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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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**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 |

# Table of Contents

**Table of Tables**

**Table of Figures**

# 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]

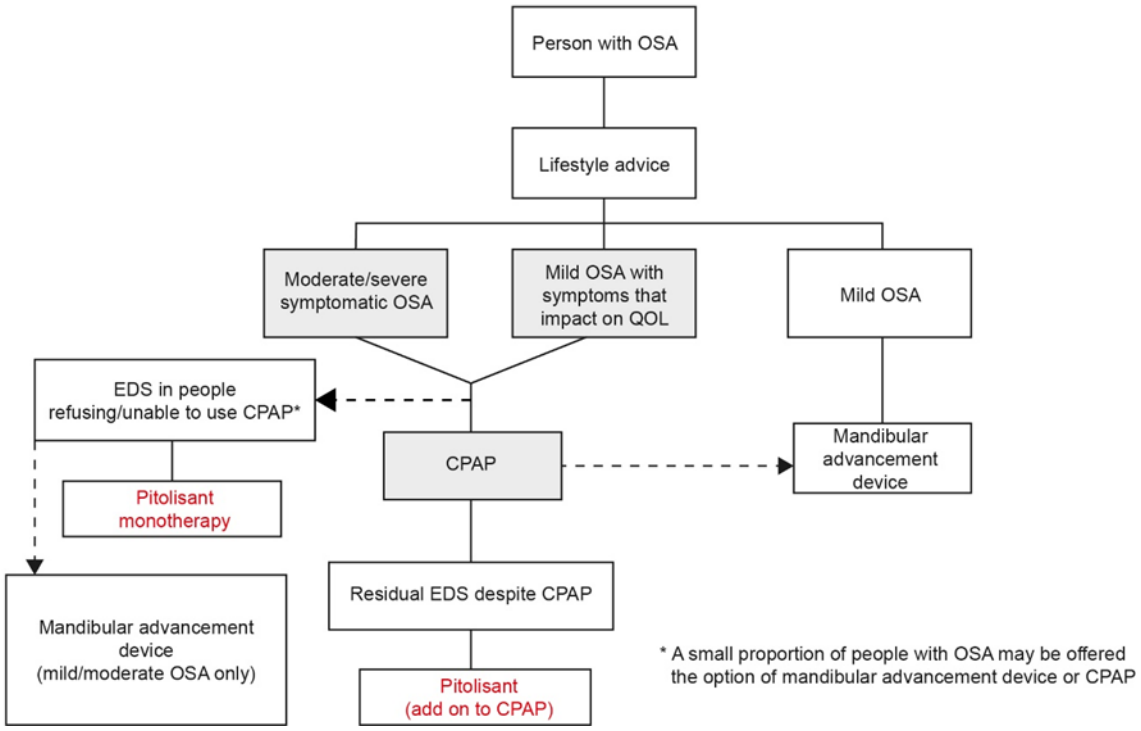
The CS states that approximately one-third of CPAP patients are not adherent or refuse CPAP, due to discomfort, inconvenience or claustrophobia, with MAD as the only alternative.[30] MADs, a gum-shield like device that holds the airway open during sleep, are an option for people with mild/moderate OSAHS 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.<br>In line with the clinical study programme, two subgroups were considered:<br>1. Patients receiving CPAP with residual EDS (HAROSA I study)[33]<br>2. Patients refusing CPAP with EDS (HAROSA II study)[34] | Pitolisant was investigated in two patient populations in two separate studies:<br>1. Patients receiving CPAP who had residual EDS (HAROSA I study)[33]<br>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<br>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<br>• Fatigue<br>• Length of life | As per scope<br>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<br>• Health-related quality of life (HRQoL) | Impression of Change (PGIC) and Patient's Global Opinion of the Effect (PGOE).<br>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.<br>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<br>• People who cannot have or have refused CPAP<br>• 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.<br>• Adults with other sleep disorders |
| Interventions | • Pitolisant<br>• Modafinil<br>• Dexamphetamine<br>• Sodium oxybate<br>• Solriamfetol<br>• CPAP | • Studies comparing different regimens of one active intervention with no other comparator |
| Comparators | • Placebo<br>• No treatment/ usual care<br>• 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<br>• Other measures of sleep amount, quality or latency<br>• Mortality<br>• Adverse events (AEs) | |
| Study design | • Randomised controlled trials<br>• Systematic reviews of randomised controlled trials (RCTs) | • Conference abstracts that report no additional data from the primary publication<br>• RCT protocols with no results<br>• 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<br>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 (%)<br>Female, n (%) | 149 (81.4%)<br>34 (18.6%) | 53 (86.9%)<br>8 (13.1%) | 151 (75.1%)<br>50 (24.9%) | 51 (76.1%)<br>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 (%)<br>No, n (%) | 117 (63.9%)<br>66 (36.1%) | 50 (82.0%)<br>11 (18.0%) | 139 (69.2%)<br>62 (30.8%) | 49 (73.1%)<br>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<br>Any significant<br>CV | <br>152 (83.1%)<br>111 (60.7%) | <br>46 (75.4%)<br>27 (44.3%) | <br>142 (70.6%)<br>110 (54.7%) | <br>47 (70.1%)<br>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<br>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. 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.<br>ANCOVA methodology was used to perform statistical analysis and all statistical tests were performed two-sided, at the 5% level of significance.<br>The final LOCF ESS score was primarily analysed using an ANCOVA model | 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 | 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 |
|---|---|---|---|
| | adjusting for ESS and BMI at visit 2 (randomisation visit) and study site as random effect. | 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) Mean difference: 2.77 p<0.001 **Treatment effect of -2.6 (95% CI: [-3.9; -1.4]) (p<0.001)** |
| | 14.9 (2.7) | 9.42 (4.66) | 14.6 (2.8) | 11.87 (5.70) | |
| **HAROSA II[34, 36]** | Pitolisant (n=201) | | Placebo (n=67) | | -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)** |
| | 15.7 (3.1) | 9.4 (4.6) | 15.7 (3.6) | 12.1 (5.8) | |
| 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)<br>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)<br>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.

