NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

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

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

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Patient expert		Para 3.2 The quoted patient expert comment "some people struggle to use it regularly because of its size, the amount of noise it makes and because it can affect sleep" is incorrect. The ACD attributes to me a statement that the size and noise of CPAP machines present problems, and the use of CPAP adversely affects sleep. This is not what I stated in my patient expert submission. I commented that CPAP machines are "now much smaller and quieter than they were a few years ago." My submission also noted that patients need to adjust to coping with the minor discomfort of having to sleep wearing a mask connected to a "small" machine. It did not state, nor did it imply, that this discomfort prevented sleep.	Thank you for your comment. Section 3.2 of the FAD has been updated to reflect that CPAP is usually well tolerated but some people may need to adjust to sleeping with a mask that's connected to a small machine.
2	Patient expert		Para 3.8 In response to patient experts concerns that availability of Pitolisant could lead to a reduction in compliance with CPAP therapy clinical experts expressed the view that "people having pitolisant hydrochloride alongside CPAP may have their use monitored more frequently than in current practice". Many sleep clinics now have the ability to monitor CPAP compliance remotely but SATA discussions with some clinics suggests that such monitoring is not routinely carried out, even on an exception reporting basis, though it may be used for the first week or so of CPAP therapy to ensure that there are no start-up problems. If Pitolisant were to be approved, it should be on the basis that CPAP use must be regularly and frequently monitored until the sleep clinic is satisfied that the patient will continue to use combined therapy.	Thank you for your comment. The committee considered the effect of pitolisant hydrochloride use on CPAP use. The committee acknowledged concerns about reduced CPAP adherence, but concluded that it had not seen evidence to change its original conclusion that pitolisant hydrochloride use is unlikely to affect CPAP use. Please see section 3.7 of the FAD.
3	Patient expert		Para 3.16 The final sentence is incorrect. People with untreated obstructive sleep apnoea and excessive daytime sleepiness are not "banned" from driving. The responsibility for deciding fitness to drive rests with the individual. If a person drives knowing they are not fit to drive through sleepiness, whatever the cause, they are breaking the law. They would also be breaking the law if they drove despite being advised not to do so by a GP, consultant or other medical professional. Conversely, a patient with moderate to severe obstructive sleep apnoea with symptoms of EDS is free to continue driving once they are diagnosed and treated, the sleep clinic is satisfied that CPAP therapy is working and the DVLA has been informed. The point at issue here is that if Pitolisant is prescribed to address the symptoms of EDS the patient could decide to carry on with Pitolisant but stop CPAP therapy. Even if Pitolisant on its own controls EDS the fact that the patient has stopped	Thank you for your comment. Section 3.14 of the FAD has been updated to reflect that people with obstructive sleep apnoea and excessive daytime sleepiness must not drive until their symptoms are under control.

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			using CPAP therapy will breach the basis on which DVLA has cleared the patient to continue driving. If Pitolisant on its own does not adequately control excessive daytime sleepiness the patient is at increased risk of a road traffic accident. Within the parameters of this paragraph, unless the Committee is convinced the various trials demonstrate that Pitolisant on its own will fully control EDS, I question the Committee decision not to include a utility decrement for road traffic accidents.	
4	Clinical expert	LIVERPOOL UNIVERSITY FOUNDATION TRUST	"Excessive daytime sleepiness caused by obstructive sleep apnoea is usually treated with a primary obstructive sleep apnoea therapy such as CPAP. Some people might not tolerate CPAP so they are offered mandibular advancement devices" MAD devices are primary therapy for OSA – they can be offered instead of rather after CPAP failure	Thank you for your comment. The FAD has been updated to reflect that people may have CPAP or a mandibular advancement device as primary therapy for obstructive sleep apnoea. Please see section 3.2 of the FAD.
5	Clinical expert	LIVERPOOL UNIVERSITY FOUNDATION TRUST	The committee concluded that the HAROSA trials were broadly generalisable for decision making but underrepresent people with psychiatric illness This is a difficult point. Many patients admitted to sleep clinics are on antidepressant medications from their primary care doctors, but many are put on this for poor quality sleep. Primary care recognises that insomnia is associated with depression, but a third of OSA patients have insomnia as their primary symptoms. So as such the percentages in HAROSA are probably fairly representive of "true depression" in a NHS clinic (albeit the poor quality of diagnosis of patients prior to referral)	Thank you for your comment. The FAD has been updated to reflect that the HAROSA trials are broadly generalisable but may underrepresent people with psychiatric illness. Please see section 3.6 of the FAD.
6	Clinical expert	LIVERPOOL UNIVERSITY FOUNDATION TRUST	It was unaware of any reasonable mechanism by which a wakefulness drug would reduce cardiovascular risk, rather than this being a result of treating the underlying cause of excessive sleepiness (obstructive sleep apnoea). I would check the literature on activity in sleepy populations eg narcolepsy and especially those with obesity (with depression or say chronic pain) and look at whether they have a lower degree of activity and as such this has a direct influence on CV risk	Thank you for your comment. The committee considered the evidence presented to it when making its recommendation for pitolisant hydrochloride. It concluded that it had not seen direct evidence of clinical or biological mechanisms by which pitolisant hydrochloride has an effect on cardiovascular events. Please see section 3.10 of the FAD.
7	Consultee (company)	Bioprojet UK Ltd	**Inconsistency around recommendations for mandibular advancement devices.** On page 3 *'Some people might not tolerate CPAP so they are offered mandibular advancement devices'.* However, later in the document (Section 3.3), clinical experts explain that people '*that people who decline CPAP or cannot tolerate it may be offered a mandibular advancement device*', that there is variation in access to mandibular advancement devices and only '*about 20% of people who do not have CPAP might be offered a mandibular advancement device*'. The concluding statement reads *'the committee concluded that mandibular advancement devices are sometimes offered to people who decline CPAP or cannot tolerate'*	Thank you for your comment. The FAD has been updated to reflect that people may have CPAP or a mandibular advancement device as primary therapy for obstructive sleep apnoea. Please see section 3.2 of the FAD.

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			We suggest that it the addition of 'sometimes' to the line on page 3 would better represent the Committee's views: *'Some people might not tolerate CPAP so they are **sometimes** offered mandibular advancement devices.*	
8	Consultee (company)	Bioprojet UK Ltd	**Patients eligible for pitolisant in the NHS** On page 3 *'They excluded some people who might be eligible for pitolisant hydrochloride in the NHS'* We feel that this statement implies that the clinical studies (HAROSA I and HAROSA II) did not provide evidence for people with pre-existing conditions. This not true. This statement is expanded upon later in the document (Section 3.7) and the following points made: '*The company clarified that people with depression were only excluded if the investigating clinician felt that it would make study participation challenging for them, rather than for any particular concern about comorbid conditions'* *'people with mild (score 5 to 7) and moderate (score 8 to 15) depression were included in the HAROSA trials. The company stated that the trials included people with depression and anxiety. 18% of patients in HAROSA 1 and 5% in HAROSA 2 had a pre-existing psychiatric illness'* Therefore, the HAROSA studies only excluded people with depression who would find study participation challenging. It is likely that these same people would not be suitable for treatment with pitolisant in clinical practice (concerns around adherence etc). We suggest that the sentence on page 3 should be deleted, as it does not reflect the clinical study programme.	Thank you for your comment. The FAD has been updated to reflect that the HAROSA trials are broadly generalisable but may have excluded some people who might be eligible for pitolisant. Please see section 3.6 of the FAD.
9	Consultee (company)	Bioprojet UK Ltd	**Quality of life in the clinical study programme** On page 3 '*There are also concerns about how they assessed quality of life, so it is uncertain if pitolisant hydrochloride improves quality of life'.* The concerns raised by the committee were not around the study assessment of quality of life, rather they focused on the mapping algorithm used to inform the model (Section 3.15). The HAROSA studies assessed quality of life using EQ-5D. As noted in Section 3.5 In terms of quality of life, '*patients in HAROSA 1 reported no difference in EQ-5D or Visual Analogue Scale during the double-blind phase of the trials. However, there was an improvement in the pain and discomfort dimension in the population of HAROSA 2 ('no problems' reported by 54.7% of patients at baseline compared with 40.6% at week 12, p=0.044)'.* As we detailed in our original submission, pitolisant does not have an impact on EQ-5D (see Document B, page 34). This is not unexpected, EQ-5D along with other generic measures of	Thank you for your comment. The committee was aware of the company's position that EQ-5D is not sensitive to changes in quality of life for people with excessive daytime sleepiness caused by obstructive sleep apnoea. It concluded that based on evidence presented to it, it was appropriate to consider an average of EQ-5D utility values from the clinical trials and ESS scores mapped to EQ-5D using the McDaid approach. Please see sections 3.12 and 3.13 of the FAD. Section 3.12 of the FAD has been

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			quality of life, does not appear to capture quality of life benefit in patients with excessive daytime sleepiness. *The lack of impact on QOL is consistent with other studies in OSA treated with CPAP[37], MADs[38,39] or modafinil[40,41]. Clinical opinion, systematic reviews and work carried out by the Assessment Group for the NICE CPAP HTA indicate that generic instruments to measure QOL, including the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and the EuroQol (EQ-5D) do not capture benefit in QOL in patients with EDS[42-44]. These instruments have not been specifically designed to assess aspects of QOL in patients with OSA or EDS and sleep is not included as a specific dimension.* (Document B, page 48) However, Clinical Global Impression of Change which measures severity of illness, global improvement/change and therapeutic response shows a significant improvement with pitolisant, as discussed in our original submission (Document B, page 33). Because EQ-5D does not appear to capture quality of life benefit in patients with excessive daytime sleepiness, we used established mapping techniques used in earlier NICE appraisals (Continuous positive airway pressure therapy for the treatment of obstructive sleep apnoea) to map Epworth Sleepiness Scale (which is the gold standard measure of sleepiness) to EQ-5D to use in our economic modelling. Indeed during Technical Engagement the NICE Technical Team stated *'The technical team agrees with the ERG that the company's approach to mapping based Mc Daid et al. could be acceptable in the absence of EQ-5D utility measures being available'.* The Committee were concerned around our mapping to EQ-5D, therefore we carried out mapping to SF-6D during Technical Engagement, which indicated an improvement in quality of life and resulted in a moderate increase in the ICER. On page 13 *After technical engagement, the company provided an analysis using utility values calculated directly from EQ-5D data in the trials. These are academic-in-confidence and cannot be presented here.* We submitted an analysis looking at mean difference by treatment group using individual patient data from EQ-5D data in the HAROSA studies. This analysis showed, as expected, that pitolisant does not have an impact on EQ-5D. This data was not used in the economic modelling, and we would like the copy in the Appraisal Consultation Document to reflect this. We suggest the following edit, which reflects more clearly the information submitted at Technical Engagement. *After technical engagement, the company provided an analysis* ***of mean difference by treatment group using individual patient data from EQ-5D data in the trials****. These are academic-in-confidence and cannot be presented here.*	updated to read "After technical engagement, the company provided an analysis of mean difference by treatment group using individual patient data from EQ-5D data in the trials."
10	Consultee (company)	Bioprojet UK Ltd	**Impact of placebo effect**	Thank you for your comment. The committee considered the company's

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			Page 3 *'And there may be a placebo effect in the standard care group (primary obstructive sleep apnoea therapy) that has not been considered and explored sufficiently'* *'There are concerns about how the trial data have been modelled to take account of a potential placebo effect in the standard care group'* Also see Section 3.6 and Section 3.14 We are extremely concerned about this issue. The placebo effect (Hawthorne effect) was not mentioned at Clarification Questions or at Technical Engagement. Indeed, it was only raised at the Committee meeting, probably because the same Committee had recently assessed solriamfetol for excessive daytime sleepiness and the manufacturer had used the Hawthorne effect in their modelling. In Section 3.6 it is stated that '*The company's analyses did not adjust for this placebo effect'.* Whilst it is true that the economic analysis did not adjust for the placebo effect, the clinical data presented in the original submission was placebo-adjusted (Table 9, page 29). The mean difference was presented as difference in ESS from baseline to week 12 in patients receiving pitolisant minus difference in ESS from baseline to week 12 in patients receiving placebo. Section 3.19 states that '*The committee agreed that it would like to see analyses that include an alternative approach to adjusting for the placebo effect*' [redacted]	new model that adjusted for the Hawthorne effect with a centring approach. It also considered scenarios from the ERG that assumed a true placebo effect, regression to the mean, or an equal mix of the 3 proposed effects. It concluded that adjusting for the Hawthorne effect was the most appropriate approach to adjust for the placebo effect. Please see section 3.11 of the FAD.
11	Consultee (company)	Bioprojet UK Ltd	**People with excessive daytime sleepiness and driving** In Section 3.16, the '*Committee concluded that people with obstructive sleep apnoea and excessive daytime sleepiness are banned from driving so it agreed not to include a utility decrement for road traffic accidents'.* We are concerned about this statement, although the Committee may have concluded that people with obstructive sleep apnoea and excessive daytime sleepiness are banned from driving, we know anecdotally from our clinical advisors that some people with obstructive sleep apnoea and excessive daytime sleepiness continue to drive despite their condition, putting them at risk of road traffic accidents, as noted in our original submission (Document B, page 16) *EDS is associated with an increased risk of accidents (particularly road traffic accidents [RTA]), indeed, the impact of EDS on RTAs is similar to that of drink driving[17]. A meta-analysis of six studies revealed that the odds ratio of the risk of a collision in drivers with OSA was 2.52[18]. It has been estimated that 40,000 RTAs/year in the UK are due to untreated OSA, given that these accidents result in injury or even fatality, the impact is considerable[10].* We believe, therefore, that the statement in Section 3.16 should be amended accordingly and the utility decrement for road traffic accidents included in the economic modelling.	Thank you for your comment. The committee concluded that people with obstructive sleep apnoea and excessive daytime sleepiness must not drive until their symptoms are under control. So it agreed not to include a utility decrement for road traffic accidents. Please see section 3.14 of the FAD.
12	Commentator	Jazz Pharmaceuticals	Section 3.6 and 3.14	Thank you for your comment. The committee considered the company's

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		UK Ltd	We are concerned that a thorough analysis of the influence of the placebo effect in the HAROSA clinical trial program has not been conducted. Although the Company Submission recognises this “strong placebo effect” (Section 2.13.1), which occurs over a time course of weeks, it has not been considered whether this could be also due to “regression towards the mean” in the whole population: a function of enrolling in the trial at a time when Epworth Sleepiness Scale was particularly severe for the patient, before returning to a natural “true” representation of the patients’ Excessive Daytime Sleepiness. We welcome the recognition that the methodology in ID1499 helps to address the observed placebo response in a meaningful and useful way, accounting for this being likely to be a true placebo effect, while acknowledging that it is not possible to rule out the influence of the Hawthorne effect (reported improvement associated with the intervention of the trial alone) and regression towards the mean.	new model that adjusted for the Hawthorne effect with a centring approach. It also considered scenarios from the ERG that assumed a true placebo effect, regression to the mean, or an equal mix of the 3 proposed effects. It concluded that adjusting for the Hawthorne effect was the most appropriate approach to adjust for the placebo effect. Please see section 3.11 of the FAD.
13	Commentator	Jazz Pharmaceuticals UK Ltd	Section 3.8 We are concerned that the influence of pitolisant on adherence to primary OSA therapy has not been adequately considered in this Technology Appraisal, with the committee concluding on this matter based on expert opinion when data exist. Although we agree that CPAP use is unlikely to be affected by treatment with pharmacotherapy for EDS (as demonstrated through data analysis in ID1499 for solriamfetol), an evidence-based approach should be considered in the ID1065 Company Submission. The omission of data on adherence to primary therapy creates uncertainty that when introducing pitolisant into clinical practice patients who are adherent to CPAP therapy could show a clinically significant reduction in CPAP usage. This may result in a return of symptoms not treated by pitolisant and therefore a introduce a significant risk to patients and an increase in resource use for those patients. Adherence to nightly CPAP was measured in the HAROSA I trial informing the data presented to the committee on pitolisant (Response to clarification questions (Lincoln Medical), page 14). This data has not been reported in the peer-reviewed manuscript associated with this study (Pepin 2021), nor in the Company Submission ID1065. Positive airway pressure, usually with CPAP, is the established primary therapy for OSA as acknowledged in the Company Submission (Section 1.3.2 "CPAP is the gold standard treatment for EDS due to OSA”). Many of the deleterious effects of OSA can be attributed to the repetitive cycles of hypoxaemia and reoxygenation association with periodic airway collapse. CPAP has consistently been shown to have a positive influence on blood pressure and other vascular risk factors (Litvin 2013, Kartali 2014, Picard 2021). The clinical importance of disease modifying therapy (e.g. CPAP) is intrinsically linked to the level of adherence in treated OSA patients, usually measured in hours per night of usage. OSA symptom control has been linked to adherent use of CPAP (Weaver 2007, Sawyer 2011, Gaisl	Thank you for your comment. The committee considered the evidence presented to it about the effect of pitolisant hydrochloride on CPAP use. At its first meeting, the committee concluded that CPAP use is unlikely to be affected by treatment with pitolisant hydrochloride because of regular monitoring. At the second meeting, the committee acknowledged concerns about reduced CPAP adherence, but concluded that it had not seen evidence to change its original conclusion that pitolisant hydrochloride use is unlikely to affect CPAP use. Please see section 3.7 of the FAD.

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			2020). More-over, withdrawal of CPAP in an adherent population has been shown to result in a rapid recurrence of OSA symptoms and re-emergence of deleterious cardiovascular biomarkers (Kohler 2011). Clinician and patient experts have raised the concern of how introducing a pharmacotherapy would influence adherence with prescribed CPAP in both ID1065 and ID1499. In ID1499 Jazz Pharmaceuticals presented a peer-reviewed analysis specifically addressing the influence of solriamfetol on adherence to PAP therapy, as well as being asked to provide additional analyses to reassure the ERG and committee that solriamfetol is unlikely to result in a decrease in adherence to CPAP. Without presenting the data that has already been gathered in the HAROSA trial program on the influence of pitolisant on adherence to CPAP being made available, considerable clinical and health economic uncertainty on this issue remains for ID1065. <u>References</u> Gaisl T, Rejmer P, Thiel S, Haile SR, Osswald M, Roos M, Bloch KE, Stradling JR, Kohler M. Effects of suboptimal adherence of CPAP therapy on symptoms of obstructive sleep apnoea: a randomised, double-blind, controlled trial. Eur Respir J. 2020 Mar 20;55(3):1901526. Kartali N, Daskalopoulou E, Geleris P, Chatzipantazi S, Tziomalos K, Vlachogiannis E, Karagiannis A. The effect of continuous positive airway pressure therapy on blood pressure and arterial stiffness in hypertensive patients with obstructive sleep apnea. Sleep Breath. 2014 Sep;18(3):635-40. Kohler M, Stoewhas AC, Ayers L, Senn O, Bloch KE, Russi EW, Stradling JR. Effects of continuous positive airway pressure therapy withdrawal in patients with obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med. 2011 Nov 15;184(10):1192-9. Litvin AY, Sukmarova ZN, Elfimova EM, Aksenova AV, Galitsin PV, Rogoza AN, Chazova IE. Effects of CPAP on vascular risk factors in patients with obstructive sleep apnea and arterial hypertension. Vasc Health Risk Manag. 2013;9:229-35. Pépin JL, Georgiev O, Tiholov R, Attali V, Verbraecken J, Buyse B, Partinen M, Fietze I, Belev G, Dokic D, Tamisier R, Lévy P, Lecomte I, Lecomte JM, Schwartz JC, Dauvilliers Y; HAROSA I Study Group. Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP: A Randomized Trial. Chest. 2021 Apr;159(4):1598-1609. Picard F, Panagiotidou P, Weinig L, Steffen M, Tammen AB, Klein RM. Effect of CPAP therapy on nocturnal blood pressure fluctuations, nocturnal blood pressure, and arterial stiffness in patients with coexisting cardiovascular diseases and obstructive sleep apnea. Sleep Breath. 2021 Mar;25(1):151-161.	

