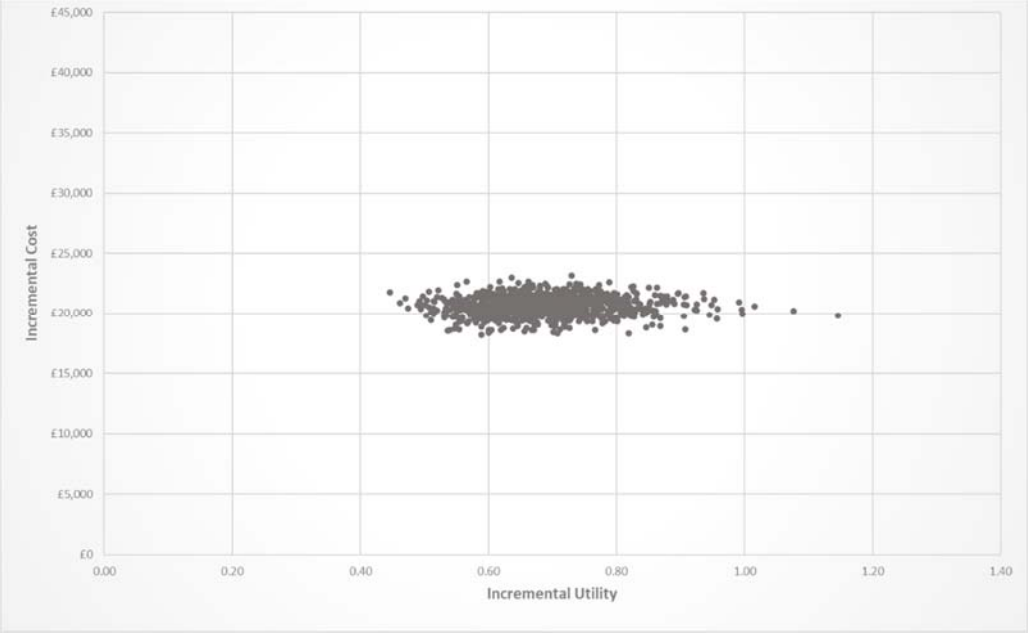
The probabilistic ICER for patients with residual EDS despite CPAP (based on HAROSA I) is £29,824 per QALY gained, and for patients with EDS due to OSA who refuse CPAP (based on HAROSA II) the probabilistic ICER is £29,932. These probabilistic ICERs are well in line with the deterministic ICERs (£29,698 and £29,803, respectively). The resulting cost effectiveness planes (CE-planes) are shown in Figures 6.1 and 6.2, and the cost effectiveness acceptability curves (CEACs) are shown in Figures 6.3 and 6.4. The CEAC shows that the probability of cost effectiveness is 0% at a threshold of £20,000 per QALY gained, and 49% at a threshold of £30,000 per QALY gained for patients with residual EDS despite CPAP (based on HAROSA I). For patients with EDS due to OSA who refuse CPAP (based on HAROSA II), the CEAC shows that the probability of cost effectiveness was also 0% at a threshold of £20,000 per QALY gained, and 48% at a threshold of £30,000 per QALY gained.

Figure 6.1: CE-plane of company's PSA results: patients with residual EDS despite CPAP (based on HAROSA I)



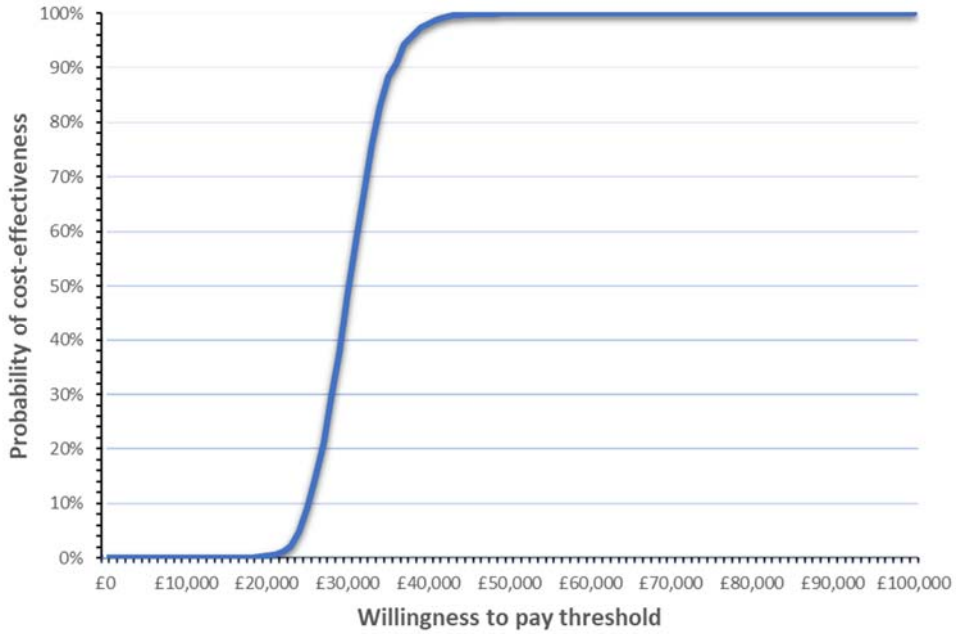
Based on the updated electronic model.
CE = cost effectiveness; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; PSA = probabilistic sensitivity analysis, QALYs = quality-adjusted life years.

Figure 6.2: CE-plane of company's PSA results: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)



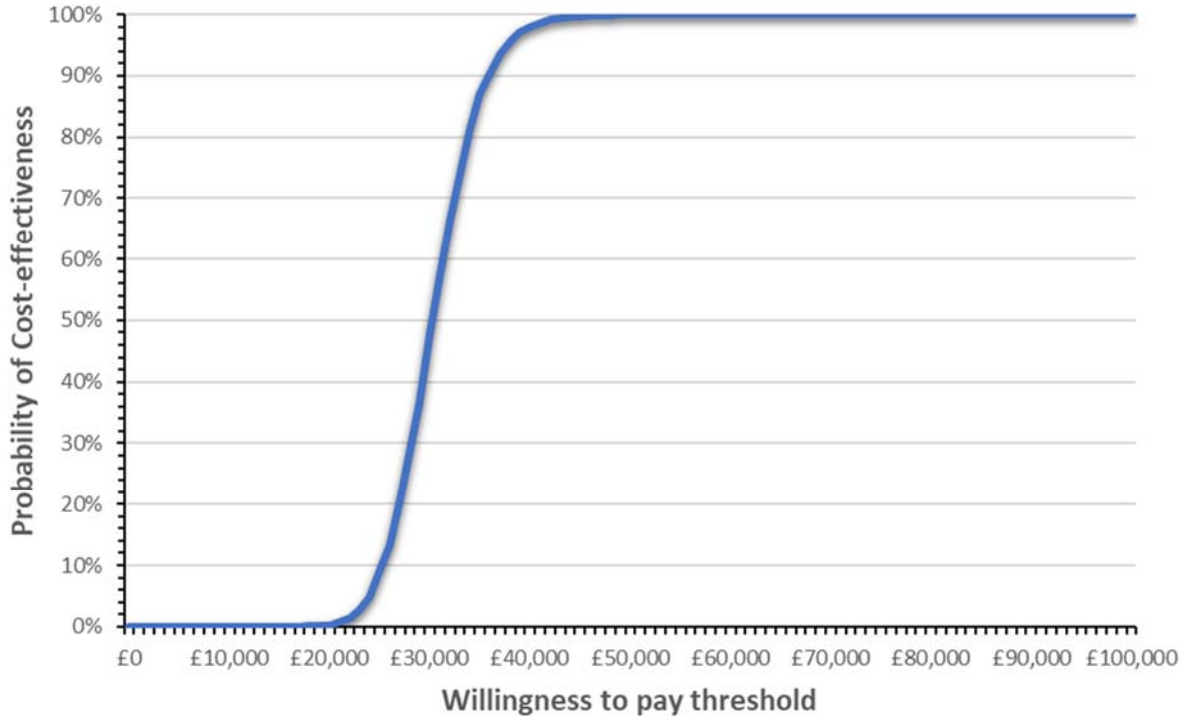
Based on the updated electronic model.
CE = cost effectiveness; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; PSA = probabilistic sensitivity analysis; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years.

Figure 6.3: CEAC of company's PSA results: patients with residual EDS despite CPAP (based on HAROSA I)



Based on the updated electronic model.
CEAC = cost effectiveness acceptability curve; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; PSA = probabilistic sensitivity analysis, QALYs = quality-adjusted life years.

Figure 6.4 CEAC of company's PSA results: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)



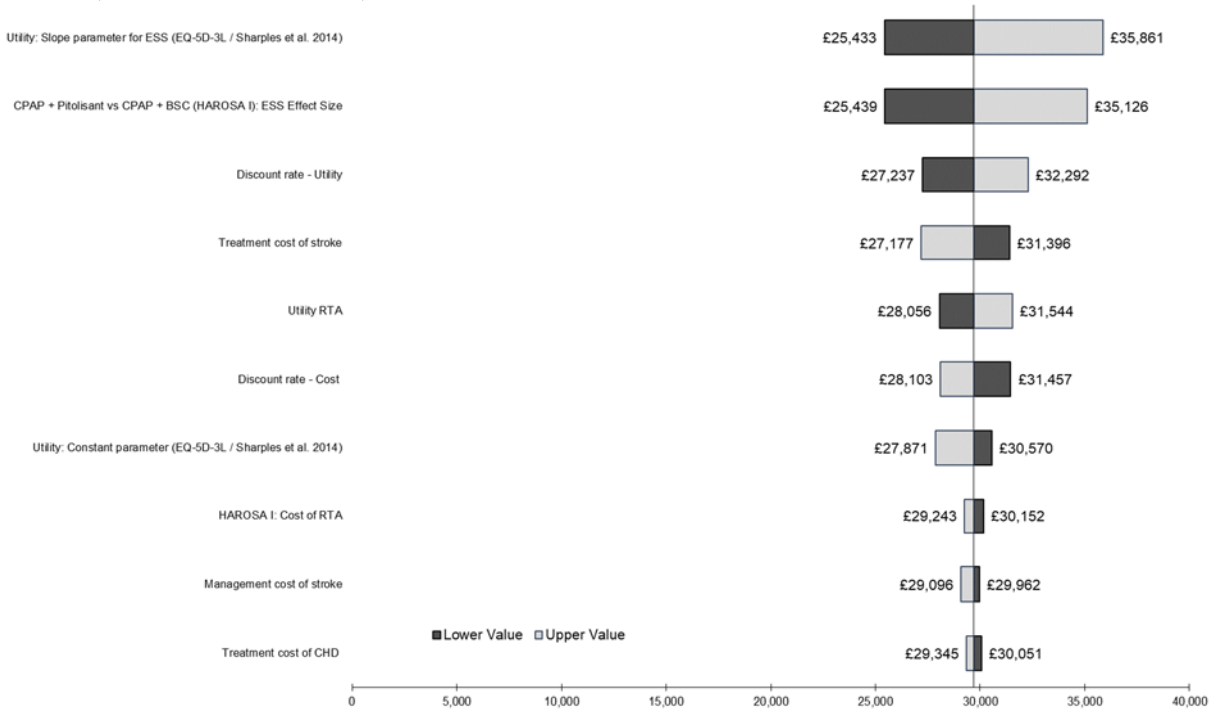
Based on the updated electronic model.
CE = cost effectiveness; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; PSA = probabilistic sensitivity analysis; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years.

6.2.2 Deterministic sensitivity analysis

A univariate, deterministic sensitivity analysis was performed by the company in which the base-case values of individual model parameters were varied. One-by-one, the parameters were independently varied according to their respective 95% CIs where available, and otherwise a range was defined based on the mean ± 20%. See also Table 38 of the CS.[1]

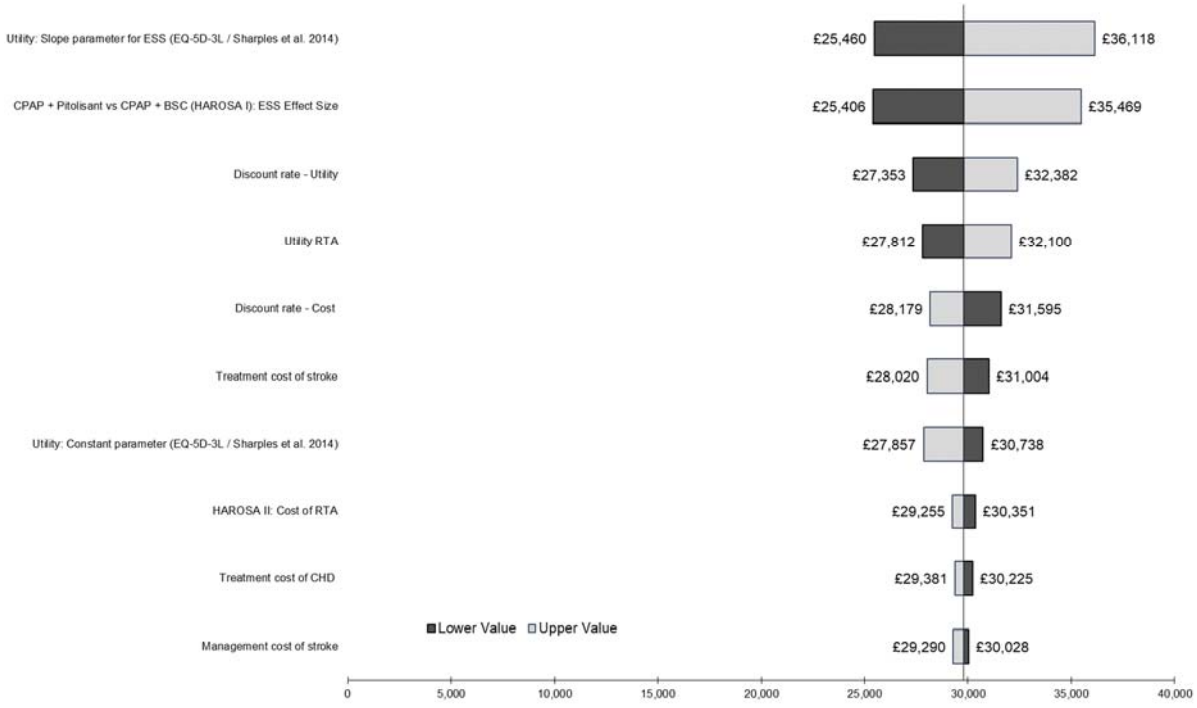
For each parameter that was varied, the ICER was calculated based on the lowest and highest value used. Figures 6.5 and 6.6 show the tornado diagrams of the 10 most influential parameters. Only two parameters (ignoring the discount rates) had a discernible impact on the ICER. i.e. the slope of the mapping function for the utilities and the ESS effect size. But even for these parameters the impact on the ICER is limited.

Figure 6.5: Tornado diagram showing impact on ICER: patients with residual EDS despite CPAP (based on HAROSA I)



Source: the updated electronic model.
CS = company submission

Figure 6.6 Tornado diagram showing impact on ICER: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)



Source: the updated electronic model.
CS = company submission

ERG comment: In general, discount rates should not be part of the univariate deterministic sensitivity analysis. This analysis is meant to explore the impact of parameter uncertainty, and discount rates are not subject to parameter uncertainty but are in many cases government determined.

For quite a few transition probabilities a range based on 20% of the mean was defined, for example for 'CPAP+Pitolisant (HAROSA I): TP from OSAHS to Acute CHD'. However, for 'CPAP+BSC (HAROSA I): TP from OSAHS to Acute CHD' a 95% confidence interval is available, which translated approximately to a range of 80% of the mean. Making use of such similarities will in general provide less arbitrary ranges. For the parameter under discussion, assuming a range of 20% leads to an underestimation of the uncertainty.

6.2.3 Scenario analyses

In order to assess the impact of key uncertainties surrounding the assumptions underlying the cost effectiveness results, a series of scenario analyses was performed by the company. The results of these scenario analyses were reported in the original CS,[1] and pertain to the following scenarios (except for scenario C; while the original CS used the Framingham equation for the base case, and QRISK 3 and QStroke for scenarios, the updated model used QRISK 3 and QStroke for the company base case. Therefore, the ERG reports the results using the Framingham equation in the updated model for scenario C, which also excludes the use of the age-dependent risk of CVE that is based on QRISK3 scores):

- Scenario A: A comparison of pitolisant versus MAD in patients with EDS due to OSA who refuse CPAP (based on HAROSA II).
- Scenario B: Use of SF-6D as the HRQOL instrument in the model.

- Scenario C: Use of Framingham equation to estimate baseline CV risk.
- Scenario D: Exclusion of costs and utilities of CV events from the model.

Unfortunately, the results of scenarios that were reported by the company following their update of the model in response to the ERG's clarification questions were not provided. Therefore, the ERG has taken the results of the scenario analyses from the electronic model after implementing the required adjustments to the company's base-case settings in the updated model. Below the results are reported for each of the scenarios listed above, alongside a summary of the motivation for the scenarios as provided by the company in the CS.[1]

6.2.3.1 Company results for Scenario A: A comparison of pitolisant versus MAD in patients with EDS due to OSA who refuse CPAP (based on HAROSA II)

The company's advisers suggested that in some NHS centres bespoke MADs may be offered to patients with EDS due to OSA. Therefore, a scenario analysis was performed comparing pitolisant to MAD. The results are presented in Table 6.5.

Table 6.5: Company results for Scenario A: comparison of pitolisant versus MAD in patients with EDS due to OSA who refuse CPAP (HAROSA II)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pitolisant + BSC	£30,923	12.57	£14,834	0.29	£51,445
MAD + BSC	£16,089	12.28			

Source: the updated electronic model.
BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; MAD = mandibular advancement device; QALYs = quality-adjusted life years.

6.2.3.2 Company results for Scenario B: Use of SF-6D as the HRQoL instrument in the model

A scenario analysis was carried out by the company to explore the impact of using the HRQoL instrument SF-6D as an alternative to the EQ-5D-3L that was used in the company base-case. The results of this analysis can be found in Table 6.6.

Table 6.6: Company results for Scenario B: Use of SF-6D as the HRQoL instrument in the model

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pitolisant + CPAP + BSC	£32,182	10.31	£21,061	0.62	£34,034
CPAP + BSC	£11,121	9.69			
Pitolisant + BSC	£30,923	10.37	£20,601	0.60	£34,534
BSC	£10,322	9.78			

Source: The updated electronic model.
BSC = best supportive care; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; OSA = obstructive sleep apnoea; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.

6.2.3.3 Company results for Scenario C: Use of Framingham equation to estimate baseline CV risk

The company used the QRISK 3 and QStroke to estimate baseline CV risk in the updated base-case model, because these are more recent algorithms, and are specific for the UK population. The company used the Framingham equation, which is based on a US population, to estimate the baseline CV risk in the original base case model, which ensures consistency with previous models. The ERG reports the results of using the Framingham equation to estimate the baseline CV risk for scenario C in Table 6.7.

Table 6.7: Company results for Scenario C: Use of Framingham equation to estimate baseline CV risk

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pitolisant + CPAP + BSC	£30,446	12.29	£20,641	0.86	£23,929
CPAP + BSC	£9,806	11.42			
Pitolisant + BSC	£29,408	12.36	£19,820	0.88	£22,5163
BSC	£9,587	11.48			

Source: The updated electronic model.
BSC = best supportive care; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; OSA = obstructive sleep apnoea; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.

6.2.3.4 Company results for Scenario D: Exclusion of costs and utilities of CV events from the model

The company performed a scenario analysis based exclusively on the impact of RTAs, thereby excluding the costs and utilities of CV events from the analysis. The results are presented in Table 6.8.

Table 6.8: Company results for Scenario D: Exclusion of the effects on CV events

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pitolisant + CPAP + BSC	£30,663	12.92	£28,555	0.37	£77,241
CPAP + BSC	£2,108	12.55			
Pitolisant + BSC	£29,404	12.93	£27,020	0.39	£69,478
BSC	£2,384	12.54			

Source: The updated electronic model.
BSC = best supportive care; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; OSA = obstructive sleep apnoea; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.