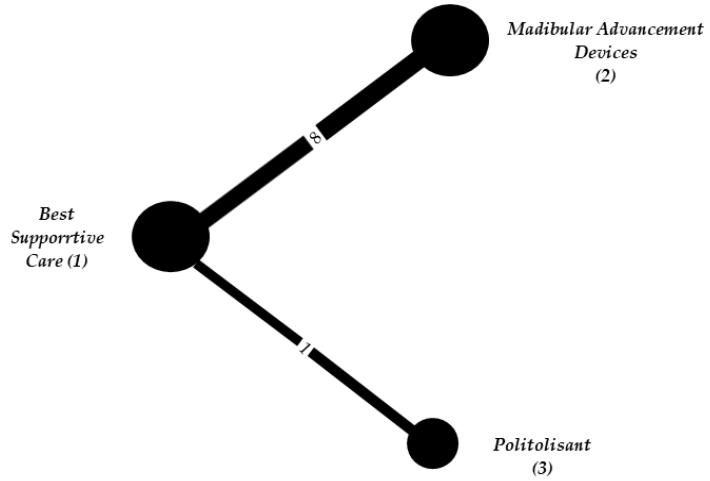
The company's systematic review of reviews identified 13 relevant systematic reviews. Based on a quality assessment of these 13 reviews, two were considered of highest quality, each having only one critical weakness (Sharples et al.[42] and Bratton et al.[43]) and a third review (Gao et al.[44]) had 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"<br>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.<br>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.<br>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.<br>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]<br>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<br>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.<br>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.<br>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]<br>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. |

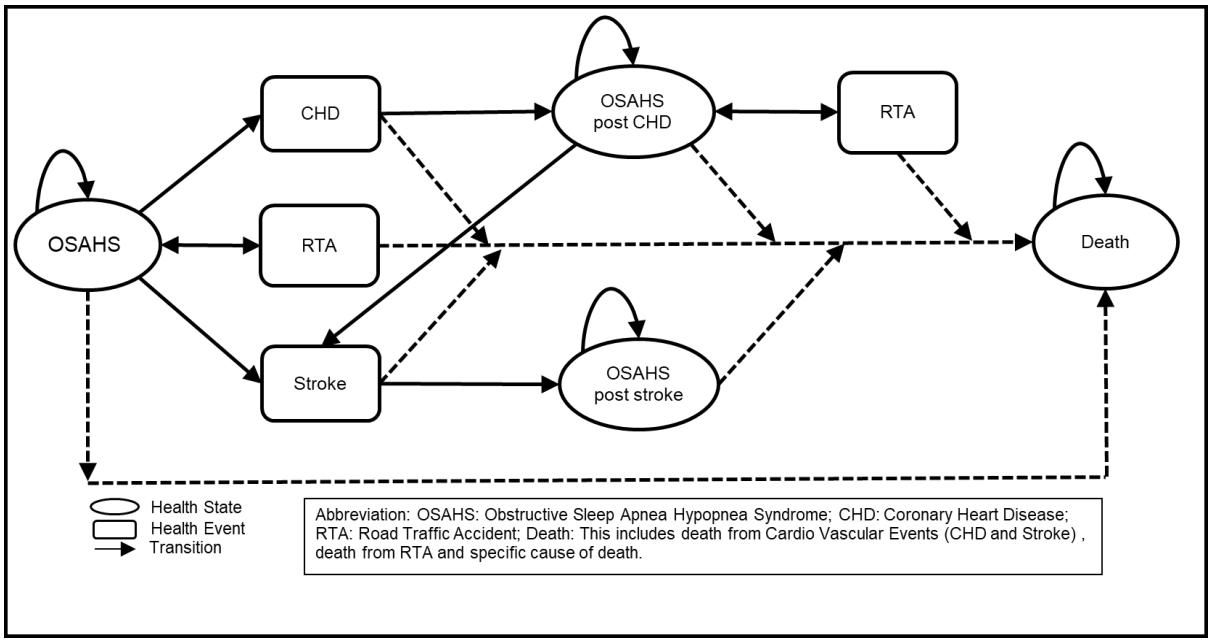
| Element of health technology assessment | Reference case | ERG comment on company's submission |
|---|---|---|
| **Discounting** | The same annual rate for both costs and health effects (currently 3.5%). | Costs and health effects are discounted at 3.5%. |

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**<br>**Any significant**<br>**CV** | <br>152 (83.1%)<br>111 (60.7%) | <br>46 (75.4%)<br>27 (44.3%) | <br>142 (70.6%)<br>110 (54.7%) | <br>47 (70.1%)<br>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<br>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 | | | |