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			Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. Sleep Med Rev. 2011 Dec;15(6):343-56. Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, Kader G, Mahowald M, Younger J, Pack AI. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. Sleep. 2007 Jun;30(6):711-9.	
14	Commentator	Jazz Pharmaceuticals UK Ltd	Section 3.15 In the absence of appropriate HRQoL trial data, we agree with the use of the McDaid algorithm as an appropriate methodology that has been used in previous NICE technology appraisals (TA139). It is recognised that there is considerable need for a well-validated and sufficiently responsive quality of life measure for evaluating people with sleep disorders (Reimer 2003). The EQ-5D and SF-6D questionnaires are both generic measures to ascertain health status and neither questionnaire includes a sleep domain nor a dimension to specifically capture the impact of EDS on quality of life in people with OSA. Clinicians describe a very substantial burden on QoL for patients with EDS due to OSA and feel that these generic scales underestimate the true burden of EDS on QoL (see ID1499). It is likely that neither the EQ-5D nor the SF-36 data collected in the pitolisant trials reflect the burden of OSA and residual EDS on QoL. The duration of the trials is also likely insufficient to capture the full effect of pitolisant on QoL. The ERG suggested that SF-6D may be more sensitive than EQ-5D in capturing QoL benefits. The Company provided a scenario that mapped ESS scores to SF-6D. The Committee agreed that the Company's scenario using SF-6D might be preferable, but stated that more understanding was needed to determine how well mapping to SF6D captures quality-of-life benefits. The Committee concluded that it preferred the EQ-5D utility values derived from the clinical trials and that more detailed evidence should be provided to explain why EQ-5D is insensitive to capturing changes in a person's quality of life. The McDaid algorithm shows similar results to the mapping algorithm developed by Jazz Pharmaceuticals across a large EU5 dataset (NHWS) in ID1499. The NHWS better reflects the real impact on patients of residual EDS in OSA compared to trial based-EQ-5D, where small number of patients and short follow up times are likely to not give a representative impact of residual EDS on quality of life. Therefore, another appropriate methodology could be to make use of a NHWS mapping to complement the McDaid approach. Reference Reimer MA, Flemons WW. Quality of life in sleep disorders. Sleep Med Rev. 2003 Aug;7(4):335-49.	Thank you for your comment. The committee considered the evidence presented to it when making its recommendation for pitolisant hydrochloride. The committee considered scenarios using ESS scores mapped to EQ-5D using McDaid, trial EQ-5D, and an average of the 2 sources. It concluded that an average of the 2 sources of utility values should be used to inform the economic model. Please see section 3.13 of the FAD.
15	Commentator	Jazz	Section 3.10	Thank you for your comment. The

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		Pharmaceuticals UK Ltd	We are concerned that the impact on the introduction of pitolisant on resource use through hospitalisation has not been adequately considered. While we agree with the observation that rates of serious TEAEs in the HAROSA I trial were relatively low, they were nonetheless reported in 6% of subjects in the pitolisant-pitolisant arm of the open-label extension of the HAROSA I trial (Company Submission, Section 2.10.3 and Table 20). As pitolisant is positioned as an add-on to primary therapy, both the direct cost and the cost related to disutility of hospitalisation could create uncertainty around the true ICER associated with pitolisant in EDS associated with OSA. Data available from the FDA Center for Drug Evaluation and Research (CDER) demonstrates that patients with OSA were hospitalised during the pitolisant clinical trial program (FDA 2019), but the Company Submission did not include these as direct resource costs nor disutilities associated with hospital admission. With the caution described by the committee in using data from the use of pitolisant for the treatment of narcolepsy in the HARMONY follow up period, we believe there is considerable uncertainty as to whether pitolisant will result in greater hospitalisation costs when prescribed for EDS associated with OSA and urge the committee to consider OSA specific hospitalisation data. <u>Reference</u> FDA Center for Drug Evaluation and Research. Joint Supervisory Memo - NDA 211150, Pitolisant, 14 July 2019. Clinical Review Application Number: 211150Orig1s000. Available at [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211150Orig1s000SumR.pdf], last accessed 24/06/2021	committee considered the evidence presented to it when making its recommendation for pitolisant hydrochloride.
16	Commentator	Jazz Pharmaceuticals UK Ltd	<u>Section 3</u> We would like to highlight some factual inaccuracies in the clinician and patient responses which have then been included in committee papers and subsequent presentation to committee. There has been some confusion of patient and clinical expert engagement forms between those for this appraisal of pitolisant (ID1065) and that of solriamfetol for treating excessive daytime sleepiness caused by obstructive sleep apnoea (ID1499). We are concerned that this may cause confusion between the two appraisals ID1605 and ID1499. It is possible that the inclusion of solriamfetol responses instead of pitolisant responses means that important clinician and patient insights into pitolisant have not been captured. For two of the three clinical expert statements for this pitolisant submission, the topic-specific questions are those set for the appraisal of solriamfetol for treating excessive daytime sleepiness caused by obstructive sleep apnoea (ID1499), not pitolisant (ID1065). The patient expert statement in this pitolisant appraisal is also subtitled “Patient expert statement Solriamfetol for treating excessive daytime sleepiness caused by obstructive sleep apnoea.” We recognise however that for the patient statement, Part 2 does have the correct Technical	Thank you for your comment. NICE is aware that some of the technical engagement forms included questions about solriamfetol. To ensure expert opinions were considered for the pitolisant hydrochloride appraisal, patient and clinical experts were invited to participate in both the first and second committee meetings.

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			Engagement questions.	

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 24 June. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Bioprojet UK Ltd (Formerly Lincoln Medical Ltd) Please note that Lincoln Medical Ltd is now Bioprojet UK Ltd and we would be grateful if you could change this on your records, many thanks in advance. The key contact remains Carol Griffiths.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links or funding from the tobacco industry
Name of commentator person completing form:	Carol Griffiths

Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Inconsistency around recommendations for mandibular advancement devices.** On page 3 *'Some people might not tolerate CPAP so they are offered mandibular advancement devices'.* However, later in the document (Section 3.3), clinical experts explain that people '*that people who decline CPAP or cannot tolerate it may be offered a mandibular advancement device*', that there is variation in access to mandibular advancement devices and only '*about 20% of people who do not have CPAP might be offered a mandibular advancement device*'. The concluding statement reads *'the committee concluded that mandibular advancement devices are sometimes offered to people who decline CPAP or cannot tolerate'* We suggest that it the addition of 'sometimes' to the line on page 3 would better represent the Committee's views: *'Some people might not tolerate CPAP so they are **sometimes** offered mandibular advancement devices.*
2	**Patients eligible for pitolisant in the NHS** On page 3 *'They excluded some people who might be eligible for pitolisant hydrochloride in the NHS'* We feel that this statement implies that the clinical studies (HAROSA I and HAROSA II) did not provide evidence for people with pre-existing conditions. This not true. This statement is expanded upon later in the document (Section 3.7) and the following points made: '*The company clarified that people with depression were only excluded if the investigating clinician felt that it would make study participation challenging for them, rather than for any particular concern about comorbid conditions'* *'people with mild (score 5 to 7) and moderate (score 8 to 15) depression were included in the HAROSA trials. The company stated that the trials included people with depression and anxiety. 18% of patients in HAROSA 1 and 5% in HAROSA 2 had a pre-existing psychiatric illness'* Therefore, the HAROSA studies only excluded people with depression who would find study participation challenging. It is likely that these same people would not be suitable for treatment with pitolisant in clinical practice (concerns around adherence etc). We suggest that the sentence on page 3 should be deleted, as it does not reflect the clinical study programme.
3	**Quality of life in the clinical study programme** On page 3 '*There are also concerns about how they assessed quality of life, so it is uncertain if pitolisant hydrochloride improves quality of life'.* The concerns raised by the committee were not around the study assessment of quality of life, rather they focused on the mapping algorithm used to inform the model (Section 3.15). The HAROSA studies assessed quality of life using EQ-5D. As noted in Section 3.5 In terms of quality of life, '*patients in HAROSA 1 reported no difference in EQ-5D or Visual Analogue Scale*

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	during the double-blind phase of the trials. However, there was an improvement in the pain and discomfort dimension in the population of HAROSA 2 ('no problems' reported by 54.7% of patients at baseline compared with 40.6% at week 12, p=0.044)'. As we detailed in our original submission, pitolisant does not have an impact on EQ-5D (see Document B, page 34). This is not unexpected, EQ-5D along with other generic measures of quality of life, does not appear to capture quality of life benefit in patients with excessive daytime sleepiness. *The lack of impact on QOL is consistent with other studies in OSA treated with CPAP[37], MADs[38,39] or modafinil[40,41]. Clinical opinion, systematic reviews and work carried out by the Assessment Group for the NICE CPAP HTA indicate that generic instruments to measure QOL, including the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and the EuroQol (EQ-5D) do not capture benefit in QOL in patients with EDS[42-44]. These instruments have not been specifically designed to assess aspects of QOL in patients with OSA or EDS and sleep is not included as a specific dimension.* (Document B, page 48) However, Clinical Global Impression of Change which measures severity of illness, global improvement/change and therapeutic response shows a significant improvement with pitolisant, as discussed in our original submission (Document B, page 33). Because EQ-5D does not appear to capture quality of life benefit in patients with excessive daytime sleepiness, we used established mapping techniques used in earlier NICE appraisals (Continuous positive airway pressure therapy for the treatment of obstructive sleep apnoea) to map Epworth Sleepiness Scale (which is the gold standard measure of sleepiness) to EQ-5D to use in our economic modelling. Indeed during Technical Engagement the NICE Technical Team stated *'The technical team agrees with the ERG that the company's approach to mapping based Mc Daid et al. could be acceptable in the absence of EQ-5D utility measures being available'.* The Committee were concerned around our mapping to EQ-5D, therefore we carried out mapping to SF-6D during Technical Engagement, which indicated an improvement in quality of life and resulted in a moderate increase in the ICER. On page 13 *After technical engagement, the company provided an analysis using utility values calculated directly from EQ-5D data in the trials. These are academic-in-confidence and cannot be presented here.* We submitted an analysis looking at mean difference by treatment group using individual patient data from EQ-5D data in the HAROSA studies. This analysis showed, as expected, that pitolisant does not have an impact on EQ-5D. This data was not used in the economic modelling, and we would like the copy in the Appraisal Consultation Document to reflect this. We suggest the following edit, which reflects more clearly the information submitted at Technical Engagement. *After technical engagement, the company provided an analysis* ***of mean difference by treatment group using individual patient data from EQ-5D data in the trials****. These are academic-in-confidence and cannot be presented here.*
4	**Impact of placebo effect** Page 3 *'And there may be a placebo effect in the standard care group (primary obstructive sleep apnoea therapy) that has not been considered and explored sufficiently'* *'There are concerns about how the trial data have been modelled to take account of a potential placebo effect in the standard care group'* Also see Section 3.6 and Section 3.14

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	We are extremely concerned about this issue. The placebo effect (Hawthorne effect) was not mentioned at Clarification Questions or at Technical Engagement. Indeed, it was only raised at the Committee meeting, probably because the same Committee had recently assessed solriamfetol for excessive daytime sleepiness and the manufacturer had used the Hawthorne effect in their modelling. In Section 3.6 it is stated that '*The company's analyses did not adjust for this placebo effect'.* Whilst it is true that the economic analysis did not adjust for the placebo effect, the clinical data presented in the original submission was placebo-adjusted (Table 9, page 29). The mean difference was presented as difference in ESS from baseline to week 12 in patients receiving pitolisant minus difference in ESS from baseline to week 12 in patients receiving placebo. Section 3.19 states that '*The committee agreed that it would like to see analyses that include an alternative approach to adjusting for the placebo effect'* Commercial in confidence information removed.
5	**People with excessive daytime sleepiness and driving** In Section 3.16, the '*Committee concluded that people with obstructive sleep apnoea and excessive daytime sleepiness are banned from driving so it agreed not to include a utility decrement for road traffic accidents'.* We are concerned about this statement, although the Committee may have concluded that people with obstructive sleep apnoea and excessive daytime sleepiness are banned from driving, we know anecdotally from our clinical advisors that some people with obstructive sleep apnoea and excessive daytime sleepiness continue to drive despite their condition, putting them at risk of road traffic accidents, as noted in our original submission (Document B, page 16) *EDS is associated with an increased risk of accidents (particularly road traffic accidents [RTA]), indeed, the impact of EDS on RTAs is similar to that of drink driving[17]. A meta-analysis of six studies revealed that the odds ratio of the risk of a collision in drivers with OSA was 2.52[18]. It has been estimated that 40,000 RTAs/year in the UK are due to untreated OSA, given that these accidents result in injury or even fatality, the impact is considerable[10].* We believe, therefore, that the statement in Section 3.16 should be amended accordingly and the utility decrement for road traffic accidents included in the economic modelling.
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more

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information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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

Extended response to ACD

August 2021

Bioprojet

Contents

Introduction

Bioprojet has previously provided a stakeholder response to the Appraisal Consultation Document (ACD) for pitolisant issued in May 2021. Following discussions between NICE, Bioprojet and the Evidence Review Group (ERG), it was agreed that two issues highlighted within the ACD – assessment of utility and the handling of placebo effect - merited a more detailed examination. This document details our further response to these issues and – as agreed with NICE – includes the results of a re-analysis of the cost-effectiveness based on an alternative modelling approach.

Derivation of utilities

Summary of committee concerns expressed within ACD:

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

Summary of company response:

Although the possibility of using SF-6D-derived utility estimates has been raised in the course of technical engagement, our interpretation of the committee response within the ACD is that the preference is for an EQ-5D based approach, in line with the NICE reference case. The concerns condense down to two issues:

1. Ideally the committee would prefer that the economic modelling should be carried out using directly elicited EQ-5D utilities from the clinical trials.
2. Indirectly derived utility estimates – arrived at through mapping from the Epworth Sleepiness Scale (ESS) – would only be acceptable in the presence of stronger evidence to support the insensitivity of directly-elicited EQ-5D utilities to changes of quality of life (QOL) in this patient group.

In Appendix 1, the results of an individual patient data regression analysis of EQ-5D outcomes are presented. This has been independently prepared by Professor Phillipe Lehert, Consulting Statistician to the Faculty of Economics, Louvain Academy, Belgium and the Faculty of Medicine, University of Melbourne, Australia.

This analysis explores the impact of assessing utility based on three distinct metrics derivable from the EQ-5D: The Health State Index score (EQ-INDEX), the Visual Analogue Scale score (EQ-VAS) and the Z-score. Although NICE mandates the use of the Health State Index in the estimation of utilities, this approach is not universal across European Health Technology Appraisal (HTA) agencies. Given that Bioprojet are involved in regulatory submissions in a number of countries with differing data requirements, understanding the association between the different QOL metrics is an important aspect of their approach to analysis and underlies the decision to commission the piece of work undertaken by Professor Lehert.

The analysis identifies the following results:

[redacted]

From the analysis, we can draw out the following conclusions:

- A straightforward between-groups comparison of EQ-INDEX yields no significant difference between pitolisant and placebo arms.
- The results when using the EQ-VAS or Z-score metrics, on the other hand, do yield statistically significant benefits.
- The VAS results are better correlated with clinical outcomes in the studies than the EQ-INDEX results.

These results are consistent with three possible interpretations:

1. That the improvement in excessive daytime sleepiness (EDS) associated with the use of pitolisant does not result in an improvement in QOL. By extension, we would have to conclude that the positive benefits demonstrated by improvements in VAS and Z-score are spurious.
2. That the EQ-5D index is insensitive to the change in QOL associated with a reduction in EDS and that the use of alternative measures (such as the EQ-VAS) would be a better way of capturing this change.
3. That the EQ-5D, regardless of the analytical method used, shows too much internal variation in results to be a reliable metric in this patient group and that an alternative mapping approach may be the best way to address the issue.

The available evidence does not allow a definitive conclusion to be drawn as to the correct interpretation. Each should therefore be considered on its merits.

1. The first option is entirely possible, although this conclusion would have significant implications for obstructive sleep apnoea (OSA) treatment as a whole, if rationally applied. The recently published TONES-3 study[1] showed a similar lack of directly-derived EQ-5D utility benefit with solriamfetol, and we are not aware of any randomised controlled trial (RCT) involving pharmaceutical or mechanical devices (continuous positive airway pressure [CPAP] or mandibular advancement device [MAD]) that have shown a benefit captured by EQ-5D index. Taking this to its logical conclusion, therefore, we would have to state that no currently used treatment for OSA yields utility gains and consequently none should be used. This goes against the narrative evidence that the Committee have heard from patients and clinicians and seems unlikely to be the whole truth.
2. The second option is supported by our evidence and Prof Lehert's analysis shows that EQ-VAS is actually better correlated with the efficacy outcomes of the study than EQ-INDEX. From the perspective of preparing a cost utility model, however, this is problematic. It is not appropriate to simply equate the value of an EQ-VAS score to a utility estimate as although the two are related, they are not identical. Although there is no reason why appropriate preference studies could not be carried out to clarify the relationship, there are currently insufficient published

evidence to support this approach. For this reason, the direct use of VAS (or Z-score) data is not an acceptable option within the NICE reference case.

3. The third option – that of mapping from ESS – therefore appears to be the only viable alternative. We recognise that there are assumptions inherent in this approach that are relatively weakly supported, but it appears to offer the only viable option. If we accept that reducing EDS is likely to result in an improvement in QOL and that the ESS is a reasonable way of quantifying this, then mapping from ESS to utility seems to be a logical jump to take. This has led to the approach being used for economic models for CPAP, MAD, solriamfetol and now pitolisant. Whilst it may not be perfect, it represents the best compromise currently available, and also allows cross-comparison between different treatment modalities to be made with a degree of confidence.

The company's conclusion at the end of this process is that, while recognising the concerns of the Committee, we believe there to be sufficient evidence to support the mapping of ESS to utility as the best currently available approach to utility estimation in this patient group. We would therefore agree with the strategy used in the ERG-preferred model considered by the committee, that this strategy should stand.

Impact of differing handling of placebo-response on ICER

Summary of committee concerns expressed within ACD:

"…The committee recalled its discussion about the need to explore the effect of a placebo response on the clinical trial results (see section 3.6). It noted the potential causes of such an effect and discussed ways to adjust for it. One way of adjusting for a placebo effect might be to remove the improvement in ESS scores observed in the placebo group from both the placebo and the pitolisant groups in the model (sometimes referred to as a centering approach). This could be combined with an approach that considers 'responders' and 'non-responders' separately, defined using individual patient data. It could also use a selection of response thresholds similar to those used in the ongoing NICE technology appraisal of solriamfetol for treating excessive daytime sleepiness. Restructuring the model in this way, and removing the effect observed in the placebo group from both groups, might reveal greater differences between the 2 groups. The committee concluded that approaches to account for the placebo effect shown in the HAROSA trials should be explored to understand the effect on the cost-effectiveness results…"

Summary of company response:

The use of a responder/non-responder model, coupled with a placebo-centring approach, based on individual patient data from their pivotal clinical trial, formed the basis of the economic model used by Jazz Pharma in their submission for the ongoing NICE solriamfetol assessment. This approach differs fundamentally from the conventional model that Bioprojet used in their submission and thus presents difficulty in comparing the two treatments alongside each other. There are general similarities between the TONES 3 study[1] for solriamfetol and the HAROSA I[2]/HAROSA II[3] studies for pitolisant, so it would seem reasonable to compare the results from comparable analytical approaches.

The economic model submitted by Bioprojet is not amenable to a simple in-model change to allow the scenario to be explored, so in order to carry out this comparison, the company had to create a de novo model to explore placebo-centred data from the HAROSA studies in the context of a responder/non-responder model structure. Full details of this model are provided in Appendix 2.

Given that the original solriamfetol model was not available to us, and details of it have not yet been published, we reconstructed the core of the model based on Jazz Pharma's original submission and the ERG appraisal of their approach. Analysis of the individual patient data from HAROSA I and HAROSA II was provided to Bioprojet by the study investigators, to allow the placebo-centred estimation to be carried out.

Given time constraints and the specific objectives of the exercise, we did not attempt to create a fully-featured cost-utility model. Instead, we generated a sufficiently complete model to answer the Committee's questions regarding placebo effect handling, albeit in simplified form. There were a number of specific differences between our approach and that adopted by Jazz Pharma in their original submission:

- In the original Jazz Pharma model, inclusion in the treatment response arm was based on achieving a change in ESS of 3 or more points. The ERG assessment considered that a change threshold of 2 points was preferred. We consequently adopted a 2-point change to define treatment response in our model.
- The ERG identified an error in the way in which placebo-centring had been carried out by Jazz Pharma in their original model: *"…The company's description of the centring exercise is incorrect, but we were able to verify centred ESS scores using raw IPD: we subtracted the mean ΔESS in patients on standard care from ΔESS for each individual patient from the solriamfetol treatment arms as described in Hawkins 2010…"* We adopted the same approach as the ERG in calculating our own placebo-centred estimates of benefit.
- The solriamfetol model approached the placebo effect from the perspective that any placebo benefit would be short-lived. In consequence, no placebo-treated patient could be considered to be a "responder". Only a solriamfetol-treated patient could occupy the responder health state ("Hawthorne effect"). Although this is an interesting idea from a statistical and health economic standpoint, we believe that it lacks a basis in normal clinical practice, where a mix of both true placebo effect and regression to the mean are likely to water down the Hawthorne effect. For our model, therefore, we elected to allow placebo-treated patients to enter the responder health-state, with the proportion being determined by the placebo-centred calculations. Whilst we recognise that this approach may have diminished the apparent clinical benefit of pitolisant, we believe it is the most reasonable approach to model clinical reality.
- In extension to our discussion above regarding the estimation of utility benefit, we used the same mapping approach as in our original model. We considered whether to use the mapping that Jazz Pharma used in their model, but ultimately rejected it for two reasons:
    1. There were a number of baseline covariates whose values was not available from the clinical trials (either TONES 3 or the HAROSA studies): the database-derived estimates of these parameters were not provided in the publicly available data relating to the solriamfetol model.
    2. It would make comparisons of the placebo-centred model results with our original model more difficult to interpret

Results

The results below compare the base-case incremental cost-effectiveness ratio (ICERs) from the ERG-preferred version of our original model, with the results derived from the placebo-centred model. Based on an NHS price of [redacted] per 30 tablet pack.