ERG comment: From the scenario analyses it is clear that exclusion of the costs and utilities of CV events more than doubles the ICER. Using the mapping of ESS to SF-6D based utilities instead of EQ-5D utilities increases the ICER somewhat, whereas using the Framingham risk score to derive the risks of CHD and stroke decrease the ICER somewhat. The first scenario, where pitolisant is compared to MAD, results in an ICER that is more than £20,000 higher than the ICER when pitolisant is compared to best supportive care.

6.3 Model validation and face validity check

In the validation section of the CS (B.3.10),[1] the company discussed some aspects of validation.

They pointed out that the current cost effectiveness analysis was carried out by adapting and extending an established, published and peer-reviewed economic model that had previously been used to inform a NICE Technology Appraisal.[19] The only significant components that have been altered, according to the company, are the efficacy inputs for pitolisant itself, combined with an updating of cost assumptions where required. In all other regards, the model mirrors the previously accepted and validated approach.

The company pointed out that the analysis had been carried out in the context of the COVID-19 outbreak, which was already under way at the time that the final scope was issued by NICE, with significant variation form the previously issued draft that was used as the basis of their preliminary model design. Given that the specialist advisors were respiratory physicians, they were unable to assist the company in the validation of many of the inputs to the model, although the company was able to access the assistance of a recently retired clinician. The company pointed out that it is possible that some assumptions were not an accurate reflection of current NHS practice, but that they have endeavoured to make conservative assumptions wherever this limitation arose.

ERG comment: The company indicated that they used a model that had already been validated, implying that at least conceptually no further validation would be required, However, it should be pointed out that, although the health states in the McDaid model[52] and the current model are the same, they differ in one important aspect. In the McDaid model[52] any effect of treatment on CVE was driven

by changes in blood pressure rather than ESS, and the ERG considers these two approaches as conceptually different.

No information was provided by the company on how the electronic model was validated, e.g. by an independent modeller testing the model, black box testing, white box testing etc. The ERG found some issues, for example, no pitolisant costs were applied to patients in other health states than the initial OSAHS state, despite the assumption from the company that patients would take pitolisant for the rest of their life.

The company indicated that due to the COVID-19 pandemic, it was not possible to have clinical experts check the face validity of that input and model outcomes, but that one recently retired clinician was able to assist. The ERG would have preferred to receive details on what was asked and what the responses were of this expert.

When comparing the outcomes of the current model to those of McDaid et al,[52] the ERG considers them quite similar, in terms of costs and QALYs for the CPAP + BSC and the BSC only groups.

7. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

7.1 Exploratory and sensitivity analyses undertaken by the ERG

7.1.1 Explanation of the company adjustments after the request for clarification

In response to the ERG's clarification questions, the company amended the model to address the issues raised by the ERG as well as additional issues identified by the company, which are all summarised below. After these amendments, the ICER for patients with residual EDS despite CPAP increased from £17,446 per QALY gained (i.e. original company base-case) to £29,698 per QALY gained (i.e. updated company base-case), and for patients with EDS due to OSA who refuse CPAP the ICER increased from £16,896 per QALY gained (i.e. original company base-case) to £29,803 per QALY gained (i.e. updated company base-case).

Below a list of bullet points is provided, broken down per category of model input parameters, to summarise the amendments that were made by the company during the clarification phase. The relevant sections that explain the amendments in more detail are indicated between brackets for each amendment.

Amendments relating to clinical effectiveness:

- The model time horizon was changed from 25 years to 47 years. (Section 5.2.5)
- The risk for CHD and stroke is now based on the QRISK 3 and QStroke risk equations, respectively (in the original model this was the Framingham risk score) (Section 5.2.6.1)
- The risk for CHD and stroke was set to increase as the age of the cohort increased (as opposed to a constant risk over the model horizon).

Amendments relating to HRQoL:

- A scenario analysis using the mapping algorithm of Sharples et al. (2014)[42] was added (Section 5.2.8.1).
- The disutility for CHD was changed from -0.064 to -0.0411 (Section 5.2.8.2).
- Uncertainty surrounding the baseline ESS and ESS effect size was included in the uncertainty around the utility for BSC and pitolisant arms, respectively, in DSA and PSA in the model (Section 5.2.8.3).

Amendments relating to resource use and costs:

- Drug acquisition costs were amended to include wastage costs (only for patients who were down-titrated from the maximal dose of 20 mg either once during the titration phase, or once during the remainder of the first year of treatment: Section 5.2.9. ERG comment).
- Drug acquisition costs were corrected to include the costs of two tablets of pitolisant for patients receiving a 10 mg dose (i.e. instead of one tablet), since tablets only exist in 5 and 20 mg per tablet doses (Section 5.2.9. ERG comment).
- The model was amended to include cost estimates for CHD costs that were based on a more recent and relevant source of information (although these were not correctly implemented, and therefore not reflected in the updated model's cost effectiveness results; Section 5.2.9. ERG comment).
- The model was amended to include the option for adding social care costs to the costs of CHD and stroke (although not used in company base-case; Section 5.2.9. ERG comment).
- The costs of stroke were updated to 2018/2019 values (Section 5.2.9. ERG comment).

7.1.2 Explanation of the ERG adjustments

The changes made by the ERG (to the model received with the response to the clarification letter) were subdivided into the following three categories, according to Kaltenthaler et al. 2016:[79]

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to).
- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred).

After these changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

7.1.2.1 Fixing errors

- The company referred to the cell of the ESS coefficient in the SF-6D model for both the SF-6D model as well as the EQ-5D model.
- In the model, the calculation of the health state utilities is dependent on the algorithm selected in the 'Global setting' sheet. In the formula of this calculation, the IF statement referred to "McDaid et al. 2009". Due to the space at the end, the wrong values were used in the calculation of the health state values based on the algorithm of McDaid et al. The space was removed in the ERG base-case.
- In the company base-case, the age decrement is subtracted from the total undiscounted QALYs per cycle. As a consequence, the age decrement is not weighted by the number of patients alive and therefore the difference between the treatment arms is not taken into account. This is corrected in the ERG base-case by weighting the utility decrement by the proportion of patients alive in the specific cycle before subtracting it from the total undiscounted QALYs per cycle.
- The costs of treatment with pitolisant were not included for patients in other health states than the OSAHS health state, and this was corrected by the ERG (i.e. by including them in the acute and post-event health states for both CHD and stroke in the scenario analysis that includes these health states).
- The social care costs that were included in the company's updated model (and which are used by the ERG for a scenario analysis), were only applied to patients in the post-CHD and post-stroke health states (i.e. not in the acute health states for CHD and stroke). This was corrected by the ERG by applying them in all CHD and stroke-related health states.
- The model was amended to include costs of stroke that were updated to 2018/2019 values, but the calculations inside the model were still based on the previous values. This was corrected by the ERG by using the updated values for the analyses.
- The model was amended by the company to include cost estimates for CHD that were based on a more recent and relevant source of information, but the calculations inside the model were still based on the previous values. This was corrected by the ERG by using the updated values for the analyses.

7.1.2.2 Fixing violations

None

7.1.2.3 Matters of judgement

The overview of the changes and the bookmarks for the justification of the ERG changes are presented in Table 7.1.

1. The time horizon of 25 years in the company model base case was adjusted to 47 years to reflect a true lifetime horizon.
2. No direct evidence is available on the effect of pitolisant on the incidence of cardiovascular events. Though there is substantial evidence that CPAP treatment reduces cardiovascular risk,[64] CPAP and pitolisant are markedly different interventions, with different modes of action. CPAP can be considered to address the symptoms and complications of OSAHS more fundamentally by improving ventilation during sleep, thereby resulting in a broad effect in alleviating OSAHS symptoms and reducing risk for (cardiovascular) complications. As pitolisant is primarily aimed at alleviating a specific symptom, daytime sleepiness, it cannot be assumed without evidence that it has broader effects such as the reduction of cardiovascular risk. Additionally, CPAP treatment has been shown to reduce known cardiovascular risk factors, predominantly blood pressure. Studies of pitolisant have no shown a change in cardiovascular risk factors. The ERG concludes that there is neither direct nor indirect evidence that treatment with pitolisant has an effect on the incidence of CHD-events and stroke. The company provided no evidence or rationale based on well understood biological mechanisms to substantiate the assumption that pitolisant has an effect on the incidence CHD-events and stroke. The company provided reasonable evidence that EDS is an independent prognostic factor for cardiovascular risk but did not provide any evidence or rationale that this is a causal relation and that the direction of causality is such that cardiovascular risk is reduced when EDS is treated. The substantiation of the assumptions made by the company are thus deemed insufficient to warrant the inclusion of an effect of pitolisant on the incidence of CHD-events and stroke. Therefore, the ERG base-case will not include such an effect.
3. In the ERG base-case, the utility for RTAs was adapted from an absolute utility of 0.62 to a utility decrement of -0.074. According to the ERG, the utility of 0.62 seems reasonable for severe RTAs (including broken neck or back, severe head and chest injuries, fractured limbs etc.). However, this utility was also applied to patients who experienced a slight RTA (i.e. shock, bruising, sprains and strains, shallow cuts, lacerations, abrasions, and whiplash or neck pain) in the company base case. The ERG has strong reservations about these slight injuries being associated with such a low utility, especially considering that in the model the utility for patients who have had a stroke is about 0.77. However, there is no data of the utility after slight RTAs. Therefore, in the ERG base case, these patients are assumed to experience a disutility equal to the most severe other event in the model, namely stroke (i.e. disutility of -0.052).
4. The company base-case included a constant utility decrement for ageing, while this utility decrement is known to increase over as people age.[74] Furthermore, the disutilities derived from the Ara and Brazier equation (varying between 0.004-0.007) are considerably larger than the annual disutility of 0.0007 applied in a scenario analysis provided by the company. In the ERG base case the equation of Ara and Brazier 2010 is used to account for the decline in utility due to ageing.

Table 7.1: Company and ERG base-case preferred assumptions (ITT population)

Base-case preferred assumptions	Company	ERG	Justification for change
Time horizon	25 years	47 years	Reflect a true lifetime horizon where patients can live up to an age of 100 years.
Impact decline ESS	Decline ESS leads to decline risk of CVD	Decline ESS has no impact on risk of CVD	No evidence was provided that a change in ESS would lead to changes in the risk of CHD and stroke
Utility RTA	Absolute utility of 0.62	Utility decrement of 0.074	The absolute utility of 0.62 was based on severe RTAs, while only 21% of the RTAs were severe. A utility decrement equal to stroke was assumed for slight RTAs. The weighted utility decrement for severe and slight RTAs was 0.074.
Utility decrements ageing	Constant utility decrement of -0.0007	Age dependent utility decrement varying from -0.004 for 50-year olds to -0.007 for 100-year olds	The equation of Ara and Brazier 2010 is used to account for the age-dependent decline in utility due to ageing.

ERG = evidence review group; RTA = road traffic accident.; CVD = cardiovascular disease, CHD = coronary heart disease; ESS = Epworth Sleepiness Scale

7.1.3 Additional scenarios conducted by the ERG

The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. These key uncertainties relate to the potential effect of ESS of CV events, the effect of inclusion of social care costs due to CV event and the impact of alternative approaches to estimating health state utilities.

7.1.3.1 Scenario set 1: CV events included

In the ERG base-case, the ERG left out the hypothesised effect of ESS on coronary heart disease and stroke that was part of the company base-case. In this scenario, the ERG includes this effect again.

7.1.3.2 Scenario set 2: Social care costs due to CV events included

The ERG performed a scenario that includes the costs and QALYs that are related to the CV events CHD and stroke, similar to the previous scenario, but now also including social care costs. The cost estimates for these social care costs are shown in Table 7.2, alongside the sources that these estimates were based on.

Table 7.2: Social care cost estimates for CHD and stroke

Health state	Social care cost estimate	Source
Acute CHD	£2,240	Xu et al.[78], Walker et al.[53], PSSRU 2019[75]
Post-CHD	£5,350	Xu et al.[78], Walker et al.[53], PSSRU 2019[75]
Acute stroke	£9,731	Xu et al.[78], PSSRU 2019[75]
Post-stroke	£5,176	Xu et al.[78], PSSRU 2019[75]

Note: In absence of a social care cost estimate for CHD, the ratio of social care to total costs for stroke from Xu et al.[78] was applied to the health care costs estimate for CHD to obtain an estimate for the social care costs.
Based on information provided in the company's response to the ERG's clarification questions.
CHD = coronary heart disease; ERG = evidence review group; PSSRU = personal social services research unit.

7.1.3.3 Scenario set 3: SF-6D used as alternative HRQoL measure

The ERG performed a scenario to explore the impact of using the HRQoL instrument SF-6D as an alternative to the EQ-5D-3L that was used in the ERG preferred base-case.

7.1.3.4 Scenario set 4: Mapping algorithm for utilities

In the clarification letter, the ERG requested a scenario analysis where the algorithm from Sharples et al.[42] instead of McDaid et al.[52] was used to show the impact of the chosen algorithm on the cost effectiveness outcomes. This scenario analysis was provided by the company in the clarification response.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

7.2.1 Results of the ERG preferred base-case scenario

The results of the ERG preferred base-case are provided in Tables 7.3 and 7.4. In the patients with residual EDS despite using a CPAP, the ICER was £67,557, based on additional costs of £35,043 whilst gaining 0.48 QALYs. For patients with EDS who refuse CPAP, a full incremental analysis was done,

which showed an ICER of MAD+BSC versus BSC alone of £36,735, whilst the ICER of pitolisant+BSC versus MAD+BSC was £97,483.

Table 7.3: ERG base-case deterministic results: patients with residual EDS despite CPAP (based on HAROSA I)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + CPAP + BSC	£35,043	17.68	14.28	£32,626	0.09	0.48	£67,557
CPAP + BSC	£2,416	17.60	13.80				

Based on the ERG preferred base case.
BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; EDS = excessive daytime sleepiness; LYG = life years gained; QALYs = quality-adjusted life years

Table 7.4: ERG base-case deterministic results: patients with EDS due to OSA who refuse CPAP (based on HAROSA II), full incremental analysis

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + BSC	£34,752	18.33	14.76	£21,322	0.03	0.22	£97,483
MAD + BSC	£13,430	18.30	14.54	£10,603	0.07	0.29	£36,735
BSC	£2,827	18.23	14.26				

Based on the ERG-preferred base case.
BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; LYG = life years gained; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years

The ERG also conducted a PSA using their preferred base-case assumptions. The probabilistic results (Tables 7.5 and 7.6) are very similar to the deterministic results.

Table 7.5: ERG base-case probabilistic results (discounted): patients with residual EDS despite CPAP (based on HAROSA I)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + CPAP + BSC	£35,135	17.74	14.34	£32,561	0.10	0.49	£66,462
CPAP + BSC	£2,574	17.65	13.85				

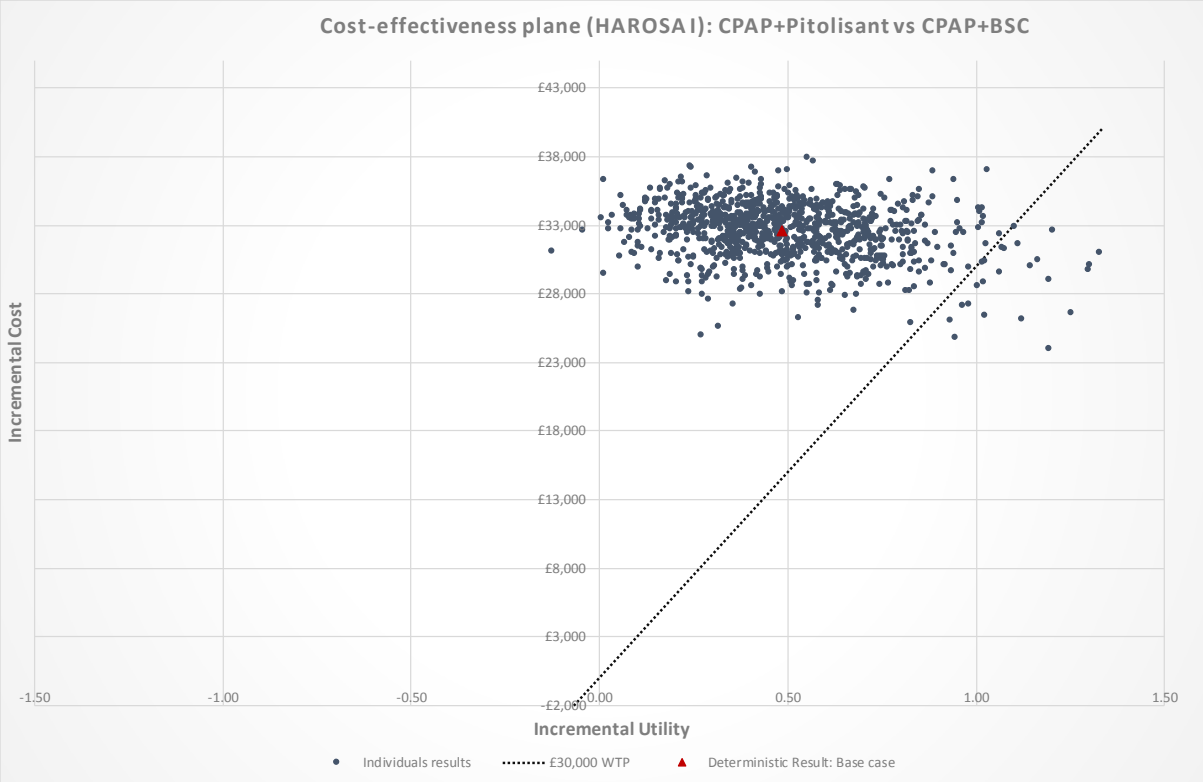
Based on the ERG-preferred model.
BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; EDS = excessive daytime sleepiness; LYG = life years gained; QALY = quality-adjusted life year.