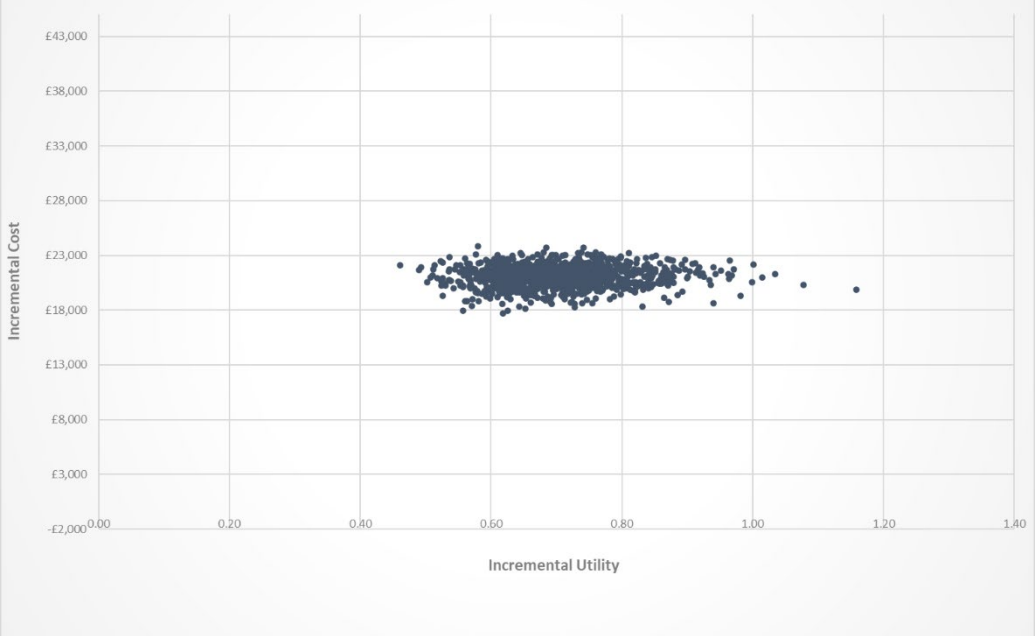
Source: Table 23 in the response to the clarification questions.[24]
BSC = best supportive care; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; ICER = incremental cost effectiveness ratio; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years.

## *6.2 Company's sensitivity analyses*

### 6.2.1 Probabilistic sensitivity analysis

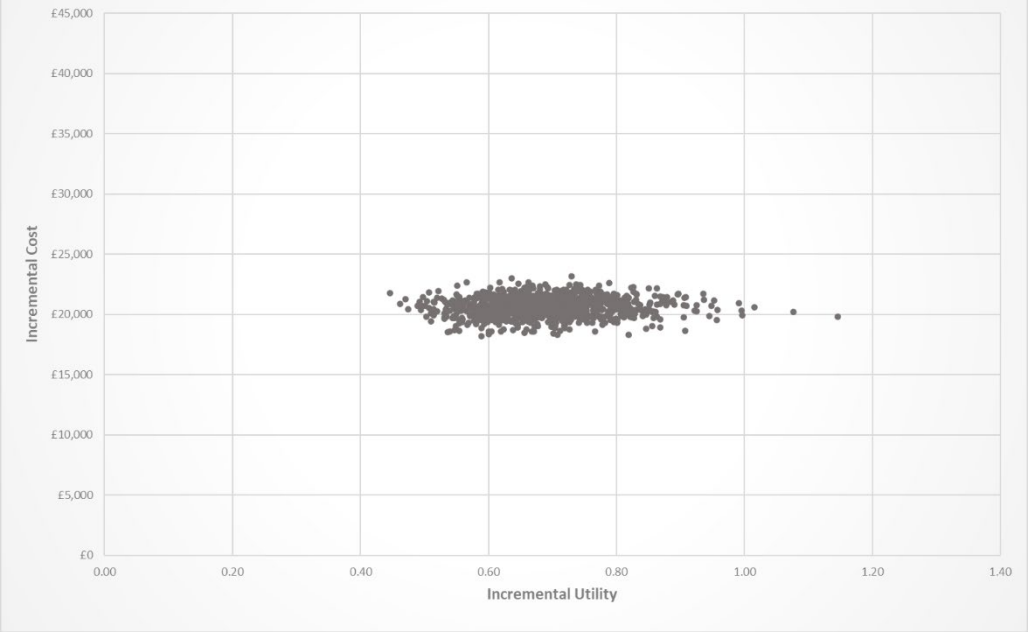
The probabilistic ICER for patients with residual EDS despite CPAP (based on HAROSA I) is £29,824 per QALY gained, and for patients with EDS due to OSA who refuse CPAP (based on HAROSA II) the probabilistic ICER is £29,932. These probabilistic ICERs are well in line with the deterministic ICERs (£29,698 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)**



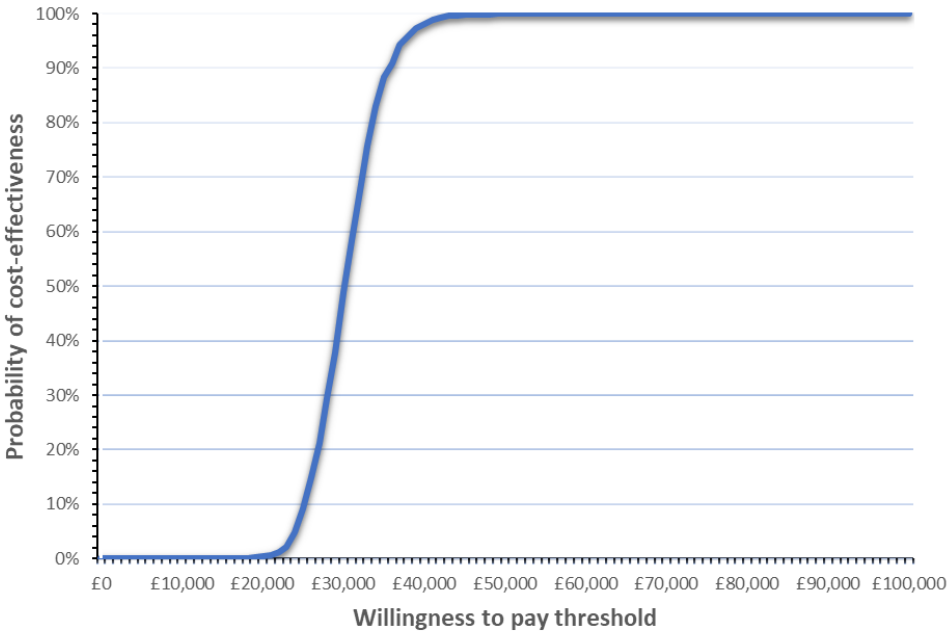

Based on the updated electronic model.
CE = cost effectiveness; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; PSA = probabilistic sensitivity analysis, QALYs = quality-adjusted life years.