Table 1: Results of new analysis vs original analysis

Population	Original model (ERG preferred)	Placebo-centred model
Add-on to CPAP (HAROSA I)	£67,557/QALY	£31,547/QALY
CPAP non-responders (HAROSA II)	£62,923/QALY	£27,262/QALY

Implications

The use of a placebo-centred model has a substantial impact on the ICER, even when the assumption of zero responders in the placebo arm is not integrated into the model. Bioprojet are currently in the process of registering a Patient Access Scheme (PAS) with PASLU, although at this stage the magnitude of the discount required has not been determined. The approach adopted by the Committee on the issues around the handling of placebo effect will clearly have a substantial impact on price for both pitolisant and solriamfetol.

Appendix 1: Efficacy of Pitolisant 20 mg in improving quality of life in patients with obstructive sleep apnoea syndrome (OSA): Results of two randomised controlled studies

Please note that this study is as yet unpublished and is AIC. We have marked the results as AIC

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Abstract

Aim: Excessive daytime sleepiness (EDS) and fatigue are major quality of life (QOL) related complaints in patients with obstructive sleep apnoea (OSA) syndrome. We assess the effect of pitolisant 20 mg (P20) on QOL in these patients.

Methods: Two randomised trials have compared P20 with placebo on efficacy and safety, and QOL was prospectively measured by the EQ-5D instrument tool. We conducted an Individual Patient Data (IPD) pooling based on a two-level (study-patient) hierarchical model on the Visual Analog Scale (VAS), the Sum-Index of the 5 items (EQ-INDEX) and the Z-score aggregating VAS and EQ-INDEX.

Results:

[redacted]

Conclusion:

[redacted]

Introduction

Description of the condition

Excessive daytime sleepiness (EDS) and fatigue are major complaints in patients with obstructive sleep apnoea (OSA) syndrome, defined as sleep-related breathing disorder (SRBD) with full or partial occlusion of the upper airway during sleep. OSA afflicts at least 2–4% of the adult population (at least 4% of males and 2% of females)[4, 5]. The proposed mechanism for EDS in OSA patients is sleep disturbance and loss of sleep resulting from micro-arousals produced by increased ventilatory effort[6, 7].

Description of the intervention

Pitolisant is an orally active selective histamine H3 receptor (H3R) antagonist/inverse agonist which enhances histaminergic transmissions in the brain and thereby elicits strong wake-promoting effects. It is the first compound of this class to be introduced in the clinic, initially to treat EDS and cataplexy in patients with narcolepsy[8-10].

Pre-clinical studies

Improvement of learning deficit and memory and the duration of waking by H3R antagonists was demonstrated experimentally in animals[11-13]. EEG results suggest improvement of the quality of arousal by reinforcing the level of vigilance and attention. Unlike other stimulating agents, P20 does not increase dopamine release in the striatum including the nucleus accumbens. In healthy volunteers, pitolisant showed good clinical and biological tolerance following single oral doses of 1 to 240 mg[8-10].

Clinical studies

The efficacy and safety of pitolisant were assessed in a first prospective multicentre, double-blind (DB) RCT of P20 (maximum dosage of 20 mg) versus placebo (HAROSA I), in patients diagnosed with moderate or severe OSA, who despite CPAP therapy for a minimum period of 3 months, were experiencing EDS[2]. This study was followed by a second RCT (HAROSA II) in OSA patients with EDS who refused CPAP therapy[3]. Apart from the difference in patient selection, the two studies had the same design and end-points, and statistical analyses of the studies have been published[2, 3]. There were no pharmacokinetics assessment in these studies, but a PET scan trial in healthy volunteers assessed the brain H3-receptor occupancy of pitolisant[14].

Study justification and objective

An integrated analysis of the two trials was planned since the beginning of this research project, each study was planned to provide a needed power for the main end-point (Epworth Sleepiness Scale [ESS]), but not the secondary and exploratory end-points. The clinical secondary end-points and the homogeneity of the studied drug effect on sub-groups defined by baseline conditions were assessed in a meta-analysis. The effect of pitolisant 20 mg on QOL was the last planned investigation and constitutes the objective of the present work.

Methods

Study selection

HAROSA I and HAROSA II were the pivotal studies for the submission of pitolisant for approval at the European Medicine Agency. As pitolisant is not yet on the market, these two studies are the only two available studies having assessed pitolisant 20 mg and constitute the exhaustive material for this meta-analysis.

Protocol

The following analysis is in conformity with the protocol and statistical analysis plan of the two studies and the used meta-analytical model for pooling the two studies was pre-determined in the statistical analysis plan (15-12-2011) blind to treatment.

Participants, Intervention

All randomised patients constitute the Intention-to-treat population (Full Analysis Set, FAS), no other selection was analysed. Intervention was defined as treatment taken fasting once daily, individual titration starting from 5 mg/day for 1 week, then 10 mg/day and 20 mg/day based on efficacy and tolerability. The best adapted and tolerated dose was administered for the 9-week stable dose period.

Outcome

Euro Qol-5D is a generic standardised instrument for use as measure of health-related QOL. It provides a simple VAS measurement and a sum-index value EQ-INDEX of 5 dimensions: Mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problem (level 1), some problems (level 2), and severe problems (level 3). EQ-5D was completed at baseline (visit 2) and final double blind visit (visit 6).

Risk of bias in individual studies

The RBT[15] addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other bias. Each item is measured on a 3-category risk of bias scale (low, high or unclear).

Assessment of the certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach[16]. The certainty rating of the studies has four levels: high, moderate, low, and very low. RCTs are initially categorized as high certainty but can be downgraded after assessment of five aspects: risk of bias, consistency, directness, imprecision, and publication bias.

Data collection, end-point calculation

This research was conducted as an Individual Patient Data (IPD) meta-analysis. The raw data from each study were requested from the manufacturer as a SAS original database. The VAS was provided at baseline and final time as a number in the range [0,100], with each of the five domains with three categories, and the sum score (EQ-INDEX) of the five categories was standardised and reversed as a QOL scale 0-100 to be directly correlated with VAS. A Z-score (EQ-Z) at baseline and final time was

calculated as the normalised centred values of VAS and EQ-INDEX by using their baseline mean and SD. The three end-points were analysed by assuming a normal distribution. A patient was considered as responding to therapy when the final-baseline change based on the Z-scores exceeded 0.2, considered as a minimum clinically relevant difference[17].

Synthesis of results

Our main analysis was based on an IPD two-level (study-patient) hierarchical model of Higgins et al[18] assuming a random treatment effect, a fixed study effect and between-study variance heterogeneity, error terms allowed to vary by study, but not by treatment group. For sensitivity purposes, we compared results of three alternative models: in fixing between study variance, in considering the fixed study effect, and the fixed treatment effect, in comparing the model relevance by the Bayesian Information Criterion (BIC)[19]. All analyses were adjusted for their baseline values through mixed models featuring linear regression for EQ scores or logistic regression for therapy response.

The secondary objective was the assessment of the homogeneity of effect across baseline conditions or subgroup analysis according to age, gender, occupation, and baseline severity of the illness. This objective was reached in testing the first-order interaction between the treatment and each baseline variable.

This analysis was based on the largest possible population (Full Analysis Set or all the randomised patients). Multiple imputation was used in calculating 15 imputed files in adjusting for age, gender, fixed, job, and clinical global impression. The Non-Missing at random MNAR Jump to reference (J2R) option was used assuming that after dropout, the participant's conditional outcomes jump to those of the reference group.

We finally evaluated the association between the two measured end-point EQ-INDEX and VAS and their interrelationships with efficacy variables as classically used in OSA : ESS, clinical global impression, and patient global opinion.

Results

Study characteristics (baseline, treatment)

A total of 512 patients, including 384 treated with P20 and 128 with placebo, comprised the FAS. The sample sizes of the two studies were similar (HAROSA I, n=244; HAROSA II, n=268). Within each study, baseline profiles (gender, employment status, age, and baseline values for ESS, OSleR and Fatigue scale) were comparable (Table 2). Between-study differences in some baseline values were apparent: the HAROSA I study included patients treated with CPAP, and baseline values of ESS and OSleR test were better than the corresponding baseline values of the HAROSA II study in which patients without CPAP were included. More women were enrolled in HAROSA II than in HAROSA I. Overall, 486 patients completed the studies (5.1% dropout rate).

Table 2: Comparison of baseline characteristics between treatment groups in the HAROSA I and HAROSA II studies. Mean±SD values

	HAROSA I (with CPAP)		HAROSA -2 (without CPAP)	
	P20	**Placebo**	**P20**	**Placebo**
Participants, n	183	61	201	67
Gender, Male: n (%)	149 (81.4)	53 (86.9)	151 (75.1)	51 (76.1)
In employment n (%)	117 (63.9)	50 (82.0)	139 (69.2)	49 (73.1)
Age (years)	53.77 ± 10.5	50.95 ± 10.6	51.94 ± 10.6	52.12 ± 11.0
Baseline ESS (scale unit)	14.9 ± 2.7	14.6 ± 2.8	15.7 ± 3.1	15.7 ± 3.6
Baseline OSleR (minutes)	20.2 ± 11.9	23.3 ± 12.1	14.8 ± 10.9	15.9 ± 11.0
Pichot Fatigue scale (scale unit)	13.2 ± 7.2	11.4 ± 7.2	13.0 ± 6.5	11.1 ± 5.9
CPAP: Continuous Positive Airway Pressure; ESS: Epworth Sleepiness Scale; OSleR: Oxford Sleep Resistance test				

Effect of P20

We first assessed the EQ-5D VAS (Table 3).

[redacted]

Table 3: VAS end-point : two level hierarchical (patient-study) meta-analysis: mixed model

	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P value	RIV	FMI
Intercept	[redacted]						
QOL (baseline)	[redacted]						
Study	[redacted]						
Age	[redacted]						
Gender	[redacted]						
Employment	[redacted]						
Treatment	[redacted]						
FMI: Fraction of Missing Information, RIV: Relative Increase in Variance							

The EQ-5D sum-score EQ-INDEX was standardised to 0-100 and reversed to have the same direction as the VAS value.

[redacted]

Table 4: EQ-INDEX end-point: two level hierarchical (patient-study) meta-analysis: mixed model

	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P value	RIV	FMI
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QOL (baseline)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Employment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FMI: Fraction of Missing Information, RIV: Relative Increase in Variance							

The EQ-5D Z-score EQ-Z at baseline and final time was calculated as the normalised centred values of VAS and EQ-INDEX by using their baseline mean and SD (Table 5).

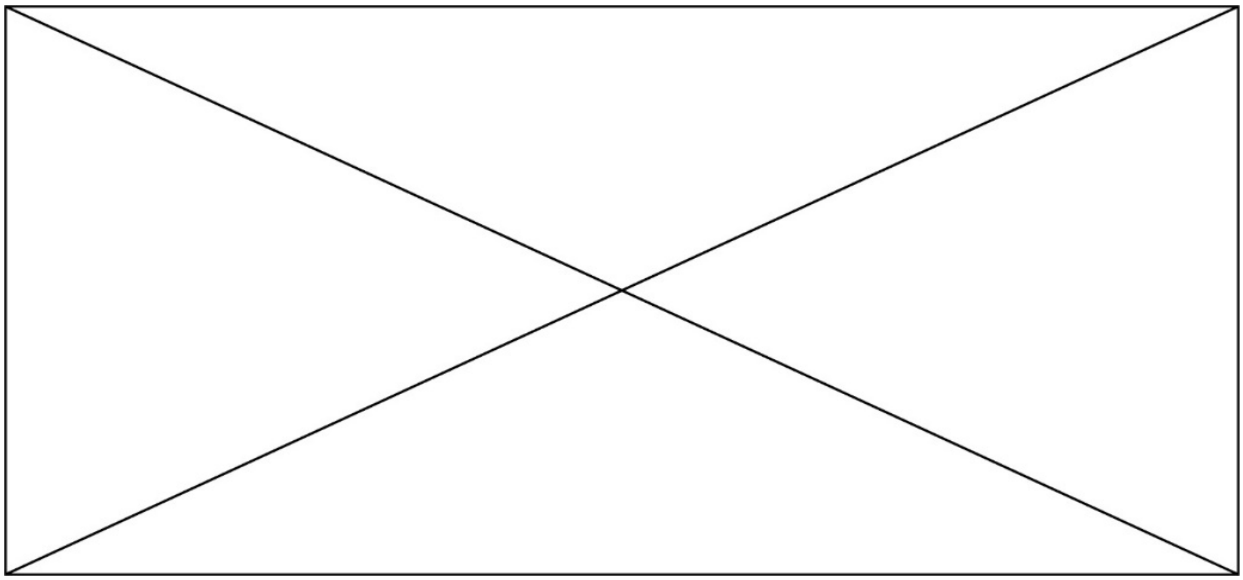
[redacted]

Table 5: EQ-Z end-point: two level hierarchical (patient-study) meta-analysis: mixed model

	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P value	RIV	FMI
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QOL (baseline)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Employment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FMI: Fraction of Missing Information, RIV: Relative Increase in Variance							

Based on the EQ Z-score, Figure 1provide the marginal estimates of the two treatments (0=red=Placebo, 1=blue=P20), for the two subgroups of patients with and without fixed employment, with increasing age.

Figure 1: Marginal estimates of the treatment effect depending on age and employment



A responder definition was defined based on the Cohen effect size[17] considering that a mean standardised change constitutes the minimum clinically relevant difference. We thus defined a responder when the change from baseline on the Z score EQ-Z exceeded 0.2. The unadjusted proportions of responders were [redacted], respectively. In adjusting for baseline conditions, odds ratio and risk ratios of [redacted] were found (Table 6).

Table 6: Responder rate - linear mixed model

.	Coefficient	95% CI		P value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
Gender	[redacted]	[redacted]	[redacted]	[redacted]
Employment	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect	[redacted]	[redacted]	[redacted]	[redacted]

The homogeneity of effect across baseline conditions or subgroup analysis according to age, gender, occupation, and baseline severity of the illness was assessed by testing the first-order interaction between the treatment and each baseline variable (table 6). [redacted]

Table 7: Homogeneity of the effect across baseline conditions. Interaction of the treatment effect with age, gender, fixed employment and baseline severity of QOL

.	Coefficient	95% CI		P value
Age: treatment effect	[redacted]	[redacted]	[redacted]	[redacted]
Gender: treatment effect	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect: employment	[redacted]	[redacted]	[redacted]	[redacted]

QOL at baseline: treatment effect	[redacted]	[redacted]	[redacted]	[redacted]

Correlation between EQ-5D Qol estimates and efficacy end-points

We studied the descriptive statistics of the three end-points (VAS, EQ-INDEX and EQ-Z) and their correlation with end-points directly linked with the efficacy of pitolisant: ESS, Clinical Global Impression (GCI), Patient Global Opinion (PGO) and Pichot Fatigue Scale (PFS).

Table 8 provides descriptive statistics for the whole sample in comparing the mean, standard deviation, median and interquartile range of VAS and EQ-Z at baseline and final values. [redacted]

Table 8: Statistical Description of EQ-INDEX and VAS at baseline and final values (Mean, standard deviation, median, Q1, Q3).

	Mean	SD	Median	Q1	Q3
Baseline					
VAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-Index	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final values					
VAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-Index	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 9 provides the Pearson correlations between EQ metrics and the main efficacy end-points: PGO at the end of the trial, CGI of the investigator at the end of the trial and ESS. [redacted]

Table 9: Pearson Correlation between QOL instruments (VAS and EQ-INDEX) and efficacy variables

	PGO	PFS	CGI	ESS	VAS	EQ-Index	EQ-Z
PGO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CGI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-Index	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-Z	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CGI: Clinical Global Impression, ESS: Epworth Sleepiness Scale , PFS: Pichot Fatigue Scale, PGO: Patient Global Opinion

Discussion

Comparison between the EQ calculations

When standardising EQ-INDEX into the range 0-100, the [redacted]

Table 9 allows for other comments:

The effect of a wakefulness drug such as pitolisant on QOL can be expected from its awakening effect: reduction of EDS, decreasing fatigue and improved vigilance. These impairments are measured in OSA trials by specific variables: ESS, PFS, PGO and CGI. The correlation between the OSA-related efficacy variables ESS, PFS, PGO and CGI provide evidence for the consistency between the efficacy variables. The correlation between the two main EQ-5D evaluations (VAS and EQ-INDEX) provide an estimate of their concordance. The inter-correlations between the two groups of variables provides evidence for the effect of stimulation effect on QOL. The comparison of the correlation between each QOL measurement (VAS or EQ-INDEX) may help to determine the best measurement in this pathology.

[redacted]

Various attempts may be brought forward to interpret these observations.

[redacted]

[redacted]

Effect of P20 on QOL

[redacted]

[redacted]

[redacted]

Results were based on a difference of Z-score of at least 0.2 corresponding to the Cohen minimum clinically relevant difference. [redacted] may provide a supplementary argument for a modest effect of pitolisant based on a clinically relevant difference.

[redacted]

Limitations

These results should be compared with the effect of other alternative OSA treatments on QOL. In particular, our results seem to confirm expert opinion that EQ-INDEX might be insensitive for some pathologies, including diurnal somnolence.

In a previous submission to NICE from the manufacturers of solriamfetol, the authors concluded that there was a lack of sensitivity for EQ-5D in EDS. [redacted]

[redacted]

A more in-depth study of the properties of the VAS compared with EQ-INDEX should be studied by structural equation modelling through the assessment of the mediation effect of EDS and fatigue on QOL.

Conclusion

Based on IPD meta-analysis of 512 patients, these results provide evidence that pitolisant favourably impacts on QOL via its effect in reducing EDS and fatigue. Further research might help to corroborate this finding.

Appendix 2: Report on responder/non-responder economic analysis, using placebo-centred efficacy data

A limited, revised economic model was developed to explore the effect on the cost-effectiveness results when adjusting for the placebo effect in the HAROSA trials, as highlighted by the Committee in the recently published NICE ACD for pitolisant in EDS caused by OSA. The revised model considers an approach using "responders" and "non-responders", in order to allow comparison with the economic model created for the recent NICE submission for solriamfetol in OSA submitted by Jazz Pharma. Unlike the original conventional model submitted by Bioprojet, this revised model does not include road traffic accidents or impact of treatment on cardiovascular events – results being solely driven by pitolisant costs and health state utilities.

Patient population

The modelled population for the revised economic model reflects the two key studies for pitolisant

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

The model estimates quality adjusted life years (QALYs) and direct cost from the perspective of the UK National Health Service (NHS).

Intervention technology and comparators

For the revised model, the intervention technology (pitolisant 20 mg) administered orally once per day was compared with best supportive care (BSC) as recommended by the ACD.

MAD were excluded from the base-case analysis as this revised model sets to simply estimate the cost-effectiveness of pitolisant when adjusting for the placebo-effect as per the solriamfetol model.

Model structure

A two-stage model composing of a decision tree (Figure 2) which reflects the first 52 weeks of treatment and a Markov model (Figure 3) for the remainder of the model time horizon was used.

Figure 2: Decision tree - first 52 weeks of treatment

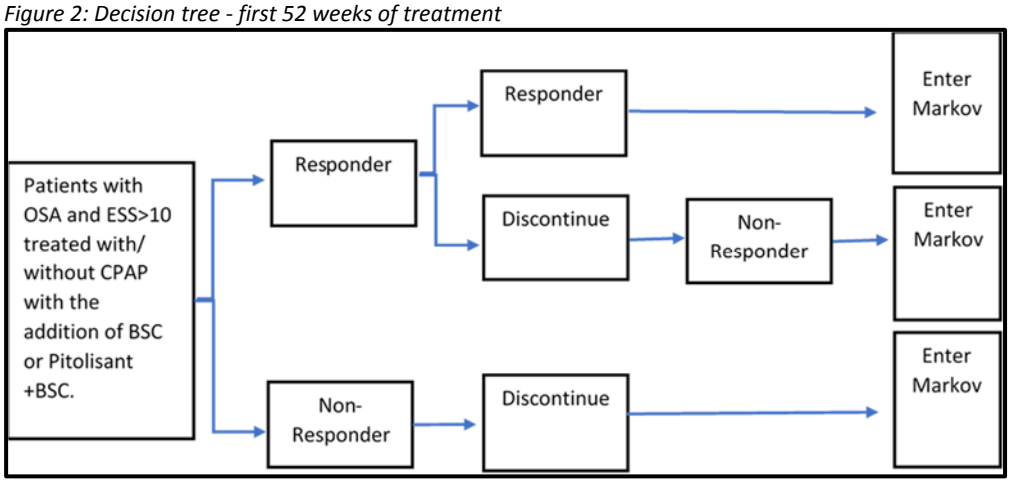


Figure 3: Markov model - 52 weeks onwards

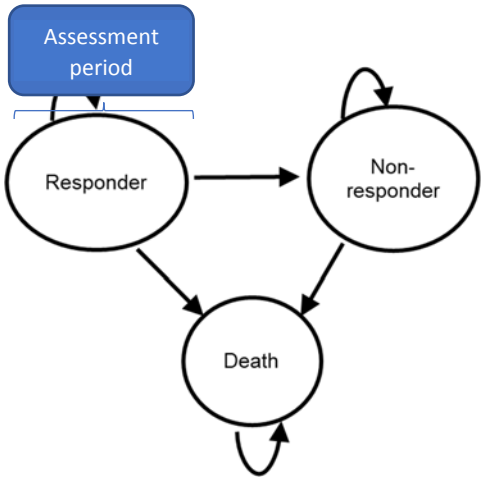


Figure 2 provides a diagrammatic representation of the first 52 weeks of the model. In the first 12 weeks of the model (Assessment period), patients with OSA and ESS>10 are treated with CPAP (HAROSA I) or without CPAP (HAROSA II) with the addition of BSC or pitolisant plus BSC, respectively. Patients identified as responders at the 12-week assessment move into the responder's health state and continue to receive pitolisant at the same dose. Non-responders are assumed to discontinue treatment.

