NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Solriamfetol for treating excessive daytime sleepiness caused by narcolepsy [ID1602]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Solriamfetol for treating excessive daytime sleepiness caused by narcolepsy [ID1602]

Contents:

The following documents are made available to consultees and commentators:

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

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   a. Narcolepsy UK

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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.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Solriamfetol for treating excessive daytime sleepiness caused by narcolepsy

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

Definitions:

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 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 determination (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, 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.

Comments received from consultees

Consultee	Comment [sic]	Response
Jazz Pharmaceuticals (manufacturer)	On the Committee's conclusions that (ACD 3.2) dexamfetamine and methylphenidate are standard treatments after modafinil and there are no established treatments after this, and (ACD 3.3) the most relevant comparators after first-line modafinil are dexamfetamine and methylphenidate and (ACD 3.9) the treatment pathway after modafinil is not fully captured in the company's model In ACD 3.2, the Committee acknowledged that there were limited data available for dexamfetamine and methylphenidate but concluded these were the most relevant comparators for solriamfetol. The Committee also removed pitolisant and sodium oxybate as comparators, stating that "treating narcolepsy with pitolisant and sodium oxybate cannot be considered established clinical practice in the NHS in England because it is limited by the need for individual funding requests." In contrast to the Committee's conclusion, the evidence outlined below strongly indicates that post modafinil there are four treatments widely used for the management of narcolepsy in the UK. In order to gain additional clinical expert input (in addition to the clinical expert opinion previously submitted (2, 8)) and further inform this assessment, the company conducted an interview programme comprising a series of in-depth interviews with healthcare professionals in the UK experienced in the management of narcolepsy (9). The methods of the interview programme are described in Appendix A	Thank you for your comment. Section 3.3 of the Final Appraisal Document (FAD) states *"The committee agreed that pitolisant and sodium oxybate could be considered as relevant comparators at that part [third line or later] of the treatment pathway despite some variability in access. The committee concluded that the relevant comparators for solriamfetol are dependent on the position in the treatment pathway."*
Jazz Pharmaceuticals	**Clinicians disagree that methylphenidate and dexamfetamine are the only established treatments for narcolepsy, and instead advise that all four treatments (dexamfetamine, methylphenidate, pitolisant, sodium oxybate) are used post modafinil in the UK** There are five treatment options used in routine practice in England for managing EDS due to narcolepsy (modafinil, dexamfetamine, methylphenidate, pitolisant, sodium oxybate). Modafinil is widely established as first line, however following modafinil there is no standard treatment option and treatment	Thank you for your comment. In section 3.2 of the FAD it states "*The committee acknowledged that modafinil is the standard first-line treatment and that there is*

	choice between the remaining four therapies differs across centres in the UK (Table 6). Advice from clinician interviews indicates that contrary to the Committee's conclusion, difficulty accessing any of these four treatments is an exception, rather than the rule, and that all four treatments are used routinely in clinical practice for the management of EDS due to narcolepsy. Clinician statements include: • "I would take issue with the NICE documents I have seen where they talk about pitolisant and sodium oxybate not being in widespread use" • "I'd say sodium oxybate is an established treatment and for pitolisant, they should have established patients. I accept dexamfetamine is established, but there are far fewer dexamfetamine patients in my clinic than there are sodium oxybate patients" • "Going forward, I would say that modafinil is first line and that all other options are second line" Clinicians disagree with the Committee conclusion that "dexamfetamine and methylphenidate were the established treatments for narcolepsy in NHS practice after modafinil and that there are no established treatments used after this." Clinicians also disagree with the statement that dexamfetamine and methylphenidate the most appropriate head-to-head comparators for solriamfetol (10). A sample of clinician descriptions of their use of methylphenidate and dexamfetamine are provided below (9): • "In a world where we have solriamfetol available, I'd look to have solriamfetol second line rather than using dexamfetamine or methylphenidate second line. Dexamfetamine and methylphenidate are fraught with a number of difficulties" • "Dexamfetamine and methylphenidate have more tachyphylaxis than modafinil. Dexamfetamine and methylphenidate have risks of dependence, addiction and rebound and if patients run out of medication, they become profoundly sleepy." • "Regarding the use of dexamfetamine, I think it's probably a 50:50 split in clinicians in the UK as to whether or not they will prescribe it. Prescription of dexamfetamine is probably more common in older physicians. I think it uncommon that physicians would choose dexamfetamine as second line" • "I'm surprised to see dexamfetamine as second line up there with methylphenidate. I can't remember the last time I prescribed dexamfetamine de novo." • "There are no data for methylphenidate and dexamfetamine. We're constantly being told to prescribe within the license. The fact is that methylphenidate doesn't have a license." • "There are a lot of patients who don't like dexamfetamine because of the 'wired' feeling it gives them." These statements indicate that clinicians have reservations about these stimulant treatments, and in	*considerable variation in the use and availability of treatments after modafinil. The committee concluded that dexamfetamine and methylphenidate were the established treatments for narcolepsy in NHS practice after modafinil, and that there is variable access to pitolisant and sodium oxybate*."

	some cases may not use them at all in clinical practice.	
Jazz Pharmaceuticals	**NHS formulary information and market share sales data demonstrate that all four comparators are widely available in the UK** As described in Section **Error! Reference source not found.**, interviews with clinicians and other relevant healthcare professionals indicated that routine access to pitolisant and sodium oxybate is widespread (9) and their advice contradicts the suggestion in the ACD that the use of these treatments cannot be considered 'routine'. In addition to the clinician interviews, publicly available NHS formulary information reveals widespread availability of all four post-modafinil treatment options (dexamfetamine, methylphenidate, pitolisant, sodium oxybate) across the UK (11-26). From this publicly available information, 14 of 19 NHS Trusts in England that treat narcolepsy have routine access to pitolisant and/or sodium oxybate for new adult patients with narcolepsy. Of these, 12 centres have direct access to prescribing and 2 further centres have commissioning arrangements to refer to a tertiary centre that can initiate pitolisant and or sodium oxybate for their patients (9, 11). Although five centres gain access to pitolisant and sodium oxybate via Individual Funding Requests (IFRs), sales data demonstrate that these treatments are prescribed across all of the 19 NHS Trusts treating narcolepsy therefore demonstrating that there have been successful IFRs at these Trusts. Furthermore, the sales data for pitolisant and sodium oxybate, both of which are currently only indicated for the management of narcolepsy (27, 28), demonstrate the extent of their current use and an increasing rate use across the UK (29). Pitolisant sales data from the 12 months covering June 2020 – May 2021 showed that [redacted] packs of pitolisant were sold in England, with a value of [redacted] This is consistent with widespread prescribing of pitolisant in its sole indication. Sodium oxybate sales for the same period totalled [redacted] units with a value of [redacted] Note that some of these sales for sodium oxybate will include paediatric and adolescent services, and therefore the sales also include both prescriptions for adult patients and the continuation of prescribing in adult patients (≥19 years) who have transitioned from these services (30, 31). A total of 12 of the 19 NHST Trusts[1] treating narcolepsy have continuation of prescribing of sodium oxybate for adults ≥19 years. Upon this transition to the adult services, commissioning of sodium oxybate moves from the responsibility of NHS England to that of Clinical Commissioning Groups, and Guidance to facilitate decision making by CCGs in whether or not to commission sodium oxybate for patients after their 19th birthday has been published by the Regional Medicines Optimisation Committee (30, 31). The sales of both pitolisant and sodium oxybate are spread across all seven regions of NHS England and provide strong evidence that these treatments are used in routine clinical practice for the management of narcolepsy. This evidence of access to these two treatments, in addition to the extensive	Thank you for your comment. In section 3.2 of the FAD it states "*The committee acknowledged that modafinil is the standard first-line treatment and that there is considerable variation in the use and availability of treatments after modafinil. The committee concluded that dexamfetamine and methylphenidate were the established treatments for narcolepsy in NHS practice after modafinil, and that there is variable access to pitolisant and sodium oxybate.*"

	clinician evidence provided over the course of this appraisal, shows that contrary to the Committee's position at ACD, access to these treatments in England is widespread, and is not "limited by the need for individual funding requests." As such, neither sodium oxybate nor pitolisant should be discounted as established clinical practice and can be considered appropriate comparators for solriamfetol	
Jazz Pharmaceuticals	**The Regional Medicines Optimisation Committee considers sodium oxybate and pitolisant to be relevant treatments for narcolepsy** Furthermore, the Regional Medicines Optimisation Committee published a commissioning statement for sodium oxybate in adult patients with narcolepsy with cataplexy in October 2019 (32). The Regional Medicines Optimisation Committee have since specified in their workplan that they will also issue a clinical commissioning framework for use of pitolisant in narcolepsy with or without cataplexy, with an expected date of 31/08/21 (33). Since the Regional Medicines Optimisation Committee published the commissioning framework for sodium oxybate in adult patients, a number of Area Prescribing Committees (APCs) and other medicines optimisation groups have since reviewed their position and adopted this guidance, allowing access for adult patients to sodium oxybate (34). The meeting minutes of other groups describe their intention to review their commissioning policies for sodium oxybate and pitolisant once both commissioning frameworks have been published by Regional Medicines Optimisation Committee (expected end of August 2021) (35, 36). A key aim of a Regional Medicines Optimisation Committee commissioning framework is to identify areas where improved consistency in the commissioning of treatments can reduce potential inequity of access across England. The inclusion of a treatment in such a commissioning framework is a strong indication that the treatment is considered established in clinical practice. As such, given that there exists a Regional Medicines Optimisation Committee commissioning framework for sodium oxybate and a framework is in development for pitolisant (expected 31/08/21), the Committee's position that sodium oxybate and pitolisant cannot be considered comparators for solriamfetol in ID1602 may contribute conflicting guidance. As described in Company submission Form B, the treatment pathway for managing narcolepsy is already highly varied likely due to relatively small patient population, the individual nature of the symptoms and the varying impact of these symptoms patients. As such, for these two wake promoting agents indicated in narcolepsy, the presence of conflicting guidance in the Regional Medicines Optimisation Committee framework versus the solriamfetol NICE guidance may cause confusion in an already varied treatment landscape, and consequently contribute to inequity of access to treatment for adult patients. This is also likely to create additional burden to healthcare professionals in the NHS who are faced with determining the position of each treatment in the pathway, taking into account the potentially conflicting recommendations alongside the highly variable and individual symptoms affecting	Thank you for your comment. The committee noted that the Regional Medicines Optimisation Committee (RMOC) published a commissioning statement for sodium oxybate in adult patients with narcolepsy with cataplexy, as highlighted in section 3.2 of the FAD. The committee noted that the RMOC guidance considered sodium oxybate treatment as a third line or later treatment.