Table 7.6: ERG base-case probabilistic results (discounted): patients with EDS due to OSA who refuse CPAP (based on HAROSA II), full incremental analysis

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + BSC	£34,847	18.40	14.83	£21,210	0.04	0.22	£96,297
MAD + BSC	£13,637	18.36	14.61	£10,366	0.09	0.30	£34,930
BSC	£3,271	18.27	14.31	-	-	-	-

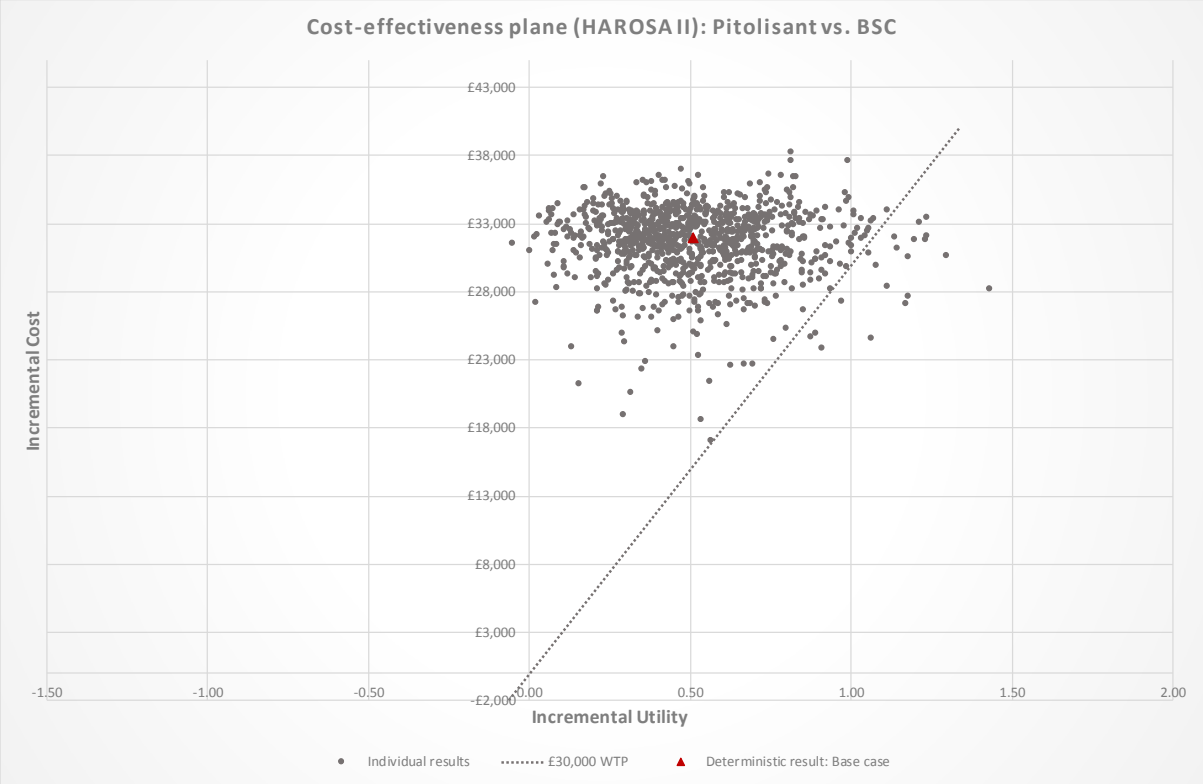
Based on the ERG-preferred base case.
BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; LYG = life years gained; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years

Figure 7.1: ERG preferred cost effectiveness plane: patients with residual EDS despite CPAP (based on HAROSA I)



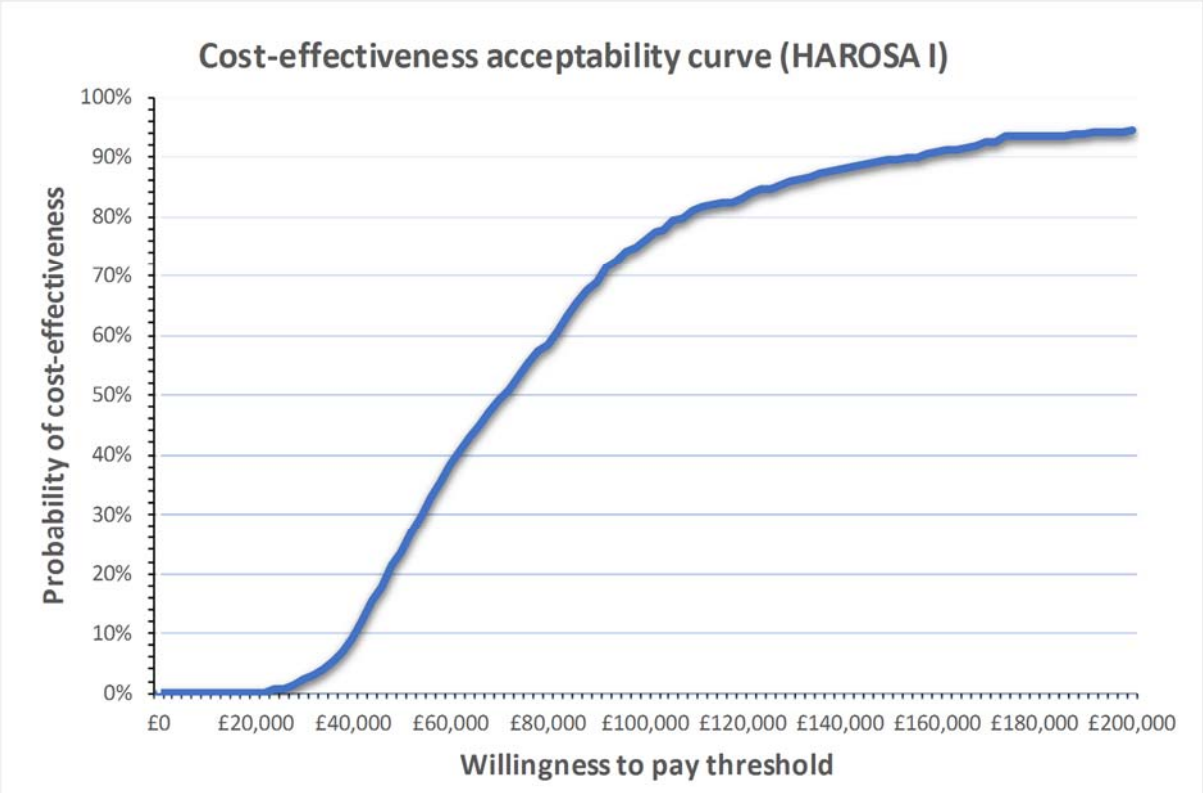
Based on the ERG-preferred model.
CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; QALYs = quality-adjusted life years.

Figure 7.2: ERG preferred cost effectiveness plane: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)



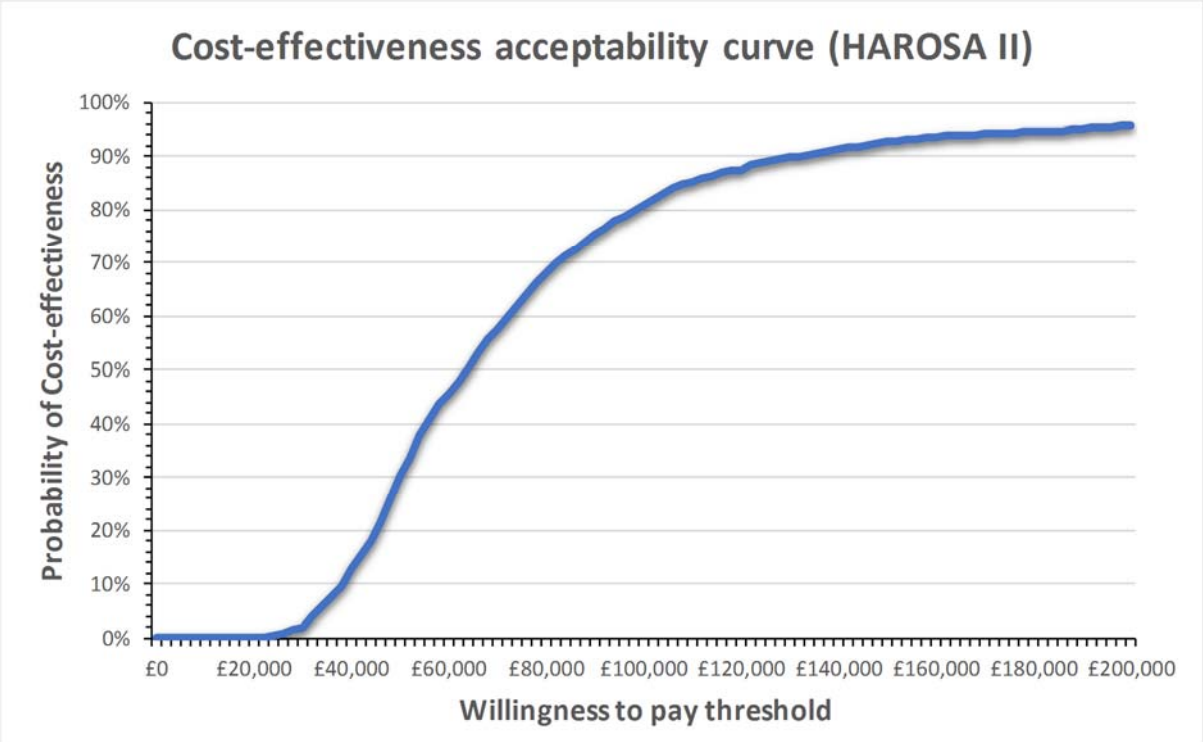
Based on the ERG-preferred model.
CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years.

Figure 7.3: ERG preferred cost effectiveness acceptability curve: patients with residual EDS despite CPAP (based on HAROSA I)



Based on the ERG-preferred model.
CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; QALYs = quality-adjusted life years.

Figure 7.4: ERG preferred cost effectiveness acceptability curve: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)



Based on the ERG-preferred model.
CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years.

The ERG performed a univariate sensitivity analyses, the results of which are reported in the tornado diagrams shown in Figures 7.5 and 7.6. The base-case values of individual model parameters were varied. One-by-one, the parameters were independently varied according to their respective 95% CIs where available, and otherwise a range was defined based on the mean ± 20%. See also Table 38 of the CS.[1]

For each parameter that was varied, the ICER was calculated based on the lowest and highest value used. The tornado diagrams show the 10 most influential parameters. Only two parameters (ignoring the discount rates) have a discernible impact on the ICER. i.e. the slope of the mapping function for the utilities and the ESS effect size. But even for these parameters the impact on the ICER is limited.

Figure 7.5: Tornado diagram showing impact on ICER: patients with residual EDS despite CPAP (based on HAROSA I)

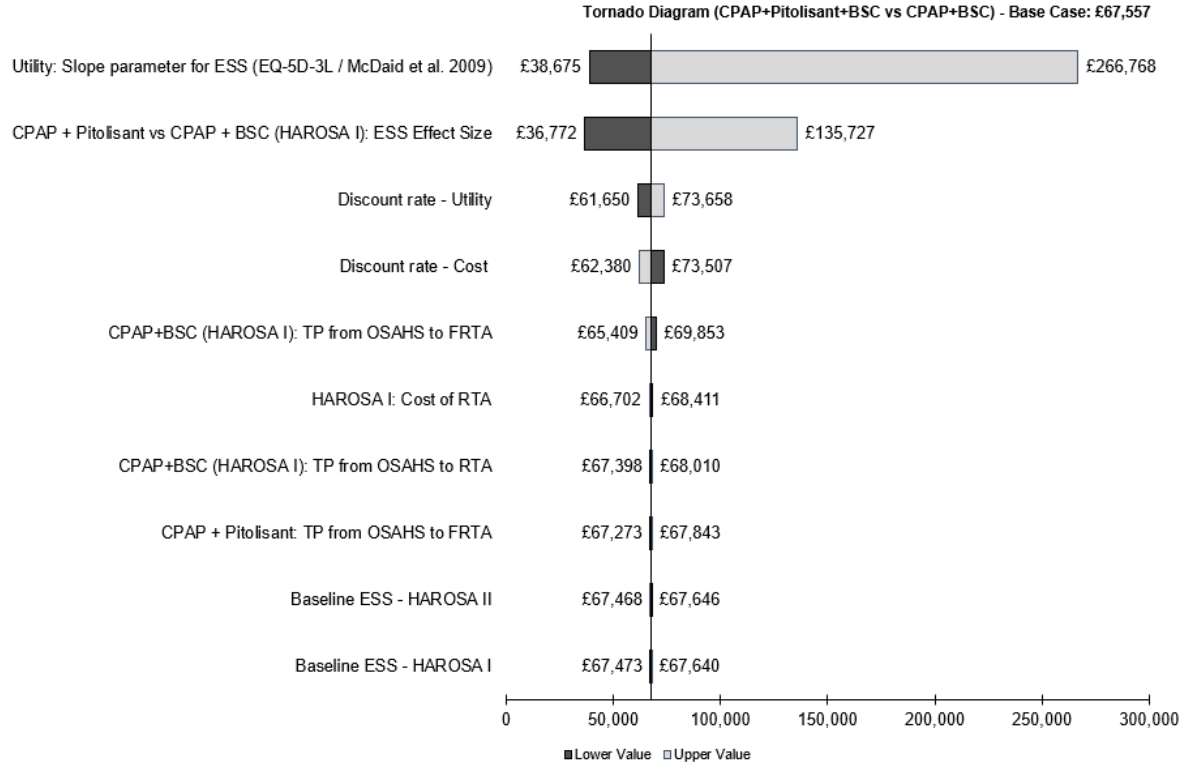
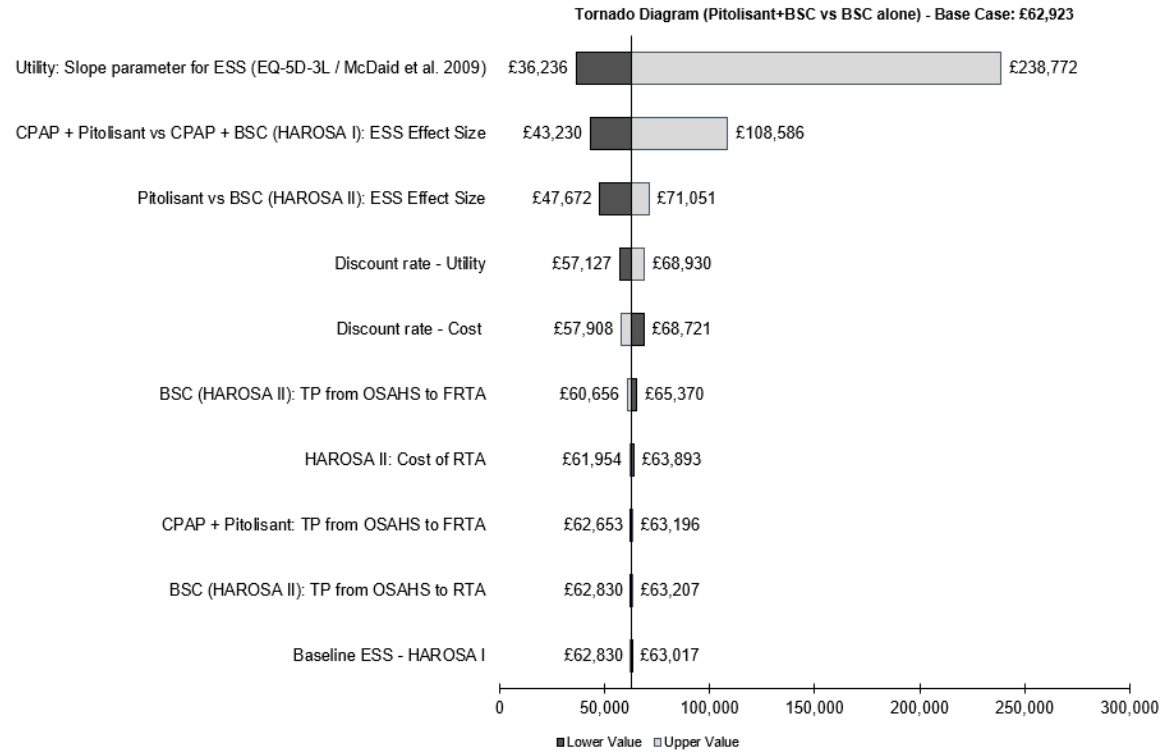


Figure 7.6: Tornado diagram showing impact on ICER: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)



7.2.2 Results of the ERG additional exploratory scenario analyses

7.2.2.1 Scenario set 1: CV events included

The ERG performed a scenario analysis in which, similar to the company's base case, CV events were included. In other words, this scenario includes the costs and QALYs for CHD and stroke. These results are shown in Tables 7.7 and 7.8.

Table 7.7: ERG results for scenario set 1: patients with residual EDS despite CPAP (based on HAROSA I)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + CPAP + BSC	£38,855	16.95	13.60	£27,224	0.67	0.98	£27,775
CPAP + BSC	£11,631	16.28	12.62				

Based on the ERG preferred version of the electronic model.
BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; EDS = excessive daytime sleepiness; LYG = life years gained; QALYs = quality-adjusted life years.

Table 7.8: ERG results for scenario set 1: patients with EDS due to OSA who refuse CPAP (based on HAROSA II), full incremental analysis

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + BSC	£36,800	17.15	13.73	£20,049	0.27	0.42	£47,335
MAD + BSC	£16,751	16.88	13.31	£6,359	0.36	0.52	£12,308
BSC	£10,391	16.52	12.79	-	-	-	-

Based on the ERG-preferred base case.
BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; LYG = life years gained; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years

7.2.2.2 Scenario set 2: Social care costs due to CV events included

The ERG performed a scenario analysis in which CV events were included, as well as the costs for social care due to CHD and stroke. These results are shown in Tables 7.9 and 7.10.

Table 7.9: ERG results for scenario set 2: patients with residual EDS despite CPAP (based on HAROSA I)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + CPAP + BSC	£49,395	16.95	13.60	£20,570	0.67	0.98	£20,986
CPAP + BSC	£28,826	16.28	12.62				
Based on the ERG preferred version of the electronic model. BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; EDS = excessive daytime sleepiness; LYG = life years gained; QALYs = quality-adjusted life years.							

Table 7.10: ERG results for scenario set 2: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)), full incremental analysis

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + BSC	£45,821	17.15	13.73	£17,045	0.27	0.42	£40,241
MAD + BSC	£28,776	16.88	13.31	£3,210	0.36	0.52	£6,212
BSC	£25,567	16.52	12.79	-	-	-	-
Based on the ERG-preferred base case. BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; LYG = life years gained; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years							

7.2.2.3 Scenario set 3: SF-6D used as alternative HRQoL measure

The ERG performed a scenario analysis in which the SF-6D was used as a measure of HRQoL, as an alternative to EQ-5D-3L. These results are shown in Tables 7.11 and 7.12.

Table 7.11: ERG results for scenario set 3: patients with residual EDS despite CPAP (based on HAROSA I)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + CPAP + BSC	£35,043	17.68	12.79	£32,626	0.09	0.47	£69,797
CPAP + BSC	£2,416	17.60	12.32				
Based on the ERG preferred version of the electronic model. BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; EDS = excessive daytime sleepiness; LYG = life years gained; QALYs = quality-adjusted life years.							

Table 7.12: ERG results for scenario set 3: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)), full incremental analysis

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + BSC	£34,752	18.33	13.22	£21,322	0.03	0.21	£102,565
MAD + BSC	£13,430	18.30	13.01	£10,603	0.08	0.28	£37,589
BSC	£2,827	18.23	12.73	-	-	-	-

Based on the ERG-preferred base case.
BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; LYG = life years gained; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years

7.2.2.4 Scenario set 4: Mapping algorithm from Sharples et al. used for utilities

The ERG performed a scenario analysis in which the mapping algorithm from Sharples et al.[42] was used as an alternative to the one from McDaid et al.[52] These results are shown in Tables 7.13 and 7.14.

Table 7.13: ERG results for scenario set 4: patients with residual EDS despite CPAP (based on HAROSA I)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + CPAP + BSC	£35,043	17.68	14.87	£32,626	0.09	0.32	£102,800
CPAP + BSC	£2,416	17.60	14.55				

Based on the ERG preferred version of the electronic model.
BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; EDS = excessive daytime sleepiness; LYG = life years gained; QALYs = quality-adjusted life years.

Table 7.14: ERG results for scenario set 4: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)), full incremental analysis

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pitolisant + BSC	£34,752	18.33	15.39	£21,322	0.03	0.14	£153,406
MAD + BSC	£13,430	18.30	15.25	£10,603	0.08	0.20	£53,870
BSC	£2,827	18.23	15.05	-	-	-	-

Based on the ERG-preferred base case.
BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; LYG = life years gained; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years

7.3 ERG's preferred assumptions

The ERG preferred changes to the updated company base-case were described in Section 7.1.2 of this report. The cost effectiveness results of the ERG preferred base-case are presented in Tables 7.15 and 7.16. Results are presented in steps, first the steps from the original company base-case to a base-case based on the assumptions of the company, but with various errors corrected. On top of that version of the model, changes are incorporated one at a time according to the ERG preferred assumptions, to show the individual impact of these assumptions. The last row of results represents the ERG base-case. From the tables below it is clear that change 2, not including a potential impact of ESS change on CHD and stroke risk, has the largest impact on the ICER, almost doubling it. This is the case for both subgroups with EDS.

Table 7.15: ERG's preferred model assumptions HAROSA I –step by step impact on results

Preferred assumption	Section in ERG report	Pitolisant + CPAP + BSC		CPAP + BSC		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case	6.1	26,379	11.77	9,743	10.80	16,635	0.97	17,140
Company base-case after clarification	6.1/ 7.1.1	32,182	12.48	11,121	11.77	21,061	0.71	29,698
Company base-case + errors corrected	7.1.2	33,567	11.98	8,942	11.17	24,625	0.82	30,173
ERG change 1: Time horizon	7.1.2	38,855	13.50	11,631	12.44	27,224	1.06	25,649
ERG change 2: No impact on CVD	7.1.2	30,663	12.41	2,108	11.91	28,555	0.50	57,647
ERG change 3: RTA disutility	7.1.2	33,567	12.00	8,942	11.26	24,625	0.74	33,340
ERG change 4: Age decrements	7.1.2	33,567	12.05	8,942	11.23	24,625	0.82	30,094
ERG base-case (changes 1-4)	7.2.1	35,043	14.28	2,416	13.80	32,626	0.48	67,557

Source: The ERG preferred version of the electronic model.
BSC = best supportive care; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; EDS = excessive daytime sleepiness; OSA = obstructive sleep apnoea; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.