**Figure 6.2: CE-plane of company's PSA results: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)**



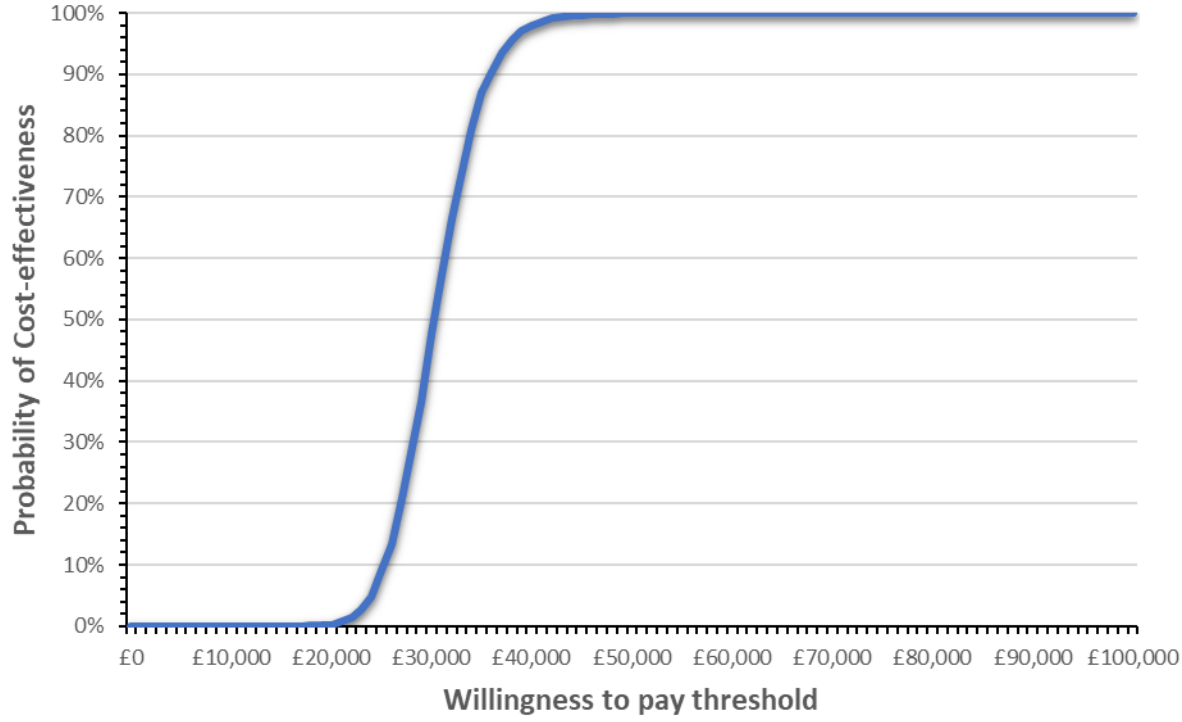

Based on the updated electronic model.
CE = cost effectiveness; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; PSA = probabilistic sensitivity analysis; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years.

**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)**



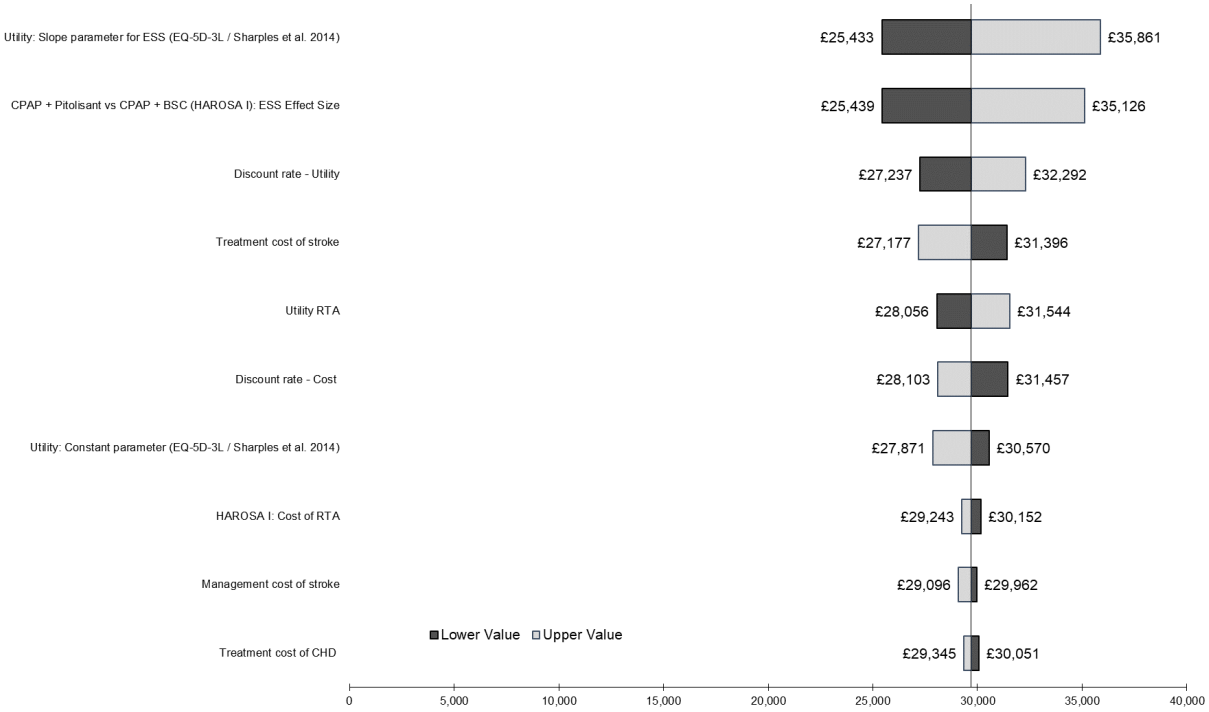

Based on the updated electronic model.
CE = cost effectiveness; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; PSA = probabilistic sensitivity analysis; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years.