	patients with narcolepsy.	
Jazz Pharmaceuticals	**On the Committee's conclusion that the Company's assumptions about treatment discontinuation due to adverse events may not be appropriate for analysis involving dexamfetamine and methylphenidate (ACD 3.12)** The company acknowledges the challenge in estimating healthcare-resource use due to adverse events associated with methylphenidate and dexamfetamine, particularly in the absence of high-quality placebo controlled safety data for these medicines. It was not feasible to compare to non-treatment and by association to make a direct comparison with solriamfetol for which placebo-controlled data and 12-month follow-up data are available. Instead, the Company has attempted to generate adverse event data for methylphenidate and dexamfetamine that would allow a comparison with solriamfetol. The Company has collated new data in three forms, in order to make an appropriate and plausible estimate of healthcare resource utilisation for use in a scenario analysis, through conducting: • A comparison of the Summary of Product Characteristics for methylphenidate, dexamfetamine and solriamfetol (Section 3.2.1) • A review of pharmacovigilance data for methylphenidate, dexamfetamine and solriamfetol in the form of a report from the Drug Safety Research Unit (Section 3.2.2) • In-depth clinician interviews with expert prescribers of these medicines (Section 3.2.3) • In addition, the scenario analysis for methylphenidate and dexamfetamine (Section 3.3.4) includes a contingent resource use for special storage, prescription, dispensing and auditing of Schedule 2 drugs, as per Schedule 2 of The Misuse of Drugs Regulations 2001. **A comparison of the Summary of Product Characteristics for methylphenidate, dexamfetamine and solriamfetol** The Summary of Product Characteristics (SmPC) forms a key part of the marketing authorisation of all medicines and is scrutinised by Regulators to ensure that the information is of high quality (43). The generation of an SmPC is a standardised procedure, associated with a rigorous and independent review of the data. Safety data within the SmPC is tabulated in a common format, often reporting the anticipated frequency of adverse events, thus allowing side-by-side comparison of the frequency rates and types of adverse events occurring for different treatments. • All of the adverse reactions listed in Section 4.8 "Undesirable effects" of the solriamfetol SmPC were also mentioned in one or both of the equivalent sections of the methylphenidate and	Thank you for your comments. The committee considered the company's adverse event costs for dexamfetamine and methylphenidate to be appropriate, see section 3.14 of the FAD.

	dexamfetamine SmPCs; this indicates that none of the anticipated adverse events are unique to solriamfetol. • Adverse events distinct and/or common to methylphenidate and dexamfetamine were: • For methylphenidate, “arrhythmia” is cited as being common (expected to occur in 1-10% of patients) • For dexamfetamine, “cardiomyopathy” is part of the expected adverse events, but not quantified • For both methylphenidate and dexamfetamine, “psychosis” is described as an expected adverse event; for methylphenidate psychosis is quantified as being uncommonly expected (expected to occur in 0.1–1% of patients) • These AEs were also consistent with the screening and monitoring requirements for prescribing listed in the SmPCs: • Methylphenidate and dexamfetamine both require pre-treatment evaluation of cardiovascular status and assessment for a family history of sudden cardiac/unexplained death. Subsequent to prescribing psychiatric and cardiovascular status should be continuously monitored **Pharmacovigilance data for methylphenidate, dexamfetamine, and solriamfetol** Pharmacovigilance data for methylphenidate, dexamfetamine and solriamfetol are available in the form of a report from the Drug Safety Research Unit. Pharmacovigilance reporting is associated with a minimal information standard, allowing an analysis on what adverse drug reactions occur specifically in real world setting in the UK. • The data source used for this analysis was the UK’s Medicines and Healthcare products Regulatory Agency (MHRA) Yellow Card scheme’s Interactive Drug Analysis Profile with a data lock point of 31 March 2021 • Descriptive statistics were produced for each drug. The raw data are not categorised by indication. Given that prescription of methylphenidate in the narcolepsy indication is not licensed, and dexamfetamine has other indications (attention-deficit hyperactivity disorder), the data are taken as indicative of the types of adverse events that are experienced in general in a real-world setting • Overall, there were 270 adverse drug reactions from 102 patients for dexamfetamine and 3,947 adverse drug reactions from 1,730 patients for methylphenidate, submitted to the UK’s Yellow Card scheme between 1964 and 31 March 2021 • Events were stratified by age, as adult patients are the focus of healthcare resource utilisation in	

	ID1602 • The majority of adverse drug reactions reported to the Yellow Card scheme are consistent with the existing safety knowledge of methylphenidate and dexamfetamine • The two reported events for solriamfetol were both classified as non-serious. The lower counts are consistent with the more recent authorisation of this medicine • 9.8% of reports in the Interactive Drug Analysis Profile for dexamfetamine, and 1.6% of those for methylphenidate, described a fatal adverse drug reaction • For both methylphenidate and dexamfetamine, the top ten adverse drug reactions (as a proportion of total reported events) are presented in Table 7. The adverse drug reactions formatted in bold are those described in the respective SmPC. The adverse drug reactions formatted in bold are those described in the respective SmPC. **Additional in-depth clinician interviews with expert prescribers of these medicines** Within the interview programme conducted post ACD stage, the Company sought additional clinical input to further understand the relative safety and healthcare resource utilisation of methylphenidate and dexamfetamine (based on the clinicians' clinical experience of these treatments), as compared with that of solriamfetol (based on the trial data); the methods of these interviews are described in Appendix A. • Advisors generally considered that methylphenidate and dexamfetamine would be associated with more healthcare resource use than solriamfetol. This use would not be large compared with the amount of healthcare resource use due to untreated narcolepsy (which was said to be a larger burden on system resource than the resource use as a consequence of treatment). • On anticipated adverse events: 3 out of 5 advisors described concern about cardiovascular side effects; 2 out of 5 describing a concern about psychiatric side effects for methylphenidate and dexamfetamine. • Discontinuation rates due to these adverse events were anticipated to be higher for methylphenidate and dexamfetamine (based on clinical experience) than for solriamfetol (based on the available clinical trial data). • Due to the nature of prescribing dexamfetamine as an adjunctive, or last line therapy: • One advisor described that patients "find a way to tolerate it", rather than discontinue • Another advisor said that in using dexamfetamine as last line, patients "are so desperate that they grin and bear it" with respect to side effects.	

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One advisor described the “cost and hassle factor” of prescribing controlled drugs
Another said that “people don’t want to try dexamfetamine because it’s a controlled drug.”

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<tr>
<td>Jazz Pharmaceuticals</td>
<td>
On the Committee’s conclusion that the costs of healthcare resource use should be appropriately included in the analysis for comparisons against dexamfetamine and methylphenidate (ACD 3.13)

Estimated healthcare resource use for adverse events associated with methylphenidate and dexamfetamine

Based on the information provided in Section Error! Reference source not found., the costs of healthcare resource use associated with hospital admission due to adverse events were calculated. This additional healthcare resource use included the anticipated hospital admissions related to arrhythmia, cardiomyopathy, and psychosis for dexamfetamine and methylphenidate, as identified in Section Error! Reference source not found.:

The frequency of adverse events was based on the midpoint value where available (e.g., a reported frequency of 1–10% used the midpoint of 5%)
For each of the NHS Reference Costs 2019/20 applied, the lowest bracket for Complication and Comorbidities (CC) score was assumed (44)

Table 1. Healthcare resource use associated with adverse drug reactions to methylphenidate or dexamfetamine and requiring hospital admissions
<table>
<tr><th></th><th>Methylphenidate</th><th>Dexamfetamine</th><th>Reference cost (44)</th></tr>
<tr><td>Arrhythmia</td><td>5.0%</td><td>0.0%</td><td>£600*</td></tr>
<tr><td>Cardiomyopathy</td><td>0.0%</td><td>0.5%</td><td>£824†</td></tr>
<tr><td>Psychosis</td><td>0.5%</td><td>0.5%</td><td>£1208‡</td></tr>
</table>
* EB07E Arrhythmia or Conduction Disorders, with CC Score 0-3
† EB14E Other Acquired Cardiac Conditions with CC Score 0-2
‡ WD08Z Mental and Behavioural Disorders Due to Drug or Alcohol Use, treated by a Non-Specialist Mental Health Service Provider
</td>
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Thank you for your comments. The committee considered the company’s adverse event costs for dexamfetamine and methylphenidate to be appropriate, see section 3.14 of the FAD.

The committee considered that the comparisons involving dexamfetamine and methylphenidate were highly uncertain due to the lack of clinical data informing them (see section 3.7 of the FAD). The committee considered that, at list price, solriamfetol was unlikely to be cost-effective compared to dexamfetamine or methylphenidate, but did consider solriamfetol to be a cost-effective option after these treatments and modafinil, at third line or later (see section 3.15 and 3.16 of the FAD).
</td>
</tr>
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Estimated healthcare resource use associated with the prescription of Schedule 2 drugs including methylphenidate and dexamfetamine

In addition to the estimated costs associated with adverse events, the analysis includes an additional healthcare resource use associated with the burden of prescribing a Schedule 2 medication, calculated to be £1.28 for each prescription (Table 2). Methylphenidate and dexamfetamine are both Schedule 2 drugs (37, 38), therefore the prescribing fee was added to their treatment costs (see Section 0).

Table 2. Tangible healthcare resource use associated with Schedule 2 drugs

Direct system costs for prescribing Schedule 2 medications	**General requirements for managing Schedule 2 medication resulting in personnel-related resource utilisation (45)** *Not an exhaustive list.*
£1.28 fee per prescription to dispense (paid to Business Services Authority to community pharmacists)	Governance arrangements and accountability
	Policies, processes, and procedures
	Processes and procedures for storage, stock checks and audits
	Processes and procedures for transportation
	Nominated person not involved in handling of controlled drugs to be appointed to oversee the management and governance of activities related to controlled drugs
	Providing information and advice to people taking or carers administering controlled drugs
	Identifying and reporting trends and barriers

Estimated daily cost for each of the four comparator treatments, including the prescribing fee associated with the prescription of Schedule 2 drugs

Given the absence of available data to compare solriamfetol with dexamfetamine and methylphenidate from a cost-effectiveness perspective, the Company investigated the maximum and minimum cost of each drug including any prescribing fees (for controlled substances) and made a direct price comparison between all post-modafinil therapies (Figure 1).

	Figure 1 depicts the minimum, average and maximum daily cost for each of the post-modafinil treatments. Note that in addition to these costs, there is a prescribing fee per 30 day prescription of £1.28 for Schedule 2 controlled substances: • Neither solriamfetol nor pitolisant are Schedule 2 drugs • Methylphenidate **and** dexamfetamine are both Schedule 2 controlled substances, therefore the associated prescribing fee was applied in the costs • Sodium oxybate is a Schedule 2 drug however as solriamfetol was cost-effective against sodium oxybate in the base case, the prescribing fee has conservatively been excluded from the analysis The maximum daily cost of [redacted] to prescribe solriamfetol is comparable with the minimum costs to prescribe pitolisant and lower than the minimum daily cost of sodium oxybate. Note that the wide range of potential doses, combined with availability of different formulations for methylphenidate and dexamfetamine result in a substantial range of daily costs. However, clinicians advise that higher doses are associated with AEs, and that to achieve similar efficacy to solriamfetol, these treatments must be titrated to the higher doses. Further, as previously discussed some patients may continue these treatments despite achieving suboptimal efficacy, in the absence of alternative options. As such, it is likely that the daily costs of solriamfetol are favourable against those of dexamfetamine and methylphenidate. It is also important to note that methylphenidate is a Schedule 2 controlled substance that does not have a license in narcolepsy, and that clinicians have concerns about this treatment (Section **Error! Reference source not found.**). **Figure 1. Minimum, average, and maximum daily cost for post-modafinil treatments in narcolepsy** Redacted Costs calculated from the range of potential doses and formulations listed on the BNF (37, 38, 46-48). Note a wide range of doses and variety of formulations are available for methylphenidate and dexamfetamine, resulting in a wide variation in potential daily doses. Even if assuming the comparators have clinical equivalence with solriamfetol, solriamfetol is a cost-saving choice for the majority of patient prescriptions. Although this would not be the case for methylphenidate, methylphenidate is unlicensed for use in narcolepsy and as outlined in Section **Error! Reference source not found.**, clinicians have concerns about the use of both methylphenidate and dexamfetamine (9).	