Figure 3 provides a diagrammatic representation of the remainder of the model time horizon. The Markov model is made up of three health states: responders, non-responders and death. Health states used in the model are based on the ERG's comments. It is assumed that after 52 weeks, patients enter the Markov model either as a responder or a non-responder.

The model assumes that there is no disease specific death (only all cause of mortality), hence transition from assessment period, responder and non-responder health states to death states are derived from the UK life tables[20]. Transition to the death state in the decision tree section of the model is applied only halfway through the first year (week 26) to account for half cycle correction.

Time horizon and cycle length

Given that OSAHS is a chronic disease, a time horizon of 25 years was deemed appropriate to capture the long-term impact of treatments on the ICER for the base case analysis.

A scenario analysis of 45 years was also implemented to accommodate the ERG's recommendation as it assumes that people in the cohort will live beyond 25 years.

A weekly cycle length was used to model the first part of the model (Decision tree) and a yearly cycle length was used for the second part of the model (Markov model).

Model inputs

Clinical efficacy data and utilities were obtained from the HAROSA I and HAROSA II trials, systematic literature reviews and meta-analysis of relevant clinical and economic literature

The HAROSA I and HAROSA II studies provided evidence on intermediary outcomes in terms of ESS score but did not measure the treatment effects in terms of their impact on utility.

Efficacy data and transition probabilities

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

Response was based on an absolute reduction of at least 2 points from baseline ESS and was assessed at 12 weeks after treatment initiation (assessment period), week 14, 16, 28, 40 and 52. Between visits, patients are assumed to remain in their state until they are assessed at the various time points of the open label extension (OLE).

Transition probabilities between health states in the first 52 weeks were derived from the double-blind (DB) phase and OLE data from the HAROSA I and HAROSA II trials.

Transition between states were dependent on response rate. Response at week 12 was estimated using "centred" ESS scores (Table 10) which assumes that the improvement in ESS score observed in the HAROSA I and HAROSA II placebo arm is due to a "Hawthorne effect" and will not occur in clinical practice[21]. Patients in the BSC arm of the model are therefore assumed to have a constant mean ESS score and change in ESS scores modelled in the pitolisant arm are relative to the placebo arm. Subsequent transition probabilities from weeks 12-52 were based on the likelihood of experiencing a response and calculated using the conditional probability based on a ratio between the number of patients at each visit and the number of patients at the previous visit (Table 11). Transition probabilities derived at week 52 were assumed to be constant over the rest of the model time horizon.

Table 10:Responder value based on centred value

	HAROSA I		**HAROSA II**	
	Pitolisant + CPAP + BSC	**BSC + CPAP**	**Pitolisant + BSC**	**BSC**
Percentage	57.4%	37.7%	53.2%	31.3%
Count	-183.00	-61.00	-201.00	-67.00

Table 11: Number of patients still on treatment at each of the trial visit

	HAROSA I		**HAROSA II**	
	Pitolisant + CPAP + BSC	**BSC + CPAP**	**Pitolisant + BSC**	**BSC**
Visit 6 / Week 12	151	48	181	55
Visit 7 / Week 14	150	47	179	55
Visit 8 / Week 16	147	44	176	54
Visit 9 / Week 28	140	43	166	51
Visit 10 / Week 40	134	42	161	49
Visit 11 / Week 52	131	41	159	47

The values in Table 11 were derived by eliminating patients that had discontinued at each visit due to withdrawal from the OLE, adverse event (AE), patient decision, protocol violation, lack of efficacy or other reasons.

The model assumes that patients who respond to pitolisant will continue to receive the same dose of pitolisant and maintain their reduction in ESS while on pitolisant. Patients who do not respond to pitolisant by week 12 are defined as non-responders and assumed to discontinue treatment but continue BSC with or without CPAP for the lifetime of the model. The "centred" mean ESS scores for responders and non-responders are based on the pooled data from HAROSA I and HAROSA II as shown in Table 13 and Table 14. The mean ESS score (centred value) for non-responders is observed to be higher than at baseline (16.40 for placebo and 15.20 for pitolisant), suggesting that there is a clinical deterioration in patients who do not receive effective treatment.

Patients who discontinue treatment due to AE or loss of response are considered non-responders and will assume an ESS score of 16.4 for placebo and 15.2 for pitolisant.

All-cause mortality used in the model was taken from the 2021 UK life tables[20] and the average age and sex distribution were based on those observed in HAROSA I and HAROSA II trials.

Health related QOL data

The Committee was concerned about the rationale for mapping ESS scores to EQ-5D because of the limitations in capturing QOL benefits and they preferred use of the EQ-5D utility values derived from the clinical trials.

EQ-5D assessments were carried out as part of the HAROSA I and HAROSA II studies. As discussed in the first section of this document and below, directly elicited EQ-5D index values are poorly correlated with clinical change and in consequence were not used in this model.

Utility values based on "centred" ESS score reflect the use of the ESS as the gold standard measurement of EDS in OSA and ESS as the most frequently reported efficacy measure. The lack of impact on QOL with pitolisant is consistent with other studies in OSA treated with CPAP[22], MADs[23, 24]or modafinil[25, 26]. Clinical opinion, systematic reviews and work carried out by the Assessment Group for the NICE CPAP HTA indicate that generic instruments to measure QOL, including the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and the EuroQol (EQ-5D) do not capture benefit in QOL in patients with EDS[27-29]. These instruments have not been specifically designed to assess aspects of QOL in patients with OSA or EDS and sleep is not included as a specific dimension.

The revised model used the mapping regression models developed in the York model which formed the basis of the NICE guidance for the use of CPAP in OSA[30, 31] shown in Table 12 (mapping from EQ-5D), the baseline utility values (0.766 for HAROSA I and 0.737 for HAROSA II) and "centred" mean ESS values derived from HAROSA I and HAROSA II shown in Table 13 and Table 14, to map incremental utility versus BSC.

The change in mean ESS score from baseline was based on centred value and was derived by subtracting the baseline value (11.9 for HAROSA I and 12.1 for HAROSA II) from the mean "centred" ESS score as shown in Table 15 and Table 16.

Table 12:Ordinary least squares (OLS model) for mapping ESS scores to utility based on EQ-5D-3L

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

Table 13:Mean ESS for responders (centred value)

	Mean	**Count**	**SD**
BSC	8.42	71	± 4.13
Pitolisant	7.76	298	± 3.46
Total	7.88	369	± 3.60

Table 14:Mean ESS for non-responders (centred value)

	Mean	Count	SD
BSC	16.40	57	± 4.06
Pitolisant	15.20	86	± 3.43
Total	15.68	143	± 3.73

Table 15:Mean ESS score from baseline based on centred value- HAROSA I

Responder	Pitolisant + CPAP + BSC	-4.11
	CPAP + BSC	-3.45
Non-responder	Pitolisant + CPAP + BSC	4.53
	CPAP + BSC	3.33

Table 16: Mean ESS score from baseline based on centred value- HAROSA II

Responder	Pitolisant + BSC	-4.34
	BSC	-3.68
Non-responder	Pitolisant + BSC	3.10
	BSC	4.30

Intervention and comparators' costs and resource use

The costs included in the model were associated with the intervention (pitolisant) which was based on the manufacturers list price of £[redacted] per 30 tablets, equating to £[redacted] per 365-day per year (£[redacted]/30*365) as shown in Table 17.

In both active and control arms in all scenarios, all patients received BSC. In the scenario evaluating data from the HAROSA I study (add-on to CPAP), all patients also received treatment with CPAP. As these are constant costs that do not differ between treatment arms, there was no incremental cost to capture in the model. The costs of control arms were consequently set at zero.

The revised model does not include costs relating to resource use and only the cost of pitolisant is included.

Table 17: Cost of pitolisant

	Monthly cost	Expected annual cost	Weekly cost
Cost of pitolisant	£[redacted]	£[redacted]	£[redacted]

Summary of base-case analysis inputs

A summary of inputs used in the model is shown below in Table 18.

Table 18:Summary of variables applied in the economic model

Variable	**Value**
Discount rate - cost	0.035
Discount rate - utility	0.035
Efficacy inputs	
CPAP + BSC + pitolisant vs CPAP + BSC (HAROSA I): ESS effect size	-2.770
Pitolisant + BSC vs BSC alone (HAROSA II): ESS effect size	-2.710
Transition probabilities at the start of the model (assessment period) BSC (HAROSA I)	
Assessment period to assessment period	1.000
responder to responders	1.000
Non-responder to non-responders	1.000
Transition probabilities at the start of the model (assessment period) Pitolisant (HAROSA I)	

Assessment period to assessment period	1.000
responder to responders	1.000
Non-responder to non-responders	1.000
Transition probabilities at the start of the model (assessment period) BSC (HAROSA II)	
Assessment period to assessment period	1.000
responder to responders	1.000
Non-responder to non-responders	1.000
Transition probabilities at the start of the model (assessment period) Pitolisant (HAROSA II)	
Assessment period to assessment period	1.000
responder to responders	1.000
Non-responder to non-responders	1.000
Transition probabilities at week 12, BSC (HAROSA I)	
Assessment period to responder	0.377
Assessment period to non-responders	0.623
responder to responder	1.000
Non-responder to non-responder	1.000
Transition probabilities at week 12, Pitolisant (HAROSA I)	
Assessment period to responder	0.574
Assessment period to non-responders	0.426
responder to responder	1.000
Non-responder to non-responder	1.000
Transition probabilities at week 12, BSC (HAROSA II)	
Assessment period to responder	0.313
Assessment period to non-responders	0.687
responder to responder	1.000
Non-responder to non-responder	1.000
Transition probabilities at week 12, Pitolisant (HAROSA II)	
Assessment period to responder	0.532
Assessment period to non-responders	0.468
responder to responder	1.000
Non-responder to non-responder	1.000
Transition probabilities at week 14, BSC (HAROSA I)	
Assessment period to non-responder	1.000
responder to responder	0.979
responder to non-responder	0.021
Non-responder to non-responders	1.000
Transition probabilities at week 14, Pitolisant (HAROSA I)	
Assessment period to non-responder	1.000
responder to responder	0.993
responder to non-responder	0.007
Non-responder to non-responders	1.000
Transition probabilities at week 14, BSC (HAROSA II)	
Assessment period to non-responder	1.000

responder to responder	1.000
responder to non-responder	0.000
Non-responder to non-responders	1.000
Transition probabilities at week 14, Pitolisant (HAROSA II)	
Assessment period to non-responder	1.000
responder to responder	0.989
responder to non-responder	0.011
Non-responder to non-responders	1.000
Transition probabilities at week 16, BSC (HAROSA I)	
Assessment period to non-responder	1.000
responder to responder	0.936
responder to non-responder	0.064
Non-responder to non-responders	1.000
Transition probabilities at week 16, Pitolisant (HAROSA I)	
Assessment period to non-responder	1.000
responder to responder	0.980
responder to non-responder	0.020
Non-responder to non-responders	1.000
Transition probabilities at week 16, BSC (HAROSA II)	
Assessment period to non-responder	1.000
responder to responder	0.982
responder to non-responder	0.018
Non-responder to non-responders	1.000
Transition probabilities at week 16, Pitolisant (HAROSA II)	
Assessment period to non-responder	1.000
responder to responder	0.983
responder to non-responder	0.017
Non-responder to non-responders	1.000
Transition probabilities at week 28, BSC (HAROSA I)	
Assessment period to non-responder	1.000
responder to responder	0.977
responder to non-responder	0.023
Non-responder to non-responders	1.000
Transition probabilities at week 28, Pitolisant (HAROSA I)	
Assessment period to non-responder	1.000
responder to responder	0.952
responder to non-responder	0.048
Non-responder to non-responders	1.000
Transition probabilities at week 28, BSC (HAROSA II)	
Assessment period to non-responder	1.000
responder to responder	0.944
responder to non-responder	0.056
Non-responder to non-responders	1.000

Transition probabilities at week 28, Pitolisant (HAROSA II)	
Assessment period to non-responder	1.000
responder to responder	0.943
responder to non-responder	0.057
Non-responder to non-responders	1.000
Transition probabilities at week 40, BSC (HAROSA I)	
Assessment period to non-responder	1.000
responder to responder	0.977
responder to non-responder	0.023
Non-responder to non-responders	1.000
Transition probabilities at week 40, Pitolisant (HAROSA I)	
Assessment period to non-responder	1.000
responder to responder	0.957
responder to non-responder	0.043
Non-responder to non-responders	1.000
Transition probabilities at week 40, BSC (HAROSA II)	
Assessment period to non-responder	1.000
responder to responder	0.961
responder to non-responder	0.039
Non-responder to non-responders	1.000
Transition probabilities at week 40, Pitolisant (HAROSA II)	
Assessment period to non-responder	1.000
responder to responder	0.970
responder to non-responder	0.030
Non-responder to non-responders	1.000
Transition probabilities at week 52, BSC (HAROSA I)	
Assessment period to non-responder	1.000
responder to responder	0.976
responder to non-responder	0.024
Non-responder to non-responders	1.000
Transition probabilities at week 52, Pitolisant (HAROSA I)	
Assessment period to non-responder	1.000
responder to responder	0.978
responder to non-responder	0.022
Non-responder to non-responders	1.000
Transition probabilities at week 52, BSC (HAROSA II)	
Assessment period to non-responder	1.000
responder to responder	0.959
responder to non-responder	0.041
Non-responder to non-responders	1.000
Transition probabilities at week 52, Pitolisant (HAROSA II)	
Assessment period to non-responder	1.000
responder to responder	0.988

responder to non-responder	0.012
Non-responder to non-responders	1.000
Transition in between probabilities BSC and pitolisant (HAROSA I and HAROSA II)	
Assessment period to non-responder	1.000
responder to responder	1.000
responder to non-responder	1.000
Non-responder to non-responders	1.000
Utility based on EQ-5D - BSC - HAROSA I	
Non-responders	0.849
Responders	0.926
Utility based on EQ-5D - Pitolisant - HAROSA I	
Non-responders	0.860
Responders	0.932
Utility based on EQ-5D - BSC - HAROSA II	
Non-responders	0.851
Responders	0.928
Utility based on EQ-5D - Pitolisant - HAROSA II	
Non-responders	0.862
Responders	0.935
Costs	
Annual cost of pitolisant (list price)	£[redacted]

Results

The corresponding total costs, QALYs and the ICER are reported for the two patient populations

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

For patients with residual EDS despite CPAP (HAROSA I), the deterministic ICER for pitolisant plus CPAP and BSC, compared with CPAP plus BSC is estimated at £32,430/QALY at 25-year time horizon (see Table 19) and £31,547/QALY at 45-year time horizon (see Table 21).

For patients with EDS due to OSA who refuse CPAP (HAROSA II), the deterministic ICER for pitolisant compared with BSC is estimated at £28,431/ QALY at 25-year time horizon (see Table 20) and £27,262/QALY at 45-year time horizon(see Table 22) both of which estimates fall below the conventionally accepted willingness to pay threshold (£30,000/QALY).

Table 19: Discounted costs and effects at 25-year time horizon – patients with residual EDS despite CPAP (HAROSA I)

Base case result: Discounted costs and effects (HAROSA I)			
	Costs	**QALYs**	**ICER (Cost/QALY)**
Pitolisant + CPAP + BSC	£10,912	13.84	
CPAP + BSC	£0	13.50	
Increment	£10,912	0.34	£32,430

Table 20: Discounted costs and effects at 25-year time horizon– patients with EDS due to OSA who refuse CPAP (HAROSA II)

Base case result: Discounted costs and effects (HAROSA II)			
	Costs	**QALYs**	**ICER (Cost/QALY)**
Pitolisant + BSC	£11,159	13.91	
BSC	£0	13.51	
Increment	£11,159	0.41	£28,431

Table 21: Discounted costs and effects at 45-year time horizon – patients with residual EDS despite CPAP (HAROSA I)

Base case result: Discounted costs and effects (HAROSA I)			
	Costs	**QALYs**	**ICER (Cost/QALY)**
Pitolisant + CPAP + BSC	£11,872	15.80	
CPAP + BSC	£0	15.43	
Increment	£11,872	0.38	£31,547

Table 22: Discounted costs and effects at 45-year time horizon– patients with EDS due to OSA who refuse CPAP (HAROSA II)

Base case result: Discounted costs and effects (HAROSA II)			
	Costs	**QALYs**	**ICER (Cost/QALY)**
Pitolisant + BSC	£12,389	15.91	
BSC	£0	15.46	
Increment	£12,389	0.48	£27,262

Conclusion

This cost-effectiveness analysis was carried out as requested by NICE to explore the impact on the cost-effectiveness of pitolisant when the effect of a placebo response in the HAROSA I and HAROSA II trials is considered.

The “centred” approach resulted in an ICER of £32,430/QALY for patients with residual EDS despite CPAP and £28,431/QALY for patients with EDS due to OSA who refuse CPAP at a 25-year time horizon. Corresponding figures for a 45-year time horizon were £31,547/QALY and £27,262/QALY respectively

The key driver of the cost-effectiveness is the utilities. The utilities used were estimated from the “centred” mean ESS scores, based on pooled data from HAROSA I and HAROSA II. Given that both trials (HAROSA I and HAROSA II) have different baseline ESS score values, using pooled data introduces bias to the analysis. Also, whilst the solriamfetol model used the centred approach, it is based on the Hawthorne effect and there is limited evidence to justify the adjustment of the BSC arm.

Baseline utility data for “responders” and “non-responders” were not available from the HAROSA studies and therefore utility values for responders and non-responders were computed using baseline ESS scores (11.9 for HAROSA I and 12.1 for HAROSA II). The “centred” mean ESS score for non-responders (16.4 for placebo and 15.2 for pitolisant) is higher than ESS score at baseline which implies that patients in the non-responder arm are worse-off at the end of the model than at the beginning. It is also important to note that data from the OLE was used to inform the transition probabilities from week 12 to week 52.

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

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Jazz Pharmaceuticals UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Section 3.6 and 3.14 We are concerned that a thorough analysis of the influence of the placebo effect in the HAROSA clinical trial program has not been conducted. Although the Company Submission recognises this “strong placebo effect” (Section 2.13.1), which occurs over a time course of weeks, it has not been considered whether this could be also due to “regression towards the mean” in the whole population: a function of enrolling in the trial at a time when Epworth Sleepiness Scale was particularly severe for the patient, before returning to a natural “true” representation of the patients’ Excessive Daytime Sleepiness. We welcome the recognition that the methodology in ID1499 helps to address the observed placebo response in a meaningful and useful way, accounting for this being likely to be a true placebo effect, while acknowledging that it is not possible to *rule out* the influence of the Hawthorne effect (reported improvement associated with the intervention of the trial alone) and regression towards the mean.
2	Section 3.8 We are concerned that the influence of pitolisant on adherence to primary OSA therapy has not been adequately considered in this Technology Appraisal, with the committee concluding on this matter based on expert opinion when data exist. Although we agree that CPAP use is unlikely to be affected by treatment with pharmacotherapy for EDS (as demonstrated through data analysis in ID1499 for solriamfetol), an evidence-based approach should be considered in the ID1065 Company Submission. The omission of data on adherence to primary therapy creates uncertainty that when introducing pitolisant into clinical practice patients who are adherent to CPAP therapy could show a clinically significant reduction in CPAP usage. This may result in a return of symptoms not treated by pitolisant and therefore a introduce a significant risk to patients and an increase in resource use for those patients. Adherence to nightly CPAP was measured in the HAROSA I trial informing the data presented to the committee on pitolisant (Response to clarification questions (Lincoln Medical), page 14). This data has not been reported in the peer-reviewed manuscript associated with this study (Pepin 2021), nor in the Company Submission ID1065. Positive airway pressure, usually with CPAP, is the established primary therapy for OSA as acknowledged in the Company Submission (Section 1.3.2 "CPAP is the gold standard treatment for EDS due to OSA”). Many of the deleterious effects of OSA can be attributed to the repetitive cycles of hypoxaemia and reoxygenation association with periodic airway

collapse. CPAP has consistently been shown to have a positive influence on blood pressure and other vascular risk factors (Litvin 2013, Kartali 2014, Picard 2021).

The clinical importance of disease modifying therapy (e.g. CPAP) is intrinsically linked to the level of adherence in treated OSA patients, usually measured in hours per night of usage. OSA symptom control has been linked to adherent use of CPAP (Weaver 2007, Sawyer 2011, Gaisl 2020). More-over, withdrawal of CPAP in an adherent population has been shown to result in a rapid recurrence of OSA symptoms and re-emergence of deleterious cardiovascular biomarkers (Kohler 2011).

Clinician and patient experts have raised the concern of how introducing a pharmacotherapy would influence adherence with prescribed CPAP in both ID1065 and ID1499.

In ID1499 Jazz Pharmaceuticals presented a peer-reviewed analysis specifically addressing the influence of solriamfetol on adherence to PAP therapy, as well as being asked to provide additional analyses to reassure the ERG and committee that solriamfetol is unlikely to result in a decrease in adherence to CPAP.