Table 7.16: ERG's preferred model assumptions HAROSA II – step by step impact on results

Preferred assumption	Section in ERG report	Pitolisant + BSC		BSC		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case	6.1	26,380	11.86	9,535	10.85	16,597	1.01	26,747
Company base-case after clarification	6.1/ 7.1.1	30,923	12.57	10,322	11.87	20,601	0.69	29,803
Company base-case + errors corrected	7.1.2	31,707	12.05	7,845	11.25	23,862	0.80	29,928
ERG change 1: Time horizon	7.1.2	36,800	13.64	10,391	12.60	26,409	1.04	25,445
ERG change 2: No impact on CVD	7.1.2	29,795	12.57	2,416	12.05	27,378	0.52	52,777
ERG change 3: RTA disutility	7.1.2	31,707	12.06	7,845	11.36	23,862	0.71	33,808
ERG change 4: Age decrements	7.1.2	31,707	12.12	7,845	11.32	23,862	0.80	29,856
ERG base-case (changes 1-4)	7.2.1	34,752	14.76	2,827	14.26	31,925	0.51	62,923

Source: The ERG preferred version of the electronic model.
BSC = best supportive care; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; EDS = excessive daytime sleepiness; OSA = obstructive sleep apnoea; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.

7.4 Conclusions of the cost effectiveness section

The company developed a health economic model to assess the cost effectiveness of the addition of pitolisant to CPAP and BSC relative to CPAP and BSC, and for the addition of pitolisant to BSC or MAD plus BSC relative to BSC for the treatment of patients with residual EDS despite CPAP, and patients with EDS due to OSA who refuse CPAP, respectively.

The model used in the cost effectiveness analysis was developed previously by the University of York.[52] The same model was also used in a previous NICE technology appraisal guidance (TA139).[19] The model was developed for the economic evaluation of CPAP versus dental devices and conservative management in OSAHS patients. The structure of the model and choice of model states was based on expert opinion on the mechanism of impact and the available evidence on the effects of CPAP in OSAHS patients. Pitolisant and CPAP differ on aspects relevant to the model structure. Pitolisant is an intervention primarily aimed at relieving the burden of one particular symptom of OSAHS, namely the daytime sleepiness. On the other hand, CPAP aims to improve the sleep of patients with OSAHS, thereby potentially intervening at a more fundamental disease level, resulting in effects on a multitude of symptoms and complications of OSAHS. As such, using a model developed for the evaluation of CPAP is not necessarily an appropriate model for the evaluation of pitolisant. In particular, no evidence is provided for the rationale to include an effect of pitolisant on cardiovascular event. On the other hand, it is likely that all the relevant consequences of the comparisons currently in question can be adequately assessed using this model (i.e. the model structure is more elaborate than necessary for the current evaluation). The ERG thus concludes that the model structure is appropriate for the current evaluation.

However, no direct evidence is available on the effect of pitolisant on the incidence of cardiovascular events. There is substantial evidence that CPAP treatment reduces cardiovascular risk.[64] However, as mentioned earlier, CPAP and pitolisant are markedly different interventions, with different modes of action. CPAP can be considered to address the symptoms and complications of OSAHS more fundamentally by improving ventilation during sleep, thereby resulting in a broad effect in alleviating OSAHS symptoms and reducing risk for (cardiovascular) complications. As pitolisant is primarily aimed at alleviating a specific symptom, daytime sleepiness, it cannot be assumed without evidence that it has broader effects such as the reduction of cardiovascular risk. Additionally, CPAP treatment has been shown to reduce known cardiovascular risk factors, predominantly blood pressure. Studies of pitolisant have shown no change in cardiovascular risk factors.

The ERG concludes that there is neither direct nor indirect evidence that treatment with pitolisant has an effect on the incidence of CHD events and stroke. The company provided reasonable evidence that EDS is an independent prognostic factor for cardiovascular risk but did not provide any evidence or rationale that this is a causal relation and that the direction of causality is such that cardiovascular risk is reduced when EDS is treated. The substantiation of the assumptions made by the company is thus considered insufficient to warrant the inclusion of an effect of pitolisant on the incidence of CHD events and stroke. Consequently, the ERG base-case does not include such an effect. Rather, these hypothesised effects were explored in a scenario analysis.

The incidence of CHD events and stroke for patients treated with pitolisant was estimated using the QRISK 3 and QStroke risk equations. These risk equations do not include OSAHS as a risk factor. As such, it is implicitly assumed that OSAHS patients treated with pitolisant have the same cardiovascular risk as non-OSAHS patients with the same risk factor profile. Given the complex nature of the pathological relation between OSAHS and cardiovascular risk, the acceptance of this assumption would require further substantiation, which was not provided.

In the original submitted version of the model, the risks of CHD and stroke were assumed to be constant over time, despite age being one of the predictors in the risk equations. After clarification the company added the option to use age-dependent risks for CHD events and stroke.

The NICE reference case states that the source of data for the measurement of HRQoL should be obtained through direct reporting by patients and valued in a representative sample of the UK general population. Instead of using the data derived from the EQ-5D assessments that were carried out as part

of the HAROSA I and HAROSA II studies to fulfil the requirements of the NICE reference case, the company used a mapping algorithm to populate the utility values of the health states in the model.

The reason that the company preferred the mapping algorithm over the EQ-5D data is that evidence showed that generic instruments to measure QoL (including EQ-5D) do not capture the true benefits of treatment in patients with EDS because they have not been specifically designed to assess aspects of QoL in patients with OSA or EDS and sleep is not included as a specific dimension.[29, 70, 71] The company concluded that the true benefits of treatment were unlikely to be captured when using the EQ-5D results. However, it is possible that a modest decrease in excessive sleepiness truly does not impact the health-related quality of life importantly. But even if the ERG agreed to some extent that generic instruments may not capture the entire benefit of treatment in patients with EDS, they would have preferred the use EQ-5D utilities in the base-case or scenario analysis to be able to compare the cost effectiveness of pitolisant with treatments for other diseases and to assure adherence to the NICE reference case. Therefore, the ERG requested a scenario analysis with utility values based on the EQ-5D assessment in the clarification letter. This was not provided by the company in the clarification response because, as they stated, the underlying EQ-5D data was not available to them. However, given the evidence presented in the CSR (i.e. EQ-5D Descriptive System Total Score, EQ-5D VAS and EQ-5D Z-score), the ERG would argue that it should be possible to request the underlying individual patient data and convert the EQ-5D responses to utilities using the UK tariff.

Disregarding the ERG's preference for using EQ-5D data assessments instead of a mapping algorithm, the ERG agreed with the choice of the mapping algorithm of McDaid et al.in the company model.[52] The population in McDaid et al. was the best match for those eligible for treatment with pitolisant who also received CPAP therapy in contrast to the population used to estimate the algorithm of Sharples et al. in which patients on CPAP were excluded.[42] Nevertheless, the ERG requested a scenario analysis using the mapping algorithm of Sharples et al., which was provided by the company in the clarification response.

The reference of the utility in the RTA health state is unclear. As stated, the EQ-5D measures from the Health Outcomes Data Repository (HODaR)[73] was used, as reported by Jenkinson et al.[69] It is unclear why the company referred to the study of Jenkinson et al. as this study was published years before the publication of HODaR EQ-5D outcomes and there was no reference to the Health Outcomes Data Repository. McDaid et al.[52] also based the utility associated with experiencing an RTA on EQ-5D measures from the HODaR. They explained that this utility was based on EQ-5D data for 56 individuals six weeks after their inpatient episode (at Cardiff Hospital, UK) for injuries experienced from an RTA (i.e. a traffic accident as a motorcycle rider, an occupant of a three-wheel motor vehicle, a car occupant or an occupant of a pick-up truck or a van (V20 to V59, ICD10 codes)).[52] However, this utility of 0.62 assumed for RTAs was not reported in the HODaR publication that was referenced by McDaid et al. and the company.

Based on the explanation provided in McDaid et al.[52] the utility of 0.62 seems reasonable for severe RTAs (including broken neck or back, severe head and chest injuries, fractured limbs etc.). However, this utility is in the model also applied to patients who experienced slight RTAs (i.e. shock, bruising, sprains and strains, shallow cuts, lacerations, abrasions, and whiplash or neck pain). The ERG has strong reservations about these slight injuries being associated with such a low utility, especially considering that in the model the utility for patients who have had a stroke is about 0.77. However, there is no data of the utility after slight RTAs. Therefore, in the ERG base-case, these patients are assumed to experience a disutility equal to the most severe other event in the model, namely stroke (i.e. disutility of -0.052).

It is standard practice within NICE appraisals to adjust utilities over the lifetime horizon of the model to account for the decline in utilities due to ageing. However, this was only included in a scenario analysis and not in the company base-case.

The study used by the company to estimate the (constant) yearly decline in utility was a US study that aimed to develop EQ-5D index scores for chronic diseases. However, the ERG prefers the UK alternative for age-adjusted utilities, i.e. a study by Ara and Brazier 2010,[74] who developed an equation which estimates the mean utility of the UK general population, adjusted for age and sex. When using the Ara and Brazier equation, the decline in utility due to ageing increases as people age.[74] In the ERG base case the equation of Ara and Brazier 2010 is used to account for the decline in utility due to ageing.

Various errors were identified by the ERG that needed correction of the model. Some of them were small errors, others more important, though the overall impact on the ICER was limited.

The major change to the company's base-case model pertained to the exclusion of CV event related costs and QALYs in the ERG's base-case model.

The ERG's base-case results indicate that the probability of cost effectiveness for the addition of pitolisant to the treatments mentioned above is 2% at the range of willingness to pay thresholds that are generally deemed acceptable by NICE. For the patient population with residual EDS whilst on CPAP we find an ICER of £67,557 for pitolisant treatment versus Best Supportive Care (BSC). For the patient population with EDS who refuse CPAP a full incremental analysis was done. This yields an ICER of almost £36,735 per QALY gained for MAD + BSC versus BSC alone, and an ICER of about £97,483 for pitolisant versus MAD.

The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. These key uncertainties were related to the inclusion of costs and QALYs related to the CV events CHD and stroke, social care costs due to the same CV events, the use of the SF-6D as an alternative to the EQ-5D-3L, and using an alternative utility mapping algorithm. The inclusion of CV events reduced the ICERs by more than half, and the inclusion of social care costs reduced the ICERs further. The use of the SF-6D only marginally increased the ICERs, and the use of the alternative mapping algorithm led to substantially higher ICERs. The other assumptions tested by the ERG had a minor impact on the model results.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Pitolisant hydrochloride for treating excessive daytime sleepiness caused by obstructive sleep apnoea [ID1065]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Monday 3 August 2020** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Exclusion of discussion around the potential mechanisms linking EDS and cardiovascular risk

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11 Additionally, CPAP treatment has been shown to reduce known cardiovascular risk factors, predominantly blood pressure The substantiation of the assumptions made by the company were deemed insufficient to warrant the inclusion of an effect of pitolisant on the incidence of coronary heart disease (CHD) and stroke. Therefore, the ERG base-case did not include such an effect.	Additionally, CPAP treatment has been shown to reduce known cardiovascular risk factors, predominantly **by exerting a modest effect on** blood pressure **in patients experiencing EDS, despite CPAP.** **Blood pressure is only one component of the complex neurohumoral mechanisms by which OSA has an impact on CV risk and EDS has been shown to be strongly associated with cardiovascular disease, even after correction for cardiovascular risk factors.** ~~The substantiation of the assumptions made by the company were deemed insufficient to warrant the inclusion of an effect of pitolisant on the incidence of coronary heart disease (CHD) and stroke. Therefore, the ERG base-case did not include such an effect.~~	It is true that CPAP treatment has been shown to reduce known CV risk factors, predominantly blood pressure. However, the relationship between EDS, CPAP and CV risk is much more complex than a simple blood pressure effect, as pointed out in our answer to clarification question B3. To summarise: • Non-sleepy patients do not experience a reduction in blood pressure even in the presence of hypertension suggesting that EDS itself may have a role in cardiovascular risk. • The presence of EDS has been shown to be strongly associated with cardiovascular disease, even after correction for known CV risk factors. • Blood pressure is only one component of the complex neurohumoral mechanisms by which OSA has an impact on CV risk The ERG is being somewhat disingenuous in excluding this important discussion and suggesting	Not a factual inaccuracy. Also, the ERG did not imply in this statement that blood pressure was the only risk factor for CHD or stroke, nor the only means by which any intervention can reduce cardiovascular risk. The ERG has reviewed the discussion of the complexity of the relation between OSHAS, EDS, and cardiovascular risk in the ERG comment in section 5.2.6.1. The possibility that a causal relation between EDS and cardiovascular risk is not dismissed completely by the ERG, and the possible effect of pitolisant through this mechanism is still explored in a scenario analysis.

		that the only way in which CPAP or any other agent can reduce cardiovascular risk is by lowering blood pressure. In excluding the discussion, the ERG is able to exclude the impact of pitolisant on CV risk factors from the base case. We believe that in reducing EDS, pitolisant reduces CV risk and suggest that the ERG should look at modifying the impact of pitolisant on CV risk, rather than dismissing it completely out of hand.	

Issue 2 Exclusion of details of epidemiology of the population suitable for pitolisant: ie people with moderate to severe OSA receiving CPAP with residual EDS and people with EDS due to OSA who refuse CPAP

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14 The ERG notes that no EDS-specific prevalence is reported in the CS.	Replace ERG statement with: Estimates from the company suggest that 21,300 people in England with moderate to severe OSA receiving CPAP have residual EDS and 21,300 people have EDS due to OSA and refuse CPAP.	This submission focuses on the population suitable for pitolisant – which comprises of people with moderate to severe OSA receiving CPAP with residual EDS and people with EDS due to OSA who refuse CPAP. Page 50-51 of the CS outline the epidemiology of these populations and it would be helpful to include this information within the ERG report, since it reassures the reader that the maximum patient pool for pitolisant is relatively small at 42,600.	Not a factual inaccuracy.

Issue 3 Exclusion of company rationale to support CPAP is the gold standard treatment for EDS due to OSA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16 The company did not provide additional references to support the statement '(…) CPAP is the gold standard treatment for EDS due to OSA'	Delete this statement	As noted in our response to Clarification question A7. CPAP is recommended in NICE TA 139 as the first-line treatment (after lifestyle modifications) for the treatment of OSA, making it a standard treatment. Furthermore, advice from clinicians working in the field stated that CPAP is the preferred first-line treatment for the treatment of OSA, once patients have tried lifestyle modifications.	Not a factual inaccuracy. The ERG has mentioned TA 139 and no references additional to this were cited.

Issue 4 The potential inclusion of MADs as a comparator in the patient group with residual EDS despite CPAP

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 Firstly because, even if CPAP is considered the gold standard treatment for OSA, this does not mean that other comparators cannot be considered. Secondly, the fact that pitolisant is always used in combination with CPAP, does not mean that all comparators should also be used	Delete this statement	As noted in our response to Clarification question A7. The licence for pitolisant is • In addition to CPAP in patients with residual EDS, in which case the comparator is CPAP. • Alone in patients with EDS who refuse CPAP, in which case the comparators are either best	Not a factual inaccuracy. Theoretically, if it is discovered that there is residual EDS on CPAP then an alternative might be a MAD.

in combination with CPAP. Therefore, the ERG still beliefs MADs could be regarded as a relevant comparator. Also see page 38 However, the company only included a comparison of pitolisant versus MAD in patients with EDS due to OSA who refused CPAP (the HAROSA II population); therefore, only the HAROSA II trial was included for pitolisant.	Delete this statement	supportive care or MADs. It should be noted that MADs are only used in patients with mild to moderate disease and are not standard of care in the UK.	

Issue 5 Language around Patient Access Scheme

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 There is no patient access scheme (PAS) in place	There is no patient access scheme (PAS) in place, **because pitolisant will be initiated in Secondary Care and continued in Primary Care, which means that it is excluded from the usual PAS scheme.**	The company initiated the PAS process with PASLU, unfortunately the way in which pitolisant will be prescribed means that it is excluded from the usual PAS arrangements. The company explored potential ways in which we could fit into the PASLU PAS scheme with PASLU, however, none were deemed appropriate. The company remain willing to offer a discount if an appropriate PAS mechanism can be arranged.	Not a factual inaccuracy.

Issue 6 Exclusion of MADs within the company's original systematic review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10 Mandibular advancement devices (MADs) could be regarded as a relevant comparator, yet they have been explicitly excluded from the systematic review for efficacy and safety studies by the company Page 27 As explained in Section 3.3 in this report, the ERG believes that MADs could be regarded as a relevant comparator, yet they have been explicitly excluded from the systematic review for efficacy and safety studies by the company. Page 41 The ERG beliefs MADs could be regarded as a relevant comparator, yet they have been explicitly excluded from the systematic review for efficacy and safety studies by the company	Mandibular advancement devices (MADs) could be regarded as a relevant comparator, yet they were excluded from the systematic review for efficacy and safety studies by the company, **since they were not included in the pre-referral scope and did not arise in early discussions with clinical advisors.** As explained in Section 3.3 in this report, the ERG believes that MADs could be regarded as a relevant comparator, yet they were excluded from the systematic review for efficacy and safety studies by the company, **since they were not included in the pre-referral scope and did not arise in early discussions with clinical advisors.** The ERG **believes** that MADs could be regarded as a relevant comparator, yet they were excluded from the systematic review for efficacy and safety studies by the company, **since they were not**	The use of MADs did not arise in our early discussions with clinical advisors and MADs were not included as comparators in the pre-referral scope which guided our systematic review. NICE TA 139 states that *Dental devices are designed to keep the upper airway open during sleep. The efficacy of dental devices has been established in clinical trials, but these devices are traditionally viewed as a treatment option only for mild and moderate OSAHS* It is therefore our understanding that MADs are not commonly used and were not considered in our original systematic review. We did carry out a later search to identify studies which evaluated MADs, this was carried out under a tight timeframe and searched for systematic reviews and meta-analyses only. The company has worked hard to understand the role of MADs in clinical practice, but has been hampered by lack of access to clinical experts due to COVID-19. We have since spoken to the Sleep Apnoea Trust who told us that MADs are	We have corrected the typo on page 41. It is important to point out that the ERG is not making a judgement about the amount of effort that the company have made to investigate the need to included MADs as comparator: these are simply intended to be statements of what the ERG believe to be relevant to the scope.

	included in the pre-referral scope and did not arise in early discussions with clinical advisors.	rarely used in the UK and seldom funded within the NHS. The company believes that MADs are only an appropriate comparator in people with EDS who refuse CPAP, see Issue 4. NICE are currently developing guidelines for obstructive sleep apnoea/hypopnoea syndrome and obesity hypoventilation syndrome in over 16s (GID-NG10098). This guidance was due in August 2020 but has been delayed due to COVID-19. We anticipate that this guidance will help to clarify the position of MADs in the treatment pathway.	

Issue 7 Critique of data extraction

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27 The authors did not perform data extraction in duplicate. There was no mention of data extraction being checked by a second author.	Delete this statement	Apologies, we should have specified, but data extraction was definitely completed by one researcher and thoroughly checked by a second researcher to avoid bias and error.	The first sentence has been deleted..

Issue 8 Half-life statement for pitolisant in the context of washout prior to pitolisant use

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27 However, the company did not provide the half-life time for pitolisant.	Delete this statement	Although we did not include the half-life for pitolisant, it is irrelevant in this context as the ERG are discussing the washout period **before** pitolisant is initiated.	The sentence had been deleted.

Issue 9 Dosing of pitolisant in the HAROSA studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30 The starting dose was 5 mg from days 1-7. From days 8-14, the 10 mg dose was introduced. The 15 mg dose was maintained or reduced at day 21 based on tolerability and dose stability	Replace ERG statement with: Pitolisant/placebo dose starting at 5 mg from day 1 to day 7, 10 mg from day 8 to day 14 and 20 mg from day 15, dose was maintained or reduced at day 21 according to tolerability and dose stable thereafter	Dose description is ambiguous in the ERG report, suggested amendment for clarity. The company is particularly concerned since pitolisant does not have a 15 mg dose and the current copy could be open to misinterpretation.	This has been corrected.