Scenario analysis comparing methylphenidate and dexamfetamine with solriamfetol

The data generated through the steps taken in Section **Error! Reference source not found.** and 0 allowed the Company to conduct a scenario analysis, comparing solriamfetol with all four post-modafinil treatments. The Company acknowledge that the adverse event data underlying this analysis are implicitly weak, however as described previously, there is an absence of clinical data for methylphenidate and dexamfetamine thus the options to conduct such an analysis were limited.

As such, the data supporting this analysis must be considered a crude analysis and the results interpreted as such. Due to the nature of this data, it cannot be considered a replacement for randomised controlled trial data nor a comprehensive description of the safety profile of methylphenidate and dexamfetamine.

The healthcare resource use costs for methylphenidate and dexamfetamine, as estimated in Section 0 and 0, may be considered conservative. Given that the costs calculated (i) include only some of the potential adverse events (as identified in Section **Error! Reference source not found.**), (ii) applied an assumed frequency using a midpoint of reported adverse event rates, (iii) applied the reference cost associated with the lowest CC score bracket, and (iv) assumed the occurrence of only a single episode of each adverse event, the costs presented likely substantially underestimate the total increase in healthcare resource use that would be associated with methylphenidate and dexamfetamine. The scenario analysis assumes:

- The cost of adverse events (calculated as *cost per adverse event x frequency rate*; Table 1) was:
  - £36.04 per year per patient for methylphenidate (£30.00 for arrhythmia; £6.04 for psychosis)
  - £10.16 per year per patient for dexamfetamine (£4.12 for cardiomyopathy; £6.04 for psychosis)
- The cost associated with prescribing a Schedule 2 drug is:
  - £1.28 per 30 day prescription applied to methylphenidate, dexamfetamine and sodium oxybate
- The efficacy of methylphenidate and dexamfetamine was assumed to be equivalent to that of sodium oxybate 4.5 g as calculated in the indirect treatment comparison (i.e., an efficacy of -2.985 ESS points relative to solriamfetol 150 mg; this was based on the updated indirect treatment comparison used in the Company response to Technical Engagement)

Other than the assumptions outlined above, the scenario analysis makes no changes to the revised base case assumptions outlined in **Error! Reference source not found.**.

Table 3. Results of a scenario analysis comparing solriamfetol with the four post-modafinil treatments (PAS PRICE)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER vs. methylphenidate	ICER vs. soliramfetol
Methylphenidate	£1,268	14.601	42.445					[redacted]
Dexamfetamine	£3,470	14.601	42.445	[redacted]	0.000	Dominated	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	42.445	[redacted]	0.103	[redacted]	[redacted]	[redacted]
Pitolisant	£19,122	14.717	42.445	[redacted]	0.013	[redacted]	[redacted]	[redacted]
Sodium oxybate	£25,860	14.676	42.445	[redacted]	-0.041	Dominated	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 10A. Results of a scenario analysis comparing solriamfetol with the four post-modafinil treatments (LIST PRICE)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER vs. solriamfetol
Methylphenidate	£1,268	14.601	42.445				£65,648
Dexamfetamine	£3,470	14.601	42.445	£2,202	0.000	Dominated	£44,284
Solriamfetol	£8,034	14.704	42.445	£4,564	0.103	£44,284	NA
Pitolisant	£19,122	14.717	42.445	£11,087	0.013	£886,555	£886,555
Sodium oxybate	£25,860	14.676	42.445	£6,739	-0.041	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

The results of the analysis are unchanged from the base case analysis, in that solriamfetol is a cost-effective treatment compared with pitolisant and sodium oxybate. In the current scenario analysis, with PAS pricing, solriamfetol would be considered cost-effective compared to dexamfetamine with an ICER of £[redacted] per QALY and is just above the £30,000 per QALY threshold when compared to methylphenidate with an ICER of £[redacted].

The initial scenario analysis assumed that the efficacy of dexamfetamine and methylphenidate was equivalent to that of sodium oxybate 4.5 g. As previously noted, there is no published data available to estimate the efficacy of dexamfetamine or methylphenidate, and the clinician interviews were unable to provide any appropriate estimates of their efficacy. Therefore, a sensitivity analysis was conducted to assess the impact of changing the relative difference in ESS compared with solriamfetol 150 mg (excluding costs of treatment in discontinuers) on the ICERs. The results are shown in Table 4. In the base case analysis, solriamfetol 150 mg has an average reduction in ESS of 5 points (based on the TONES 2 individual patient level data) from baseline thus the analysis was limited to this range.

Table 4. Sensitivity analysis to assess the impact of the relative difference in ESS compared with solriamfetol 150 mg on the ICERs (PAS PRICE)

ΔESS relative to solriamfetol 150 mg	ICER vs. methylphenidate	ICER vs. dexamfetamine
-1.00	[redacted]	[redacted]
-2.00	[redacted]	[redacted]
-3.00	[redacted]	[redacted]
-4.00	[redacted]	[redacted]
-5.00	[redacted]	[redacted]

Abbreviations: ΔESS, Difference in ESS; ICER, incremental cost effectiveness ratio; SW, southwest quadrant.

Table 11A. Sensitivity analysis to assess the impact of the relative difference in ESS compared with solriamfetol 150 mg on the ICERs (LIST PRICE)

ΔESS relative to solriamfetol 150 mg	ICER vs. methylphenidate	ICER vs. dexamfetamine
-1.00	Methylphenidate dominates	Dexamfetamine dominates
-2.00	£183,216	£86,406
-3.00	£66,575	£44,234
-4.00	£48,806	£37,694
-5.00	£42,618	£35,230

Abbreviations: ΔESS, Difference in ESS; ICER, incremental cost effectiveness ratio; SW, southwest quadrant.

Note that these results must be interpreted with caution. Solriamfetol 75 mg was less effective than solriamfetol 150 mg in the ITC therefore when methylphenidate or dexamfetamine are considered to be less effective than solriamfetol 150 mg by ≥1 ESS point, the comparison against solriamfetol combined results in counterintuitive ICERs. As such, on average the comparators appear more effective than solriamfetol combined but are not necessarily so against solriamfetol 150 mg.

As the relative efficacy of the comparators versus solriamfetol increase (i.e. the comparators become less effective compared to solriamfetol 150 mg), the utility gain for solriamfetol increases but so does relative cost. Compared with dexamfetamine, solriamfetol is cost-effective at all levels of assumed efficacy; this is due to the small difference in costs between the two products. When compared to methylphenidate the ICER drops below £30,000 per QALY when methylphenidate efficacy is ≥4 lower than that of solriamfetol 150 mg.

Due to the lack of treatment options available and the limitations associated with methylphenidate and dexamfetamine (Section **Error! Reference source not found.**), clinicians suggested that many patients will continue to receive stimulant treatment even when the patient does not perceive a clinical benefit. A threshold analysis was performed to assess the impact of continuing methylphenidate or dexamfetamine treatment in a proportion of non-responding patients. The analysis assumes there are no costs for patients who discontinue solriamfetol, as in contrast to dexamfetamine/methylphenidate, patients are assumed to discontinue solriamfetol if they do not respond to treatment.

AT PAS PRICE:

- For solriamfetol to be cost neutral against methylphenidate, 24.6% of patients need to continue their methylphenidate treatment despite a suboptimal clinical response

- For solriamfetol to be cost-effective at £20,000 per QALY, 10% of patients need to continue their methylphenidate treatment despite a suboptimal clinical response
- For solriamfetol to be cost-neutral against dexamfetamine, 11.4% of patients need to continue their dexamfetamine treatment despite a suboptimal clinical response

AT LIST PRICE:

- For solriamfetol to be cost neutral against methylphenidate, 48.0% of patients need to continue their methylphenidate treatment despite a suboptimal clinical response
- For solriamfetol to be cost-effective at £20,000 per QALY, 31.1% of patients need to continue their methylphenidate treatment despite a suboptimal clinical response
- For solriamfetol to be cost-neutral against dexamfetamine, 11.8% of patients need to continue their dexamfetamine treatment despite a suboptimal clinical response
-

Scenario analysis for an excess mortality associated with use of methylphenidate and dexamfetamine

There is evidence that the use of stimulants is associated with excess mortality (49, 50), thus an analysis investigating the effect of excess mortality on the ICERs was conducted. The analysis assumed a standardised mortality rate of 1.01 applied to dexamfetamine and methylphenidate. As expected, this excess mortality impacted the total QALYs for the stimulant treatments and reduced the ICERs for all treatments vs methylphenidate (Table 5). Note that in order to generate an ICER of £20,000 per QALY for solriamfetol versus methylphenidate, i.e. for solriamfetol to become cost-effective, the excess mortality due to methylphenidate treatment would only need to increase very slightly to 1.04, however, this scenario has the same challenges as all dexamfetamine and methylphenidate scenarios due to a lack of evidence.

Table 5. Scenario analysis outlining the impact of excess mortality associated wtih stimulants on the ICERs (PAS PRICE)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER vs. solriamfetol
Methylphenidate	£1,268	14.585	42.352				[redacted]
Dexamfetamine	£3,470	14.585	42.352	[redacted]	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	42.445	[redacted]	0.120	[redacted]	NA

Pitolisant	£19,122	14.717	42.445	[redacted]	0.013	[redacted]	[redacted]
Sodium oxybate	£25,860	14.676	42.445	[redacted]	-0.041	Dominated	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 6. Scenario analysis outlining the impact of excess mortality associated wtih stimulants on the ICERs (LIST PRICE)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER vs. solriamfetol
Methylphenidate	£1,268	14.585	42.352				£56,601
Dexamfetamine	£3,470	14.585	42.352	£2,202	0.000	Dominated	£38,183
Solriamfetol	£8,034	14.704	42.445	£4,565	0.120	£38,183	NA
Pitolisant	£19,122	14.717	42.445	£11,087	0.013	£886,555	£886,555
Sodium oxybate	£25,860	14.676	42.445	£6,739	-0.041	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Jazz Pharmaceuticals	**On the Committee's consideration that most appropriate dose splits were uncertain (ACD 3.11)**	Thank you for your comments. The committee considered that the most appropriate dose splits were uncertain, particularly for

	Since the time of response to Technical Engagement (January 2021), the Company have collected further sales data from the French and German markets. Solriamfetol has been prescribed in France since April 2020 (in the narcolepsy indication only from April 2020 to February 2021, and in both the narcolepsy and OSA indications from February 2021) and in Germany since May 2020 (in the narcolepsy indication only from May 2020 to July 2021, the OSA indication was approved in July 2021). After the point of initiation of prescribing to patients with OSA in France (February 2021), it is not possible to stratify the sales data by indication and determine whether a sale reflects a prescription for the narcolepsy or OSA indication. As such, the German data (reflecting sales in the narcolepsy indication only) have been used to inform a new dose split for the Company's revised base case. The Company's original base case analysis (Form B, November 2020) assumed a 50:50 dosing split between 75 mg and 150 mg doses of solriamfetol. At the time of the response to Technical Engagement, the dosing split based on German sales data was calculated as [redacted] for the 75 mg and 150 mg doses, respectively. With the addition of a further 6 months of data, this dosing split has changed slightly to a dose split of [redacted] for the 75 mg to 150 mg doses, respectively. However, as solriamfetol is a new treatment option, the data are weighted towards the lower dose, new patients are anticipated to start on the 75 mg dosage and depending upon their clinical response, may subsequently titrate up to the higher 150 mg dosage; this is consistent with the solriamfetol SmPC (51). In order to reduce the impact of the initial weighting towards lower doses, the Company has specifically assessed the dosing split for prescriptions made between January 2021 and June 2021. This data cut reflects prescriptions made after 8 months of solriamfetol availability in the narcolepsy indication in Germany, and therefore are assumed to be more representative of a steady state of prescribing in clinicians with first-hand experience with solriamfetol. Based on this representative data cut, the real-world dosing split for solriamfetol was [redacted] for the 75 mg and 150 mg doses, respectively. This dosing split has been applied in the Company's revised base case analysis.	dexamfetamine and methylphenidate (see section 3.12 of the FAD).
Jazz Pharmaceuticals	**Comment 5. On the Committee's conclusion that mapping from the ESS to the EQ-5D may not adequately capture changes in quality of life (ACD 3.10)**	Thank you for your comments. The committee acknowledged the