Without presenting the data that has already been gathered in the HAROSA trial program on the influence of pitolisant on adherence to CPAP being made available, considerable clinical and health economic uncertainty on this issue remains for ID1065.

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

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	Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. Sleep Med Rev. 2011 Dec;15(6):343-56. Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, Kader G, Mahowald M, Younger J, Pack AI. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. Sleep. 2007 Jun;30(6):711-9.
3	Section 3.15 In the absence of appropriate HRQoL trial data, we agree with the use of the McDaid algorithm as an appropriate methodology that has been used in previous NICE technology appraisals (TA139). It is recognised that there is considerable need for a well-validated and sufficiently responsive quality of life measure for evaluating people with sleep disorders (Reimer 2003). The EQ-5D and SF-6D questionnaires are both generic measures to ascertain health status and neither questionnaire includes a sleep domain nor a dimension to specifically capture the impact of EDS on quality of life in people with OSA. Clinicians describe a very substantial burden on QoL for patients with EDS due to OSA and feel that these generic scales underestimate the true burden of EDS on QoL (see ID1499). It is likely that neither the EQ-5D nor the SF-36 data collected in the pitolisant trials reflect the burden of OSA and residual EDS on QoL. The duration of the trials is also likely insufficient to capture the full effect of pitolisant on QoL. The ERG suggested that SF-6D may be more sensitive than EQ-5D in capturing QoL benefits. The Company provided a scenario that mapped ESS scores to SF-6D. The Committee agreed that the Company's scenario using SF-6D might be preferable, but stated that more understanding was needed to determine how well mapping to SF6D captures quality-of-life benefits. The Committee concluded that it preferred the EQ-5D utility values derived from the clinical trials and that more detailed evidence should be provided to explain why EQ-5D is insensitive to capturing changes in a person's quality of life. The McDaid algorithm shows similar results to the mapping algorithm developed by Jazz Pharmaceuticals across a large EU5 dataset (NHWS) in ID1499. The NHWS better reflects the real impact on patients of residual EDS in OSA compared to trial based-EQ-5D, where small number of patients and short follow up times are likely to not give a representative impact of residual EDS on quality of life. Therefore, another appropriate methodology could be to make use of a NHWS mapping to complement the McDaid approach. Reference Reimer MA, Flemons WW. Quality of life in sleep disorders. Sleep Med Rev. 2003 Aug;7(4):335-49.
4	Section 3.10 We are concerned that the impact on the introduction of pitolisant on resource use through hospitalisation has not been adequately considered.

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	While we agree with the observation that rates of serious TEAEs in the HAROSA I trial were relatively low, they were nonetheless reported in 6% of subjects in the pitolisant-pitolisant arm of the open-label extension of the HAROSA I trial (Company Submission, Section 2.10.3 and Table 20). As pitolisant is positioned as an add-on to primary therapy, both the direct cost and the cost related to disutility of hospitalisation could create uncertainty around the true ICER associated with pitolisant in EDS associated with OSA. Data available from the FDA Center for Drug Evaluation and Research (CDER) demonstrates that patients with OSA were hospitalised during the pitolisant clinical trial program (FDA 2019), but the Company Submission did not include these as direct resource costs nor disutilities associated with hospital admission. With the caution described by the committee in using data from the use of pitolisant for the treatment of narcolepsy in the HARMONY follow up period, we believe there is considerable uncertainty as to whether pitolisant will result in greater hospitalisation costs when prescribed for EDS associated with OSA and urge the committee to consider OSA specific hospitalisation data. <u>Reference</u> FDA Center for Drug Evaluation and Research. Joint Supervisory Memo - NDA 211150, Pitolisant, 14 July 2019. Clinical Review Application Number: 211150Orig1s000. Available at [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211150Orig1s000SumR.pdf], last accessed 24/06/2021
5	<u>Section 3</u> We would like to highlight some factual inaccuracies in the clinician and patient responses which have then been included in committee papers and subsequent presentation to committee. There has been some confusion of patient and clinical expert engagement forms between those for this appraisal of pitolisant (ID1065) and that of solriamfetol for treating excessive daytime sleepiness caused by obstructive sleep apnoea (ID1499). We are concerned that this may cause confusion between the two appraisals ID1605 and ID1499. It is possible that the inclusion of solriamfetol responses instead of pitolisant responses means that important clinician and patient insights into pitolisant have not been captured. For two of the three clinical expert statements for this pitolisant submission, the topic-specific questions are those set for the appraisal of solriamfetol for treating excessive daytime sleepiness caused by obstructive sleep apnoea (ID1499), not pitolisant (ID1065). The patient expert statement in this pitolisant appraisal is also subtitled “Patient expert statement Solriamfetol for treating excessive daytime sleepiness caused by obstructive sleep apnoea.” We recognise however that for the patient statement, Part 2 does have the correct Technical Engagement questions.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	Graham Hill
Comment number	**Comments**

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

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 24 June. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Para 3.2 The quoted patient expert comment "some people struggle to use it regularly because of its size, the amount of noise it makes and because it can affect sleep" is incorrect. The ACD attributes to me a statement that the size and noise of CPAP machines present problems, and the use of CPAP adversely affects sleep. This is not what I stated in my patient expert submission. I commented that CPAP machines are "now much smaller and quieter than they were a few years ago." My submission also noted that patients need to adjust to coping with the minor discomfort of having to sleep wearing a mask connected to a "small" machine. It did not state, nor did it imply, that this discomfort prevented sleep.
2	Para 3.8 In response to patient experts concerns that availability of Pitolisant could lead to a reduction in compliance with CPAP therapy clinical experts expressed the view that "people having pitolisant hydrochloride alongside CPAP may have their use monitored more frequently than in current practice". Many sleep clinics now have the ability to monitor CPAP compliance remotely but SATA discussions with some clinics suggests that such monitoring is not routinely carried out, even on an exception reporting basis, though it may be used for the first week or so of CPAP therapy to ensure that there are no start-up problems. If Pitolisant were to be approved, it should be on the basis that CPAP use must be regularly and frequently monitored until the sleep clinic is satisfied that the patient will continue to use combined therapy.
3	Para 3.16 The final sentence is incorrect. People with untreated obstructive sleep apnoea and excessive daytime sleepiness are not "banned" from driving. The responsibility for deciding fitness to drive rests with the individual. If a person drives knowing they are not fit to drive through sleepiness, whatever the cause, they are breaking the law. They would also be breaking the law if they drove despite being advised not to do so by a GP, consultant or other medical professional. Conversely, a patient with moderate to severe obstructive sleep apnoea with symptoms of EDS is free to continue driving once they are diagnosed and treated, the sleep clinic is satisfied that CPAP therapy is working and the DVLA has been informed. The point at issue here is that if Pitolisant is prescribed to address the symptoms of EDS the patient could decide to carry on with Pitolisant but stop CPAP therapy. Even if Pitolisant on its own controls EDS the fact that the patient has stopped using CPAP therapy will breach the basis on which DVLA has cleared the patient to continue driving. If Pitolisant on its own does not adequately control excessive daytime sleepiness the patient is at increased risk of a road traffic accident. Within the parameters of this paragraph, unless the Committee is convinced the various trials demonstrate that Pitolisant on its own will fully control EDS, I question the Committee decision not to include a utility decrement for road traffic accidents.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**LIVERPOOL UNIVERISTY FOUNDATION TRUST**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Previous education lecture on behalf of Jazz Pharmaceuticals]**
Name of commentator person completing form:	Ari Manuel

Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	"Excessive daytime sleepiness caused by obstructive sleep apnoea is usually treated with a primary obstructive sleep apnoea therapy such as CPAP. Some people might not tolerate CPAP so they are offered mandibular advancement devices" MAD devices are primary therapy for OSA – they can be offered instead of rather after CPAP failure
2	The committee concluded that the HAROSA trials were broadly generalisable for decision making but underrepresent people with psychiatric illness This is a difficult point. Many patients admitted to sleep clinics are on antidepressant medications from their primary care doctors, but many are put on this for poor quality sleep. Primary care recognises that insomnia is associated with depression, but a third of OSA patients have insomnia as their primary symptoms. So as such the percentages in HAROSA are probably fairly representive of "true depression" in a NHS clinic (albeit the poor quality of diagnosis of patients prior to referral)
3	It was unaware of any reasonable mechanism by which a wakefulness drug would reduce cardiovascular risk, rather than this being a result of treating the underlying cause of excessive sleepiness (obstructive sleep apnoea). I would check the literature on activity in sleepy populations eg narcolepsy and especially those with obesity (with depression or say chronic pain) and look at whether they have a lower degree of activity and as such this has a direct influence on CV risk
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- Complete the disclosure about links with, or funding from, the tobacco industry.
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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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

ADDENDUM: Critique of the company's response to ACD

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

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Date completed 24/09/2021

Company's response to ACD

The purpose of this addendum is to provide a critique of the company's response to the appraisal consultation document (ACD).

Introduction

As an extension of their stakeholder response to the Appraisal Consultation Document (ACD) for pitolisant issued in May 2021, the company has provided a document with the results of a more detailed examination of the assessment of utility and the handling of placebo effect, including an updated cost-effectiveness model based on an alternative modelling approach. This document and the updated model were assessed by the Evidence Review Group (ERG), whose summaries and comments are provided below.

Issue 1: Derivation of utilities

To address the committee's concerns about the use of a mapping approach to estimate EQ-5D utility values using the Epworth Sleepiness Scale (ESS) scores, the company commissioned an analysis of EQ-5D outcomes by Professor Phillipe Lehert.

The company indicated in their original submission that the choice for the use of a mapping approach was based on limitations in capturing quality-of-life benefits due to the insensitivity of the EQ-5D to changes in the quality of life (QoL) of patients who experienced improvements in excessive daytime sleepiness (EDS) following the use of pitolisant.

The committee indicated their preference for directly elicited EQ-5D utilities from the clinical trials and that stronger evidence regarding the insensitivity of directly elicited EQ-5D utilities was required to support the use of indirectly estimated utilities using a mapping approach from ESS scores.

The analysis by Prof. Lehert consisted of an individual patient data regression analysis of the following EQ-5D outcomes: The Health State Index score (EQ-INDEX; defined as a sum score over the 5 dimensions of the EQ-5D), the Visual Analogue Scale score (EQ-VAS) and the Z-score. The results indicated that there was no significant difference between the pitolisant and placebo arms for the EQ-INDEX. In contrast, significant differences were found for the EQ-VAS and the Z-score. The results for the EQ-VAS were better correlated with clinical outcomes than those for the EQ-INDEX.

In light of the narrative evidence from patients and clinicians, the company deemed an interpretation that the improvement in excessive daytime sleepiness (EDS) associated with the use of pitolisant, as well as other treatments for obstructive sleep apnoea (OSA), did not lead to improvements in QoL, and that consequently improvements indicated by EQ-VAS and the Z-score were spurious, unlikely to be the whole truth. Instead, the company interpreted the results to be in support of the interpretation that the EQ-5D INDEX is insensitive to the change in QoL associated with a reduction in EDS, and that alternative measures such as the EQ-VAS are better able of capturing this change. However, the company also recognized that the direct use of the EQ-VAS data (or Z-score) is not in line with the NICE Reference case, and therefore not acceptable, and that currently no evidence exists to support the interpretation of an EQ-VAS score as a utility estimate. A third interpretation that was coined by the company was that the EQ-5D, regardless of the analytical method used, showed too much internal variation and therefore is an unreliable metric for use in this patient group. According to the company, addressing this issue by using an alternative mapping approach from ESS scores would be the only viable option despite there being relatively weak support for the assumptions that are inherent to such an approach. As such, the company concluded that an estimation of utilities based on a mapping from

ESS scores, similar to the approach that was used for economic models for CPAP, MAD and solriamfetol, was the best compromise currently available for use in the economic model for pitolisant.

ERG comment:

The ERG notes that the EQ-5D INDEX variable that was used in the additional analyses refers to an EQ-5D sum-score (i.e., a summation of the scores for each level of the five dimensions) that was standardised and reversed to a scale of 0-100. As such, it is unknown what results would have been obtained if EQ-5D utilities (e.g. based on the UK value set[1]) were used. Therefore, the results for the additional analysis using EQ-5D INDEX (i.e. sum score) do not provide evidence that the EQ-5D utility is insensitive to improvements in QoL in this patient group. It is unknown to what extent the results using EQ-INDEX (i.e. sum score) would be consistent with results that would be obtained using EQ-5D utilities.

The ERG agrees that the results of the additional analyses based on EQ-VAS are indicative of improvements in QoL based on patients' subjective perception of what constitutes QoL. However, the ERG notes that this is a different concept than QoL measured with the EQ-5D using utilities. As such, the results using EQ-VAS cannot be used in support of claims regarding the EQ-5D scored with utilities not being capable of capturing change in this population.

In the ACD, the committee highlighted that if EQ-5D does not capture quality-of-life benefits adequately the results should not be mapped to EQ-5D, because it will remain insensitive. In spite of this comment, the company has used the mapping from ESS to EQ-5D also in the updated economic model.

[1] Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095–108.

Issue 2: Impact of differing handling of placebo-response on ICER

Model structure

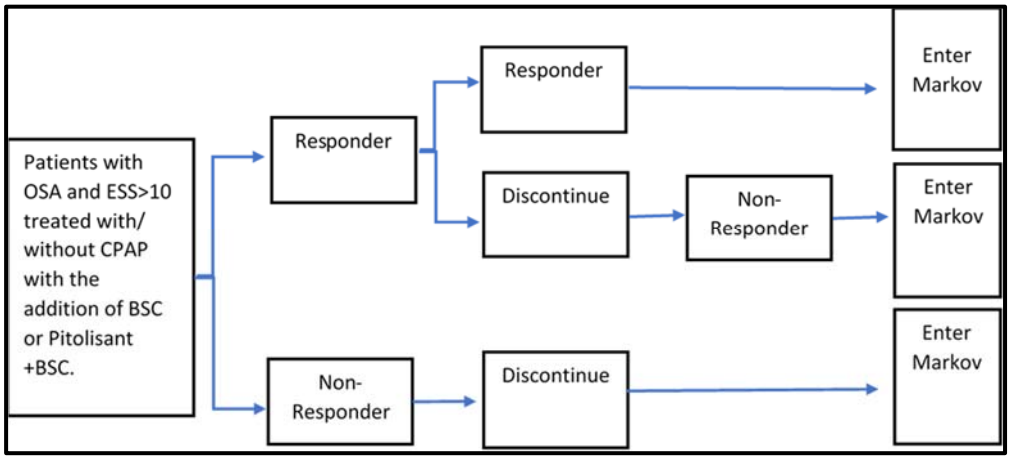
In response to the committee's suggestion and in line with the approach used by Jazz Pharma in their economic model for solriamfetol, the company constructed a *de novo* model that considers 'responders' and 'non-responders' separately, coupled with a placebo-centering approach (i.e. in which the improvement in ESS scores observed in the placebo group is removed from both the placebo and the pitolisant groups in the model).

The company notes a number of differences between their approach and the one by Jazz Pharma:

- In line with ERG comments to the original model by Jazz Pharma, the company adopted a 2-point change (i.e. instead of a 3-point change) in ESS score in defining a treatment response.
- In line with ERG comments to the original model by Jazz Pharma, centred ESS scores were calculated by subtracting the mean ΔESS in patients on standard care from ΔESS for each individual patient from the pitolisant treatment arm.
- In contrast to the model by Jazz Pharma, placebo-treated patients could enter the responder health state (with the proportion being determined by the placebo-centred calculations).
- The company adhered to the same mapping approach from ESS scores to utilities as used in their original submission (and mentioned above), instead of the mapping approach used by Jazz Pharma. This was due to a number of baseline covariates not being available and to facilitate comparisons with the results from the original model.

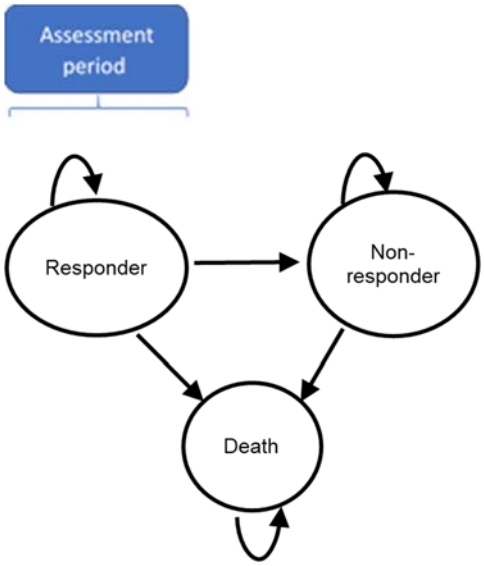
In terms of model structure, a two-stage model was composed that included a decision tree (Figure 1.1), reflecting the first 52 weeks of treatment, and a Markov model (Figure 1.2), consisting of the health states Responder, Non-responder, and Death, was used for the remainder of the model time horizon.

Figure 1.1: Model structure for decision tree – first 52 weeks of treatment



Source: Figure 2 in the company's extended ACD response.
ACD = appraisal consultation document; BSC = best supportive care; CPAP = continuous positive airway pressure; OSA = obstructive sleep apnoea; ESS = Epworth Sleepiness Scale.

Figure 1.2: Model structure for Markov model – 52 weeks onwards



Source: Figure 3 in the company's extended ACD response.
ACD = appraisal consultation document.

In the first 12 weeks of the model (Assessment period), patients with OSA and ESS>10 are treated with CPAP (HAROSA I) or without CPAP (HAROSA II) with the addition of BSC or pitolisant plus BSC, respectively. Patients identified as responders at the 12-week assessment move into the Responder health state and continue to receive pitolisant at the same dose. Non-responders are assumed to discontinue treatment. After 52 weeks, patients enter the Markov model either as a responder or a non-responder.

A weekly cycle length was used to model the first part of the model (Decision tree) and a yearly cycle length was used for the second part of the model (Markov model). A time horizon of 25 years was used for the base-case analysis, and scenario analyses were performed using 45 years as preferred by the ERG.

Patient population, intervention and comparators

In short, the patient population considered in the revised model consisted of adult patients with moderate or severe OSAHS, with residual EDS despite treatment with CPAP for a minimum period of 3 months (i.e. HAROSA I) and adult patients with EDS due to OSA who refuse CPAP (i.e. HAROSA II). The studied intervention was pitolisant 20 mg administered orally once per day, which was compared with best supportive care (BSC) as recommended by the ACD. A scenario including MAD was not performed.

Model inputs

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

Transitions between health states were dependent on response rate. Response was based on an absolute reduction of at least 2 points from baseline ESS and was assessed at week 12 (assessment period) using "centred" ESS scores. It was assumed that patients in the BSC arm of the model have a constant mean ESS score and change in ESS scores in the pitolisant arm was modelled relative to the placebo arm.

Patients who do not respond to pitolisant by week 12 are defined as non-responders and assumed to discontinue treatment but continue BSC with or without CPAP for the lifetime of the model. The proportions of responders and non-responders in HAROSA I and HAROSA II are shown in Table 1.1.

Table 1.1 Proportions of responders in HAROSA I and HAROSA II

	HAROSA I		HAROSA II	
	Pitolisant + CPAP + BSC (n=183)	**BSC + CPAP (n=61)**	**Pitolisant + BSC (n=201)**	**BSC (n=67)**
Percentage of responders	**57.4%**	**37.7%**	**53.2%**	**31.3%**
Based on Table 10 in the company's extended ACD response. ACD = appraisal consultation document; BSC = best supportive care; CPAP = continuous positive airway pressure.				

For week 14, 16, 28, 40 and 52 (open label extension period), response rates were based on the number of patients still on treatment (i.e. who are assumed to be responders and maintain their reduction in ESS while on pitolisant) at each visit relative to the previous visit and are shown in Table 1.2. Treatment discontinuation could be due to withdrawal from the OLE, adverse event (AE), patient decision, protocol violation, lack of efficacy or other reasons. From week 52 onwards, transition probabilities were assumed to be constant over the rest of the time horizon.

Table 1.2 Numbers of patients still on treatment at each of the trial visits

	HAROSA I		HAROSA II	
	Pitolisant + CPAP + BSC (n=183)	**BSC + CPAP (n=61)**	**Pitolisant + BSC (n=201)**	**BSC (n=67)**
Visit 6 / Week 12	151	48	181	55
Visit 7 / Week 14	150	47	179	55
Visit 8 / Week 16	147	44	176	54
Visit 9 / Week 28	140	43	166	51
Visit 10 / Week 40	134	42	161	49
Visit 11 / Week 52	131	41	159	47
Source: Table 11 in the company's extended ACD response. ACD = appraisal consultation document; BSC = best supportive care; CPAP = continuous positive airway pressure.				

The "centred" mean ESS scores for responders and non-responders are based on the pooled data from HAROSA I and HAROSA II as shown in **Error! Reference source not found.**. The mean ESS score (centred value) for non-responders was higher than at baseline (16.40 for placebo and 15.20 for pitolisant), suggesting that there is a clinical deterioration in patients who do not receive effective treatment.

Table 1.3 Mean ESS for responders and non-responders (centred value)

	Mean	Count	SD
Responders			
BSC	8.42	71	± 4.13
Pitolisant	7.76	298	± 3.46
Total	7.88	369	± 3.60
Non-responders			
BSC	16.40	57	± 4.06
Pitolisant	15.20	86	± 3.43
Total	15.68	143	± 3.73

Source: Tables 13 and 14 in the company's extended ACD response.
ACD = appraisal consultation document; BSC = best supportive care; SD = standard deviation.