Issue 10 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32 The reduction in ESS score was	The reduction in ESS score was greater with pitolisant compared to placebo in HAROSA I (mean difference (MD) -2.6,	Typographical error $p<0.002$ to be replaced by $p<0.001$	Corrected.

greater with pitolisant compared to placebo in HAROSA I (mean difference (MD) -2.6, 95% CI -3.9 to -1.4, p<0.001) and in HAROSA II patients, who refused CPAP, (MD -2.8, 95% CI -4.0 to -1.5, p <0.002).	95% CI -3.9 to -1.4, p<0.001) and in HAROSA II patients, who refused CPAP, (MD -2.8, 95% CI -4.0 to -1.5, **p <0.001).**		

Issue 11 Language around the minimal important difference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32 According to the company, the minimal important difference (MID) for ESS is two points in patients with OSA and EDS, Page 41 The company noted that the minimal important difference for ESS was two points, which indicated clinical and statistical significance	~~According to the company,~~ The minimal important difference (MID) for ESS is two points in patients with OSA and EDS, ~~The company noted that~~ the minimal important difference for ESS was two points, which indicated clinical and statistical significance	By using the phrase 'According to the company', and 'The company noted' the ERG is casting doubt on the MID for ESS. The MID for ESS is taken from a robust study by Crook et al Crook S, Sievi NA, Bloch KE, et al. Minimum important difference of the Epworth Sleepiness Scale in obstructive sleep apnoea: estimation from three randomised controlled trials. Thorax 2019; 74(4): 390-6 The methodology used by Crook is vigorous and is described in detail in Clarification question A12.	Not a factual inaccuracy. It should be noted that MID is a subjective notion, and so it would not be reasonable to state what the company presented as if it were objective fact: that reference was also cited by the ERG.

Issue 12 Incorrect statement re evidence for impact of pitolisant on CV risk

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 50 In particular, no evidence is provided for the rationale to include an effect of pitolisant on cardiovascular event. Page 75 The company provided no evidence or rationale based on well understood biological mechanisms to substantiate the assumption that pitolisant has an effect on the incidence CHD-events and stroke. The company provided reasonable evidence that EDS is an independent prognostic factor for cardiovascular risk but did not provide any evidence or rationale that this is a causal relation and that the direction of causality is such that cardiovascular risk is reduced when EDS is treated The substantiation of the assumptions made by the company are thus deemed insufficient to warrant the inclusion of an effect of pitolisant	Delete this statement Delete this statement	This is incorrect, detailed rationale is outlined in clarification question B3 and in Issue 1.	Not a factual inaccuracy. The rationale presented by the company is not equivalent to evidence of an effect of pitolisant on a risk factor, the change in which has been shown to effect a change in risk of a cardiovascular event. The answer to clarification question B3 predominantly highlights that the complex relationship between OSHAS, EDS and cardiovascular risk is currently not well understood. The answer to B3 itself provides multiple possible explanations for the currently available evidence and acknowledges that a causal association between EDS and cardiovascular risk has not been established. The ERG is therefore of the opinion that the statements in the ERG report are an accurate representation of the statements in the company submission and clarification questions.

on the incidence of CHD-events and stroke Page 91 In particular, no evidence is provided for the rationale to include an effect of pitolisant on cardiovascular event The substantiation of the assumptions made by the company is thus considered insufficient to warrant the inclusion of an effect of pitolisant on the incidence of CHD events and stroke.	Delete this statement Delete this statement		

Issue 13 The trial populations are representative of the UK population eligible for pitolisant

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51 It is not clear to the ERG to what extent the trial populations are representative of the UK population eligible for pitolisant. At the same time, it is also unclear to what extent the estimate of the primary outcome (ESS) would change if the UK OSA population differed	**The trial populations are representative of the UK population eligible for pitolisant.** At the same time, it is also unclear to what extent the estimate of the primary outcome (ESS) would change if the UK OSA population differed substantially regarding the baseline characteristics.	The company discussed the study populations with a clinical expert. He confirmed that *The population of the HAROSA studies is relevant to the English population* (page 49 of CS) Telephone conversation: Tricia Dixon (JB Medical) and John O'Reilly (Consultant Physician in Respiratory and Sleep Medicine) 17 September 2019 was provided as a reference. The	Not a factual inaccuracy. This is a matter of judgement.

substantially regarding the baseline characteristics.		clinical expert states that the demographics of the HAROSA studies *largely reflects what we see in practice: frequently middle aged, obese men, most of whom are still working.*	

Issue 14 Exclusion of company rationale for inclusion of an effect of pitolisant on CHD events and stroke

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 54 In the clarification letter, the ERG questioned the decision to include a treatment effect of pitolisant on CHD events and stroke in the model. The answer to this question did not provide a strong rationale for the inclusion of an effect of pitolisant on CHD events and stroke. Page 55 The substantiation of the assumptions made by the company are thus deemed insufficient to warrant the inclusion of an effect of pitolisant on the incidence of CHD events and stroke. Therefore, the ERG base-case will not include such an effect. Rather, these effects are explored in a scenario	Delete this statement Delete this statement	As outlined in Issue 1 and in clarification question B3 we believe that there is a strong rationale to suggest that pitolisant may have an impact on CV risk via the reduction of daytime sleepiness.	Not a factual inaccuracy. The rationale presented by the company is not equivalent to evidence of an effect of pitolisant on a risk factor, the change in which has been shown to effect a change in risk of a cardiovascular event.

analysis.			

Issue 15 Error in all-cause mortality for CPAP refusers

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 58 The all-cause mortality for the OSAHS patients who refused treatment with CPAP appeared to have a two-year lag compared to the OSAHS patients treated with CPAP with residual EDS. As the ERG could not find a plausible explanation for this, this was corrected in the model.	No amendment	The ERG is correct, there is a 2-year lag for the all-cause mortality for OSAHS patients who refused treatment with CPAP. We initially considered using the 2016-2018 UK life table starting at 54 years for HAROSA I and 52 years for HAROSA II to account for the mean age each study. We later opted for the use of the VLOOKUP function in Excel, which meant that we could use the same 2016-2018 UK life table for both studies. We did eventually use the VLOOKUP, but omitted to remove the 2016-2018 UK life table for HAROSA II from the model. This is an error on our part, however, it has a marginal impact on the model result.	No response required.

Issue 16 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 65 Table 5.11 Based on Table 14 in the company's response to clarification questions.[24]	Based on Table **15** in the company's response to clarification questions.[24]	Typo	Corrected.

Issue 17 Clinical expert response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 The ERG would have preferred to receive details on what was asked and what the responses were of this expert.	Delete this statement	Telephone conversation: Tricia Dixon (JB Medical) and John O'Reilly (Consultant Physician in Respiratory and Sleep Medicine) 17 September 2019 was provided as a reference and detailed the questions we asked John and his answers	Not a factual inaccuracy.

Issue 18 Use of discount rates as part of the univariate deterministic sensitivity analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73	In general, discount rates should not be part of the univariate deterministic	Although it is true that discount rates are not subject to parameter uncertainty but	Not a factual inaccuracy.

In general, discount rates should not be part of the univariate deterministic sensitivity analysis. This analysis is meant to explore the impact of parameter uncertainty, and discount rates are not subject to parameter uncertainty but are in many cases government determined.	sensitivity analysis. **However, in situations where there is a significant cost associated with one treatment arm (Pitolisant + BSC) and no treatment cost associated with the other (BSC) inclusion of discount rates can be very helpful.**	are in many cases government determined, it is useful to assess how variation in cost might impact on the ICER, especially in situations where there is a significant cost associated with one treatment arm (Pitolisant + BSC) and no treatment cost associated with the other (BSC).	

Issue 19 The company use of assuming a range based on 20% of the mean for transition probabilities where no 95% CI data is available

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73 For the parameter under discussion, assuming a range of 20% leads to an underestimation of the uncertainty.	Delete this statement	The company agrees that it is difficult to determine a range which is representative of the data when the 95% CI is not available. For example, for "MAD (HAROSA II): transition probability from OSAHS to Acute Stroke" a 95% CI was available and was equivalent to 20% range around the mean. Whereas, for "CPAP+BSC (HAROSA I): transition probability from OSAHS to Acute Stroke" a 95% confidence interval was also available and was equivalent to 40% range around the mean. We would like to point out that the 20% range is conventionally used when the 95% CI is missing.	The statement on Page 73 was changed to: "For the parameter under discussion, assuming a range of 20% might lead to an underestimation of the uncertainty."

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Technical engagement response form

Pitolisant hydrochloride for treating excessive daytime sleepiness caused by obstructive sleep apnoea [ID1065]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments 5pm on Tuesday 2 February 2021

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bioprojet**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Issue 1: Trial population and its generalisability.	
1. Is there evidence to support the efficacy of pitolisant in these groups who were not included in the trial?	In common with many clinical studies in obstructive sleep apnoea, the HAROSA studies excluded patients with specific co-morbidities – the Evidence Review Group have raised concern over the efficacy of pitolisant in patients with co-existing cardiovascular disease and psychiatric illness. Patients with serious cardiovascular disease in the opinion of the treating physician (defined as recent myocardial infarction, angina, hypertension or dysrhythmias [within the previous 6 months], QT interval longer than 450 ms, history of left ventricular hypertrophy or mitral valve prolapse) were excluded from the HAROSA studies. However, just over one-half of people in the HAROSA studies had pre-existing cardiovascular disease (HAROSA I: 138/244, 56% and HAROSA II: 145/268, 54%, Document B, Table 5) providing clear evidence for the efficacy of pitolisant in patients with cardiovascular disease. Furthermore, most patients in the HAROSA studies were obese (mean body mass index was >30 in both HAROSA studies, Document B, Table 5), suggesting that many of the trial participants had type 2 diabetes and metabolic disorders such as insulin resistance and glucose intolerance. The table below indicates that 39% of patients in HAROSA I and 30% in HAROSA II had pre-existing metabolic disorders. Patients with psychiatric illness were excluded if the physician felt that their psychiatric condition would make study participation challenging, rather than any particular concern re co-morbid conditions. As shown in the table below, 18% of patients in HAROSA I and 5% in HAROSA II had pre-existing psychiatric illness. The HAROSA studies included patients with depression and

anxiety if, in the opinion of their physician, their condition would not impact on study participation. A Beck Depression Inventory (13 item short form) score of <16 was an inclusion criterion, meaning that people with mild (score 5-7) and moderate (score 8-15) depression were included in the HAROSA studies.

The Beck Depression Inventory was used to assess depression in study participants at the beginning of the studies. In HAROSA I mean score was 4.5 in the pitolisant arm and 4.0 in the placebo arm, for HAROSA II the scores were 4.7 and 4.4 respectively. However, there was a wide range in scores (0-15 in HAROSA I and 0-13 in HAROSA II) indicating that some patients had scores >7 and therefore were experiencing mild or moderate depression at the start of the study, as per the inclusion criterion. The table below details co-morbid conditions in both studies:

Co-morbidity	**HAROSA I (n=244)**	**HAROSA II (n=268)**
Cardiovascular	138 (56.6%)	145 (54.1%)
Metabolic	96 (39.3%)	80 (29.9%)
Neurological/psychiatric	43 (17.6%)	14 (5.2%)
Urogenital	34 (13.9%)	10 (3.7%)
Ear/nose/throat	29 (11.9%)	14 (5.2%)
Dermatology	18 (7.4%)	5 (1.9%)
Respiratory	44 (18.0%)	34 (12.7%)
Gastrointestinal	47 (19.3%)	25 (9.3%)
Allergy	21 (8.6%)	7 (2.6%)
Haematology	7 (2.9%)	1 (0.4%)
Others	72 (29.5%)	45 (16.8%)

The clinical advisor consulted for this submission confirmed that patients enrolled in the HAROSA studies are relevant to the UK population (Document B, page 49).

There is reason to suggest that pitolisant would not be efficacious in people with excessive

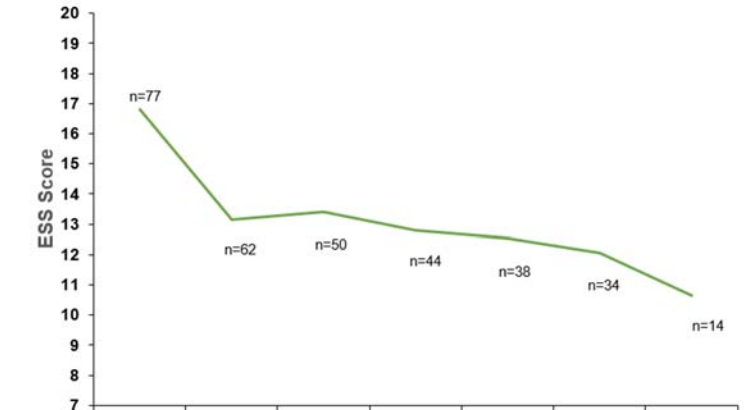
	daytime sleepiness and co-morbid cardiovascular disease or depression. Indeed, the mode of action of pitolisant (orally active histamine H3-receptor antagonist/inverse agonist which, via its blockade of histamine auto-receptors, enhances the activity of brain histaminergic neurones resulting in improved wakefulness) is not impacted by co-morbidities. Furthermore, safety data from the two pivotal trials did not indicate any cardiovascular or psychiatric issues.
2. What is the prevalence of these conditions in people who have OSA?	*Depression* Patients with obstructive sleep apnoea have higher rates of depressive disorders (15-56%) than the healthy population (6-7%)[1] Lang and colleagues used Beck's Depression Inventory and the Center for Epidemiological Studies Depression Scale to assess 1,875 men aged 35 to 83 years to determine whether undiagnosed excessive daytime sleepiness and obstructive sleep apnoea were associated with depression. Depression was present in 11.5% of men without obstructive sleep apnoea vs 15% of those with mild to moderate disease and 21.3% of those with severe disease. The presence of excessive daytime sleepiness significantly increased the incidence of depression from 12.2% in patients without excessive daytime sleepiness to 26.7% in those with the condition, $p<0.001$. Previously undiagnosed and untreated severe obstructive sleep apnoea alone was associated with an increased prevalence of depression (adjusted odds ratio=1.69; 95% CI, 0.85-3.36), as was excessive daytime sleepiness alone (adjusted odds ratio=1.19; 95% CI, 0.49-3.05). However, the interplay between the two conditions is demonstrated by men with both excessive daytime sleepiness and severe obstructive sleep apnoea being almost 3-times more likely to have depression than those with either diagnosis (adjusted odds ratio=4.82; 95% CI, 1.42-16.35. $p<0.05$[2]). *Diabetes* The prevalence of obstructive sleep apnoea in people with type 2 diabetes has been estimated at between 18% (Primary Care) and 86% (obese populations with type 2 diabetes)[3]. Five studies of almost 1,200 people with type 2 diabetes found that approximately 71% (range 58% to 86%) of

	people had co-existing obstructive sleep apnoea as diagnosed on polysomnography[4]. The variation in prevalence rates is due to differences in study population and in methods of detecting sleep apnoea, however, it is clear that there is significant co-morbidity, much of which is undiagnosed. The prevalence of type 2 diabetes is significantly higher in people with obstructive sleep apnoea than in the general population, prevalence estimates of type 2 diabetes range from 15% to 30% in people with a diagnosis of obstructive sleep apnoea[4]. Data from the National Sleep Foundation's Sleep and Aging poll revealed that older people with type 2 diabetes were significantly more likely to have excessive daytime sleepiness than people without type 2 diabetes. Of the sample, 20% of the people with diabetes had excessive daytime sleepiness vs 13.4% of those without diabetes, p=0.009. Sleepy people with diabetes also reported more frequent feelings of depression, decreased pleasure in life, naps, feeling drowsy or dozing off while driving than people with diabetes alone (all $p<0.05$)[5]. It seems that the prevalence of diabetes is significantly higher in people with excessive daytime sleepiness and obstructive sleep apnoea than in those with obstructive sleep apnoea or excessive daytime sleepiness alone. A study of 6,779 women aged 20-99 years found that the prevalence of diabetes was 1.6% in people without excessive daytime sleepiness and obstructive sleep apnoea, rising to 5.0% in those with excessive daytime sleepiness and to 5.8% in those with both excessive daytime sleepiness and obstructive sleep apnoea[6]. The prevalence of diabetes in women with obstructive sleep apnoea alone was 2.9%. *Cardiovascular disease* Daytime sleepiness plays an important role in cardiovascular disease. People with obstructive sleep apnoea and excessive daytime sleepiness are at higher risk of cardiovascular disease than those with without obstructive sleep apnoea. Data from the Sleep Heart Study (n=1,207) showed that people with excessive daytime sleepiness have a significantly increased risk of prevalent cardiovascular disease (odds ratio=2.00 [1.21–3.31], p=0.007) and heart failure (odds ratio=4.64

	[2.17–9.92], p=0.0001) vs people without obstructive sleep apnoea. The increased risk of cardiovascular disease highest in those people who have both obstructive sleep apnoea and excessive daytime sleepiness[7]. Obstructive sleep apnoea and hypertension commonly co-occur: the reported prevalence of obstructive sleep apnoea in patients with hypertension is between 20% to 40%, increasing to 70% in those with drug resistant hypertension[8] The risk of hypertension increases with the severity of obstructive sleep apnoea – the Wisconsin Sleep Cohort showed a linear relationship between hypertension and obstructive sleep apnoea with the risk of hypertension increasing by 4% for every 1 event/hour increase in apnoea hypopnea index[9]. It seems that the prevalence of hypertension is significantly higher in people with excessive daytime sleepiness and obstructive sleep apnoea than in those with obstructive sleep apnoea or excessive daytime sleepiness alone. A study of 6,779 women aged 20-99 years found that the prevalence of hypertension was 8.7% in people without excessive daytime sleepiness and obstructive sleep apnoea, rising to 12.8% in those with excessive daytime sleepiness alone and to 26.3% in those with both excessive daytime sleepiness and obstructive sleep apnoea[6]. The prevalence of diabetes in women with obstructive sleep apnoea alone was 15.5%.
Issue 2: Comparators	
Is it reasonable to include mandibular devices as a relevant comparator in people who have OSA but refuses CPAP?	Mandibular devices are traditionally viewed as a treatment option only for mild and moderate disease and are generally used earlier in the pathway than continuous positive airway pressure. If mandibular devices are used, they are offered to the patient prior to offering continuous positive airway pressure. Therefore, a patient who refuses continuous positive airway pressure may well have already been offered a mandibular device. This means that mandibular devices are not used in the same position in the treatment pathway as pitolisant, meaning that mandibular devices are not a relevant comparator to pitolisant.

Issue 3: Comparators	
Is the indirect treatment comparison, conducted by the company comparing pitolisant and mandibular devices, reliable for decision making given the ERG's concerns?	Given the comments from the Evidence Review Group on our existing systematic literature review and indirect treatment comparison comparing pitolisant with mandibular devices we have carried out an updated systematic literature review and indirect treatment comparison, which are provided as new sources of evidence. The systematic literature review identified 11 randomised controlled trials of mandibular advancement devices. However, none of the studies identified recruited a patient population directly matching that in the pitolisant trials. The closest match is the study by Gagnadoux et al. (2017)[10], which included patients with severe obstructive sleep apnoea who were intolerant of continuous positive airway pressure, but excessive daytime sleepiness was not a requirement in this study[11]. Patients in Gagnadoux et al, had a mean Epworth Sleepiness Scale score of 9.3 at baseline. One of the studies identified in the systematic literature review was excluded due to small patient numbers (n=13), leaving 10 studies of mandibular advancement devices and the two studies of pitolisant (HAROSA I and HAROSA II) to be included in a mixed treatment comparison[12]. Severity of both obstructive sleep apnoea and excessive daytime sleepiness varied across the populations and none of the studies matched the pitolisant HAROSA studies in terms of severity of obstructive sleep apnoea (moderate and severe) and excessive daytime sleepiness (Epworth Sleepiness Scale score weighted mean of 15.21 across both HAROSA studies). All the included studies of mandibular advancement devices had Epworth Sleepiness Scale <14 (weighted mean 10.36), with the severity of obstructive sleep apnoea ranging from mild (n=1), mild and moderate (n=3), moderate and severe (n=5) and severe (n=1). Therefore, there was significant clinical heterogeneity across the included studies in terms of the baseline characteristics. Six out of the eleven included studies were crossover randomised trials and the remaining five were parallel randomised controlled trials. Six of the eleven studies had low risk of bias, and the

	remaining five studies did not report information on the quality of the randomised controlled trial. Most of the studies which did not report on randomisation and concealment methods were crossover trials. Regardless of the model used (fixed effect or random effect), the mixed treatment comparison assessing efficacy (Epworth Sleepiness Scale change from baseline) suggests that pitolisant had a significantly larger impact on Epworth Sleepiness Scale than placebo and no treatment, but no significant difference when compared with mandibular advancement devices and continuous positive airway pressure, although the effect sizes were large. Surface under the cumulative ranking curve indicated that pitolisant was most likely to be the most effective treatment in both analyses (surface under the cumulative ranking score of 97.5% for the fixed effects model and 96.1% for the random effects model). However, this analysis has several limitations: 1. Critical appraisal indicates that methods used to generate random allocation sequence and concealment were only provided in five of the eleven studies. 2. The populations in the mandibular advancement device trials do not match those in the pitolisant trials (patients had less severe daytime sleepiness in the mandibular advancement device studies than in the pitolisant studies, weighted mean Epworth Sleepiness Scale: 10.36 vs 15.21) and the severity of obstructive sleep apnoea ranged from mild to severe in the mandibular advancement device studies vs moderate to severe in the pitolisant studies. 3. The duration of treatment varied from 4 weeks to 16 weeks, this is a potential cause of bias, since evidence from the HAROSA studies suggests that Epworth Sleepiness Scale response improves over time with pitolisant. 4. The studies assessing the efficacy of mandibular advancement devices used different mandibular advancement devices, introducing uncertainty into the results.