	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 (52). In addition, a recent systematic review and meta-analysis highlights this, and confirms the lack of an appropriate, validated method to capture health-related quality of life in people with narcolepsy (53). 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 narcolepsy. Neither the EQ-5D nor the SF-36 data collected in the TONES trials reflected the substantial burden of EDS in narcolepsy on quality of life. Despite the high burden of illness in patients with such a disabling symptom (see Company submission, Form B.1.3), baseline utility scores collected in the trials were inconsistent with the widely accepted negative impact of EDS and narcolepsy. The reasons why these health questionnaires were incapable of capturing changes in quality of life in the trials are discussed at length in the Company submission Form B and Technical Engagement response (e.g., a lack of a sleep domain, inability to capture impact on relationships, high baseline utility scores, patient adaptation to sleepiness over time). Furthermore, the 12-week trial duration was likely insufficient to capture the effect of solriamfetol on quality of life. Therefore, in the absence of appropriate health-related quality of life trial data, the Company maintain that the best method for describing the quality of life improvement for patients with narcolepsy is the use of the EQ-5D from the NHWS mapping formula in the base case, with an analysis using the McDaid algorithm provided in a scenario. The Committee commented that changes in quality of life may not be adequately captured by mapping the Epworth Sleepiness Scale to the EQ-5D. The Committee also commented that the results from the mapping algorithm estimated a high valuation of quality of life even at extremely high ESS scores (higher ESS scores equal higher levels of excessive daytime sleepiness), which did not appear to be valid. The Committee concluded that mapping from the ESS to the EQ-5D may not adequately capture changes in quality of life. The Company agrees that the improvement in quality of life is likely to be an underestimate, and it is likely that the analyses underestimate the cost-effectiveness of solriamfetol. Following the ACD, the Company discussed with clinicians the topic of using generic health questionnaires to measure changes in quality of life associated with changes in EDS (9). Please see the Discussion Guide (provided in the reference pack) for details. Based on these discussions, the	limitations in the analysis which estimated impact of excessive sleepiness caused by narcolepsy in the appraisal (see section 3.12 of the FAD)

	Company's resolve to the use of the mapping approach was strengthened. Clinicians described a very substantial burden on quality of life for patients with EDS. Statements from the clinicians include: • "If you're not dealing with these patients day to day you don't understand the severity and impact on life. The patient could get an A grade in the morning and an E grade in the afternoon, due to their narcolepsy." • "Even at their very best, [patients with narcolepsy] perform as someone who hasn't slept for 22 hours, but they think they're doing OK. The tools are so crude for measuring this – how do you measure that a patient doesn't fall asleep at the cinema?" The Company discussed the mapping with clinicians (see the interview 'Pre Read' in the reference pack for details). Clinicians confirmed they expected to see a correlating decrease in quality of life as a patient's sleepiness increased. In general, clinicians agreed that the shape of the NHWS and McDaid graphs were an appropriate reflection of the impact of EDS on quality of life but believed the graphs to underestimate the detrimental impact of EDS on the patient. For example: • "Quality of life increases as ESS decreases. I'm surprised it's not more steep. The trend is correct, but it should be more steep" • "The inflection point looks at the right place, but it doesn't sit right in that the QoL is as high as it is when they patients are so sleepy – these QoL scores are high for such sleepy patients" Clinicians highlighted that these (EQ-5D, SF-36) are generic scales and not tailored for EDS, and the clinicians felt that these generic scales underestimate the true burden of EDS on quality of life, thus the QALY gain with solriamfetol is likely an underestimate of the true cost-effectiveness of solriamfetol, as supported by the scenario using the time trade off study utility values.	
Jazz Pharmaceuticals	On the clinical experts' statement that if someone's condition did not respond to dexamfetamine or methylphenidate, usually they had no further treatment options and had to continue on treatment with those drugs (ACD 3.2) The company acknowledges the limitation arising from the lack of head-to-head comparisons between solriamfetol and other medications used in the treatment of narcolepsy. This limitation is particularly	Thank you for your comments. The committee considered that the comparisons involving dexamfetamine and methylphenidate were

	acute for dexamfetamine and methylphenidate, for which two systematic literature reviews failed to identify any studies reporting methods and sufficient quality data to include in an indirect treatment comparison (see Company submission, Form B.2.9.1). This absence of data for methylphenidate and dexamfetamine is acknowledged in the evidence-based recommendations of the recent European guideline and expert statements on the management of narcolepsy in adults and children (a joint guideline from the European Academy of Neurology, European Sleep Research Society, and European Narcolepsy Network (54)). In this comprehensive expert statement, the quality of data for both methylphenidate and amphetamine derivatives (which encompasses dexamfetamine) are deemed “weak.” The Company acknowledge the limitations associated with drawing conclusions about the relative clinical effectiveness of the treatment options given the absence of relevant and valid data. Consistent with NICE guidance, the Company has not presented a naïve analysis and has instead restricted to a narrative overview (55). As such, in order to contribute further clinical expert input to understand relative efficacy of solriamfetol compared with methylphenidate and dexamfetamine, the company conducted a series of in-depth interviews (9), the methods of which are described in **Error! Reference source not found.**. This is in addition to clinical expert opinion previously submitted (2, 8). In this interview programme, Clinicians consistently described the practice of titrating both methylphenidate and dexamfetamine not just to clinical effect, as measured by ESS, but also to the emergence of adverse events. The dose-response relationship was described as “not a linear relationship” and “[not] predictable at all.” In addition, the patient experience was described as “incredibly variable.” Where possible, clinicians gave an estimate of the treatment effect for each of methylphenidate and dexamfetamine with respect to ESS. A reduction in ESS in the range of 3-5 points was reported for methylphenidate and 3-6 points was reported for dexamfetamine. In one of these interviews, a clinician who is a current prescriber of solriamfetol estimated the reduction of ESS to be 5–6 points and when describing the relative effect of solriamfetol stated:	highly uncertain due to the lack of clinical data informing them (see section 3.7 of the FAD). The committee also noted that the company’s model did not fully capture the treatment pathway, in which pitolisant and sodium oxybate were usually given, if available, as a third line or later treatment (see section 3.10).

	"I don't think it's inferior to dexamfetamine or methylphenidate" Clinical expert opinion was that an adequate therapeutic response to methylphenidate and dexamfetamine occurs in only 50-60% of patients at the maximum tolerated dose. A direct quote from this set of expert interviews was: "Solriamfetol is likely to be better tolerated… than dexamfetamine or methylphenidate" This clinician input supports the assumption in the Company's revised model that methylphenidate and dexamfetamine may achieve similar efficacy as solriamfetol, with the added context that in order to achieve this level of efficacy, patients may experience adverse events due to titrating to a sufficiently high dose to achieve therapeutic response. Solriamfetol will be confined to secondary care prescribing Solriamfetol prescribing will be limited to secondary care. The summary of product characteristics for solriamfetol states that treatment with solriamfetol requires specialist initiation (51). Further, it is common for patients with narcolepsy to remain within secondary and sometimes tertiary care, given the nature of the disease. In addition, as a newly licensed medication, solriamfetol carries a black triangle, severely limiting (in many cases precluding) its use in primary care at this time. The restriction of solriamfetol to secondary care is also consistent with the anticipated prescribing of pitolisant hydrochloride in secondary care per the ACD for NICE ID1065 (56). Discussions with NHS stakeholders (clinicians and pharmacists) revealed the preferred route for continuation of prescribing of solriamfetol is outsourced outpatient pharmacy from secondary care; however, some areas will prefer to adopt NHS contracted homecare medicines services. The NHS England Specialist Pharmacy Service has published clear principles on routes of supply for medicines to outpatients, ratified by the Regional Medicines Optimisation Committee (57). The document uses sodium oxybate as an example of a drug that is suitable for Outsourced Outpatient Dispensing or Homecare Delivery for continuation of prescribing to outpatients. During the COVID-19 pandemic, many Outsourced Outpatient Dispensing services have been couriering drugs to patients. In discussions with	

	NHS customers, these routes have been validated as well-suited for solriamfetol. In addition, in areas where early access has been approved, solriamfetol is listed as a restricted 'Red' drug in formularies, meaning its prescription is limited to hospital only (14, 15, 17, 19-21, 23-26). Clinical expert statements further support the expectation that ongoing prescribing will remain with sleep physicians. Dr Martin Allen's clinical expert statement in the Committee meeting stated that "Patients should be under the regular review of a specialist sleep centre where the treatment can be both initiated, observed for effect and then stopped if necessary" (58). Dr Sonya Craig's clinical expert statement, representing the British Thoracic Society, for NIC TA ID1499 (Solriamfetol for treating excessive daytime sleepiness caused by OSA) stated "It is very unlikely that primary care would be willing to take on prescribing of this drug"(59). There are 14 NHS Hospital Trusts with commissioning agreements for access to pitolisant, and 11 of these have classified pitolisant as a "Red" drug, meaning that it is considered to be a specialist medicine with prescribing responsibility remaining with the consultant or specialist clinician (11-26). In alignment with its secondary care prescribing, Jazz has listed solriamfetol as 'hospital only' in the British National Formulary (48).	
Narcolepsy UK	We are concerned that this recommendation may discriminate against people with narcolepsy compared to people with more common, better researched conditions. Narcolepsy is a disability and people with narcolepsy are protected from discrimination as a result of their condition by legislation enshrined within the Equality Act 2010. This is recognised in the appraisal consultation document, and in Narcolepsy UK's Charter*, both of which describe the chronically debilitating impact of narcolepsy on every aspect of our lives including education, employment, family and social lives. As people with narcolepsy, we suffer disadvantages related to the lack of recognition of our condition, lack of healthcare services and lack of scientific research. This, together with the relative rarity of narcolepsy limits the development of, and access to, new health technologies.	Thank you for your comments. The committee heard from the patient experts at the meeting and considered the evidence submitted on the impact of narcolepsy on people with the condition (see sections 3.1 and 3.11 of the FAD). At the second committee meeting, the committee considered that, at list price,