The change in mean ESS score from baseline was based on the centred value and was derived by subtracting the baseline value (from the mean "centred" ESS score, which resulted in the values shown in Table 1.4 and Table 1.5 for HAROSA I and HAROSA II, respectively.

Table 1.4 Mean change in ESS from baseline based on centred value: HAROSA I

	Treatment arm	Mean ΔESS from baseline (centred value)
Responder	Pitolisant + CPAP + BSC	-4.11
	CPAP + BSC	-3.45
Non-responder	Pitolisant + CPAP + BSC	4.53
	CPAP + BSC	3.33

Source: Table 15 in the company's extended ACD response.
ACD = appraisal consultation document; BSC = best supportive care; CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Scale.

Table 1.5 Mean change in ESS from baseline based on centred value: HAROSA II

	Treatment arm	Mean ΔESS from baseline (centred value)
Responder	Pitolisant + BSC	-4.34
	BSC	-3.68
Non-responder	Pitolisant + BSC	3.10
	BSC	4.30

Source: Table 16 in the company's extended ACD response.
ACD = appraisal consultation document; BSC = best supportive care; ESS = Epworth Sleepiness Scale.

All-cause mortality used in the model was taken from the 2021 UK life tables and the average age and sex distribution were based on those observed in HAROSA I and HAROSA II trials. Transition to Death

in the decision tree section of the model is applied only halfway through the first year (week 26) to account for half cycle correction.

Quality of life inputs

Utility estimates for responders and non-responders were estimated using mapping regression models developed in the York model for NICE TA139, using the coefficients as shown in shown in **Error! Reference source not found.**, the baseline utility values (0.766 for HAROSA I and 0.737 for HAROSA II) and "centred" mean ESS values derived from HAROSA I and HAROSA II.

Table 1.6 Ordinary least squares model for mapping ESS scores to utility based on EQ-5D-3L

	Coefficient	SE	95% CI
ESS	-0.01	0.004	-0.018 to -0.002
Baseline ESS	0.003	0.003	-0.004 to 0.01
Constant	0.893	0.029	0.836 to 0.949

Source: Table 12 in the company's extended ACD response.
ACD = appraisal consultation document; CI = confidence interval; ESS = Epworth Sleepiness Scale; SE = standard error.

Table 1.7 shows the utility estimates that were mapped from ESS scores and used in the company's model for responders and non-responders in both treatment arms in HAROSA I and HAROSA II.

Table 1.7 Utility values mapped from ESS to EQ-5D

	Utility value HAROSA I	Utility value HAROSA II
BSC		
Responder	0.926	0.928
Non-responder	0.849	0.851
Pitolisant		
Responder	0.932	0.935
Non-responder	0.860	0.862

Source: Table 18 in the company's extended ACD response.
ACD = appraisal consultation document; BSC = best supportive care; ESS = Epworth Sleepiness Scale; EQ-5D = EuroQol-5 dimensions.

Cost inputs

The model included no costs other than the drug acquisition costs of pitolisant, which was based on the list price of £[redacted] per 30 tablets, equating to £[redacted] per year (£[redacted]/30*365).

Results

The company's base-case cost effectiveness results are shown in Table 1.8 for patients with residual EDS despite CPAP (HAROSA I), indicating an ICER of £32,430 per QALY gained.

Table 1.8: Updated company base-case deterministic cost effectiveness results (discounted): HAROSA I

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pitolisant + CPAP + BSC	£10,912	13.84	£10,912	0.34	£32,430
CPAP + BSC	£0	13.50			

Source: Table 19 in the company's extended ACD response.
ACD = appraisal consultation document; BSC = best supportive care; CPAP = continuous positive airway pressure; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.

For patients with EDS due to OSA who refuse CPAP (HAROSA II) the company's base-case cost effectiveness results are shown in Table 1.9, indicating an ICER of £28,431 per QALY gained.

Table 1.9: Updated company base-case deterministic cost effectiveness results (discounted): HAROSA II

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pitolisant + BSC	£11,159	13.91	£11,159	0.41	£28,431
BSC	£0	13.51			

Source: Table 20 in the company's extended ACD response.
ACD = appraisal consultation document; BSC = best supportive care; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.

The company did not perform a probabilistic sensitivity analysis but did include scenario analyses in which the time horizon was extended from 25 to 45 years. These resulted in ICERs of £31,547 per QALY gained for patients with residual EDS despite CPAP (HAROSA I), and £27,262 per QALY gained for patients with EDS due to OSA who refuse CPAP (HAROSA II).

ERG comment:

The ERG considers the company's approach to their updated model in line with the suggestions in the ACD regarding categorization of responders and non-responders and correction for the placebo effect as appropriate in general. However, there are a number of aspects in the updated model that in the opinion of the ERG require further justification and explanation.

Transition probabilities after 12 weeks

The transition probabilities from responder to non-responder from week 12 onwards (i.e. at which point treatment response is determined) were calculated from the numbers of patients in each arm that were still on treatment and attending study visits during the open-label extension periods of the trials. However, it is not clear to what extent we may assume that th derived rate of discontinuation can be used to estimate the rate of losing treatment response. In their document the company provides no justification to support this assumption.

The ERG further notes that the number of patients that were still on treatment and attended the study visits at week 12, e.g. 151 patients receiving pitolisant in HAROSA I, is substantially higher than the number of patients that were categorized as responders at that time (e.g. 57.4% of 181 patients is 104 patients). It is unclear why also non-responders entering the open-label extension period, were included in the derivation of the discontinuation rate.
Finally, the approach described above, where the company used the open-label extension periods of the trials to estimate the transition probability from responder to non-responder was also applied to the BSC groups. However, during the open-label period these patients received pitolisant, and thus, the observed discontinuation rate in this group cannot be used to estimate the discontinuation rate if these patients had continued to receive BSC, let alone to estimate the rate of losing treatment response.

Baseline utility

The updated model includes baseline utility values for HAROSA I and HAROSA II (i.e. on sheet 'Clinical inputs', cells K11 and K12). It is not clear how these were derived but they cannot be reproduced using the baseline ESS scores as presented on the 'Efficacy & Risk inputs'.

Utilities responders and non-responders

The utilities derived for responders and non-responders using the mapping algorithm appear very high; for HAROSA I in the BSC group the utility is 0.851 for non-responders and 0.928 for responders, and for the pitolisant group 0.862 and 0.935, respectively. Compared to the baseline utility of 0.766 this is a sharp increase for both responders and non-responders. This is caused by an error in the formulae for these utilities, since the company multiplies the baseline utility with the coefficient labelled 'baseline ESS' and adds this to the intercept + coefficient ESS * change in ESS. However, if we follow the same approach as in McDaid et al,[2] the source of the mapping algorithm, the correct approach would be to estimate the utilities by adding a value of coefficient ESS * change in ESS to the baseline utility. The resulting utility values are in table 1.10.

Table 1.10 ERG derived utility values mapped from ESS to EQ-5D

	Utility value HAROSA I	Utility value HAROSA II
BSC		
Responder	0.799	0.773
Non-responder	0.722	0.695
Pitolisant		
Responder	0.806	0.779
Non-responder	0.734	0.707
ACD = appraisal consultation document; BSC = best supportive care; ESS = Epworth Sleepiness Scale; EQ-5D = EuroQol-5 dimensions.		

[2] McDaid C, Griffin S, Weatherly H, et al. Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis. Health Technol Assess 2009;13(4).

Utility first 12 weeks

The ERG noted inconsistencies in the model regarding the application of utility values during the assessment period (i.e. the first 12 weeks). For the HAROSA I population the company applied the utility values of non-responders in the BSC arm in HAROSA I for the first 12 weeks to both treatment arms, except for the first week in the pitolisant arm the utility value for a non-responder in the pitolisant arm was applied (i.e. and subsequent values of non-responders in the BSC arm). For the HAROSA II population the company applied the utility values of non-responders in the pitolisant + BSC arm and BSC arm correspondingly to each arm. The ERG prefers that in the first 12 weeks both treatment arms are assigned the baseline utility, rather than the responder or non-responder utility after 12 weeks.

Other modelling errors

The ERG also noted several errors in the Markov trace sheets (HAROSA I pitolisant, HAROSA II pitolisant, HAROSA II BSC) where the utility values to be used where duplicated from the 'Clinical Inputs' sheet. Here several times a reference was made to the lower limit of the confidence interval rather than the mean utility.

Costs

In contrast to the previous model, the company's updated model does not account for patients who receive pitolisant in a dosage of 10 mg (i.e. as two 5 mg tablets) and wastage costs due to down- titration.

Sensitivity analysis

In absence of a probabilistic sensitivity analysis, the uncertainty that surrounds the cost effectiveness results has not been explored. The probability that pitolisant is cost effective, under the updated model's assumptions, therefore remains unknown.

Results after model corrections

The ERG re-calculated the updated model's cost effectiveness results after implementing the abovementioned changes to the implementation of the mapping from ESS scores to utilities, by applying the corresponding baseline utility values (i.e. as provided in the model) to the assessment periods in HAROSA I and HAROSA II, and after correcting the cell references to the utility values on the Clinical Inputs sheet. This resulted in ICERs of £32,957 per QALY gained for HAROSA I and £25,752 per QALY gained for HAROSA II. Importantly, the ERG emphasizes that the validity of these results depends on the validity of the values for the baseline utilities as provided in the model for which no explanation was provided on how these values were arrived at.

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

Base case models at PAS price

October 2021

Bioprojet

Contents

Introduction

To date, all the economic models submitted to NICE by Bioprojet for pitolisant for treating excessive daytime sleepiness caused by obstructive sleep apnoea [ID1065] have used the list price, since a Patient Access Scheme (PAS) price had not been confirmed at the time of submission.

Bioprojet are in the process of applying for a PAS. In order to facilitate decision making at the second Committee meeting on 13 October, we would like to take this opportunity to submit the results of the economic modelling using the proposed PAS price. Bioprojet are considering a [redacted] PAS discount which is pending final agreement with PASLU.

Price of pitolisant

The list price of pitolisant is £[redacted] per 30 tablets, equating to £[redacted] per 365-day per year (£[redacted] /30*365) as shown in Table 1.

The PAS price is set at £[redacted] per 30 tablets, equating to £[redacted] per 365-day per year (£[redacted]/30*365).

Table 1: Price of pitolisant – list and PAS

	Monthly cost	Expected annual cost	Weekly cost
List price pitolisant	[redacted]	[redacted]	[redacted]
PAS price pitolisant	[redacted]	[redacted]	[redacted]

In both active and control arms in all scenarios, all patients received BSC. In the scenario evaluating data from the HAROSA I study (add-on to continuous positive airway pressure [CPAP]), all patients also received treatment with CPAP. As these are constant costs that do not differ between treatment arms, there was no incremental cost to capture in the model. The costs of control arms were consequently set at zero.

Economic models

Original Bioprojet model

The original economic modelling submitted by Bioprojet was based on the economic modelling approach used in the NICE Technology Appraisal for CPAP for the treatment of obstructive sleep apnoea/hypopnoea syndrome (TA139)[1].

A resubmission of this economic modelling was made in January 2021 due to a price change for pitolisant.

ERG-preferred model

The ERG-preferred model made several adjustments to the company base case (see Section 7.1.2 of the ERG report) which are 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.

The ERG-preferred model is ID1065 Pitolisant CEM – ERG base case ACIC.xls

Placebo-centred model

The use of a responder/non-responder model, coupled with a placebo-centring approach, based on individual patient data from their pivotal clinical trial, formed the basis of the economic model used by Jazz Pharma in their submission for the ongoing NICE solriamfetol assessment. This approach differs fundamentally from the conventional model that Bioprojet used in their submission and thus presents difficulty in comparing the two treatments alongside each other. There are general similarities between the TONES 3 study[2] for solriamfetol and the HAROSA I[3]/HAROSA II[4] studies for pitolisant, so it would seem reasonable to compare the results from comparable analytical approaches.

The original economic model submitted by Bioprojet is not amenable to a simple in-model change to allow the scenario to be explored, so in order to carry out this comparison, the company had to create a de novo model to explore placebo-centred data from the HAROSA studies in the context of a responder/non-responder model structure.

Given that the original solriamfetol model was not available to us, and details of it have not yet been published, we reconstructed the core of the model based on Jazz Pharma's original submission and the ERG appraisal of their approach. Analysis of the individual patient data from HAROSA I and HAROSA II was provided to Bioprojet by the study investigators, to allow the placebo-centred estimation to be carried out.

The new placebo-centred model was submitted to NICE in August 2021.

Results

The base case results at list and PAS price are shown below in Table 2.

We have also included a scenario for the placebo-centred model, which extends the time horizon from 25 years to 47 years to reflect a lifetime horizon as recommended by the ERG in their preferred model.

Table 2: Results with and without PAS

Model	Add-on to CPAP (HAROSA I)		CPAP non-responders (HAROSA II)	
	List price	PAS price	List price	PAS price
Base case				
ERG-preferred model	£67,557/QALY	[redacted]	£62,923/QALY	[redacted]
Placebo-centred model (25-year time horizon)	£32,430/QALY	[redacted]	£28,431/QALY	[redacted]
Scenario				
Placebo-centred model (47-year time horizon)	£31,542/QALY	[redacted]	£27,257/QALY	[redacted]

The results using the PAS price are shown in more detail below:

ERG-preferred model

Table 3: ERG-preferred model (PAS price) – patients with residual EDS despite CPAP (HAROSA I)

ERG-preferred model	**Add-on to CPAP (HAROSA I)**		
	Costs	**QALYs**	**ICER (Cost/ QALY)**
Pitolisant + CPAP + BSC	[redacted]	[redacted]	
CPAP + BSC	[redacted]	[redacted]	
Increment	[redacted]	[redacted]	[redacted]

Table 4: ERG-preferred model (PAS price) – patients with EDS due to OSA who refuse CPAP (HAROSA II)

ERG-preferred model	**CPAP non-responders (HAROSA II)**		
	Costs	**QALYs**	**ICER (Cost/ QALY)**
Pitolisant + BSC	[redacted]	[redacted]	
BSC alone	[redacted]	[redacted]	
Increment	[redacted]	[redacted]	[redacted]

Placebo-centred model

Table 5: Placebo-centred model (PAS price) – patients with residual EDS despite CPAP (HAROSA I)

Placebo-centred model	**Add-on to CPAP (HAROSA I)**		
	Costs	**QALYs**	**ICER (Cost/ QALY)**
Base case			
Pitolisant + CPAP + BSC	[redacted]	[redacted]	
CPAP + BSC	[redacted]	[redacted]	
Increment	[redacted]	[redacted]	[redacted]
Scenario (47-year time horizon)			
Pitolisant + CPAP + BSC	[redacted]	[redacted]	
CPAP + BSC	[redacted]	[redacted]	
Increment	[redacted]	[redacted]	[redacted]

Table 6: Placebo-centred model (PAS price) – patients with EDS due to OSA who refuse CPAP (HAROSA II)

Placebo-centred model	**CPAP non-responders (HAROSA II)**		
	Costs	**QALYs**	**ICER (Cost/ QALY)**
Base case			
Pitolisant + BSC	[redacted]	[redacted]	
BSC alone	[redacted]	[redacted]	
Increment	[redacted]	[redacted]	[redacted]
Scenario (47-year time horizon)			
Pitolisant + BSC	[redacted]	[redacted]	
BSC alone	[redacted]	[redacted]	
Increment	[redacted]	[redacted]	[redacted]

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

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Question 1: EQ-5D utility values

EQ-5D utility values (based on the UK tariff by Dolan et al.) collected in HAROSA I and HAROSA II that are categorised by response status. This is to allow the trial EQ-5D utility values to be used in the ACD model, where people are separated into responders and non-responders.

There is a body of evidence that ED-5D is not a suitable tool to measure utility in people with excessive daily sleepiness. This has been well documented in our earlier responses and supported by clinical opinion.

The lack of impact on QOL is consistent with other studies in OSA treated with CPAP[1], MADs[2, 3] or modafinil[4, 5]. Clinical opinion, systematic reviews and work carried out by the Assessment Group for the NICE CPAP HTA indicate that generic instruments to measure QOL, including the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and the EuroQol (EQ-5D) do not capture benefit in QOL in patients with EDS[6-8]. These instruments have not been specifically designed to assess aspects of QOL in patients with OSA or EDS and sleep is not included as a specific dimension. (Document B, page 48)

Indeed, in the recent Solriamfetol Committee meeting, the majority of the Committee concluded that ED-5D is not a suitable tool in the context of excessive daily sleepiness.

The EQ-5D utility values by response status as requested above were provided to NICE in an Excel spreadsheet on October 6 (HAROSA EQ5D data by response.xls)

Please note that the EQ-5D in the spreadsheet are based on the French tariff rather than the UK tariff by Dolan et al. Given that the output is mean difference in EQ-5D the tariff used does not impact significantly on results and we were keen to expediate our response.

As a reminder, the locations of the study centres for HAROSA I and HAROSA II are shown below.

Table 1: Study locations of the HAROSA studies

	HAROSA I	**HAROSA II**
Location	38 centres in 9 European countries: Belgium (6), Bulgaria (6), Denmark (2), Finland (3), France (8), Germany (3), Macedonia (2), Spain (6), Sweden (2)	29 centres in 10 European countries: Belgium (2), Bulgaria (6), Denmark (1), Finland (3), France (5), Germany (1), Macedonia (3), Serbia (3), Spain (3), Sweden (2)

Question 2: Individual patient ESS values

Individual patient ESS values (baseline and at 12 weeks) from HAROSA I and HAROSA II that would allow the ERG to explore alternative placebo adjustments.

This is provided on an accompanying spreadsheet which was sent to NICE on 6 October (Harosa ESS values individual data.xls).

Please note that this spreadsheet includes patients with ESS score at baseline and week 12. Those without an ESS score at week 12 were not included.

Question 3: ESS scores mapped to SF-6D

ESS scores mapped to SF-6D utility values categorised by response status. This is to allow the SF-6D utility values to be used in the ACD model.

We would like to point out that SF-6D was not mentioned in the ERG's review of our responder/non responder model.

The requested data is shown below in Table 2 and Table 3.

Table 2: HAROSA I– ESS mapped to SF-6D categorised by response status

	HAROSA I	
	Mean	95% CI
Pitolisant + CPAP + BSC		
ESS non-responder	0.662	0.598, 0.726
ESS responder	0.733	0.689, 0.777
Best supportive care + CPAP		
ESS non-responder	0.651	0.583, 0.718
ESS responder	0.732	0.688, 0.776

Table 3: HAROSA II– ESS mapped to SF-6D categorised by response status

	HAROSA II	
	Mean	95% CI
Pitolisant + BSC		
ESS non-responder	0.662	0.636, 0.747
ESS responder	0.733	0.689, 0.777
Best supportive care		
ESS non-responder	0.651	0.583, 0.718
ESS responder	0.727	0.681, 0.772

Please note that ESS scores mapped to SF-6D utility values were used in our original modelling as a scenario (results below). SF-6D results in a slightly lower QALY – the increment is 0.08 lower for HAROSA I and 0.09 for HAROSA II.

Table 4: Discounted costs and effects – patients with residual EDS despite CPAP (HAROSA I)

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

Table 5: Scenario – use of SF-6D as the HRQOL instrument in patients with residual EDS despite CPAP (HAROSA I), discounted costs and effects

Scenario, residual EDS (HAROSA I), base case ICER: £24,237			
	Costs	**QALYs**	**ICER (Cost/QALY)**
Pitolisant + CPAP + BSC	£33,266	10.53	
CPAP + BSC	£9,743	9.64	
Increment	£23,523	0.89	£26,569

Table 6: Discounted costs and effects – patients with EDS due to OSA who refuse CPAP (HAROSA II)

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

Table 7: Scenario – use of SF-6D as the HRQOL instrument in patients with EDS due to OSA who refuse CPAP (HAROSA II), discounted costs and effects

Scenario, CPAP refuser (HAROSA II), base case ICER: £23,538			
	Costs	QALYs	ICER (Cost/QALY)
Pitolisant + BSC	£33,426	10.61	
BSC alone	£9,535	9.69	
Increment	£23,891	0.92	£25,861

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Table 1: HAROSA I – ESS mapped to SF-6D categorised by response status

	HAROSA I	
	Mean	95% CI
Pitolisant + CPAP + BSC		
ESS non-responder	0.662	0.598, 0.726
ESS responder	0.733	0.689, 0.777
Best supportive care + CPAP		
ESS non-responder	0.651	0.583, 0.718
ESS responder	0.732	0.688, 0.776

Table 2: HAROSA II – ESS mapped to SF-6D categorised by response status

	HAROSA II	
	Mean	95% CI
Pitolisant + BSC		
ESS non-responder	0.662	0.636, 0.747
ESS responder	0.733	0.689, 0.777
Best supportive care		
ESS non-responder	0.651	0.583, 0.718
ESS responder	0.727	0.681, 0.772

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Query received from NICE

We would like to clarify a point that was raised during the meeting. The ERG noted that the files provided for individual patient ESS and trial EQ-5D contained no missing values. The ERG also noted they had been unable to reproduce the company's calculated number of responders per group. We would therefore be grateful if you could note any differences in the datasets used by the company and those provided to NICE for the ERG scenarios. Particularly, please explain any types of imputation that were used for missing data.