Issue 4: Follow-up period in the clinical trials	
Is it plausible that pitolisant will continue to have the same beneficial treatment effects beyond the studied period?	Yes Patients receiving pitolisant for narcolepsy show sustained effect of treatment. The Harmony study assessed the use of pitolisant in narcolepsy over the long term. One-year data has been published[13] and reveals that excessive daytime sleepiness as measured by the Epworth Sleepiness Score decreased during the 12-month period (decrease of −3.37 ± 0.42; n=93 after month 1 and −4.6 ± 0.59, n=60 after 12 months). Harmony III will run for 5 years, to date data is available on 48 French patients, 14 (29%) of whom continued on treatment for 5 or more years[14]. The reduction in Epworth Sleepiness Score was maintained over the 5 year period. By the end of 5 years follow-up a decrease in mean ESS score of -6.07 from baseline was seen, see Figure.  |	Baseline	Month 3	Year 1	Year 2	Year 3	Year 4	Year 5
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ESS Score	16.8	13.16	13.42	12.8	12.53	12.06	10.64

	The responder rate (defined as reduction in Epworth Sleepiness Scale of ≥3 or final score ≤10 increased from 54.4% by the end of month 3 of treatment to 71.4% by the end of year 5. Bioprojet are also conducting a 5-year post-authorisation study of pitolisant in narcolepsy. Data collected from December 2016 to January 2020 is available in an interim study report. Data is available from [15]…. **Academic in confidence information removed.**
Issue 5: Evidence of effects on cardiovascular events	
Is it reasonable to remove the assumption of a utility benefit associated with pitolisant reducing cardiovascular events given the available evidence?	Yes We believe that there is insufficient evidence to exclude a cardiovascular benefit for treatment of excessive daytime sleepiness with pitolisant on the grounds that it has no effect on resting blood pressure. The relationship between obstructive sleep apnoea, excessive daytime sleepiness and cardiovascular disease is complex and the consensus from the literature is that it is mediated by more than the modest reduction in blood pressure associated with continuous positive airway pressure therapy. We addressed this issue in our previous response to the Evidence Review Group clarification questions, which we have reproduced below for your convenience. Original response to clarification questions *A number of studies have shown an association between OSA and increased CV risk, particularly in patients with EDS[16-22]. Hypertension is an easily identifiable CV risk factor that has been shown to be more frequent in people with OSA and EDS[23,24]. The use of CPAP has been shown to exert a modest beneficial effect on blood pressure[25]. It is proposed that this effect underlies the observed improvement in CV events, at least in those patients with hypertension[26].* *However, two studies have shown that CPAP only exerts a lowering effect on blood pressure in the presence of EDS, non-sleepy patients showing no change in blood pressure, even in the presence of hypertension[27,28]. This suggest that EDS either has a direct causative role in raising*

	blood pressure or is a marker of a third unknown factor, that may mediate the CV changes in a more subtle way than simply elevating blood pressure. *This not an unreasonable hypothesis, given that OSA appears to exert its CV effect via a range of different neurohumoral mechanisms, with the effect on blood pressure being one component of a complex autonomic interaction[29,30]. Additionally, the presence of EDS has been shown to be strongly associated with the risk of myocardial infarction, heart failure and stroke, even after correction for the effect of a wide range of known CV risk factors, including hypertension[7,31,32].* *There is therefore reason to believe that the interaction between OSA with EDS is considerably more complex than a simple blood pressure effect. Although it is difficult to demonstrate a causal association between EDS and CV risk, there is sufficient evidence to justify modelling CV outcomes based on the surrogate measure of ESS score. Even in the absence of an impact of pitolisant on blood pressure, this is consequently a plausible strategy.* Clearly, in order to resolve this issue, large, high quality randomised controlled trials are required. Unfortunately, owing to the undoubted symptomatic benefits of treatment in patients with excessive daytime sleepiness, the few randomised controlled trials published in the field have largely limited themselves to patients without excessive daytime sleepiness[33]. Indeed, in these patients there is little sign of any reduction in cardiovascular events with continuous positive airway pressure. However, excessive daytime sleepiness has been shown to be an independent predictor of cardiovascular disease risk, regardless of any co-existing general cardiovascular risk factors[34]. Randomised studies of continuous positive airway pressure in excessive daytime sleepiness are lacking, for the reasons outlined above. Oral amphetamine-derived stimulant therapy has been used on an ad hoc basis for a number of years in the absence of either a licence or any prospective evidence at all in any relevant patient group. Modafinil has a moderate evidence base in obstructive sleep apnoea and has been shown to improve excessive daytime sleepiness[35]. However, concerns about its impact on cardiovascular

	risk have led to the European Medicines Agency withdrawing its licence for obstructive sleep apnoea[36], so there is no possibility of a long-term trial investigating its impact on cardiovascular outcomes. The two newest drugs in the field – pitolisant and solriamfetol – have been investigated in short-term efficacy studies in excessive daytime sleepiness due to obstructive sleep apnoea, with confirmed ongoing benefit for up to 1 year. However, the studies are too small and of too limited duration to demonstrate any impact on cardiovascular risk. Additionally, because they have only been used in excessive daytime sleepiness due to obstructive sleep apnoea in the context of regulatory studies, there is insufficient clinical experience in this patient group to allow retrospective studies to have been carried out. The Technical Engagement document asks: *"Is it reasonable to remove the assumption of a utility benefit associated with pitolisant reducing cardiovascular events given the available evidence?"* • Excessive daytime sleepiness is an independent risk factor for cardiovascular disease – that is clear. • Pitolisant has been shown to reduce the magnitude of excessive daytime sleepiness due to obstructive sleep apnoea. What we cannot do is link these two statements together and claim, in the absence of evidence, that pitolisant will reduce the risk of cardiovascular events. However, there is a reasonable circumstantial case to be made that it may exert a benefit. In our original submission, we assumed a benefit comparable with that assigned to continuous positive airway pressure in the past. In their response, the Evidence Review Group assumed no benefit at all. It seems likely that both these positions are wrong and that the true impact of pitolisant on cardiovascular risk lies between the two extremes. We would therefore request that this uncertainty be made clear to the committee and that a scenario analysis be presented,

	incorporating the cardiovascular benefit, to inform the discussion between the expert and lay members.
Issue 6: Mapping algorithm	
Is the company's approach to mapping utility values from the literature [McDaid et al.] appropriate given that EQ5D data was collected in the clinical trials?	Yes EQ-5D data was collected in the HAROSA studies. As we detailed in our submission, pitolisant does not have an impact on EQ-5D (see Document B, page 34). This is not unexpected, EQ-5D along with other generic measures of quality of life, does not appear to capture quality of life benefit in patients with excessive daytime sleepiness. *The lack of impact on QOL is consistent with other studies in OSA treated with CPAP[37], MADs[38,39] or modafinil[40,41]. Clinical opinion, systematic reviews and work carried out by the Assessment Group for the NICE CPAP HTA indicate that generic instruments to measure QOL, including the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and the EuroQol (EQ-5D) do not capture benefit in QOL in patients with EDS[42-44]. These instruments have not been specifically designed to assess aspects of QOL in patients with OSA or EDS and sleep is not included as a specific dimension.* (Document B, page 48) However, Clinical Global Impression of Change which measures severity of illness, global improvement/change and therapeutic response shows a significant improvement with pitolisant, as discussed in our original submission (Document B, page 33). We have provided further analysis of the patient level EQ-5D[45] … **academic in confidence information removed….**in either HAROSA I or HAROSA II.
Issue 7: Utility value of reducing RTA by using pitolisant	

Is it reasonable to take into account that there could be a utility benefit of reducing road traffic accidents when taking pitolisant? Is there any available evidence to support this?	Yes Excessive daytime sleepiness has a significant impact on road traffic accidents, as discussed in our submission. *EDS is associated with an increased risk of accidents (particularly road traffic accidents [RTA]), indeed, the impact of EDS on RTAs is similar to that of drink driving[46]. A meta-analysis of six studies revealed that the odds ratio of the risk of a collision in drivers with OSA was 2.52[47]. It has been estimated that 40,000 RTAs/year in the UK are due to untreated OSA, given that these accidents result in injury or even fatality, the impact is considerable[48].* (Document B, page 16) Other studies have confirmed the impact of sleepiness on road traffic accidents. It is important to note that self-reporting of road traffic accidents due to sleepiness may be unreliable as drivers are reluctant to report accidents because of the potential of losing their driving licence. It has been suggested that two-thirds of people with obstructive sleep apnoea did not report their accidents[49], meaning that true rates of road traffic accidents are likely to be higher than those reported in the literature. A recent systemic review and meta-analysis including 10 cross sectional studies (n=51,520), six case control studies (n=4,904) and one cohort study (n=13,674) found that sleepiness at the wheel was associated with an increased risk of motor vehicle accidents (pooled odds ratio 2.51 [95% CI 1.87; 3.39])[50]. A large Swedish study found a similar increase in risk of road traffic accidents in patients with obstructive sleep apnoea (risk ratio of 2.45)[51]. Severity of daytime sleepiness, but not severity of sleep apnoea, was identified as a risk factor for road traffic accidents in patients with obstructive sleep apnoea, with risk of road traffic accident increasing with Epworth Sleepiness Scale[51]. A study comparing 38 patients with untreated obstructive sleep apnoea with 14 healthy controls, showed that increasing sleepiness (measured by Maintenance of Wakefulness, Epworth Sleepiness Scale and Karolinska Sleepiness Scale) correlated with objective measures of poor

	driving (inappropriate line crossings during a 90 minute, real-life driving session). As one might expect very sleepy and sleepy participants had significantly more inappropriate line crossings than non-sleepy control drivers[52]. A later study by the same group in people driving >5,000 km per year revealed that 74/176 (42%) of people with sleep disorders reported an accident or a near miss over a 1 year period. Of the people who experienced an accident/near miss, over one-third (37.8%) reported feeling sleepy at the wheel more than once a week. The risk of an accident/near miss increased with increasing sleepiness as measured by Maintenance of Wakefulness and Epworth Sleepiness Scale. People with Maintenance of Wakefulness latency <19 minutes (unable to remain awake for more than 19 minutes under test conditions) were 5.5 x more likely to report an accident/near miss than those with normal wakefulness[53]. Increasing daytime wakefulness by using a wakefulness agent, such as pitolisant, solriamfetol or modafinil, or by using continuous positive airway pressure should reduce the risk of road traffic accidents. There is evidence to support continuous positive airway pressure, solriamfetol and modafinil in improving driving performance (solriamfetol and modafinil) and reducing road traffic accidents (continuous positive airway pressure). There is strong evidence that treatment with continuous positive airway pressure reduces road traffic accidents by increasing wakefulness[47,49]. Data from the Swedish Traffic Accident Registry (n=635,786) revealed that treatment with continuous positive airway pressure (adherence to treatment for ≥4 hours per night) significantly reduced the incidence of road traffic accidents from 7.6 per 1,000 individuals per year to 2.5, a 70% reduction. However, in patients with poor adherence (0-4 hours continuous positive airway pressure per night) rates of road traffic accidents rose from 6.6 to 12.2[51]. Solriamfetol has also been shown to improve driving performance in patients with excessive daytime sleepiness due to obstructive sleep apnoea and narcolepsy. In two randomised, double-blind, placebo-controlled, crossover studies driving performance during an on-road driving test (a 1-hour drive on a public road) solriamfetol/placebo were assessed at 2 hours and 6 hours post-

	dose following 7 days of treatment with solriamfetol or placebo in people with excessive daytime sleepiness due to obstructive sleep apnoea[54] and narcolepsy[55]. For assessment of driving performance, the primary end-point was standard deviation of lateral position, a measure of "weaving," at 2 hours post-dose[54,55]. In people with excessive daytime sleepiness due to obstructive sleep apnoea, treatment with solriamfetol significantly improved driving performance vs placebo at 2 hours and 6 hours post-dose[54]. In people with excessive daytime sleepiness due to narcolepsy there was a significant improvement in driving performance with solriamfetol when measured 2 hours post-dose[55]. A similar study assessed the impact of treatment with the wake-promoting agent, modafinil, on driving performance in people with narcolepsy and idiopathic hypersomnia[56]. Patients were randomly assigned to receive modafinil (400 mg) or placebo for 5 days prior to the driving tests (inappropriate line crossings, standard deviation of lateral position). Modafinil significantly reduced the number of inappropriate line crossings and standard deviation of lateral position vs placebo. Sleepiness, as measured by the maintenance of wakefulness test was significantly correlated with the mean number of inappropriate line crossings, showing that sleepiness has a significant impact on driving ability. Indeed, the model developed by the University of York to inform prior NICE guidance on the use of continuous positive airway pressure in excessive daytime sleepiness due to obstructive sleep apnoea included the impact of continuous positive airway pressure treatment on the incidence of road traffic accidents. Pitolisant and continuous positive airway pressure both improve excessive daytime sleepiness, it is the improvement in excessive daytime sleepiness which is important to reduce the risk of road traffic accidents, rather than the way in which wakefulness is achieved.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Pitolisant for treating excessive daytime sleepiness caused by obstructive sleep apnoea

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Friday 12 February 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with OSA and current treatment options	
About you	
1.Your name	Graham Hill
2. Are you (please tick all that apply):	**X☐X** a patient with OSA? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with OSA? X☐ X a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement X☐ X Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement X ☐ X I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	**X**☐ **X** I am drawing from personal experience. **X**☐ **X** I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: I have been a SATA Committee member for 10 years, and Vice Chairman for 5 years. I represent SATA on the OSA Partnership Group and the Association for Respiratory Technology and Physiology Sleep Apnoea Committee. I have also attended annual or biennial conferences of ARTP, Royal College of GPs and the British Sleep Society as a SATA exhibitor, so I have had many discussions with medical professionals, manufacturers and others on OSA and sleep disordered breathing. **X**☐ **X** I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with OSA? If you are a carer (for someone with OSA) please share your experience of caring for them.	I was diagnosed with Obstructive Sleep Apnoea, and issued with a CPAP, in July 2000. However, I had experienced symptoms for several years prior to 2000, and was diagnosed with mild OSA, with no treatment indicated, in late 1993. Becoming accustomed to the CPAP took a few days, but since 2000 I have used my CPAP continuously, only not using it when suffering from, for example, a heavy cold, when breathing was difficult. It has been very effective, both in terms of minimising sleep disturbance, and in eliminating excessive daytime sleepiness. Bearing in mind my general health at the time of diagnosis, coupled with a family history of

	cardiac issues, CPAP has been life changing, and I have absolutely no doubt that CPAP treatment has saved my life.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for OSA on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	7a. Patient access to diagnosis and treatment of OSA is erratic. SATA has monitored NHS Sleep Clinic performance for many years, and though a number of excellent sleep clinics, pre-Covid, were able to diagnose and treat patients within reasonably short wait times, many had excessive waiting times for diagnosis, and an unreasonably long interval between diagnosis, and setting patients up on CPAP treatment. In some cases this was due to CCGs failing to fully understand their obligation under NICE TA139 to provide adequate funding for clinics in their area of responsibility. In addition SATA considers that too many GPs do not fully understand OSA. SATA believes that the key to making much greater inroads into the more than 3 million undiagnosed OSA sufferers is greater understanding and involvement in the diagnostic pathway by the primary care sector. 7b. These views are shared by my colleagues within SATA.
8. If there are disadvantages for patients of **current NHS treatments** for OSA (for example how the treatment is given or taken, side effects of treatment etc) please describe these	Pitolisant is not a current treatment for OSA with EDS. I am not aware of its use in other conditions.
Advantages of this treatment	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these.	There are no current treatments I am aware of for EDS associated with OSA which is not controlled by CPAP treatment

For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe these? For example, are there any risks with this treatment? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	See previous answer

Patient population	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	This proposed treatment is targeted at a particular group of patients. Which patients within this group who might benefit more or less is a matter for clinical judgement.
Equality	
12. Are there any potential equality issues that should be taken into account when considering OSA and treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race,	No. If approved the treatment should be offered to all eligible patients.

religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	No

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14. **Could a decline in ESS score lead to a lower risk of cardiovascular events?** o What are the main pathological reasons as of why these patients show increased cardiovascular risk compared to the general population? o Could the increase in awakeness cause a reduction of	I am not a clinician and cannot therefore comment.

cardiovascular events on this population? If so, how could this occur physiologically?	
15. **Generalisability of the population in the clinical trials to the UK setting.** The exclusion criteria of HAROSA I and HAROSA II clinical trials excluded patients with cardiovascular disease and psychiatric illness. However, literature states that the condition is associated with depression, metabolic and cardiovascular co-morbidities. o Do you think that the exclusion of these groups could impact	

upon the generalisability of the trial results? o Would you recommend the use of this drug to patients who have cardiovascular or psychiatric illnesses despite these groups not being studied in the trial? 16. **Mandibular advancement device in the treatment of OSA** o How relevant are mandibular advancement devices in the treatment of OSA in the UK? o Would you consider that mandibular advancement devices	

need to be combined with medication like pitolisant to gain relief from the condition?	
17. Would the increase in staying awake by taking pitolisant represent a benefit/utility in reducing road traffic accidents?	If a patient with EDS which was not being controlled by CPAP therapy, and if taking Pitolisant increased wakefulness in these circumstances, there is a theoretical likelihood of a reduction in road traffic accidents. However if the patient still experienced EDS with CPAP therapy, they should not be driving at all, so road traffic accidents would not occur unless the patient was breaking the law by driving whilst sleep impaired. The CS states that Pitolisant takes 5 weeks to become fully effective, so a patient should not be driving within that 5 week period, or subsequently, unless and until a consultant is satisfied that the patient's EDS is under control.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

-
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

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

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **2 March 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with excessive daytime sleepiness caused by obstructive sleep apnoea and current treatment options	
About you	
1. Your name	**ARI MANUEL**
2. Name of organisation	**LIVERPOOL UNIVERSITY FOUNDATION TRUST**
3. Job title or position	**CONSULTANT IN SLEEP AND VENTILATION**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with excessive daytime sleepiness caused by obstructive sleep apnoea? ☐ a specialist in the clinical evidence base for excessive daytime sleepiness caused by obstructive sleep apnoea or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**nil**
The aim of treatment for excessive daytime sleepiness caused by obstructive sleep apnoea	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Reduce EDS in patients with OSA already on maximal therapy (CPAP or JAD eg) who do not have another cause of EDS eg medication or other medical condition
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	Reduction in ESS of 2 Patient related outcome measure which reflects improvement in EDS

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in excessive daytime sleepiness caused by obstructive sleep apnoea?	OSA services in the UK are over stretched with diagnosis and treatment of OSA with CPAP (especially post-COVID-19) There is a significant proportion of patients who remain with EDS despite maximal NHS available therapy (in the most cases CPAP therapy) which the patient is currently compliant. There is very little/no option for this group of patients currently
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	No treated, or modafinil in rare cases. Some are labelled with secondary sleep diagnosis – Idiopathic hypersomnolence (perhaps incorrectly)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	No. Clinical guidelines is to investigate EDS in patients on CPAP, but practice varies around the UK. No treatments limit investigation pathways
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No clear pathway in the UK. Likely large variation based on exposure of cases eg bigger centres with access to advanced testing eg PSG/MSLT who treat patients with sleep conditions eg Narcolepsy may be different to other centres No pathway in US European (France) may have pathways; potentially liked to payments based on performance (payment dependent on compliance with CPAP)