	These disadvantages are demonstrated in this appraisal consultation document through a recognition of the absence of evidence that would normally be available to NICE to assess the cost effectiveness of new treatments. This includes evidence that could be costly and time consuming to produce such as the development of a method to appropriately capture quality of life changes in this population, other sources of evidence for the efficacy of the comparator drugs (dexamfetamine and methylphenidate), and appropriate estimates of healthcare resource use for treatment with these comparators compared with solriamfetol. Whilst dexamfetamine and methylphenidate have never been subject to a NICE Technical Appraisal and, to our knowledge, have never been trialled in people with narcolepsy, they have been deemed second line by NICE as they represent cheaper alternatives to drugs specifically developed for our condition. In reviewing their decision, the committee should ask themselves what level of evidence would be needed to recommend a new narcolepsy drug, whether it would be possible for a pharmaceutical company to produce this evidence, and whether the company would make sufficient returns to justify generating this evidence. If not, the reports recommendation will have a negative impact on people with narcolepsy compared to people with other more common and well recognised conditions. This will leave us to be treated with high doses of drugs that may well be harmful when taken with the frequency and longitude necessary for our condition, having more side-effects than solriamtetol, including adverse cardiovascular events. *We submitted Narcolepsy UK's Charter as evidence in the consultation. The Charter is a written statement of the rights of people with narcolepsy and their families and friends to have a full and rounded life without having to fight to make this happen. It is based on responses to an externally created, validated online survey of 302 people with narcolepsy and 149 supporters. The Charter and supporting documentation are available here: https://www.narcolepsy.org.uk/resources/narcolepsy-charter	solriamfetol was unlikely to be cost-effective compared to dexamfetamine or methylphenidate, but did consider solriamfetol to be a cost-effective option after these treatments and modafinil, which would be third line or later (see section 3.15 and 3.16 of the FAD).
Narcolepsy UK	We believe that the response provided substantiates the view that a higher % of rare disease patient groups fail to have medicines approved by the standard NICE Technology Appraisal and that there is a pressing need for rare disease treatments to be subject to a specialised appraisal. Failure to do this results in a Catch-22 situation where rare disease patients are unable to access medicines for treatment unless there is evidence to support cost effectiveness. This evidence proving virtually impossible to collect due to the inability to access medicines. We believe this to be discriminatory, based purely on the nature of our disability.	Thank you for your comment. At the second committee meeting, the committee considered that, at list price, solriamfetol was unlikely to be cost-effective compared to dexamfetamine or methylphenidate, but did consider solriamfetol to be a

		cost-effective option after these treatments and modafinil, which would be third line or later (see section 3.15 and 3.16 of the FAD).
Narcolepsy UK	Solriamfetol was granted Orphan Drug Status by the FDA but we understand that this was not sought by Jazz as they are also seeking an appraisal for sleep apnoea by NICE. This has the effect of making the drug available sooner & cheaper than might otherwise occur yet this recognition of potential earlier than normal patient access for a novel medicine has been overlooked. In fact, we believe that this standard method of appraisal does not suit a condition where treatments are both novel & re-purposed & often mixed.	Thank you for your comment. At the second committee meeting, the committee considered that, at list price, solriamfetol was unlikely to be cost-effective compared to dexamfetamine or methylphenidate, but did consider solriamfetol to be a cost-effective option after these treatments and modafinil, which would be third line or later (see section 3.15 and 3.16 of the FAD).
Narcolepsy UK	NHS England costs are not accurately reflected in the cost models as whilst there is some reference to the legally dubious process of Individual Funding Requests, no account has been taken of their cost per CCG if clinicians and patient groups choose to request treatment. These costs are inevitable if this is the only route open to patients who would benefit from solriamfetol.	Thank you for your comment. The committee were not presented with additional costs for treatment which may require an individual funding request. At the second committee meeting, the committee was presented with additional data to show that pitolisant and sodium

		oxybate are available across various regions of the NHS but access is usually subject to various restrictions (see FAD section 3.3).
Narcolepsy UK	Various comparisons were made to sodium oxybate & its general lack of availability but this has not been subject to analysis or scrutiny by NICE and neither of the clinicians present at the appraisal committee were representative of an area where sodium oxybate is routinely commissioned and so a more pessimistic view of the availability of treatment was offered The fact that post pubertal children who are refractory to older narcolepsy treatments are now routinely commissioned sodium oxybate is predicated on (as set out in the NHS England commissioning policy 2016) the effectiveness of sodium oxybate as a narcolepsy treatment for adults. It is perverse to have such a treatment for children and apply a different view for adults. You may wish to consider the judgment of Collins J in R (on the application of S (a child) v NHS England [2016] EWHC 1395 (Admin) on the meaning of "exceptional", as it also applied to a refusal of funding of sodium oxybate for narcolepsy with cataplexy within the IFR procedure. An appeal against that decision was refused by the Court of Appeal on 2nd March 2017. We would estimate the total costs associated with this judgement to be c. 20 times the annual cost of treatment of £13,000 per annum.	Thank you for your comments. At the second committee meeting, the committee was presented with additional data to show that pitolisant and sodium oxybate are available across various regions of the NHS but access is usually subject to various restrictions (see FAD section 3.3). Section 3.3 of the FAD states "*The committee agreed that pitolisant and sodium oxybate could be considered as relevant comparators at that part of the treatment pathway despite some variability in access. The committee concluded that the relevant comparators for solriamfetol are dependent on the position in* the treatment pathway."
Narcolepsy UK	The MHRA has recently issued a warning that modafinil, the first line drug to treat excessive daytime sleepiness in people with narcolepsy, has been linked to increased risk of birth defects and also to	Thank you for your

	reduced effectiveness of oral contraception. Doctors are reluctant to prescribe modafinil to women who are not using alternative methods of birth control. Women who do not want to use alternatives to oral contraception, or do not want or need to use any form of contraception, need access to alternative, safe, treatments for narcolepsy.	comments. The committee considered this potential equalities issue and noted that the recommendations for solriamfetol would not negatively impact people who could not have modafinil as the recommendations allows use in this group of people (see FAD section 3.17).
Narcolepsy UK	We would like NICE to consider in what circumstances the following scheme was acceptable in the context of all that has been put forward as part of this appraisal as we believe it shows that patients with narcolepsy are subject to conflicting treatment options by the Department of Health & Social Security. **https://www.narcolepsy.org.uk/resources/sodium-oxybate-xyrem-–-ex-gratia-provision-victims-pandemrix** **Ex gratia provision of Xyrem** The Government operates a scheme under which the Department of Health will fund, on an ex gratia and time-limited basis, provision of Xyrem to personal injury claimants suffering from narcolepsy with cataplexy, who have made claims against GSK that they developed the condition after immunisation with Pandemrix vaccine. The Government has recently confirmed in Parliament that this scheme will remain in place until all the personal injury claims have been settled. The health departments in Scotland, Wales and Northern Ireland are also participating in the Scheme. Details of this scheme, including an application form for funding under the scheme, can be found here.	Thank you for your comment. At the second committee meeting, the committee was presented with additional data to show that pitolisant and sodium oxybate are available across various regions of the NHS but access is usually subject to various restrictions (see FAD section 3.3). Section 3.3 of the FAD states "*The committee agreed that pitolisant and sodium oxybate could be considered as relevant comparators at that part of the treatment pathway despite some variability in access. The committee concluded that the relevant comparators for solriamfetol are dependent on the position in the treatment*

		pathway."
The British Sleep Society	**Has all of the relevant evidence been taken into account?** 1) In relation to the medications used as comparators in the modelling: a. (3.2) Modafinil may be the first choice of treatment but is typically not potent enough at the maximal dose to treat narcolepsy sufficiently. Additional therapeutic options are therefore required; b. (3.3) While Dexamphetamine and Methylphenidate are used second line, this is not a satisfactory situation. As the committee recognises, there is limited evidence of effectiveness and safety as they are older drugs. They have known serious cardiovascular and psychiatric side effects. Their potential for habituation is also important to consider. They are used by default for symptomatic patients who do not benefit from or cannot tolerate modafinil, because clinicians lack access to other drugs. As a Society, we do not believe this should be considered a satisfactory state of affairs and does not justify using them as the main comparators. c. (3.12) The Committee comments that "the adverse effects of Dexamphetamine and Methylphenidate are thought to have been underestimated". We consider it surprising that in this context, an alternative and licensed, and thus safe, alternative treatment is not recommended. d. (3.2) Sodium Oxybate is not used primarily just for refractory cataplexy. It is effective in, and used for, either sleepiness or cataplexy symptoms that remain debilitating and refractory to first- and second-line medications. In fact, one of the Regional Medicines Optimisation Committees (RMOCs) issued guidance in October 2019 recommending Sodium Oxybate for refractory narcolepsy (https://www.sps.nhs.uk/articles/rmoc-sodium-oxybate-in-adult-patients/). RMOCs are an integral part of NHS England and NHS Improvement. Therefore, Sodium Oxybate should be considered standard of care although the message has been slow to reach all CCGs, possibly due to Covid. The catalyst for this guidance was the approval of funding of sodium oxybate for children with refractory narcolepsy (https://www.england.nhs.uk/publication/clinical-commissioning-policy-sodium-oxybate-for-symptom-control-of-narcolepsy-with-cataplexy-children/). There is more evidence for the effectiveness of Sodium Oxybate in adults and it is a key tool when available. The risk of patients losing access to effective treatment once they reach adulthood was agreed to be unacceptable. As a Society, we believe that the fact that some CCGs have not yet implemented the RMOC guidance should not be used as a reason for adopting the 'deprived' treatment pathway as the basis on which to evaluate Solriamfetol. RMOC guidance for Pitolisant is a work in progress but we suggest NICE also take this into account to future proof the relevance of their recommendations. Sodium Oxybate and Pitolisant are thus already established treatments and in some cases, are first line treatment. In Liverpool, for example, no Individual Funding Request (IFR) is needed as there is an agreement in place with 13 CCGs for their prescription.	Thank you for your comment. Section 3.3 of the Final Appraisal Document (FAD) states "The committee *agreed that pitolisant and sodium oxybate could be considered as relevant comparators at that part [third line or later] of the treatment pathway despite some variability in access. The committee concluded that the relevant comparators for solriamfetol are dependent on the position in the treatment pathway."* The committee noted that the Regional Medicines Optimisation Committee (RMOC) published a commissioning statement for sodium oxybate in adult patients with narcolepsy with cataplexy, as highlighted in section 3.2 of the FAD. The committee noted that the RMOC guidance considered sodium oxybate treatment as a third line or later treatment.

	e. As a Society, we therefore respectfully suggest NICE consider using Sodium Oxybate and Pitolisant as comparators in the modelling, rather than Dexamphetamine and Methylphenidate. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** 2) In relation to the use of the Epworth Sleepiness Scale to assess efficacy and cost-effectiveness: a. (3.8) The Epworth Sleepiness Scale (ESS) has not been developed for narcolepsy. It was originally created and validated to assess sleepiness in the context of obstructive sleep apnoea. The minimally clinically important difference (MCID) for the ESS is thought to be more than 2 points (Patel et al, ERJ 2017; Patel et al, Am J Resp Crit Care Med 2018). Although the ESS may have be an easier comparative research tool, it is very difficult to make direct comparisons of "wake promoting" efficacy between the main agents using this scale. b. (3.8) Sleepiness is a multi-dimensional symptom and the ESS does not seem to capture the entire breadth of the problem. As a Society, we suggest that the cost-effectiveness analysis should include other measures of sleepiness, such as objective outcomes (e.g. Multiple Sleep Latency Tests, Maintenance of Wakefulness Test). This could also help with an adjusted cost-effectiveness, as some of the other medications that have been suggested as comparators have been studied for longer periods and may provide further data for these calculations. c. (3.8) ESS and current measures of wakefulness underestimate benefit on quality of life in treatment of wakefulness in narcolepsy - patients report this themselves and experience clinicians say this themselves **Are the recommendations sound and a suitable basis for guidance to the NHS?** Based on our other comments, we respectfully request that the Committee review its guidance as we do not believe the current recommendations are sound, or a suitable basis for guidance to the NHS. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** 3) In relation to equality of access to treatments: a. As a Society, we are concerned this recommendation reinforces the already poor availability of licenced treatment options that have been specifically developed for patients with narcolepsy with and without cataplexy. The current recommendation may potentiate geographic inequality of access to treatments as some centres (as indicated above) have special agreement with CCGs for other licenced narcolepsy treatments.	The committee noted that quality of life changes may not have been captured appropriately due to the use of the ESS and statistical mapping approaches (see FAD section 3.11). Thank you for your comment. At the second committee meeting, the committee considered that, at list price, solriamfetol was unlikely to be cost-effective compared to dexamfetamine or methylphenidate, but did consider solriamfetol to be a cost-effective option after these treatments and modafinil, which would be third line or later (see section 3.15 and 3.16 of the FAD).