Answer

Individual patient data EQ-5D

Yes, that is correct, the dataset provided 8 October only includes patients with an EQ-5D reading at baseline and at week 12. This dataset was the one we used to determine baseline EQ-5D from the trial data used in our placebo-centred model.

Individual patient data ESS

Our placebo-centred model used the entire population (intention to treat [ITT]) with missing data accounted for using last observation carried forward (LOCF). Patients were classified as responders if they experienced a decrease of 2 or more in ESS. Importantly, the model used an analysis for **responders based on centred values**, which means that the mean benefit (ESS change from baseline) observed in the placebo arm has been removed from both arms. This analysis was carried out by Professor Phillipe Lehert, Faculty of Economics, UCL Mons, Louvain, Belgium and at the time of submission we did not have access to the raw data.

The dataset provided on the 8 October was the per protocol (PP) dataset and only includes those patients with ESS at baseline and at week 12. Patients were classified as responders if they experienced a decrease of 2 or more in ESS. We are unclear how the ERG used this data in their analysis, whether or not they counted responders based on centred values (as we did in our placebo-centred model) or simply the number of responders/number of patients (noted as simple analysis in the table below).

Regardless of the approach used to estimate the proportion of responders in each arm and the dataset used, the difference between the proportion of responders in the placebo and pitolisant arms is similar (around 19% for HAROSA 1 and 22-23% for HAROSA 2).

Table 1: ESS responders in the HAROSA studies

	Population	**Method**	**Pitolisant**		**Placebo**		**Difference between responder rate**
HAROSA 1							
Original centred model	ITT population	Responders based on centred values	105/183	57.4%	23/61	37.7%	19.7%
Dataset sent in response to NICE query October	PP population	Simple	143/173	82.65%	37/59	62.71%	19.9%
HAROSA 2							
Original centred model	ITT population	Responders based on centred values	107/201	53.2%	21/67	31.3%	22.1%
Dataset sent in response to NICE query October	PP population	Simple	161/186	86.56%	40/63	63.49%	23.1%

in collaboration with:

Erasmus School of Health Policy & Management

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

ADDENDUM: Additional analyses before and after ACM2 at the request of NICE

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

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Introduction

The purpose of this addendum is to provide various scenarios with regards to the definition of responders and with regards to utility estimates used in the cost effectiveness analysis of pitolisant. These scenarios were requested by NICE both ahead and after the second Committee meeting (ACM2). The scenarios cover two important issues, i.e. the placebo effect observed in HAROSA I and II and the utilities to be used for responders and non-responders to treatment. For the placebo effect three options had been discussed. The first is the so-called Hawthorne effect, where patients behave differently because they know they are being watched. In this instance, one would expect the change from baseline to be larger in the study setting than what will be observed in daily practice, in both study arms. The second reason why a strong placebo effect was observed could be due to regression to the mean. If a certain outcome like ESS fluctuates over time, and many patients enter the study at their worst (e.g. due to inclusion criteria) then it is reasonable to expect an improvement in many patients, regardless of treatment. As such, the level of ESS reached in the studies after 12 weeks would be a fair reflection of daily practice and no adjustment are necessary. Finally, there could be a true placebo effect, where only in the placebo group we see an effect that is unlikely to be replicated in daily practice.

Regarding the utilities to be used, the committee regarded it of interest to see how the ICER would change if the utilities as measured with the EQ-5D in the HAROSA I and II had been used, rather than a published mapping algorithm converting ESS scores in EQ-5D utilities.

Please note that this addendum should be read in conjunction with our earlier addendum (24 September 2021). In that earlier addendum the ERG discussed various issues regarding the response-based model that the company supplied in response to the appraisal consultation document.

The requests

As mentioned in the introduction, NICE requested scenarios with regards to the placebo effect observed in HAROSA I and II, asking for one scenario in which the Hawthorne effect was assumed (scenario 1, see Table 1), and one in which an average was taken of the Hawthorne effect, regression to the mean and the true placebo effect (scenario 2). It should be noted that scenario 2 necessitated the calculation of scenario 3, 'regression to the mean', and scenario 4, 'true placebo'.

Within each of these scneario's variations on the approach to utility estimation were requested. The mapping based on McDaid would represent option a, and utilies based on the EQ5D measurements from HAROSA I and II were option b. In addition, NICE requested on behalf of the committee the average of the coefficients for trial derived EQ-5D and ESS mapped to EQ-5D using McDaid. They suggested two approaches to averaging: the direct average of the utility gain from each method (option c) and the average of the coefficients of two mapping algorithms (option d). This led to the following list of scenarios for both the HAROSA I and HAROSA II populations.

Table 1 **Scenarios for HAROSA I & II using pitolisant list price**

Hawthorne model for placebo effect	
1a	McDaid mapped utilities (company base case)
1b	EQ-5D from trial
1c	50% McDaid / 50% trial EQ-5D (average of utility values)

1d	50% McDaid / 50% trial EQ-5D (average of coefficients)
Equal mix of models for placebo effect	
2a	McDaid mapped utilities
2b	EQ-5D from trial
2c	50% McDaid / 50% trial EQ-5D (average of utility values)
2d	50% McDaid /50% trial EQ-5D (average of coefficients)

The ERG added an extra row to scenario 1, to represent the ERG corrected version of the company base case. Option d for the utilities proved not applicable for this technology assessment, since the only one mapping algorithm was considered (McDaid). Furthermore, the company base case only included the Hawthorne approach, so for the other approaches (scenario 3 and 4) only the ERG-corrected version of the model was available.

After ACM2, NICE requested scenarios 1a, 1b and 1c with utility values that were only health state specific, but not treatment specific, these will be denoted later with a *.

Data

In order to fulfil the requests from NICE, the ERG requested patient-level data from the HAROSA I and II studies presenting the ESS score at baseline and at 12 weeks. This was provided as excel file named *ID1065 Harosa ESS values individual data [ACIC].* Additionally, the raw EQ-5D descriptives per patient were requested. The latter data set had already been provided at the technical engagement stage of the project (*45. HAROSA EQ-5D analyses (AIC)*), and could be used by the ERG. In that dataset, the EQ-5D measurements were valued using the French tariff, so the ERG applied the UK tariff to the measurements.

Ahead of ACM2, the company had provided the ESS data for the patients who had observations both at baseline and at 12 weeks. After ACM2, the ITT data were provided with the explanation that missing values at 12 weeks had been imputed based on last observation carried forward.

Data analyses

Data analysis took place at two moments, before the ACM2 and after that meeting. Before ACM2, the ERG only had datasets with complete cases. Using these datasets, the ERG performed the following steps:

- Calculate change from baseline for all patients on week 12.
- In the placebo group, calculate the average change from baseline
- Subtract this average, that represents the Hawthorne effect, from all changes from baseline, both in the pitolisant and the placebo arm of the HAROSA I and II studies.
- Define responders, where a response required a change from baseline larger than 2 on the ESS scale. This was done three times, based on the:
    1. the Hawthorne corrected changes;
    2. the as observed changes from baseline (this represents the regression to the mean scenario).

3. A computations of the Hawthorne corrected changes for patients in the pitolisant arm, and the as observed changes in the placebo arm (this represents the true placebo scenario)

- Calculate response rates for both study arms, for HAROSA I and II, using the above 3 definitions of responder.
- Calculate utilities for responders and non-responders, per treatment.

After ACM2, most of these steps were repeated, but now using the data from ITT population. However, based on the discussion in the ACM2, response was now defined only based on Hawthorne corrected changes from baseline and the utilities were based only on response status, and no longer on treatment.

The before ACM2 results, based on complete cases, are presented in Table 2 and 3. In both tables we also show the values as calculated by the company (with corrections from the ERG is the calculation of the mapped utilities). We see a small difference in the response rate between the ERG analysis of the data and the company's approach. Whilst at first the ERG assumed that the difference in response rate could be explained by the use of complete cases by the ERG versus the ITT population by the company, it will later be shown (Table 4 and 5) that this does not provide a complete explanation. More striking is the difference in the estimated ESS change from baseline between the company's and the ERG's analysis. The ERG was unable to find an explanation for this difference. In order to check the ERG estimated for the ESS change from baseline, we calculated the weighted average ESS change of the responders and non-responders. This value was zero, both for HARISA I and II, in line with expectations, given that we had subtracted the average ESS change from baseline from the placebo group from all individual changes from baseline. For the company's values of ESS change from baseline, the weighted average in the placebo group was 1.5 and 1.8 for HAROSA I and II, respectively.

An important difference between the results of the HAROSA I and II can be seen in the EQ5D utility values. In table 2 we observe that both responders and non-responders in the CPAP + BSC arm have a higher utility than patients in the pitolisant + CPAP + BSC arm. This is the opposite of what can be seen in Table 3, where the utilities for pitolisant + BSC are hight than for BSC, both for responders and non-responders

Table 2 Results from data analysis HAROSA I – complete cases data

Assumed explanation placebo effect	Response status	Treatment arm	ESS change from baseline CC	Utility UK EQ5D CC	Response rate CC
Hawthorne	Responder	Pitolisant + CPAP + BSC	-6.16	0.869	62.6%
		CPAP + BSC	-6.77	0.912	37.3%
	Non-Responder	Pitolisant + CPAP + BSC	1.29	0.797	37.4%
		CPAP + BSC	4.02	0.813	62.7%
Regression to the mean	Responder	Pitolisant + CPAP + BSC	-7.82	0.868	75.9%
		CPAP + BSC	-7.47	0.883	54.2%
	Non-Responder	Pitolisant + CPAP + BSC	-0.14	0.760	24.1%
		CPAP + BSC	3.19	0.811	45.8%
True placebo	Responder	Pitolisant + CPAP + BSC	-7.82	0.868	75.9%
		CPAP + BSC	-6.77	0.912	37.3%
	Non-Responder	Pitolisant + CPAP + BSC	-0.14	0.760	24.1%
		CPAP + BSC	4.02	0.813	62.7%
Hawthorne	**Company base case with ERG corrections**		**ESS change from baseline ITT**	**Mapping McDaid***	**Response rate ITT**
	Responder	Pitolisant + CPAP + BSC	-4.11	0.806	57.4%
		CPAP + BSC	-3.45	0.799	37.7%
	Non-Responder	Pitolisant + CPAP + BSC	3.33	0.734	42.6%
		CPAP + BSC	4.53	0.722	62.3%

* these values are based on corrections made by the ERG to the technical implementation of the mapping algorithm
ESS = Epworth Sleepiness Scale; CC: complete cases; BSC = best supportive care; CPAP = continuous positive airway pressure

Table 3 Results from data analysis HAROSA II – complete cases data

Assumed explanation placebo effect	Response status	Treatment arm	ESS change from baseline CC	Utility UK EQ5D CC	Response rate CC
Hawthorne	Responder	Pitolisant + BSC	-6.33	0.855	58.4%
		BSC	-5.74	0.816	35.9%
	Non-Responder	Pitolisant + BSC	1.21	0.801	41.6%
		BSC	3.22	0.797	64.1%
Regression to the mean	Responder	Pitolisant + BSC	-8.22	0.847	80.5%
		BSC	-7.65	0.803	53.1%
	Non-Responder	Pitolisant + BSC	-0.08	0.774	19.5%
		BSC	1.33	0.804	46.9%
True placebo	Responder	Pitolisant + BSC	-8.22	0.847	80.5%
		BSC	-5.74	0.816	35.9%
	Non-Responder	Pitolisant + BSC	-0.08	0.774	19.5%
		BSC	3.22	0.797	64.1%
Hawthorne	**Company base case with ERG corrections**			**Mapping McDaid***	
	Responder	Pitolisant + BSC	-4.34	0.799	53.2%
		BSC	-3.68	0.773	31.3%
	Non-Responder	Pitolisant + BSC	3.10	0.707	46.8%
		BSC	4.30	0.695	68.7%

* these values are based on corrections made by the ERG to the technical implementation of the mapping algorithm
ESS = Epworth Sleepiness Scale; CC: complete cases; BSC = best supportive care

When we compare the results of the ITT analysis in Tables 4 and 5 with the company results in Tables 2 and 3, we see that the ERG analyses yield slightly different response rates, but these are not the same as those reported by the company. The ERG cannot explain this remaining difference. The difference between the company reported ESS change from baseline and the ERG derived ESS change from baseline remains large, without any idea to the cause of this difference. Note that the utilities reported in Table 4 and 5 are still based on complete cases, as the ERG did not have the ITT dataset for the EQ5D measurements.

Table 4 Results from data analysis HAROSA I – ITT data

Assumed explanation placebo effect	Response status	Treatment arm	ESS change from baseline ITT*	Mapped Utility	Treatment independent utility UK EQ5D CC	Response rate ITT*
Hawthorne	**Responder**	Pitolisant + CPAP + BSC	-6.33	0.827	0.876	60.1%
		CPAP + BSC				36.1%
	Non-Responder	Pitolisant + CPAP + BSC	2.20	0.745	0.803	39.9%
		CPAP + BSC				63.9%

* Missing ESS score at 12 weeks was imputed using last observation caried forward
ESS = Epworth Sleepiness Scale; ITT = intention to treat; BSC = best supportive care; CPAP = continuous positive airway pressure; CC=complete cases

Table 5 Results from data analysis HAROSA II – ITT data

Assumed explanation placebo effect	Response status	Treatment arm	ESS change from baseline ITT*	Mapped Utility	Treatment independent utility UK EQ5D CC	Response rate ITT*
Hawthorne	**Responder**	Pitolisant + BSC	-6.28	0.798	0.848	56.7%
		BSC				35.8%
	Non-Responder	Pitolisant + BSC	1.99	0.718	0.800	43.3%
		BSC				64.2%

* Missing ESS score at 12 weeks was imputed using last observation caried forward
ESS = Epworth Sleepiness Scale; ITT = intention to treat; BSC = best supportive care; CC=complete cases

Table 6

		HAROSA I							HAROSA II						
		Costs			QALYs			ICER	Costs			QALYs			ICER
Hawthorne model for placebo effect - CC		**Pitolisant + CPAP + BSC**	**CPAP + BSC**	**Incr.**	**Pitolisant + CPAP + BSC**	**CPAP + BSC**	**Incr.**	**£/QALY**	**Pitolisant + BSC**	**BSC**	**Incr.**	**Pitolisant + BSC**	**BSC**	**Incr.**	**£/QALY**
1a	McDaid mapped utilities (company base case)	£10,912	£0	£10,912	13.84	13.5	0.34	£32,430	£11,159	£0	£11,159	13.91	13.51	0.41	£28,431
1b	McDaid mapped utilities (ERG corrected company base case)	£12,913	£0	£12,913	13.91	13.35	0.55	£23,410	£13,562	£0	£13,562	13.49	12.88	0.61	£22,294
1c	EQ-5D from trial	£12,913	£0	£12,913	14.67	14.84	-0.17	pitolisant dominated	£13,562	£0	£13,562	14.68	14.25	0.43	£31,787
1d	Average of utility values from 1b and 1c	£12,913	£0	£12,913	14.29	14.10	0.19	£67,604	£13,562	£0	£13,562	14.08	13.57	0.52	£26,207
1e	Average of ESS coefficients mapping	not applicable							not applicable						
Equal mix of models for placebo effect - CC															
2a	McDaid mapped utilities Company BC	not available							not available						
2b	McDaid mapped utilities ERG corrected company BC	£14,687	£0	£14,687	14.16	13.47	0.69	£21,260	£16,885	£0	£16,885	13.82	13.04	0.78	£21,519
2c	EQ-5D from trial	£14,687	£0	£14,687	14.53	14.84	-0.30	pitolisant dominated	£16,885	£0	£16,885	14.61	14.27	0.34	£50,041
2d	Average of utility values from 1b and 1c	£14,687	£0	£14,687	14.35	14.15	0.19	£76,069	£16,885	£0	£16,885	14.21	13.65	0.56	£30,096
2e	Average of ESS coefficients mapping	not applicable							not applicable						

Regression to the mean model for placebo effect - CC														
3a	McDaid mapped utilities Company BC	not available							not available					
3b	McDaid mapped utilities ERG corrected company BC	£15,574	£0	£15,574	14.28	13.69	0.59	£26,319	£18,547	£0	£18,547	13.99	13.35	0.64	£29,093
3c	EQ-5D from trial	£15,574	£0	£15,574	14.46	14.83	-0.37	pitolisant dominated	£18,547	£0	£18,547	14.57	14.30	0.27	£69,307
3d	Average of utility values from 1b and 1c	£15,574	£0	£15,574	14.37	14.26	0.11	£138,472	£18,547	£0	£18,547	14.28	13.83	0.45	£40,982
3e	Average of ESS coefficients mapping	not applicable							not applicable						
True placebo effect - CC														
4a	McDaid mapped utilities Company BC	not available							not available					
4b	McDaid mapped utilities ERG corrected company BC	£15,574	£0	£15,574	14.28	13.35	0.93	£16,763	£18,547	£0	£18,547	13.99	12.88	1.11	£16,736
4c	EQ-5D from trial	£15,574	£0	£15,574	14.46	14.84	-0.38	pitolisant dominated	£18,547	£0	£18,547	14.57	14.25	0.32	£58,320
4d	Average of utility values from 1b and 1c	£15,574	£0	£15,574	14.37	14.10	0.28	£56,480	£18,547	£0	£18,547	14.28	13.57	0.71	£26,008
4e	Average of ESS coefficients mapping	not applicable							not applicable						
Hawthorne model for placebo effect - ITT														
1b*	McDaid mapped utilities - treatment independent	£12,412	£0	£12,412	13.81	13.56	0.25	£50,154	£13,178	£0	£13,178	13.39	13.07	0.33	£40,240
1c*	EQ-5D from trial - treatment independent	£12,412	£0	£12,412	14.76	14.54	0.22	£56,837	£13,178	£0	£13,178	14.60	14.41	0.20	£67,239
1d*	Average of utility values from 1b* and 1c*	£12,412	£0	£12,412	14.28	14.05	0.23	£53,287	£13,178	£0	£13,178	14.00	13.74	0.26	£50,348

Cost effectiveness results

In Table 6 the results of all the various scenarios are shown. Scenarios 1 to 4 were prepared ahead of ACM2, scenarios 1b*, 1c* and 1d* after ACM2.

In scenario 1 to 4 it is noteworthy that the use of the EQ5D values as obtain from the clinical studies leads for the HAROSA I population to a loss of QALYs when receiving pitolisant. As a result, CPAP + BSC dominates pitolisant + CPAP + BSC. A similar result is not seen in the HAROSA II population.

This can be explained by the utility values derived from the EQ5D measurements, as reported in table 2 and 3. There we observe that for HAROSA I the utility values of CPAP + BSC are slightly higher than for pitolisant + CPAP + BSC, both for responders and non-responders. As a result, the number of QALYs accumulated with CPAP + BSC is also higher than with pitolisant + CPAP + BSC. In the HAROSA II population, the utility values for pitolisant + CPAP + BSC were higher than for CPAP + BSC.

Furthermore, we see that, in line with expectations, ICERs are most favourable when the observed reduction of ESS in the placebo group is assumed to be a true placebo effect, and least favourable when this reduction is attributed to regression to the mean.

When comparing the costs in scenario 1b to 1b*, we see the effect of using the ITT population, rather than only the complete cases. The impact of the population is, for the costs, only through the response rates, and in table 2 and 4 for HAROSA I and table 3 and 5 for HAROSA II we see that there is a small difference in the response rate between the ITT and complete cases.

When we look at the QALY gains, we see that these are smaller when using utility values that are only dependent on response status (except for HAROSA I 1c*, where the gain is higher). Consequently, the ICERs for those scenarios are higher.

It should be noted, as in the addendum from 29 September 2021, that this version of the model does not include a probabilistic sensitivity analysis, so it is unclear what the extent is of parameter uncertainty, on top of the here explored structural uncertainty.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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

2nd ADDENDUM: Additional analyses after ACM2 at the request of NICE

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

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Introduction

In the addendum of 29 October 2021, the ERG provided various scenarios with regards to the definition of responders and with regards to utility estimates used in the cost effectiveness analysis of pitolisant. These scenarios were requested by NICE both ahead and after the second Committee meeting (ACM2). That addendum contained scenario analyses where the utilities as measured with the EQ-5D-3L in the HAROSA I and II had been used, rather than a published mapping algorithm converting ESS scores in EQ-5D utilities.

The current addendum contains another analysis of the EQ-5D data as measured in HAROSA I and II, this time to estimate the relationship between an improvement in ESS and the subsequent improvement in health-related utility. Furthermore, we explored the impact of the baseline utility, that is applied until patients become responder or non-responder and is the intercept when calculating the utilities for responders and non-responders when the McDaid mapping is used. In the company's approach, the baseline utility was derived from the trial EQ-5D data, using the French tariff. In the ERG scenario's the same data was used, whilst applying the UK tariff.

Please note that this addendum should also be read in conjunction with our earlier addendum of 24 September 2021. In that earlier addendum the ERG discussed various issues regarding the response-based model that the company supplied in response to the appraisal consultation document.

Data

In order to fulfil the requests from NICE, the ERG used the patient-level data from the HAROSA I and II studies presenting the ESS score at baseline and at 12 weeks in combination with the dataset containing the raw EQ-5D descriptives per patient, for which the ERG had already calculated the UK utilities.