### 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]

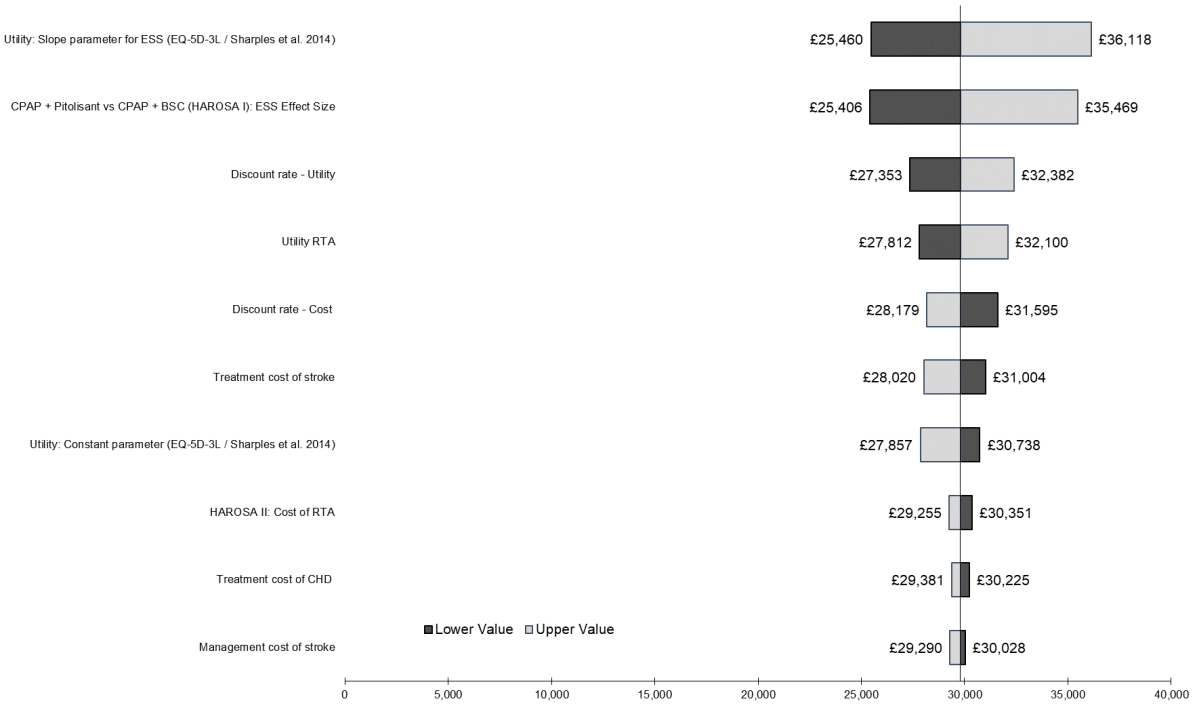
For each parameter that was varied, the ICER was calculated based on the lowest and highest value used. Figures 6.5 and 6.6 show the tornado diagrams of the 10 most influential parameters. Only two parameters (ignoring the discount rates) had a discernible impact on the ICER. i.e. the slope of the mapping 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.<br>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.<br>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)**

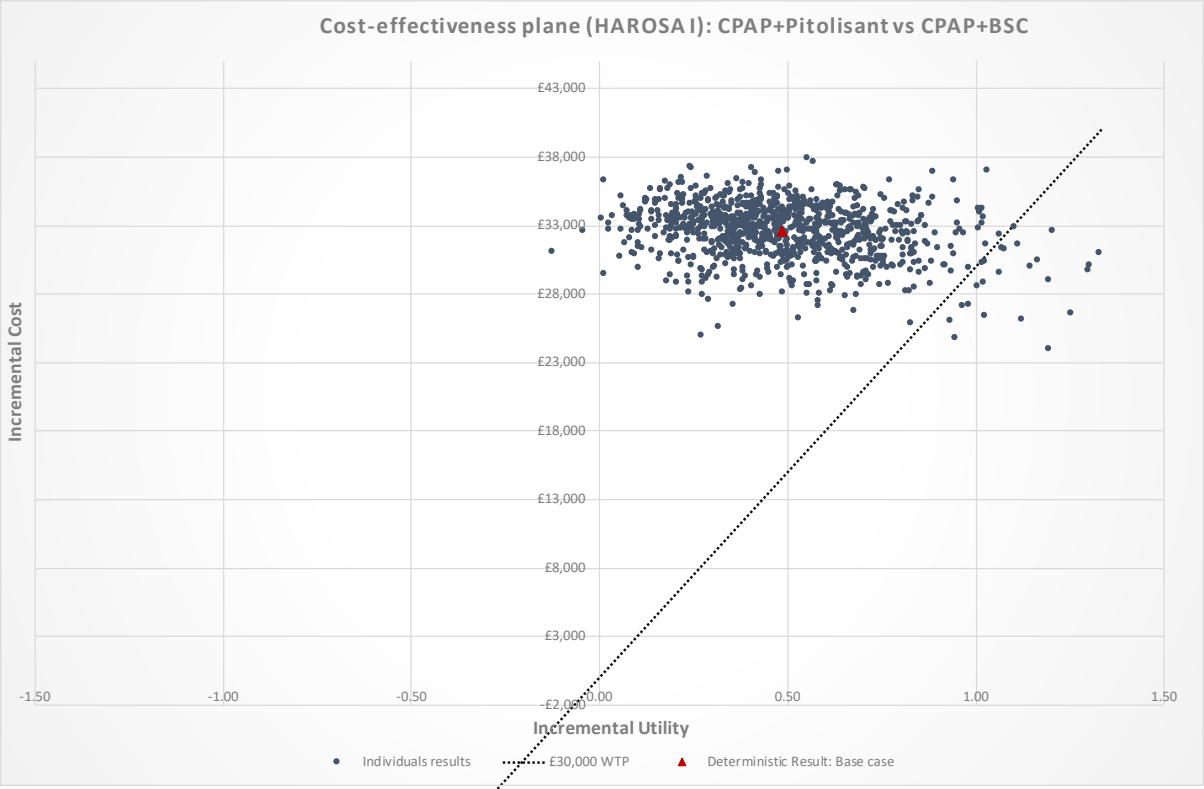
| Technologies | Total costs (£) | Total LYGs | Total QALYs | Incr. costs (£) | Incr. LYGs | Incr. QALYs | ICER versus baseline (£/QALY) |
|---|---|---|---|---|---|---|---|
| Pitolisant + CPAP + BSC | £35,135 | 17.74 | 14.34 | £32,561 | 0.10 | 0.49 | £66,462 |
| CPAP + BSC | £2,574 | 17.65 | 13.85 | | | | |
| Based on the ERG-preferred model.<br>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 | - | - | - | - |