	General comments: We are grateful to the Committee for inviting us to comment on this draft guidance. Our comments are as laid out below. 1) In relation to the medications used as comparators in the modelling: a. (3.2) Modafinil may be the first choice of treatment but is typically not potent enough at the maximal dose to treat narcolepsy sufficiently. Additional therapeutic options are therefore required; b. (3.3) While Dexamphetamine and Methylphenidate are used second line, this is not a satisfactory situation. As the committee recognises, there is limited evidence of effectiveness and safety as they are older drugs. They have known serious cardiovascular and psychiatric side effects. Their potential for habituation is also important to consider. They are used by default for symptomatic patients who do not benefit from or cannot tolerate modafinil, because clinicians lack access to other drugs. As a Society, we do not believe this should be considered a satisfactory state of affairs and does not justify using them as the main comparators. c. (3.12) The Committee comments that "the adverse effects of Dexamphetamine and Methylphenidate are thought to have been underestimated". We consider it surprising that in this context, an alternative and licensed, and thus safe, alternative treatment is not recommended. d. (3.2) Sodium Oxybate is not used primarily just for refractory cataplexy. It is effective in, and used for, either sleepiness or cataplexy symptoms that remain debilitating and refractory to first- and second-line medications. In fact, one of the Regional Medicines Optimisation Committees (RMOCs) issued guidance in October 2019 recommending Sodium Oxybate for refractory narcolepsy (https://www.sps.nhs.uk/articles/rmoc-sodium-oxybate-in-adult-patients/). RMOCs are an integral part of NHS England and NHS Improvement. Therefore, Sodium Oxybate should be considered standard of care although the message has been slow to reach all CCGs, possibly due to Covid. The catalyst for this guidance was the approval of funding of sodium oxybate for children with refractory narcolepsy (https://www.england.nhs.uk/publication/clinical-commissioning-policy-sodium-oxybate-for-symptom-control-of-narcolepsy-with-cataplexy-children/). There is more evidence for the effectiveness of Sodium Oxybate in adults and it is a key tool when available. The risk of patients losing access to effective treatment once they reach adulthood was agreed to be unacceptable. As a Society, we believe that the fact that some CCGs have not yet implemented the RMOC guidance should not be used as a reason for adopting the 'deprived' treatment pathway as the basis on which to evaluate Solriamfetol. RMOC guidance for Pitolisant is a work in progress but we suggest NICE also take this into account to future proof the relevance of their recommendations. Sodium Oxybate and Pitolisant are thus already established treatments and in some cases, are first line treatment. In Liverpool, for example, no	

	Individual Funding Request (IFR) is needed as there is an agreement in place with 13 CCGs for their prescription. e. As a Society, we therefore respectfully suggest NICE consider using Sodium Oxybate and Pitolisant as comparators in the modelling, rather than Dexamphetamine and Methylphenidate. 2) In relation to the use of the Epworth Sleepiness Scale to assess efficacy and cost-effectiveness: a. (3.8) The Epworth Sleepiness Scale (ESS) has not been developed for narcolepsy. It was originally created and validated to assess sleepiness in the context of obstructive sleep apnoea. The minimally clinically important difference (MCID) for the ESS is thought to be more than 2 points (Patel et al, ERJ 2017; Patel et al, Am J Resp Crit Care Med 2018). Although the ESS may have be an easier comparative research tool, it is very difficult to make direct comparisons of "wake promoting" efficacy between the main agents using this scale. b. (3.8) Sleepiness is a multi-dimensional symptom and the ESS does not seem to capture the entire breadth of the problem. As a Society, we suggest that the cost-effectiveness analysis should include other measures of sleepiness, such as objective outcomes (e.g. Multiple Sleep Latency Tests, Maintenance of Wakefulness Test). This could also help with an adjusted cost-effectiveness, as some of the other medications that have been suggested as comparators have been studied for longer periods and may provide further data for these calculations. c. (3.8) ESS and current measures of wakefulness underestimate benefit on quality of life in treatment of wakefulness in narcolepsy - patients report this themselves and experience clinicians say this themselves 3) In relation to equality of access to treatments: a. As a Society, we are concerned this recommendation reinforces the already poor availability of licenced treatment options that have been specifically developed for patients with narcolepsy with and without cataplexy. The current recommendation may potentiate geographic inequality of access to treatments as some centres (as indicated above) have special agreement with CCGs for other licenced narcolepsy treatments. In conclusion, we respectfully request that the Committee review its guidance as we do not believe the current recommendations are sound, or a suitable basis for guidance to the NHS. [redacted] For and on behalf of the British Sleep Society	

Comments received from clinical experts and patient experts

No comments received

Comments received from commentators

No comments received

Comments received from members of the public

Nominating organisation	Comment [sic]	Response
Web comment	**Has all of the relevant evidence been taken into account?** Nothing to add **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Dear Sir/Madam , As a clinician who frequently treats patients with narcolepsy, and as a researcher who has captured the relevant clinical practice in one of the biggest sleep centres in our country, I would like to highlight that using stimulant medications with no RCT data, makes me feel unease. That feeling is heightened when medications with sound scientific and research documentation are available but restricted or limited, on the basis of lack of comparison data with the medications that lacks RCT data anyway (methylphenidate/dexamphetamine). As a result sleep clinicians feel trapped in their clinical practice, and patients unfairly treated compared to patients in other countries , who enjoy the availability of these extra treatment options. The treatment of narcolepsy is problematic, hence we should strive to be able to offer all available treatment options to our patients, following proper and agreed clinical decision making. **Are the recommendations sound and a suitable basis for guidance to the NHS?** Please check the answer above **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Nothing to add	Thank you for your comment. The committee considered that the comparisons involving dexamfetamine and methylphenidate were highly uncertain due to the lack of clinical data informing them (see section 3.7 of the FAD). Thank you for your comment. At the second committee meeting, the committee considered that, at list price, solriamfetol was unlikely to be cost-effective compared to dexamfetamine or methylphenidate, but did consider solriamfetol to be a cost-effective option after these treatments and modafinil, which would be third line or later (see section 3.15 and 3.16 of the FAD).

Web comment	General Comments: The document rightly highlights the potentially disabling nature of narcolepsy, a neurological condition that is frequently under-diagnosed and generally affects young populations across the full 24 hour daily period. In section 3.1, the comment "people ... often feel extremely tired" does not capture the situation and I suspect most patients would react adversely to this seemingly trite description. Patients with narcolepsy frequently do not fulfill their potential, partly due to the relative ineffectiveness of currently available drug therapy but also as a result of the patchy nature of neurological sleep services in the UK. In turn, this reflects the relative under-development of sleep medicine as a speciality in the UK compared to the majority of European countries and the USA where treatment protocols have been fully established for some time. It is perhaps surprising that this NICE assessment is the first to fully address any drug treatment in narcolepsy, a neurological condition with an accepted prevalence of around 0.05%. I suspect this reflects the "cinderalla" status of UK sleep medicine. In my view, the unwillingness of the committee to compare solriamfetol with pitolisant and sodium oxybate is inappropriate. To comment that these drugs are not "widely available" is disingenuous as this simply reflects the relative lack of NHS facilities and expertise in managing narcolepsy. Pitolisant has been used in specialist centres fairly routinely for over 3 years and sodium oxybate, widely and rightly recognised as the single most effective drug for narcolepsy, was licenced in 2006 and, again, is widely used whenever commissioning bodies have sanctioned it. It is somewhat ironic that the drug is not formally licenced for use in children yet is easily available to prescribe in this group in contrast to the situation in adults where it is generally deemed not to be cost-effective (as an aside, there are now generic formulations that deserve to be assessed fully in any economic analysis). The data on Pitolisant and especially sodium oxybate are now significant and most authorities in narcolepsy would consider solriamfetol as an alternative to these increasingly established agents. In section 3.6 there is a clear typo - sodium oxybate doses should be in grams, not milligrams. In this section, it is also commented that beneficial effects of sodium oxybate can take 12 weeks to accrue. However, this applies to reduction of cataplexy attacks, not symptoms of excessive sleepiness or severe sleep maintenance insomnia where positive effects are generally immediate. In summary, I can state with confidence that there is a desperate need for better services and treatments for those unfortunate enough to suffer from narcolepsy. I do not think this NICE document captures the current best practice for narcolepsy treatment in the UK. This largely reflects the limited and patchy availability of expertise/experience in narcolepsy management. This gap in service provision should not be used as an excuse to ignore the considerable available data on the newer	Thank you for your comment. The highlighted error in sodium oxybate dosing has now been corrected in the FAD. At the second meeting, the committee were presented with additional information relating to the use of pitolisant and sodium oxybate. Section 3,2 of the FAD states,“*The committee acknowledged that modafinil is the standard first-line treatment and that there is considerable variation in the use and availability of treatments after modafinil. The committee concluded that dexamfetamine and methylphenidate were the established treatments for narcolepsy in NHS practice after modafinil, and that there is variable access to pitolisant and sodium oxybate.”* At the second committee meeting, the committee considered that, at list price, solriamfetol was unlikely to be cost-effective compared to dexamfetamine or methylphenidate, but did consider solriamfetol to be a cost-effective option after these

	treatments in narcolepsy compared to traditional psycho-stimulant therapy that became available before the era of evidence-based medicine and detailed scrutiny.	treatments and modafinil, which would be third line or later (see section 3.15 and 3.16 of the FAD).

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.	None
Name of commentator person completing form:	Dr Patricia Keegan

1. Executive Summary

The Committee concluded in the ACD that "narcolepsy is a debilitating disease that significantly affects many aspects of daily life and that people with narcolepsy would welcome a new treatment option." There are five treatment options used in routine practice in England for managing EDS due to narcolepsy (modafinil, dexamfetamine, methylphenidate, pitolisant, sodium oxybate). Modafinil is widely established as first-line, however following modafinil there is no standard treatment option. A key point of concern for both the Committee and the Company was how to inform a comparison of dexamfetamine and methylphenidate with solriamfetol, given the absence of data for dexamfetamine and methylphenidate. As outlined in the Company submission, neither a systematic literature review nor an extended literature search identified any clinical data for dexamfetamine nor methylphenidate that would allow an indirect treatment comparison with solriamfetol.

Therefore, following receipt of the ACD, the Company had an informal discussion with NICE on 17th March 2021 to better understand the Committee's requests regarding new/additional methylphenidate and dexamfetamine analysis, and the Committee's position that neither pitolisant nor sodium oxybate were standard of care. The informal discussion with NICE led to a decision to re-engage with clinicians to test plausible assumptions and scenarios regarding the efficacy and adverse events associated with dexamfetamine and methylphenidate (see Appendix A for details on this interview programme).

After carrying out this second set of clinician interviews (in addition to prior clinician interviews to support the original submission), the Company had a further informal discussion with NICE on 8th July 2021. During this meeting, the Company explained to NICE that despite further in-depth clinician interviews, there remained an absence of data for dexamfetamine and methylphenidate and that these clinician interviews (consistent with the initial set of interviews) revealed widespread use of pitolisant and sodium oxybate in clinical practice.