Data analyses

The ERG calculated the change in utility per change in ESS for HAROSA I and II separately, and also for the pooled data, but did not distinguish between treatment arms or response status, see Table 1.

It can be seen that the slopes as estimated from the observed EQ-5D utilities for the HAROSA I and II separately are very close to the slope as estimated by McDaid, which was -0.0097. When we use the pooled HAROSA data, the slope is nearly identical to that of McDaid.

Table 1 Estimation of the change in utility per change in ESS score – HAROSA EQ-5D-3L data

	HAROSA I		HAROSA II		Pooled	
	ESS	Utility	ESS	Utility	ESS	Utility
Baseline	14.8607	0.7946	15.6978	0.7711	15.2988	0.7822
12 weeks	9.8730	0.8441	9.9590	0.8252	9.9180	0.8442
Difference	4.9877	-0.0495	5.7388	-0.0541	5.3809	-0.0521
Slope	-0.0099		-0.0094		-0.0097	

In Table 2 the baseline utilities are presented. These values are used at 2 places in the model. First, they are used to value the first 12 weeks, in which patients are assessed for response. After that (for scenarios based on a regression equation) the baseline value represents the intercept of the mapping equation.

In the previous addendum, the French utility was used in scenario a and b, which represent the company approach using McDaid. The UK utility was used in scenario c, in which all utilities are estimated directly from the EQ-5D-3L data collected during HAROSA I and II. The average baseline utility was used in scenario d, where an average of scenario b and c was used.

Whilst working on the current analysis, the ERG realized that a scenario is missing, in which the company approach is followed (scenario b), but using the baseline utilities based on the UK rather than the French tariff (see Table 2). Thus, this scenario will be added to the set of scenarios. It should be realized that this change only impacts the accumulated QALYs in each treatment arm, the incremental QALYs are independent on the baseline value.

For the requested scenario in which the slopes from McDaid and from HAROSA are averaged, we will use the UK base line utilities.

Table 2 Baseline utility values used in the model

	French utility	UK utility	Average
HAROSA I	0.766	0.787	0.777
HAROSA II	0.737	0.771	0.754

In tables 3 and 4 the utility values used for the various scenarios are presented.

Table 3 Utilities used – treatment independent - HAROSA I

	Response status	Mapped utility – French	Mapped Utility - UK	Treatment independent utility UK EQ5D CC	Average slopes McDaid & observed HI – HII separate	Average slopes McDaid & observed HI – HII pooled
Hawthorne	**Responder**	0.827	0.849	0.876	0.849	0.849
	Non-Responder	0.745	0.766	0.803	0.766	0.766
Regression to the mean	**Responder**	0.841	0.862	0.871	0.863	0.862
	Non-responder	0.756	0.777	0.780	0.777	0.777
True placebo	**Responder**	0.840	0.862	0.875	0.862	0.862
	Non-responder	0.750	0.771	0.785	0.771	0.771

Table 4 Utilities used – treatment independent - HAROSA II

	Response status	Mapped utility – French	Mapped Utility - UK	Treatment independent utility UK EQ5D CC	Average slopes McDaid & observed HI – HII separate	Average slopes McDaid & observed HI – HII pooled
Hawthorne	**Responder**	0.798	0.832	0.848	0.831	0.832
	Non-Responder	0.718	0.752	0.800	0.752	0.752
Regression to the mean	**Responder**	0.816	0.851	0.839	0.849	0.850
	Non-responder	0.732	0.767	0.788	0.767	0.767
True placebo	**Responder**	0.814	0.848	0.843	0.847	0.848
	Non-responder	0.722	0.756	0.786	0.756	0.756

Table 5 Full comparison methods for utility estimation - Hawthorne models

		HAROSA I							HAROSA II						
		Costs			QALYs			ICER	Costs			QALYs			ICER
Hawthorne model for placebo effect - CC		**Pitolisant + CPAP + BSC**	**CPAP + BSC**	**Incr.**	**Pitolisant + CPAP + BSC**	**CPAP + BSC**	**Incr.**	**£/QALY**	**Pitolisant + BSC**	**BSC**	**Incr.**	**Pitolisant + BSC**	**BSC**	**Incr.**	**£/QALY**
1a	McDaid mapped utilities (company base case)	£10,912	£0	£10,912	13.84	13.5	0.34	£32,430	£11,159	£0	£11,159	13.91	13.51	0.41	£28,431
1b	McDaid mapped utilities (ERG corrected company base case)	£12,913	£0	£12,913	13.91	13.35	0.55	£23,410	£13,562	£0	£13,562	13.49	12.88	0.61	£22,294
1c	EQ-5D from trial	£12,913	£0	£12,913	14.67	14.84	-0.17	pitolisant dominated	£13,562	£0	£13,562	14.68	14.25	0.43	£31,787
1d	Average of utility values from 1b and 1c	£12,913	£0	£12,913	14.29	14.10	0.19	£67,604	£13,562	£0	£13,562	14.08	13.57	0.52	£26,207
1e	Average of ESS coefficients mapping	not available							Not available						
Hawthorne model for placebo effect - ITT															
1b*-F	McDaid mapped utilities - treatment independent – baseline utilities French tariff	£12,412	£0	£12,412	13.81	13.56	0.25	£50,154	£13,178	£0	£13,178	13.39	13.07	0.33	£40,240
1b*-UK	McDaid mapped utilities - treatment independent – baseline utilities UK tariff	£12,412	£0	£12,412	14.18	13.93	0.25	£50,154	£13,178	£0	£13,178	14.00	13.67	0.33	£40,240
1c*	EQ-5D from trial - treatment independent	£12,412	£0	£12,412	14.76	14.54	0.22	£56,837	£13,178	£0	£13,178	14.60	14.41	0.20	£67,239
1d*	Average of utility values from 1b* and 1c*	£12,412	£0	£12,412	14.28	14.05	0.23	£53,287	£13,178	£0	£13,178	14.00	13.74	0.26	£50,348
1e*	Average of ESS coefficients mapping – HI and HII separate	£12,412	£0	£12,412	14.19	13.94	0.25	£49,574	£13,178	£0	£13,178	14.00	13.68	0.32	£40,800
1e*-pooled	Average of ESS coefficients mapping – HI and HII pooled	£12,412	£0	£12,412	14.18	13.94	0.25	£50,214	£13,178	£0	£13,178	14.01	13.68	0.33	£40,288

Table 6 Comparison various models for placebo effect and treatment independent methods for utility estimation

		HAROSA I							HAROSA II						
		Costs			QALYs			ICER	Costs			QALYs			ICER
Hawthorne model for placebo effect - ITT		**Pitolisant + CPAP + BSC**	**CPAP + BSC**	**Incr.**	**Pitolisant + CPAP + BSC**	**CPAP + BSC**	**Incr.**	**£/QALY**	**Pitolisant + BSC**	**BSC**	**Incr.**	**Pitolisant + BSC**	**BSC**	**Incr.**	**£/QALY**
1b*-UK	McDaid mapped utilities - treatment independent – baseline utilities UK tariff	£12,412	£0	£12,412	14.18	13.93	0.25	£50,154	£13,178	£0	£13,178	14.00	13.67	0.33	£40,240
1c*	EQ-5D from trial - treatment independent	£12,412	£0	£12,412	14.76	14.54	0.22	£56,837	£13,178	£0	£13,178	14.60	14.41	0.20	£67,239
1d*	Average of utility values from 1b* and 1c*	£12,412	£0	£12,412	14.28	14.05	0.23	£53,287	£13,178	£0	£13,178	14.00	13.74	0.26	£50,348
1e*	Average of ESS coefficients mapping – HI and HII separate	£12,412	£0	£12,412	14.19	13.94	0.25	£49,574	£13,178	£0	£13,178	14.00	13.68	0.32	£40,800
1e*-pooled	Average of ESS coefficients mapping – HI and HII pooled	£12,412	£0	£12,412	14.18	13.94	0.25	£50,214	£13,178	£0	£13,178	14.01	13.68	0.33	£40,288
Regression to the Mean model for placebo effect - ITT		**Pitolisant + CPAP + BSC**	**CPAP + BSC**	**Incr.**	**Pitolisant + CPAP + BSC**	**CPAP + BSC**	**Incr.**	**£/QALY**	**Pitolisant + BSC**	**BSC**	**Incr.**	**Pitolisant + BSC**	**BSC**	**Incr.**	**£/QALY**
2b*-UK	McDaid mapped utilities - treatment independent – baseline utilities UK tariff	£15,154	£0	£15,154	14.53	14.31	0.22	£70,012	£18,119	£0	£18,119	14.53	14.07	0.45	£39,950
2c*	EQ-5D from trial - treatment independent	£15,154	£0	£15,154	14.64	14.41	0.23	£65,438	£18,119	£0	£18,119	14.56	14.29	0.28	£65,714
2d*	Average of utility values from 1b* and 1c*	£15,154	£0	£15,154	14.58	14.36	0.22	£67,648	£18,119	£0	£18,119	14.55	14.18	0.36	£49,691
2e*	Average of ESS coefficients mapping – HI and HII separate	£15,154	£0	£15,154	14.54	14.32	0.22	£69,202	£18,119	£0	£18,119	14.53	14.08	0.45	£40,506
2e*-pooled	Average of ESS coefficients mapping – HI and HII pooled	£15,154	£0	£15,154	14.53	14.32	0.22	£70,095	£18,119	£0	£18,119	14.54	14.08	0.45	£39,998

True placebo model for placebo effect - ITT		**Pitolisant + CPAP + BSC**	**CPAP + BSC**	**Incr.**	**Pitolisant + CPAP + BSC**	**CPAP + BSC**	**Incr.**	**£/QALY**	**Pitolisant + BSC**	**BSC**	**Incr.**	**Pitolisant + BSC**	**BSC**	**Incr.**	**£/QALY**
3b*-UK	McDaid mapped utilities - treatment independent – baseline utilities UK tariff	£15,154	£0	£15,154	14.47	14.06	0.42	£36,294	£18,119	£0	£18,119	14.43	13.78	0.65	£27,932
3c*	EQ-5D from trial - treatment independent	£15,154	£0	£15,154	14.72	14.30	0.42	£36,412	£18,119	£0	£18,119	14.59	14.19	0.40	£45,245
3d*	Average of utility values from 1b* and 1c*	£15,154	£0	£15,154	14.59	14.18	0.42	£36,353	£18,119	£0	£18,119	14.51	13.99	0.52	£34,541
3e*	Average of ESS coefficients mapping – HI and HII separate	£15,154	£0	£15,154	14.48	14.06	0.42	£35,874	£18,119	£0	£18,119	14.43	13.79	0.64	£28,321
3e*-pooled	Average of ESS coefficients mapping – HI and HII pooled	£15,154	£0	£15,154	14.48	14.06	0.42	£36,337	£18,119	£0	£18,119	14.44	13.79	0.65	£27,966
Average 3 placebo models		**Pitolisant + CPAP + BSC**	**CPAP + BSC**	**Incr.**	**Pitolisant + CPAP + BSC**	**CPAP + BSC**	**Incr.**	**£/QALY**	**Pitolisant + BSC**	**BSC**	**Incr.**	**Pitolisant + BSC**	**BSC**	**Incr.**	**£/QALY**
A-b*-UK	McDaid mapped utilities - treatment independent – baseline utilities UK tariff	£14,240	£0	£14,240	14.39	14.10	0.30	£48,000	£16,472	£0	£16,472	14.32	13.84	0.48	£34,557
A-c*	EQ-5D from trial - treatment independent	£14,240	£0	£14,240	14.71	14.42	0.29	£49,103	£16,472	£0	£16,472	14.58	14.30	0.29	£56,155
A-d*	Average of utility values from 1b* and 1c*	£14,240	£0	£14,240	14.48	14.20	0.29	£49,103	£16,472	£0	£16,472	14.35	13.97	0.38	£43,347
A-e*	Average of ESS coefficients mapping – HI and HII separate	£14,240	£0	£14,240	14.40	14.11	0.30	£48,000	£16,472	£0	£16,472	14.32	13.85	0.47	£35,047
A-e*-pooled	Average of ESS coefficients mapping – HI and HII pooled	£14,240	£0	£14,240	14.40	14.11	0.30	£48,000	£16,472	£0	£16,472	14.33	13.85	0.48	£34,557

Cost effectiveness results

In Table 5 the results of all the various scenarios based on the Hawthorne models are shown. The results that are new compared to Table 6 in the previous addendum are the last two rows, scenario 1e* and 1e*-pooled, and scenario 1b*-UK.

From this, it is clear that when the EQ-5D data as collected in the HAROSA trials is used to estimate the slope of a linear relationship between ESS and utility, using the average of the McDaid slopes and the observed slopes has hardly any impact on the results. This is not surprising when looking at the observed slopes in Table 1, which are nearly identical to the slope estimated by McDaid et al.

In Table 6 we see the impact of the approach for dealing with the placebo effect. Looking at the average across approaches, the ICER for the HAROSA I population (on CPAP) is around £50,000, regardless of the method to estimate utilities. For the HAROSA II population the ICER is about £35.000 when a mapping approach is used and £55,000 when the observed utilities are used.

It should be noted, as in the previous addenda, that this version of the model does not include a probabilistic sensitivity analysis, so it is unclear what the extent is of parameter uncertainty, on top of the here explored structural uncertainty.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Response to ERG additional analyses after ACM2 at the request of NICE

December 2021

Overview

The ERG carried out additional modelling at the request of NICE both before and after the Second Committee Meeting held on 13 October 2021.

Three Addenda were provided to Bioprojet on 29 November for review which assessed different scenarios, which focused on the two key outstanding issues.

- The most appropriate method to account for the placebo effect observed in HAROSA I and HAROSA II.
- The most appropriate method to calculate the utilities to be used for responders and non-responders to treatment with pitolisant.

Addendum 1

Assessed four potential ways to account for the placebo effect.

- Hawthorne model for placebo effect (the base case).
- Regression to the mean model for placebo effect.
- True placebo effect.
- Equal mix of models for placebo effect.

Assessed four potential ways to estimate utilities.

- McDaid mapped utilities (company base case).
- McDaid mapped utilities (ERG-corrected company base case).
- EQ-5D from trial.
- Average of McDaid mapped utilities (ERG corrected company base case) and EQ-5D from trial.

The scenarios were run using the complete case (CC) population, which is equivalent to the per protocol population.

An additional scenario was also run using the intention to treat (ITT) population for the Hawthorne model for placebo effect.

Addendum 2

Only assessed the Hawthorne model (both CC and ITT).

The ERG calculated the change in utility per change in Epworth Sleepiness Score (ESS) for HAROSA I and II separately, and also for the pooled data, but did not distinguish between treatment arms or response status.

Table 1: Estimation of the change in utility per change in ESS score – HAROSA EQ-5D-3L data (page 3) shows that the slopes from the observed EQ-5D utilities for HAROSA I and II are very close to the slope estimated using mapping (0.0097).

The CC population used the utilities estimated in Addendum 1.

Assessed six additional potential ways to estimate utilities for the ITT population using treatment independent methods for utility estimation.

- Mapped utility (French tariff).
- Mapped utility (UK tariff).
- Treatment independent utility using observed EQ5D data from the trials (CC).
- Average of McDaid mapped utilities and EQ-5D from trial.
- Average of mapping and observed EQ-5D data from the trials (HAROSA I and II separate).
- Average of mapping and observed EQ-5D data from the trials (HAROSA I and II pooled).

Addendum 3

This final addendum pulled all the information together and presented:

- Hawthorne model for placebo effect (CC and ITT) – as presented in Addendum 2.

Assessed four potential ways to account for the placebo effect in the ITT population.

- Hawthorne model for placebo effect.
- Regression to the mean model for placebo effect.
- True placebo effect.
- Equal mix of models for placebo effect.

Assessed six additional potential ways to estimate utilities for the ITT population using treatment independent methods for utility estimation.

- McDaid mapped utilities - treatment independent – baseline utilities UK tariff.
- Treatment independent utility using observed EQ5D data from the trials.
- Average of McDaid mapped utilities and EQ-5D from trial (CC).
- Average of mapping and observed EQ-5D data from the trials (HAROSA I and II separate).
- Average of mapping and observed EQ-5D data from the trials (HAROSA I and II pooled).

Looking at the average across all approaches, the incremental cost effectiveness ratio (ICER) for the HAROSA I population is around [redacted] regardless of the method to estimate utilities. For the HAROSA II population the ICER is about [redacted] when a mapping approach is used and [redacted] when the observed utilities are used.

Bioprojet comments

Thank you for such a comprehensive scenario analysis.

We would like to emphasise several points:

1. There is striking similarity in results between the EQ-5D data as collected in the HAROSA trials and mapping data when used to estimate the slope of a linear relationship between ESS and utility. This is helpful in validating the mapping approach, thank you.

2. When ITT data is used rather than CC data (as per our original base case and the ERG original base case) the ICERs are higher. This is not unexpected because the number of responders in the ITT population will be lower than that in the CC population since not all patients completed the placebo-controlled study. The question is whether the CC population or the ITT population represents current clinical practice.

3. During the Second Committee Meeting, the ERG suggested that that 50% Hawthorne and 50% true placebo might be the best approach to modelling the placebo effect and that fluctuation in ESS would make regression to the mean inappropriate. Members of the Committee (Matt, Peter and Rob) all felt that Hawthorne was the most appropriate measure to use. Therefore, we suggest that the Hawthorne effect would be the most appropriate option for model choice.

4. During the Second Committee Meeting for pitolisant the Committee did not come to a robust conclusion regarding the most appropriate approach to estimating utilities. The clinical expert (Sonya) confirmed that studies of continuous positive airway pressure (CPAP) show that there is no impact on EQ-5D with CPAP and another clinical expert (Adrian) mentioned that people with excessive daytime sleepiness (EDS) have poor quality of life (QOL) and that improving EDS improves patient QOL.

   Similar points were made during the Second Committee Meeting for solriamfetol. The clinical experts (Sonya and Ari) confirmed that EQ-5D is insensitive in EDS. Overall, the Committee agreed that EQ-5D collected from clinical trials in EDS does not reflect the improvement in QOL.

   The ERG stated that '*absolutely accept that this drug has benefit, however our query is around the magnitude of utility benefit*'

   Therefore, it is clear that improving EDS improves QOL, but it has been challenging to quantify the benefit. Interestingly, the methods used to estimate utility benefit all show broadly similar results, with the exception of treatment independent utility UK EQ5D using the CC population, see **Table 1**. This can also be seen in Table 6 of Addendum 3, where the incremental quality adjusted life years (QALYs) are similar within each of the various models, particularly so for HAROSA I. This makes sense since EQ-5D does not capture QOL in EDS, as discussed in our original submission.

   The lack of impact on QOL is consistent with other studies in OSA treated with CPAP[37], MADs[38,39] or modafinil[40,41]. Clinical opinion, systematic reviews and work carried out by the Assessment

Group for the NICE CPAP HTA indicate that generic instruments to measure QOL, including the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and the EuroQol (EQ-5D) do not capture benefit in QOL in patients with EDS[42-44]. These instruments have not been specifically designed to assess aspects of QOL in patients with OSA or EDS and sleep is not included as a specific dimension. (Document B, page 48)

Furthermore, in Table 5 of Addendum 3, which considers the Hawthorne model (CC and ITT), the incremental QALY in the ITT model are similar (around 0.25 for HAROSA I and around 0.33 for HAROSA II).

We suggest that given the consistency of results in Table 1, together with striking similarity in results between trial EQ-5D data and mapping data when used to estimate the slope of a linear relationship between ESS and utility (point 1) that mapping is the most appropriate approach to estimating utilities.

Table 1: HAROSA – utility estimates

	Response status	Mapped utility – French	Mapped Utility - UK	Treatment independent utility UK EQ5D CC	Average slopes McDaid & observed HI – HII separate	Average slopes McDaid & observed HI – HII pooled
HAROSA I						
Hawthorne	Responder	0.827	0.849	0.876	0.849	0.849
	Non-Responder	0.745	0.766	0.803	0.766	0.766
	Difference	**0.082**	**0.083**	**0.073**	**0.083**	**0.083**
Regression to the mean	Responder	0.841	0.862	0.871	0.863	0.862
	Non-responder	0.756	0.777	0.78	0.777	0.777
	Difference	**0.085**	**0.085**	**0.091**	**0.086**	**0.085**
True placebo	Responder	0.84	0.862	0.875	0.862	0.862
	Non-responder	0.75	0.771	0.785	0.771	0.771
	Difference	**0.09**	**0.091**	**0.09**	**0.091**	**0.091**
HAROSA II						
Hawthorne	Responder	0.798	0.832	0.848	0.831	0.832
	Non-Responder	0.718	0.752	0.8	0.752	0.752
	Difference	**0.08**	**0.08**	**0.048**	**0.079**	**0.08**
Regression to the mean	Responder	0.816	0.851	0.839	0.849	0.85
	Non-responder	0.732	0.767	0.788	0.767	0.767
	Difference	**0.084**	**0.084**	**0.051**	**0.082**	**0.083**
True placebo	Responder	0.814	0.848	0.843	0.847	0.848
	Non-responder	0.722	0.756	0.786	0.756	0.756
	Difference	**0.092**	**0.092**	**0.057**	**0.091**	**0.092**