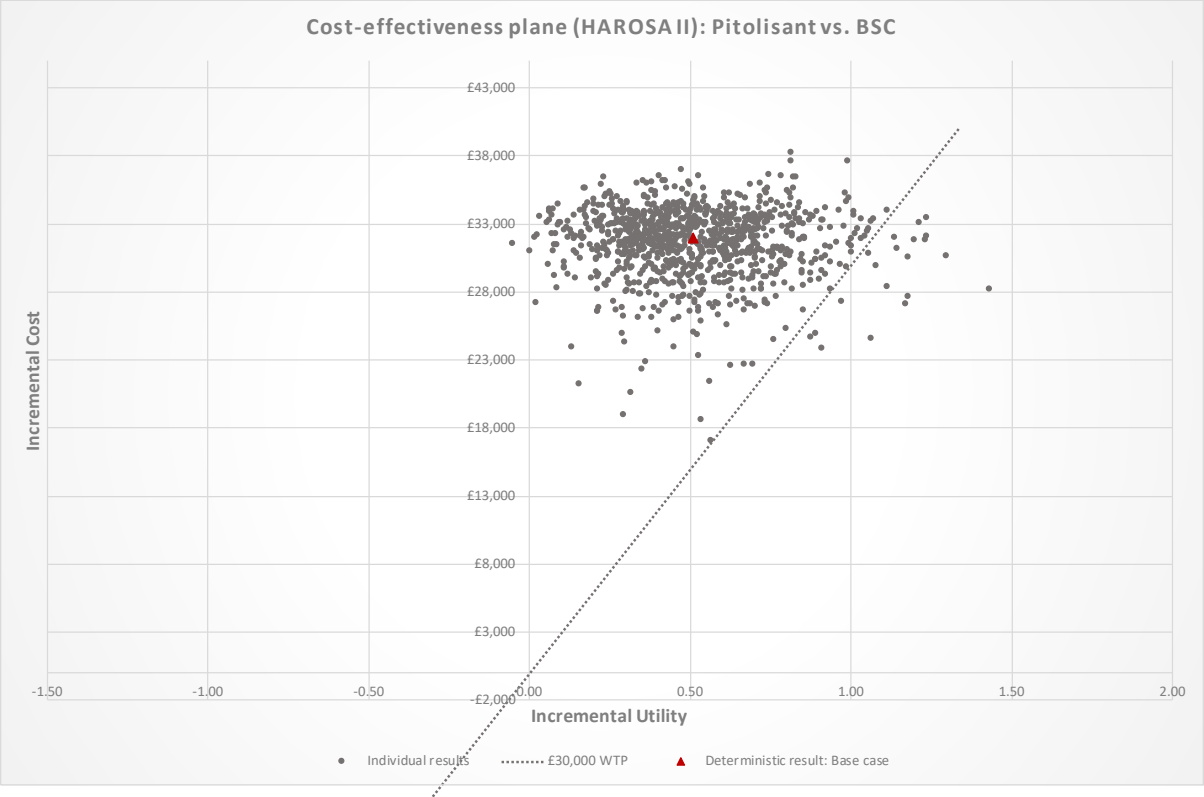
Based on the ERG-preferred base case.
BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; LYG = life years gained; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years