The Company has, therefore, maintained a base case comparison of solriamfetol with the two comparators for which there are available clinical data, namely pitolisant and sodium oxybate. However, in response to the Committee's requests, and taking into account the Committee's acknowledgement of the absence of relevant clinical data for these treatments, the Company has also provided an enhanced scenario analysis investigating the cost-effectiveness of methylphenidate and dexamfetamine.

To summarise, following the initial appraisal Committee meeting the company have made some amendments to the original model assumptions and present a revised base case analysis.

- Amendments to the base case analysis:
  - an updated dose split for solriamfetol 75/150 mg to reflect recent sales data
  - use of an updated NHWS mapping algorithm based on a UK value set
  - a Patient Access Scheme (PAS) price for solriamfetol

- In addition, the company presents an enhanced scenario analysis to investigate the cost-effectiveness of methylphenidate and dexamfetamine for managing EDS due to narcolepsy

2. Description of updates to the Company's base case analysis

The original company base case results (reflecting the Company's position at Technical Engagement stage) are shown in Table 1. This analysis was based on a [redacted] dose split for solriamfetol 75/150 mg, the original NHWS algorithm (see Company Submission Form B.3.4.3) and the List price for solriamfetol.

Table 1. Base-case results for solriamfetol combined – sent to NICE at Technical Engagement stage (List price)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,322	13.368	42.445			
Pitolisant	£19,242	13.376	42.445	£10,920	0.008	£1,352,843
Sodium oxybate	£25,860	13.336	42.445	£6,618	-0.040	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

The Company's revised base case analysis reflects:

- updates to the solriamfetol dose split (based on real-world market sales data)
- an updated NHWS algorithm based on a UK value set (1)
- the solriamfetol List price

These changes are summarised in Table 2. Other than these amendments, there were no other changes to the Company's revised base case as compared with the Company base case presented at Technical Engagement stage. A summary of the revised base case assumptions is listed in Table 3.

Table 2. Rationale for updating the assumptions in the Company's model

	Company's original base case assumption	Company's revised base case assumption	Rationale
Dose split for solriamfetol	[redacted] dose split for solriamfetol 75 and 150 mg	[redacted] dose split for solriamfetol 75 and 150 mg	The dose split for the Company model has been updated to reflect new sales data for solriamfetol (described in Section 3.4)
NHWS algorithm	NHWS algorithm for mapping ESS to EQ-5D was based on an EU5 data set	The NHWS algorithm from the base case was updated using a UK value set	Using a UK value set to derive utility values increases the relevance of to the UK population (1)
Cost of solriamfetol	£177.52 per pack of 28 x 75 mg film-coated tablets (i.e. £6.34 per tablet). £248.64 per pack of 28 x 150 mg film-coated tablets (i.e. £8.88 per tablet)	[redacted] per pack of 28 x 75 mg film coated tablets (i.e. [redacted] per tablet).[redacted] per pack of 28 x 150 mg film coated tablets (i.e. [redacted] per tablet).	The price in the revised Company model reflects a commercially confidential PAS price for solriamfetol.

Abbreviations: CE, cost effectiveness; EQ-5D, 5 dimension EuroQoL health survey; ESS, Epworth Sleepiness Scale; EU5, (collectively) France, Germany, Italy, Spain, and the UK; NHWS, National health and wellness survey; PAS, patient access scheme.

Table 3. Summary of model assumptions used in the base case analysis (unchanged from the original base case)

Assumption	Brief justification	Relevant section in CS Form B
Model structure		
Response was defined as a change from baseline ESS of 3 or more	Clinicians advised that they do not generally require patients to achieve a pre-specified absolute change in ESS (2), however the literature supports a reduction of 2–4 points in ESS as being clinically meaningful thus the midpoint of ESS ≥3 points was chosen (3-5).	Table 2 B.3.3.1 B.3.8.4
The absolute change in ESS from baseline varied between the treatments and as such the level of response will vary amongst responders.	Response, defined as a 3-point reduction in ESS from baseline, was simply a criterion for continuation of treatment. The absolute change from baseline was the true measure of treatment efficacy. This is reflective of previous economic evaluations include TA139 (6, 7). The impact of a response of 2 or 4 points was assessed in scenario analyses.	B.3.3.1
This analysis did not consider the impact of EDS on RTAs	Although EDS is associated with an increased risk of RTA, narcolepsy is a 'notifiable' medical condition and patients with uncontrolled EDS must surrender their driving license. As such they would not be considered at risk of being involved in an RTA and consequently RTAs were not considered within the analysis.	B.3.2
This analysis did not consider the impact of CVEs.	Previous economic models associated with EDS considered the impact of CVEs using the Framingham risk equation via changes in systolic BP. These relative changes in systolic BP between treatments were small and there is a lack of conclusive evidence linking the treatment related blood pressure changes to CVEs and consequently are not considered within this analysis.	B.3.2
Clinical inputs		
The model used TONES 2 IPD for those patients who received solriamfetol 150 mg and then applied a relative change in ESS to the change from baseline achieved in the IPD.	This approach implicitly assumed that all patients responded equally, irrespective of baseline severity and this was recognised as a limitation of the approach taken. Although there may be a skew in the way data shifted, no other data was identified that could inform such a shift. A scenario analysis evaluated any potential skew and the impact of this on the cost-effectiveness results.	B.3.3.1
When patients stopped treatment, their ESS returned to baseline levels.	The randomised withdrawal phase of TONES 5 demonstrated that when patients cease treatment, there is a rapid increase in EDS, as measured by ESS, suggesting a return towards baseline. As such, this analysis assumed that patients return to their baseline ESS when they stopped receiving an active treatment.	B.3.3.2

Assumption	Brief justification	Relevant section in CS Form B
Treatment related AEs that did not lead to discontinuation were not associated with any costs or disutilities.	All treatment related AEs, not leading to treatment discontinuation, are transient and generally quick to resolve. As AEs are monitored during routine visits, they were assumed not to be associated with additional HRU costs, and they have not been considered within the analysis.	B.3.3.4
Utility inputs		
The NHWS mapping algorithm is used to estimated utilities in responders and non-responders	The NHWS represents the largest ex-US dataset of narcolepsy and OSA patients allowing for the most robust elicitation of EQ-5D based utility values linked to ESS, the primary measure of efficacy in the analysis **Updated for ACD** to use a UK value set, to generate utility values more reflective of the UK population	B.3.4.5 **and** Table 2 in this document
Medical resource use and cost inputs		
Administration and monitoring costs associated with the pharmacological interventions were excluded from the analysis	All treatments are oral formulation and as all monitoring occurs during regular visits there are no specific monitoring requirements for any of the treatments considered. The analysis assumed that treatment initiation and subsequent assessment at week 8 would be identical for all therapies considered and as such the cost of initiation and assessment of response was excluded from the analysis.	Table 2 B.3.5.2
There were no health state related costs considered within the analysis	This analysis focuses on the treatment of EDS in patients with narcolepsy, and not the underlying narcolepsy itself. Patients are routinely reviewed and monitored by HCPs and based on the KOL Clinical Practice Interviews, the impact of EDS is unlikely to influence the frequency of regular follow-ups. It could be assumed that those patients who do not respond to treatment and continue to experience EDS may require higher healthcare utilisation but there is limited evidence available to quantify this. As a consequence, and for simplicity, this analysis conservatively excludes health state related costs.	B.3.5.2

Abbreviations: ACD, Appraisal Consultation Document; AE, adverse event; BP, blood pressure; CS, Company Submission; CVE, cardiovascular events; EDS, excessive daytime sleepiness; EQ-5D, 5 dimension EuroQol Health Survey; ESS, Epworth sleepiness scale; HCP, healthcare practitioner; HRU, healthcare resource use; IPD, individual patient level data; KOL, key opinion leader; NHWS, National Health and Wellness Survey; OSA, obstructive sleep apnoea; RTA, road traffic accident; TA, technology appraisal; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness; UK, United Kingdom; US, United States.

The results of the revised base case are shown in Table 4. The updated assumptions in the revised model generated reduced incremental cost-effectiveness ratios (ICERs) compared with the original base case (Table 1), and although not presented here, under the same parameters, any analyses originally presented in the Company submission Form B would be expected to generate reduced ICERs.

Table 4. Revised base-case results – solriamfetol doses combined (List price)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	£8,034	14.704	42.445			
Pitolisant	£19,122	14.717	42.445	£11,087	0.013	£886,555
Sodium oxybate	£25,860	14.676	42.445	£6,739	-0.041	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

The Company's revised base case results applying the solriamfetol PAS price are shown in Table 5. As expected, the PAS price reduced the ICERs even further compared with those shown in Table 4. Similarly, although not presented here, applying the same parameters *and* the PAS price, the ICERs for any analyses presented in the Company submission would be expected to be substantially reduced.

Table 5. Revised base-case results – solriamfetol doses combined (PAS price)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Solriamfetol	[redacted]	14.704	42.445			
Pitolisant	£19,122	14.717	42.445	[redacted]	0.013	[redacted]
Sodium oxybate	£25,860	14.676	42.445	[redacted]	-0.041	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

3. Company comments on ACD and additional analyses

Number	Comments
1	For comment on ACD 3.2, 3.3 and 3.9, that dexamfetamine and methylphenidate are the most relevant comparators for solriamfetol, that there are no established treatments after dexamfetamine and methylphenidate and that the treatment pathway is not fully captured in the company's model, see Section 3.1
2	For comment on ACD 3.12, that the company's treatment discontinuation due to adverse events assumptions may not be appropriate for analysis involving dexamfetamine and methylphenidate, see Section 3.2
3	For comment on ACD 3.13, on the conclusion that the costs of healthcare resource use should be appropriately included in the analysis for comparisons against dexamfetamine and methylphenidate, see Section 3.3
4	For comment on ACD 3.11 regarding the uncertainty around the dose split assumptions for solriamfetol in clinical practice, see Section 3.4
5	For comment on ACD 3.10, on the conclusion that mapping from the ESS to the EQ-5D may not adequately capture changes in quality of life, see Section 3.5
6	Comments on other issues are provided in Section 3.6: • On the clinical experts' statement that if someone's condition did not respond to dexamfetamine or methylphenidate, usually they had no further treatment options and had to continue on treatment with those drugs (ACD 3.2) • Solriamfetol will be confined to secondary care prescribing • Additional clinician advice to ensure representative opinions from across England

3.1. Comment 1. On the Committee's conclusions that (ACD 3.2) dexamfetamine and methylphenidate are standard treatments after modafinil and there are no established treatments after this, and (ACD 3.3) the most relevant comparators after first-line modafinil are dexamfetamine and methylphenidate and (ACD 3.9) the treatment pathway after modafinil is not fully captured in the company's model

In ACD 3.2, the Committee acknowledged that there were limited data available for dexamfetamine and methylphenidate but concluded these were the most relevant comparators for solriamfetol. The Committee also removed pitolisant and sodium oxybate as comparators, stating that "treating narcolepsy with pitolisant and sodium oxybate cannot be considered established clinical practice in the NHS in England because it is limited by the need for individual funding requests."

In contrast to the Committee's conclusion, the evidence outlined below strongly indicates that post-modafinil there are four treatments widely used for the management of narcolepsy in the UK.

In order to gain additional clinical expert input (in addition to the clinical expert opinion previously submitted (2, 8)) and further inform this assessment, the company conducted an interview programme comprising a series of in-depth interviews with healthcare professionals in the UK experienced in the management of narcolepsy (9). The methods of the interview programme are described in Appendix A.