• What impact would the technology have on the current pathway of care?	Would need a total change in the pathway as patients with EDS would need to be followed up and also those already on CPAP would also need to be captured
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	There is no treatment in this area currently used (perhaps the combination of CPAP with JAD or modafinil but this is rare)
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care specialist clinics (ie those which have the ability to perform the more advance testing for EDS on CPAP as well those which are use to titration of medication in sleep disorders) Potential for shared care with primary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Will need more sleep labs with the capability to perform tests to assess – eg MSLT/actigraphy More physiologists to perform and interpret tests potentially More physical sleep labs to performs tests More training (to primary and secondary care) to identify patients on CPAP with residual EDS
13. Do you expect the technology to provide clinically meaningful	Yes – there is no current care in this area

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	There has to be a tangible link between improving EDS and life expectance – I am not sure of the evidence base in that area
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – EDS is the primary compliant for patient with OSA – could have a profound benefit
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	More difficult – as mentioned earlier these patients may not be followed up currently (potential unmet need) – there is likely a need for more staff, training, equipment and physical space

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Informally – likely failure to work (i.e. no improvement with EDS) or significant side effects
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Unclear but likely some benefits with reduced hospital admission or visits to primary care or potential use of medications such as sedatives, anti-depressants and opiate based drugs
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes – no current treatment in this area so could have subsequential benefit (which needs to be offset with the substantial infrastructure improvement needed)

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes – as noted above
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Depends on side-effect – need to consider CVS SE but this needs to be considered in the increased activity of patients when EDS improves
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	The tests used are not freely available in the UK but data can be extrapolated

• What, in your view, are the most important outcomes, and were they measured in the trials?	Improvements in ESS
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA139?	No

23. How do data on real-world experience compare with the trial data?	Limited real world data
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Need to ensure
24b. Consider whether these issues are different from issues with current care and why.	Not different from current care
Topic-specific questions	
25. What would be the effect on patient compliance with first line therapy such as CPAP if soliramfetol improved OSA symptoms?	Patients who were already non compliant – remain non compliant Those who were compliant – likely remain compliant although some would potential reduce CPAP usage

26. What is the ESS level that best reflects 'normal' level of daytime sleepiness, and the group of patients who would most benefit from solriamfetol treatment?	Normal Below 9-10 (I guess the range would be 9-12; dependant on age sex social class ethnicity) Likely 12 – 20 range (anyone over 20 may not have EDS just from OSA)
27. What would you say is the appropriate definition of treatment response, in terms of ESS reduction or other measurable factors concerned in OSA?	ESS – 2 OR PROMS regarding sleepiness
28. How is ESS seen to vary over time in patients from this population from the initial consultation, without solriamfetol treatment?	Massive individual variation (between people or within the same individual over a short time frame) Influence by age, gender, social class, ethnicity Very unclear if EDS increases over time in a clinical population (maybe some anthropology evidence)

PART 2 – Technical engagement questions for clinical experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

Issue 1: Trial population and its generalisability.	
1. Is there evidence to support the efficacy of pitolisant in these groups who were not included in the trial?	
2. What is the prevalence of these conditions in people who have OSA?	
Issue 2: Comparators	
Is it reasonable to include mandibular devices as a relevant comparator in people who have OSA but refuses CPAP?	

Issue 3: Comparators	
Is the indirect treatment comparison, conducted by the company comparing pitolisant and mandibular devices, reliable for decision making given the ERG's concerns?	
Issue 4: Follow-up period in the clinical trials	
Is it plausible that pitolisant will continue to have the same beneficial treatment effects beyond the studied period?	
Issue 5: Evidence of effects on cardiovascular events	
Is it reasonable to remove the assumption of a utility benefit associated with pitolisant reducing cardiovascular events given the available evidence?	
Issue 6: Mapping algorithm	
Is the company's approach to mapping utility values from the literature [McDaid et al.] appropriate given that EQ5D data was collected in the clinical trials?	
Issue 7: Utility value of reducing RTA by using pitolisant	
Is it reasonable to take into account that there could be a utility benefit of reducing road traffic accidents when taking pitolisant? Is there any available evidence to support this?	

PART 3 -Key messages
16. In up to 5 sentences, please summarise the key messages of your statement: • • • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

Your privacy

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

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

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

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- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **2 April 2021**

Completing this form

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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with excessive daytime sleepiness caused by obstructive sleep apnoea and current treatment options	
About you	
1. Your name	**Adrian williams**
2. Name of organisation	**Queen Victoria Hospital**
3. Job title or position	**consultant**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? +☐ a specialist in the treatment of people with excessive daytime sleepiness caused by obstructive sleep apnoea? ☐ a specialist in the clinical evidence base for excessive daytime sleepiness caused by obstructive sleep apnoea or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	+☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
The aim of treatment for excessive daytime sleepiness caused by obstructive sleep apnoea	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve Q o L
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity	Reduction in ESS of 3 from baseline

by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in excessive daytime sleepiness caused by obstructive sleep apnoea?	yes
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	CPAP
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	yes
• What impact would the technology have on the	cost

current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	yes
• How does healthcare resource use differ between the technology and current care?	Medication rather than devices or often no treatment
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	secondary
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	none
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	yes

• Do you expect the technology to increase length of life more than current care?	no
• Do you expect the technology to increase health-related quality of life more than current care?	yes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	?
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	no

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes; using or tried to use CAP or MAD
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Employment isssues
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need	yes

is met?	
• Is the technology a 'step-change' in the management of the condition?	yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes- currently no Rx for those failing CPAP
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	?
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes,	Treating the patient's impaired Q o L

and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	?
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I know
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA139?	no
23. How do data on real-world experience compare with the trial	?

data?	
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	? equality- link won't open
24b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
25. What would be the effect on patient compliance with first line therapy such as CPAP if soliramfetol improved OSA symptoms?	Soliramfetol??
26. What is the ESS level that best reflects 'normal' level of	Unclear question: normal ESS <10; patients most likely to benefit >14

daytime sleepiness, and the group of patients who would most benefit from solriamfetol treatment?	And ? SOLRIAMFETOL??
27. What would you say is the appropriate definition of treatment response, in terms of ESS reduction or other measurable factors concerned in OSA?	3
28. How is ESS seen to vary over time in patients from this population from the initial consultation, without solriamfetol treatment?	little

PART 2 – Technical engagement questions for clinical experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

Issue 1: Trial population and its generalisability.	
1. Is there evidence to support the efficacy of pitolisant in these groups who were not included in the trial?	
2. What is the prevalence of these conditions in people who have OSA?	
Issue 2: Comparators	
Is it reasonable to include mandibular devices as a relevant comparator in people who have OSA but refuses CPAP?	yes

Issue 3: Comparators	
Is the indirect treatment comparison, conducted by the company comparing pitolisant and mandibular devices, reliable for decision making given the ERG's concerns?	
Issue 4: Follow-up period in the clinical trials	
Is it plausible that pitolisant will continue to have the same beneficial treatment effects beyond the studied period?	yes
Issue 5: Evidence of effects on cardiovascular events	
Is it reasonable to remove the assumption of a utility benefit associated with pitolisant reducing cardiovascular events given the available evidence?	
Issue 6: Mapping algorithm	
Is the company's approach to mapping utility values from the literature [McDaid et al.] appropriate given that EQ5D data was collected in the clinical trials?	
Issue 7: Utility value of reducing RTA by using pitolisant	
Is it reasonable to take into account that there could be a utility benefit of reducing road traffic accidents when taking pitolisant? Is there any available evidence to support this?	Yes; CPAP reduces RTAs

PART 3 -Key messages
16. In up to 5 sentences, please summarise the key messages of your statement: • Need for alternative treatments for residual sleepiness in patients on CPAP • Need to treat sleepiness in those who fail other OSA treatments • Q o L should not be ignored • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

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

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **2 April 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with excessive daytime sleepiness caused by obstructive sleep apnoea and current treatment options	
About you	
1. Your name	**Sonya Craig**
2. Name of organisation	**British Thoracic Society**
3. Job title or position	**Consultant Respiratory and Sleep physician, Chair of BTS Specialist Advisory Group for Sleep**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with excessive daytime sleepiness caused by obstructive sleep apnoea? **x**☐ a specialist in the clinical evidence base for excessive daytime sleepiness caused by obstructive sleep apnoea or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x**☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for excessive daytime sleepiness caused by obstructive sleep apnoea	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce daytime sleepiness associated with Obstructive Sleep Apnoea with or without CPAP therapy
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity	A reduction in Epworth Sleepiness score of at least two points and also an improvement in quality of life and daytime functioning.

by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in excessive daytime sleepiness caused by obstructive sleep apnoea?	Yes, there are no options currently for the relatively small group of patients with OSA who have residual sleepiness (rEDS). However, it is important that other causes such as shift work, mental health, medication and sleep hygiene are taken into account. It is difficult to separate this from idiopathic hypersomnia without specialist tests.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	OSA is treated with CPAP if moderate to severe. There is increasing evidence that even patients with very mild OSA on a sleep study get symptomatic improvement with CPAP if they present to their doctor with sleep disturbance or other symptoms associated with poor sleep quality.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, NICE guidelines for CPAP in OSA TA 139 2008
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The current guidance is for treatment with CPAP if AHI>15 (sleep study severity moderate to severe). Below this level lifestyle changes such as weight loss are advised. However many sleep centres would try CPAP at a lower level of severity if the patient reports significant daytime symptoms or sleep disturbance. This is based on a number of UK RCT such as MOSAIC and MERGE which have shown improvement in ESS and HRQoL at much lower levels of sleepiness (MOSAIC) and sleep study severity (MERGE). Most Sleep physicians would advocate a trial of CPAP but there is some variability in reimbursement in some areas of the country. The pathway for set up and followup for CPAP in OSA is varied and maybe mainly nurse led, consultant led or physiologist led. Services will have developed the most efficient pathway based on local resources and referral rates. Referrals into Sleep centres have greatly increased over the last 5 years due to the increase in obesity. Most sleep

	centres report long waits for diagnostic tests, CPAP set up and follow up. Some centres use industry partners to follow up their patients and they don't have the resource to carry out servicing or mask management. Therefore the ability to detect rEDS may be different in some areas and there would likely be long delays to see a specialist.
• What impact would the technology have on the current pathway of care?	Potentially hugely disruptive. In general, Sleep services in the UK are profitable to their local trust but not always well resourced despite this. There are already delays in seeing consultants/sleep specialist nurses and although there is remote monitoring to help with compliance reviews this is not universal. It is not clear from the company submission how rEDS would be defined and what tests would be required prior to starting Pitolisant. However it would be useful for patients who cannot use CPAP.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No this is a new technology in this field but is in use for treatment of Narcolepsy with cataplexy.
• How does healthcare resource use differ between the technology and current care?	At present patients with raised ESS on CPAP would have a compliance check either remotely or direct contact with download of their CPAP machine. Any mask issues or pressure changes would be instigated by the sleep physiology or technical team. Sleep studies on CPAP would be carried out to check for other causes. In some cases referral to a more specialist centre may be required with the suggestion of more complex sleep testing such as actigraphy or PSG. Consultant or nurse review would likely take place in most settings. Often compliance with CPAP is the issue or other medical conditions such as depression, chronic pain or chronic fatigue.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Most likely this would be specialist centres due to the potential need for further tests.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or	This is an unmet need and previously patients were unlikely to have had adequate investigation or follow up due to lack of resource and general underinvestment in sleep centres. The societal improvements are huge but investment in better staffing with monitoring of CPAP usage (which would improve CPAP compliance across the board and greatly improve cost effectiveness for the whole OSA population) are required. It is likely that non consultant medical

training.)	staff such as specialist nurses would be required to prescribe and monitor effectiveness or specialist pharmacists similar to the ILD model. As this drug is expensive then it is likely to need to be specially commissioned which could help sleep services in general to ensure there is adequate staffing.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, to some degree. It may also be useful for some patients who are only partly or non compliant with CPAP due to mental health issues or behavourial problems. For these patients they are extremely disabled by daytime somnolence and often put on weight due to their medication, they develop OSA but due to their mental health are unable to tolerate CPAP at a level that would improve sleepiness. As a result their mental health deteriorates and they are unable to function in society and are a great burden to themselves and their families. Therefore for some groups this could be life changing.
• Do you expect the technology to increase length of life more than current care?	Generally no but in some groups such as patients with extreme somnolence due to OSA and mental health issues this could improve quality of life to the point where they are able to follow a healthier lifestyle and reduce weight and engage with other lifestyle improvement activities.
• Do you expect the technology to increase health-related quality of life more than current care?	Not to a great extent for the general OSA population. CPAP shows good levels of HRQoL improvements even in mild patients and is greatest for the sleepiest patients. However some groups may benefit greatly from this.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As described above there are some groups who cannot tolerate CPAP despite best efforts. These are mainly those with mental health issues who are extremely claustrophobic and unable to tolerate any mask. They are on medication that causes weight gain and sleepiness. Often CPAP is attempted and then discarded. It is possible that this drug with good side effect profile could benefit this population and improve mental health functioning to the point that CPAP can then be tried again. Other groups could be those with neurodegenerative conditions who tolerate CPAP poorly but are very sleepy. This could help their quality of life and potentially reduce their cognitive decline (some evidence in mouse models for modafinil and armodafinil).
The use of the technology	
15. Will the technology be easier	Generally more difficult. It is likely that small sleep centres specialising in OSA only would need to rule out other

or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	causes of EDS first which may require objective tests of sleepiness (due to the concern of patients saying they are sleepy; this is likely to be easily reversed by a face to face consultation however) not available at their centres. This may already happen in their area where they refer to the specialist sleep centre for help or it may increase the number of referrals to the specialist centre (more likely). This means that patients may have to travel for this medication and subsequent prescriptions. Taking a tablet is easier than CPAP but for most patients ensuring compliance with CPAP would be important. Therefore more compliance monitoring would be required which is unlikely to be able to be absorbed into the specialist centre workload unless this was a specialist complex sleep pathway where this additional workload was factored in. Patients will generally accept this medication if they perceive benefit but would stop if side effects are too great.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Generally patients would be expected to continue with CPAP therapy and be compliant in order to start. This does increase the workload of checking compliance in order to prescribe the drug. In addition other more complex testing maybe required to rule out other causes of daytime sleepiness. Although this should be happening currently, it is not clear how or when this happens in some sleep centres (possibly as no treatment for rEDS currently exists). It is likely that the presence of this drug could stimulate greater referrals for testing for rEDS . It is not clear how sleep centres would decide when patients not able to tolerate CPAP would be eligible for this drug.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in	Those with cognitive problems.

the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes this is a novel drug with novel action. It is easy to take with few side effects and much improved compared with modafinil.
• Is the technology a 'step-change' in the management of the condition?	It is not clear how many patients have rEDS as they perhaps aren't investigated or looked for in the current OSA population. Therefore difficult to say if this is a step change.
• Does the use of the technology address any particular unmet need of the patient population?	Yes as described. Those with health conditions that genuinely prevent them using CPAP effectively.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Potentially worsen those with anxiety although the numbers are small in the clinical trials.

Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Cognitive functioning which wasn't addressed.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	It is difficult to extrapolate the effects of sleepiness long term and ESS is a subjective measure.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial	no

evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA139?	no
23. How do data on real-world experience compare with the trial data?	Patients in the trials were sleepier than most patients who are treated with CPAP. We would consider other conditions such as depression, chronic pain or poor sleep hygiene first before suggesting r EDS. It not clear when we would consider calling this idiopathic hypersomnia rather than r EDS.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Ability of CCGs to pay for treatment. Those areas with high levels of poverty tend to do badly with CPAP and have higher rates of obesity and mental health issues. It is very unlikely that CCGs would take on this additional cost and would be detrimental to the poorest areas.
24b. Consider whether these issues are different from issues with current care and why.	This drug could potentially help these groups most. However they already do poorly on CPAP and are referred late for investigation so having this drug available would not affect that inequality.
Topic-specific questions	

25. Is there any information from your clinical perspective that explains why reducing ESS score on patients with sleep apnoea can decrease their risk of cardiovascular events?	There is a link with high ESS and raised nocturnal BP. Treatment with CPAP reduces BP the most in the sleepiest patients(Pepperell, Lancet 2003). It is likely this is due to increased arousal at night due to apnoeas. However this does not mean that sleepiness is causally implicated in CV risk. Therefore just reducing sleepiness is unlikely to reduce CV risk especially if not using CPAP to reduce apnoeas.
26.Do you think that the exclusion of patients with psychiatric illness could impact upon the generalisability of the trial results? Would you recommend the use of this drug to patients who have cardiovascular or psychiatric illnesses despite these groups not being studied in the trial?	Yes, I think this is the group most in need of this type of medication due to their inability to tolerate CPAP. Yes, there is no evidence of raised BP or heart rate.
27.How relevant are mandibular advancement devices in the treatment of OSA in the UK?	Small numbers.

Would you consider that mandibular advancement devices need to be combined with medication like pitolisant to gain relief from the condition?	I would suggest that some device to alleviate the airway closing is used rather than pitolisant by itself. However MAD are not available on the NHS throughout the country.
28. The trial comparing pitolisant with placebo lasted 12 weeks after that all patients who wanted to continue received pitolisant for 40 weeks. Is this sufficient time to capture the effects of it?	Yes
29. Would the increase in staying awake by taking pitolisant represents a benefit/utility in reducing road traffic accidents?	Difficult to say if this is a large effect as the number of RTAs has reduced in general. I don't think this is a large effect.

PART 2 – Technical engagement questions for clinical experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

Issue 1: Trial population and its generalisability.	
1. Is there evidence to support the efficacy of pitolisant in these groups who were not included in the trial?	There is no reason why those not included wouldn't benefit.
2. What is the prevalence of these conditions in people who have OSA?	There are large numbers of patients with mental health problems who also have OSA
Issue 2: Comparators	
Is it reasonable to include mandibular devices as a relevant comparator in people who have OSA but refuses CPAP?	Yes

Issue 3: Comparators	
Is the indirect treatment comparison, conducted by the company comparing pitolisant and mandibular devices, reliable for decision making given the ERG's concerns?	MA devices also correct the underlying health condition (ie reduce apnoeas) which pitolisant doesn't so Pitilosant wouldn't affect CV risk for instance.
Issue 4: Follow-up period in the clinical trials	
Is it plausible that pitolisant will continue to have the same beneficial treatment effects beyond the studied period?	Yes. There is evidence from narcolepsy treatment for sustained effect.
Issue 5: Evidence of effects on cardiovascular events	
Is it reasonable to remove the assumption of a utility benefit associated with pitolisant reducing cardiovascular events given the available evidence?	Yes
Issue 6: Mapping algorithm	
Is the company's approach to mapping utility values from the literature [McDaid et al.] appropriate given that EQ5D data was collected in the clinical trials?	I think the EQ5D data should have been provided to compare costs but other QoI measures are more appropriate for showing improvements in sleepiness.
Issue 7: Utility value of reducing RTA by using pitolisant	
Is it reasonable to take into account that there could be a utility benefit of reducing road traffic accidents when taking pitolisant? Is there any available evidence to support this?	This is based on reduction of ESS as a measure of sleepiness. There are other objective measures such as OSLER- this could have been used as vigilance tests have been used in other trial to predict driving performance. It is reasonable to assume that a subjective improvement leads to improved driving performance. This has been shown in modafinil studies.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- This is a novel drug that could help some groups of patients with residual sleepiness on CPAP therapy especially those who are excessively sleepy due to mental health or cognitive issues resulting in partial compliance.
- It is effective and has few side effects.
- It is not clear how the diagnosis of residual EDS will be defined and investigated nor who will carry out these tests.
- It is likely to increase the workload of specialist centres as smaller centres may not have the resources to carry out these tests.
- It is also likely that extra resource would be required to monitor CPAP more effectively and to prescribe the drug based on these observations.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Technical engagement response form

Pitolisant hydrochloride for treating excessive daytime sleepiness caused by obstructive sleep apnoea [ID1065]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm on Tuesday 2 February 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Jazz Pharmaceuticals**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Trial population and its generalisability.	
1. Is there evidence to support the efficacy of pitolisant in these groups who were not included in the trial?	It is important to consider that patients with OSA is frequently associated with comorbidities, including depression (Steier, 2014). Symptoms common to OSA and depression, such as sleepiness and fatigue make this a large and overlapping population, with diagnostic challenge. Patients with depression as well as OSA may experience a higher symptom burden (Harris et al, 2009 Sleep Med Rev. 2009). Depression could be a treatment effect modifier for pitolisant in rEDS related to OSA, and evidence in a representative population with co-existing depression should be presented. The intended population of this technology review includes a group labelled as “patients with EDS due to OSA who refuse CPAP”. We would welcome a clearer description of this population and how they are defined. The importance of CPAP as a potentially disease-modifying therapy could be undermined, with pharmacotherapy being positioned as a favoured option. Pharmacotherapy as presented, has no demonstrated role in modifying the underlying disease profile and the multisystem consequences of persistent, airway collapse related intermittent hypoxia.
2. What is the prevalence of these conditions in people who have OSA?	A recent meta-analysis (Garbarino, S et al. Behavioral Sleep Medicine 2020) suggested that the prevalence of depressive symptoms in patients with OSA was 35% (95% CI, 28–41%). Some of these patients were excluded from the HAROSA trials.