**Figure 7.1: ERG preferred cost effectiveness plane: patients with residual EDS despite CPAP (based on HAROSA I)**



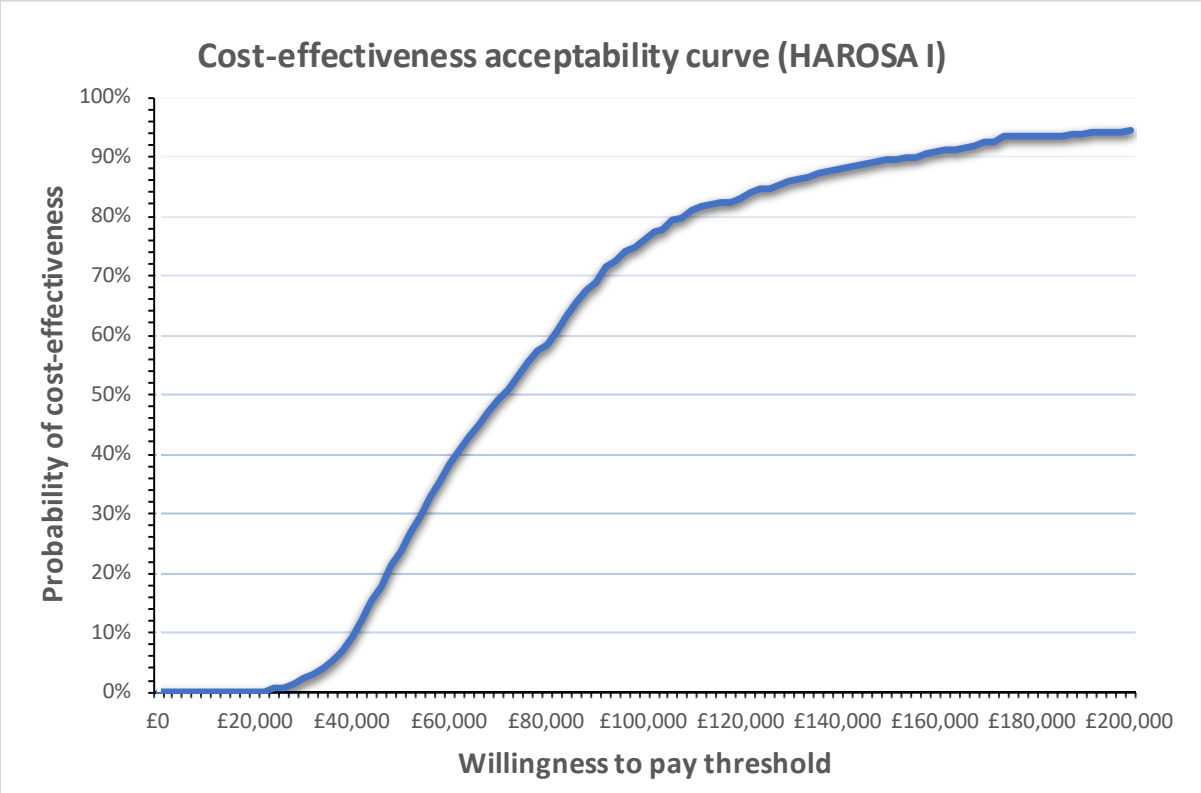

Based on the ERG-preferred model.
CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; QALYs = quality-adjusted life years.

**Figure 7.2: ERG preferred cost effectiveness plane: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)**



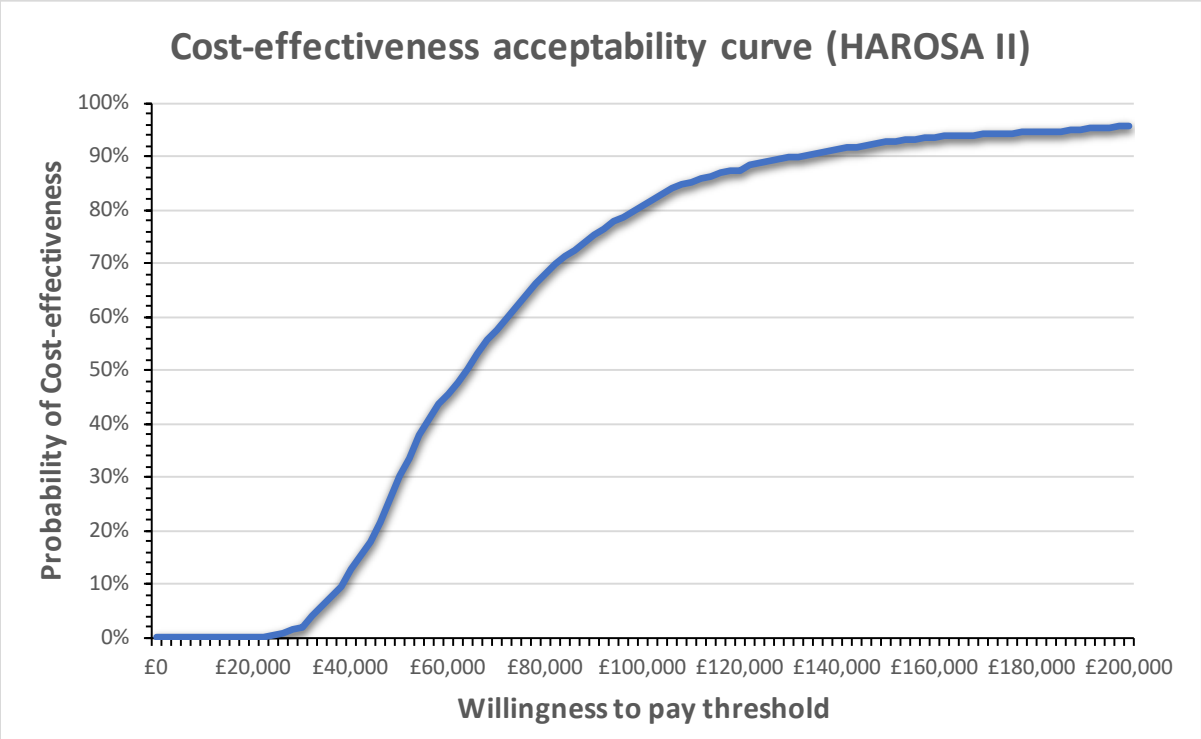

Based on the ERG-preferred model.
CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years.