Issue 2: Comparators	
Is it reasonable to include mandibular devices as a relevant comparator in people who have OSA but refuses CPAP?	We believe that mandibular devices are a relevant comparator in people with OSA who refuse CPAP. Mandibular devices have been reported in meta-analyses to have a positive treatment effect with respect to OSA and compliance rates that may be higher than for CPAP (Sharples, L et al. Sleep medicine reviews 2016). In this population, particularly where CPAP has been refused, a mandibular device may be more tolerable and would therefore be considered as a primary and efficacious therapy. We also note that when describing the clinical landscape, there is repeated reference to there being “no licensed treatment options to reduce EDS in patients adherent to CPAP with residual EDS”. Solriamfetol was granted marketing authorisation in the United Kingdom in February 2020 (predating the submission of the Technical Engagement Papers for ID1065), having received a positive CHMP opinion from the EMA in November 2019. We would like this highlighted to the committee for two reasons: (1) It represents an incomplete assessment of the current treatment landscape in the United Kingdom for people with OSA and residual excessive daytime sleepiness (2) Pitolisant has yet to receive either a CHMP opinion or marketing authorisation in excessive daytime sleepiness associated with OSA.

Issue 3: Comparators	
Is the indirect treatment comparison, conducted by the company comparing pitolisant and mandibular devices, reliable for decision making given the ERG's concerns?	It is important to consider that wake promoting agents do not treat the underlying OSA in the same way that CPAP or Mandibular Advancement Devices do. It is considered that treating the underlying OSA first is clinically the most appropriate action, and that a wake promoting agent (WPA) should only be considered if a patient is treated with primary therapy and still experiences EDS. It is probably therefore inappropriate to compare a WPA to a device which treats the underlying OSA, and it would be more appropriate to examine the cost effectiveness of pitolisant added to MAD. If the comparison is to be carried out, a comprehensive SLR would likely give more certainty on the efficacy of MAD. However it is likely that any ITC which combines trials of WPAs versus placebo and devices where best supportive care is the comparator will likely overvalue the efficacy of the device; placebo is not the same as best supportive care. The placebo arm in the HAROSA and TONES programmes is very effective in comparison to that seen in device trials for a variety of reasons that it would be difficult to adjust for.
Issue 4: Follow-up period in the clinical trials	
Is it plausible that pitolisant will continue to have the same beneficial treatment effects beyond the studied period?	We acknowledge the challenges of studying this therapy in a long-term population. With the data provided for pitolisant ranging to 1-year of follow up, it is likely that any pharmacologically-mediated waning of effect would have been apparent in that time.
Issue 5: Evidence of effects on cardiovascular events	
Is it reasonable to remove the assumption of a utility benefit associated with pitolisant reducing cardiovascular events given the available evidence?	We agree that it is reasonable to remove the assumption of a utility benefit associated with pitolisant reducing cardiovascular events. We are aware of no evidence that supports this

	important clinical endpoint. In the proposed population, long-term cardiovascular morbidity is unfortunately common. Modelling using a utility benefit of this kind could suggest to patients or the clinical community that pitolisant alone improves cardiovascular outcomes.
Issue 6: Mapping algorithm	
Is the company's approach to mapping utility values from the literature [McDaid et al.] appropriate given that EQ5D data was collected in the clinical trials?	The use of the McDaid algorithm is an appropriate methodology and has been used in previous NICE technology appraisals (TA139). The McDaid algorithm shows similar results to the mapping algorithm developed by Jazz across a large EU5 dataset (NHWS). The NHWS better reflects the real impact on patients of residual EDS in OSA compared to trial based-EQ-5D, where small number of patients and short follow up times are likely to not give a representative impact of residual EDS on quality of life. Therefore, another appropriate methodology could be to make use of a NHWS mapping to complement the McDaid approach.
Issue 7: Utility value of reducing RTA by using pitolisant	
Is it reasonable to take into account that there could be a utility benefit of reducing road traffic accidents when taking pitolisant? Is there any available evidence to support this?	This issue should be broadened to both costs and utilities. Driving and RTA risk is an important issue in residual EDS in OSA. DVLA guidance states that patients whose EDS is not controlled must not drive until symptoms are under control and a patient is strictly following treatment (https://www.gov.uk/excessive-sleepiness-and-driving: last accessed 2nd March 2021). It is believed that this has a substantial implication on the lives of patients with EDS and rEDS in OSA. The difference between the rules in the UK and the US is one of the reasons why US derived utility measures are not appropriate in this therapy area. Including RTAs in a population who are not allowed to drive overstates the benefits of pitolisant.

	However, there may be some patients whose physicians feel that compliance with CPAP is sufficient to warrant the return of a driving licence, and therefore including a proportion of patients at an elevated risk could be a reasonable approach. It is also likely patients with rEDS suffer from an increase in workplace accidents (Gharibi V, et al. Int J Occup Environ Med. 2020), although as above a proportion of more severe patients will no longer be able to work and would therefore not be at an elevated risk. Quantifying this into the framework of an economic model is difficult, and hence why it was not included within Jazz's modelling but could be considered to offer further value for money for any wake promoting agent in rEDS.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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

ADDENDUM: Critique of the company's response to Technical Engagement

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Company's response to technical engagement

The purpose of this addendum is to provide a critique of the new evidence submitted by the company as part of their response to the technical engagement report.[1]

In their response to technical engagement, the company submitted responses to the key issues raised in the Technical Report written by the NICE technical team, and some additional evidence relevant to these issues.[1]

1. Trial population and its generalisability

According to the Technical Report written by the NICE technical team, "literature states that the condition is associated with depression, metabolic and cardiovascular co-morbidities (Mason, 2013). Additionally, this condition is more prevalent in people with type 2 diabetes and metabolic disorders such as insulin resistance and glucose intolerance (Moon, 2015)".[2] Exclusion of these groups could impact upon the generalisability of the trial results.

The exclusion criteria of HAROSA I and HAROSA II clinical trials exclude patients with cardiovascular disease and psychiatric illness. Therefore, the NICE technical team considered that further input from clinical experts is needed to understand whether the results are generalisable to the population that would be treated in the NHS.

There were two specific questions regarding the generalisability of the trial populations in the HAROSA studies:

1. Is there evidence to support the efficacy of pitolisant in these groups who were not included in the trial?
2. What is the prevalence of these conditions in people who have OSA?

In their response,[1] the company argued that "just over one-half of people in the HAROSA studies had pre-existing cardiovascular disease (HAROSA I: 138/244, 56% and HAROSA II: 145/268, 54%, Document B, Table 5)" and "that 39% of patients in HAROSA I and 30% in HAROSA II had pre-existing metabolic disorders".

Regarding psychiatric illness, the company stated that "patients with psychiatric illness were excluded if the physician felt that their psychiatric condition would make study participation challenging, rather than any particular concern re co-morbid conditions" and that "18% of patients in HAROSA I and 5% in HAROSA II had pre-existing psychiatric illness. The HAROSA studies included patients with depression and anxiety if, in the opinion of their physician, their condition would not impact on study participation. A Beck Depression Inventory (13 item short form) score of <16 was an inclusion criterion, meaning that people with mild (score 5-7) and moderate (score 8-15) depression were included in the HAROSA studies."

ERG comment: The company did not provide any new evidence and further input from clinical experts was not provided either. Instead, the company referred to the evidence presented in their original submission.

Regarding the prevalence of these conditions in people who have OSA, the company stated that "patients with obstructive sleep apnoea have higher rates of depressive disorders (15-56%) than the healthy population (6-7%)",[3] and that "the prevalence of type 2 diabetes is significantly higher in people with obstructive sleep apnoea than in the general population, prevalence estimates of type 2 diabetes range from 15% to 30% in people with a diagnosis of obstructive sleep apnoea.[4]

Regarding cardiovascular disease, the company provided data from the Sleep Heart Study (n=1,207), which showed that people with excessive daytime sleepiness have a significantly increased risk of

prevalent cardiovascular disease (odds ratio=2.00 [1.21–3.31], p=0.007) and heart failure (odds ratio=4.64 [2.17–9.92], p=0.0001) vs people without obstructive sleep apnoea. The increased risk of cardiovascular disease highest in those people who have both obstructive sleep apnoea and excessive daytime sleepiness.[5]

ERG comment: The ERG checked the numbers presented by the company, and they are as referenced in the sources reported. However, it should be noted that Slater 2012[3] is not a systematic review. It does not delve into which studies or sources were used. Mazzotti 2019[5] is a cohort study of over 1200 patients. It does not refer to excessive daytime sleepiness as a condition. Instead, it refers to an excessively sleepy subtype according to the Obstructive Sleep Apnea Symptom Subtype. In this study the compared subtypes are Disturbed Sleep, Minimally Symptomatic, and Moderately Sleepy.

In addition, Jazz Pharmaceuticals (the comparator company for solriamfetol) mentioned a recent meta-analysis by Garbarino et al. (2020)[6] which suggested that the prevalence of depressive symptoms in patients with OSA was 35% (95% CI, 28–41%).

2. Comparators - mandibular devices as a comparator in people who have OSA but refuse CPAP

The NICE technical team stated that mandibular devices seem to be a relevant comparator for people with OSA who refuse CPAP and that the indirect treatment comparison presented was of poor quality because of the methodology used by the company for the search.

In their response, the company reiterated that they believe "that mandibular devices are not used in the same position in the treatment pathway as pitolisant, meaning that mandibular devices are not a relevant comparator to pitolisant".[1]

ERG comment: As stated by the NICE technical team, mandibular devices seem to be a relevant comparator for people with OSA who refuse CPAP.

3. Comparators - indirect treatment comparison

The company did carry out an updated systematic literature review and indirect treatment comparison, which are provided as new sources of evidence in their response to Technical Engagement.[1]

ERG comment: The company provided two documents describing a systematic literature review,[7] and a mixed treatment comparison.[8]

The systematic literature review reported searches for the following resources:

Search strategy element	Resource	Host/Source	Date Range	Date searched
Electronic Databases	MEDLINE/Pubmed	Embase.com		4/8/20
	Embase			
	Cochrane Library	Not reported	All years	
Conference Proceedings	ISPOR	www.ispor.org	(2017-2019)	
	World sleep congress	www.worldsleepcongress.com	2017 & 2019	
	Sleep meeting	www.sleepmeeting.org	2017-2020	
	Sleep and breathing conference	Accessed via the ERJ: www.openres.ersjournals.com	2017 & 2019	

	European respiratory society international congress	Accessed via the ERJ: www.erj.ersjournals.com	(2017-2019)	
	British Thoracic society	Accessed via thorax journal: www.thorax.bmj.com	2018-2019	
	American thoracic society	www.atsjournals.org	2018-2020	
Trials Registries	ClinicalTrials.gov	www.clinicaltrials.gov	All years	

ERG comments:

- Searches were conducted on a good range of resources and strategies were clear and reproducible.
- Table 13 of the literature review reports a search of Embase, MEDLINE and Pubmed via Embase.com.[7] A similar approach was reported in the original submission for which the ERG asked the company to clarify if this was referring to a search of Embase conducted on the understanding that it now contains all records from Medline and conducted at the same time as the Embase search, or if it was a separate search of the MEDLINE database. The company responded, "We confirm that we searched Medline and Embase at the same time via the embase.com platform and not via a separate search of the Medline database."[9] As previously reported the ERG is concerned that this approach has limitations when using subject heading terms which could affect recall of results. Embase subject heading terms (Emtree) were used in the search strategy, and although simultaneous searching of Embase should automatically identify and search for equivalent MEDLINE subject heading terms (MeSH), it is not clear if this is the case for all potentially useful MeSH terms. Given the possible limitations of this approach, the ERG considered it preferable to search each database separately, or at least to ensure inclusion of both Emtree and MeSH terms in the search strategy.
- Both the Embase.com and Cochrane searches contained limited use of synonyms and truncation (examples of missing free text terms include mouth or dental guard/s). The combination of lines #2 and #3 in the Embase.com search with line #1 using AND (i.e. 1 AND 2 AND 3) appeared overly restrictive and the ERG is concerned that relevant studies may have been missed. Whilst some limitations may have been mitigated by the other searches, the ERG is unable to say what impact this may have had on the overall recall of results as they are unable to rerun the searches due to lack of access to that host.
- As in the previous submission the MEDLINE/Embase search contained a limit to only those records that contained abstracts. When asked to confirm if this was the case the company responded, "We confirm that the final search was limited to studies conducted in humans that had abstracts. As studies without abstracts are mainly those that do not report primary research, such as editorials and opinion-piece publications".[9] A more cautious approach might have been to remove unwanted publication types rather than limiting to abstracts, a limit which may exclude relevant non-English language or e-print papers which do not always carry abstracts.

The company stated that "the systematic literature review identified 11 randomised controlled trials of mandibular advancement devices. However, none of the studies identified recruited a patient population directly matching that in the pitolisant trials." The company mentioned one study by Gagnadoux et al. (2017),[10] which they described as 'the closest match'.

The company excluded one of the studies identified in the systematic literature review due to small patient numbers (n=13), leaving 10 studies of mandibular advancement devices and the two studies of pitolisant (HAROSA I and HAROSA II) to be included in a mixed treatment comparison.[8]

ERG Comments: The original systematic literature review (SLR) presented in the CS identified 8 mandibular advancement device (MAD) studies which were then compared with results of the HAROSA II study.[11] Of these, 8 MAD studies, 4 were included in the new SLR. Two MAD studies were already discarded in the original CS because they were small studies reporting much larger treatment differences in ESS compared to the other studies. However, it is not clear to the ERG why the other two MAD studies have not been included in the new SLR:

- It is unclear why Aarab (2011)[12] was included in the original indirect comparison with results for the difference in ESS score for MAD versus BSC (See CS, Appendix D, Table 13), but not included in the new indirect comparison. A different paper by Aarab et al. (2011)[13] was excluded due to 'No relevant outcomes' (Response to TE, Reference 11, Table 15).
- And it is unclear why Lam et al. 2007[14] was included in the original indirect comparison with results for the difference in ESS score for MAD versus BSC (See CS, Appendix D, Table 13), but not included in the new indirect comparison.

Overall, the ERG would agree with the company that the results of the indirect comparison comparing MADs with pitolisant are unreliable; mainly because the populations in the MAD trials do not match those in the pitolisant trials (patients had less severe daytime sleepiness in the mandibular advancement device studies than in the pitolisant studies, weighted mean Epworth Sleepiness Scale: 10.36 vs 15.21) and the severity of obstructive sleep apnoea ranged from mild to severe in the mandibular advancement device studies vs moderate to severe in the pitolisant studies. In addition, the duration of treatment varied from 4 weeks to 16 weeks in the trials, which is also a potential cause of bias.

4. Follow-up period in the clinical trials

The company provided long-term results from the Harmony study, which assessed the use of pitolisant in narcolepsy with up to 5 years follow-up. The company stated that "Harmony III will run for 5 years, to date data is available on 48 French patients, 14 (29%) of whom continued on treatment for 5 or more years.[15] The reduction in Epworth Sleepiness Score was maintained over the 5 year period. By the end of 5 years follow-up a decrease in mean ESS score of -6.07 from baseline was seen."[1]

ERG comment: Although the results of pitolisant in narcolepsy are encouraging, these results are based on small numbers of patients with a different disease. Therefore, the ERG is not convinced the same applies to pitolisant in excessive daytime sleepiness caused by obstructive sleep apnoea.

5. Evidence of effects on cardiovascular events

In the original company submission, the observed reduction in ESS resulting from treatment with pitolisant was linked to a reduction in cardiovascular events. Due to a lack of evidence to support this effect, the ERG proposed that in the base-case analyses such effects should not be included. The NICE technical team posed the question in their technical report whether this was reasonable. In their response, the company discussed the relation between EDS and cardiovascular risk, part of which was also provided in response to the ERG's clarification questions. They concluded this discussion as follows: *'Excessive daytime sleepiness is an independent risk factor for cardiovascular disease – that is clear. Pitolisant has been shown to reduce the magnitude of excessive daytime sleepiness due to*

obstructive sleep apnoea. What we cannot do is link these two statements together and claim, in the absence of evidence, that pitolisant will reduce the risk of cardiovascular events. However, there is a reasonable circumstantial case to be made that it may exert a benefit. Furthermore, the company states that the magnitude of this effect is uncertain and they '*would therefore request that this uncertainty be made clear to the committee and that a scenario analysis be presented, incorporating the cardiovascular benefit, to inform the discussion between the expert and lay members.'*

ERG comment:

The ERG agrees with the company's conclusion that there is good evidence for EDS as an independent risk factor for cardiovascular disease, and also with their statement that there is no evidence that a reduction of EDS will result in a reduction in cardiovascular risk. Precisely for this reason the ERG argues that this effect should therefore not be included in the base case scenario. The ERG agrees with the company that, although evidence is currently lacking, such an effect might be possible and therefore agrees that exploring it in a sensitivity analysis scenario could be informative, which is why we included a scenario with the potential reduction in cardiovascular events in the ERG report, Tables 7.7 and 7.8.

6. Mapping algorithm

The NICE technical team questioned the use of a mapping algorithm for utilities as EQ-5D data was collected in the HAROSA I and II trials. In their response, the company referred to their original submission that stated that generic measures of quality of life, such as the EQ-5D, do not capture quality of life benefit in patients with excessive daytime sleepiness. This is reflected in the EQ-5D results in the HAROSA I and II trial that showed that pitolisant did not have an impact on EQ-5D. The company will provide additional analyses on the patient-level EQ-5D data that confirms that pitolisant does not have an impact on EQ-5D.

ERG comment: The ERG already raised this question of the NICE technical team in the clarification phase. The ERG requested a scenario analysis with utility values based on the EQ-5D assessment in the clarification letter, but this was not provided by the company because the underlying data were not available to them. As it seems the company can provide additional analyses on patient-level EQ-5D data in response to the question of the NICE technical team, the ERG would like to request the scenario analyses with utility values based on the EQ-5D assessment again.

7. Utility value of reducing RTA by using pitolisant

The NICE technical team raised the question whether it is reasonable to take into account a utility benefit of reducing RTA when taking pitolisant. The company responded that excessive daytime sleepiness has a significant impact on RTA and referred to the evidence provided in the original submission. In their response, the company provides additional evidence of the association between daytime sleepiness and RTA or objective measures of poor driving.[16-19] In addition, they refer to evidence of other methods to reduce daytime sleepiness in improving driving performance (solriamfetol[20, 21] and modafinil[22]) and reducing RTA (CPAP[17, 23, 24]). However, there is no direct evidence of the impact of pitolisant on the occurrence of RTA.

ERG comment: The ERG would have preferred direct evidence of the impact of pitolisant on RTA or at least on objective measures of poor driving. However, the ERG agrees with the company that it is reasonable to assume a similar association between RTA and objective measures of poor driving for pitolisant as with other methods to reduce daytime sleepiness.

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