**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)**

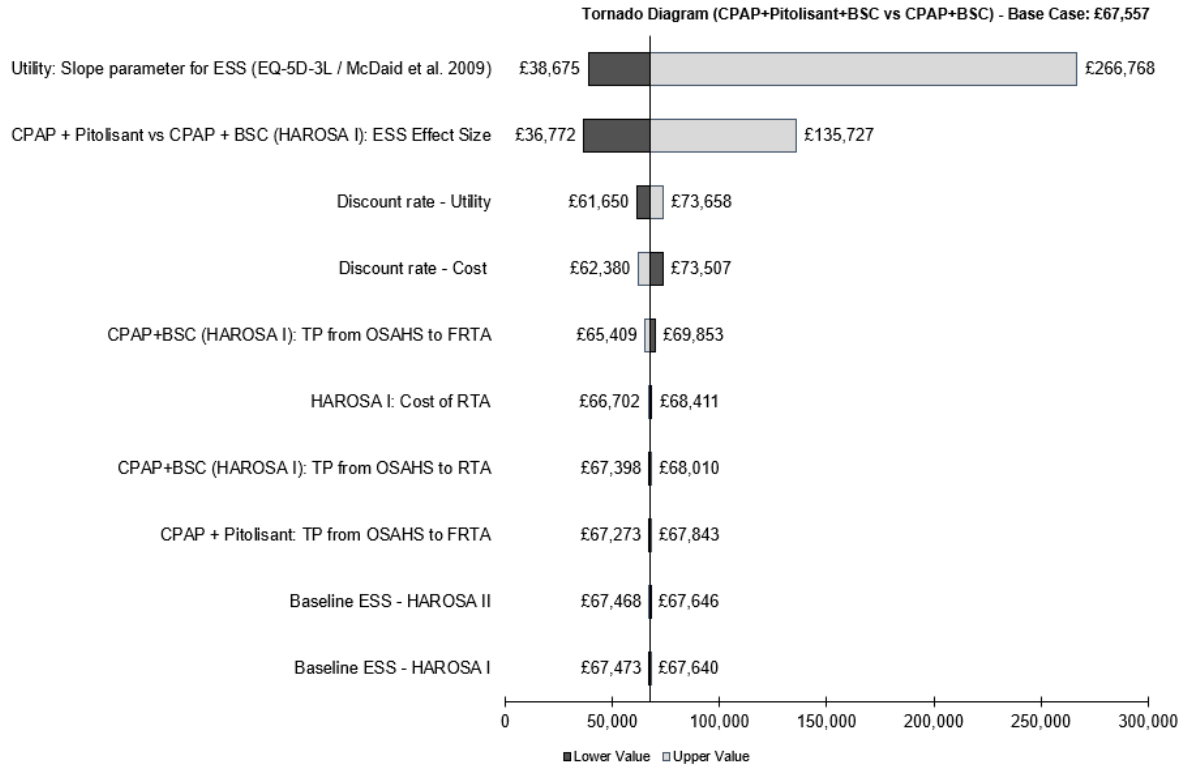
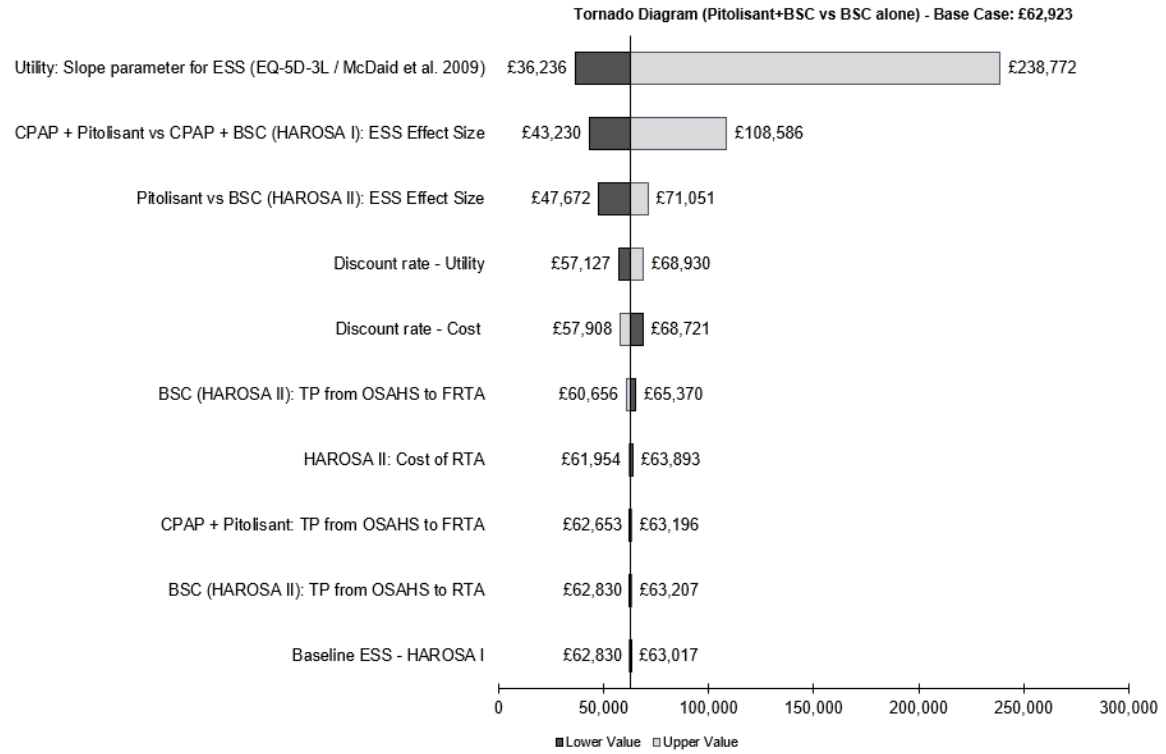



**Figure 7.6: Tornado diagram showing impact on ICER: patients with EDS due to OSA who refuse CPAP (based on HAROSA II)**



### 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.<br>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.<br>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.<br>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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