3.1.1. Clinicians disagree that methylphenidate and dexamfetamine are the only established treatments for narcolepsy, and instead advise that all four treatments (dexamfetamine, methylphenidate, pitolisant, sodium oxybate) are used post-modafinil in the UK

There are five treatment options used in routine practice in England for managing EDS due to narcolepsy (modafinil, dexamfetamine, methylphenidate, pitolisant, sodium oxybate). Modafinil is widely established as first-line, however following modafinil there is no standard treatment option and treatment choice between the remaining four therapies differs across centres in the UK (Table 6).

Advice from clinician interviews indicates that contrary to the Committee's conclusion, difficulty accessing any of these four treatments is an exception, rather than the rule, and that all four treatments are used routinely in clinical practice for the management of EDS due to narcolepsy. Clinician statements include:

- "I would take issue with the NICE documents I have seen where they talk about pitolisant and sodium oxybate not being in widespread use"
- "I'd say sodium oxybate is an established treatment and for pitolisant, they should have established patients. I accept dexamfetamine is established, but there are far fewer dexamfetamine patients in my clinic than there are sodium oxybate patients"
- "Going forward, I would say that modafinil is first-line and that all other options are second-line"

Clinicians disagree with the Committee conclusion that "dexamfetamine and methylphenidate were the established treatments for narcolepsy in NHS practice after modafinil and that there are no established treatments used after this." Clinicians also disagree with the statement that dexamfetamine and methylphenidate the most appropriate head-to-head comparators for solriamfetol (10). A sample of clinician descriptions of their use of methylphenidate and dexamfetamine are provided below (9):

- "In a world where we have solriamfetol available, I'd look to have solriamfetol second-line rather than using dexamfetamine or methylphenidate second-line. Dexamfetamine and methylphenidate are fraught with a number of difficulties"
- "Dexamfetamine and methylphenidate have more tachyphylaxis than modafinil. Dexamfetamine and methylphenidate have risks of dependence, addiction and rebound and if patients run out of medication, they become profoundly sleepy."
- "Regarding the use of dexamfetamine, I think it's probably a 50:50 split in clinicians in the UK as to whether or not they will prescribe it. Prescription of dexamfetamine is probably more common in older physicians. I think it uncommon that physicians would choose dexamfetamine as second line"
- "I'm surprised to see dexamfetamine as second-line up there with methylphenidate. I can't remember the last time I prescribed dexamfetamine de novo."
- "There are no data for methylphenidate and dexamfetamine. We're constantly being told to prescribe within the license. The fact is that methylphenidate doesn't have a license."
- "There are a lot of patients who don't like dexamfetamine because of the 'wired' feeling it gives them."

These statements indicate that clinicians have reservations about these stimulant treatments, and in some cases may not use them at all in clinical practice.

3.1.2. NHS formulary information and market share sales data demonstrate that all four comparators are widely available in the UK

As described in Section 3.1.1, interviews with clinicians and other relevant healthcare professionals indicated that routine access to pitolisant and sodium oxybate is widespread (9) and their advice contradicts the suggestion in the ACD that the use of these treatments cannot be considered 'routine'. In addition to the clinician interviews, publicly available NHS formulary information reveals widespread availability of all four post-modafinil treatment options (dexamfetamine, methylphenidate, pitolisant, sodium oxybate) across the UK (11-26).

From this publicly available information, 14 of 19 NHS Trusts in England that treat narcolepsy have routine access to pitolisant and/or sodium oxybate for new adult patients with narcolepsy. Of these, 12 centres have direct access to prescribing and 2 further centres have commissioning arrangements to refer to a tertiary centre that can initiate pitolisant and or sodium oxybate for their patients (9, 11). Although five centres gain access to pitolisant and sodium oxybate via Individual Funding Requests (IFRs), sales data demonstrate that these treatments are prescribed across all of the 19 NHS Trusts treating narcolepsy therefore demonstrating that there have been successful IFRs at these Trusts.

Furthermore, the sales data for pitolisant and sodium oxybate, both of which are currently only indicated for the management of narcolepsy (27, 28), demonstrate the extent of their current use and an increasing rate use across the UK (29). Pitolisant sales data from the 12 months covering June 2020 – May 2021 showed that [redacted] packs of pitolisant were sold in England, with a value of [redacted]. This is consistent with widespread prescribing of pitolisant in its sole indication. Sodium oxybate sales for the same period totalled [redacted] units with a value of [redacted].

Note that some of these sales for sodium oxybate will include paediatric and adolescent services, and therefore the sales also include both prescriptions for adult patients and the continuation of prescribing in adult patients (≥19 years) who have transitioned from these services (30, 31). A total of 12 of the 19

NHST Trusts[a] treating narcolepsy have continuation of prescribing of sodium oxybate for adults ≥19 years. Upon this transition to the adult services, commissioning of sodium oxybate moves from the responsibility of NHS England to that of Clinical Commissioning Groups, and Guidance to facilitate decision making by CCGs in whether or not to commission sodium oxybate for patients after their 19th birthday has been published by the Regional Medicines Optimisation Committee (30, 31).

The sales of both pitolisant and sodium oxybate are spread across all seven regions of NHS England and provide strong evidence that these treatments are used in routine clinical practice for the management of narcolepsy. This evidence of access to these two treatments, in addition to the extensive clinician evidence provided over the course of this appraisal, shows that contrary to the Committee's position at ACD, access to these treatments in England is widespread, and is not "limited by the need for individual funding requests." As such, neither sodium oxybate nor pitolisant should be discounted as established clinical practice and can be considered appropriate comparators for solriamfetol.

3.1.3. The Regional Medicines Optimisation Committee considers sodium oxybate and pitolisant to be relevant treatments for narcolepsy

Furthermore, the Regional Medicines Optimisation Committee published a commissioning statement for sodium oxybate in adult patients with narcolepsy with cataplexy in October 2019 (32). The Regional Medicines Optimisation Committee have since specified in their workplan that they will also issue a clinical commissioning framework for use of pitolisant in narcolepsy with or without cataplexy, with an expected date of 31/08/21 (33).

Since the Regional Medicines Optimisation Committee published the commissioning framework for sodium oxybate in adult patients, a number of Area Prescribing Committees (APCs) and other medicines optimisation groups have since reviewed their position and adopted this guidance, allowing access for adult patients to sodium oxybate (34). The meeting minutes of other groups describe their intention to review their commissioning policies for sodium oxybate and pitolisant once both commissioning frameworks have been published by Regional Medicines Optimisation Committee (expected end of August 2021) (35, 36).

A key aim of a Regional Medicines Optimisation Committee commissioning framework is to identify areas where improved consistency in the commissioning of treatments can reduce potential inequity of access across England. The inclusion of a treatment in such a commissioning framework is a strong indication that the treatment is considered established in clinical practice. As such, given that there exists a Regional Medicines Optimisation Committee commissioning framework for sodium oxybate and a framework is in development for pitolisant (expected 31/08/21), the Committee's position that sodium oxybate and pitolisant cannot be considered comparators for solriamfetol in ID1602 may contribute conflicting guidance.

[a] Guys & St Thomas NHS FT, Queen Victoria NHS FT (East Grinsted), East Sussex Health Care NHS FT(Conquest), Papworth NHS FT, United College Hospital London NHS FT, University Hospitals Leicester NHS FT, Liverpool University NHS FT, Manchester University NHS FT, Salford Royal NHS FT, Sheffield Teaching NHS FT, Newcastle NHS FT, South Tees NHS FT

As described in Company submission Form B, the treatment pathway for managing narcolepsy is already highly varied likely due to relatively small patient population, the individual nature of the symptoms and the varying impact of these symptoms patients. As such, for these two wake promoting agents indicated in narcolepsy, the presence of conflicting guidance in the Regional Medicines Optimisation Committee framework versus the solriamfetol NICE guidance may cause confusion in an already varied treatment landscape, and consequently contribute to inequity of access to treatment for adult patients. This is also likely to create additional burden to healthcare professionals in the NHS who are faced with determining the position of each treatment in the pathway, taking into account the potentially conflicting recommendations alongside the highly variable and individual symptoms affecting patients with narcolepsy.

3.1.4. Conclusion

Prior to the availability of products specifically investigated in patients with narcolepsy in randomised controlled trials (sodium oxybate, pitolisant, solriamfetol), methylphenidate and dexamfetamine were typically used second-line to modafinil. However, with the availability of new treatments, clinicians are looking to the clinically-proven therapies (pitolisant, sodium oxybate, solriamfetol) as treatment options for their patients with narcolepsy.

There are no randomised controlled trials that demonstrate the clinical benefit nor safety of methylphenidate and dexamfetamine in treating EDS due to narcolepsy. Methylphenidate is unlicensed in narcolepsy and dexamfetamine achieved its MHRA licence based on expert clinical opinion. Furthermore, dexamfetamine, and methylphenidate are Schedule 2 drugs (37, 38), well-known for their addictive profiles (39), and amphetamines are associated with a rebound effect (increased sleep following increased wake, often referred to as a “crash”) (40, 41).

Clinician interviews in 2020 (for the original submission), and subsequently in 2021 (after the ID1602 Committee meeting) are consistent in their position that modafinil is the established first-line option for narcolepsy but that there is no established second-line treatment option (2, 8, 9). The evidence in Sections 3.1.1 to 3.1.3 above demonstrate that there is widespread access to four therapies in the post-modafinil position, and a summary of the evidence available for each of these four treatments is provided in Table 6.

Table 6. Evidence for four therapies used in routine clinical practice for patients with narcolepsy

Therapy	Efficacy and safety evidence identified in extensive literature searches	NICE appraisal
Methylphenidate	None Not licensed in narcolepsy	None
Dexamfetamine	None	None
Pitolisant	Randomised controlled trial data	Evidence Summary 8 (which lists modafinil, dexamfetamine, methylphenidate and sodium oxybate as medicines used to treat narcolepsy) (42)
Sodium oxybate	Randomised controlled trial data	None

In summary, to reflect the current landscape and taking into account the absence of clinical evidence for methylphenidate and dexamfetamine, the Company revised model compares solriamfetol to pitolisant and sodium oxybate.

However, in response to the Committee's request, the Company conducted a limited and heavily assumption-based scenario analysis to attempt a comparison of solriamfetol with dexamfetamine and methylphenidate (Section 3.3.4). The Company acknowledge that the data supporting this scenario are implicitly weak, however in the absence of published evidence for these treatments, the Company used data from the Medicines and Healthcare products Regulatory Agency (MHRA) Yellow Card scheme's Interactive Drug Analysis Profile in an attempt to generate data to inform the scenario analysis requested by the Committee.

3.2. Comment 2. On the Committee's conclusion that the Company's assumptions about treatment discontinuation due to adverse events may not be appropriate for analysis involving dexamfetamine and methylphenidate (ACD 3.12)

The company acknowledges the challenge in estimating healthcare-resource use due to adverse events associated with methylphenidate and dexamfetamine, particularly in the absence of high-quality placebo-controlled safety data for these medicines. It was not feasible to compare to non-treatment and by association to make a direct comparison with solriamfetol for which placebo-controlled data and 12-month follow-up data are available. Instead, the Company has attempted to generate adverse event data for methylphenidate and dexamfetamine that would allow a comparison with solriamfetol. The Company has collated new data in three forms, in order to make an appropriate and plausible estimate of healthcare resource utilisation for use in a scenario analysis, through conducting:

- A comparison of the Summary of Product Characteristics for methylphenidate, dexamfetamine and solriamfetol (Section 3.2.1)
- A review of pharmacovigilance data for methylphenidate, dexamfetamine and solriamfetol in the form of a report from the Drug Safety Research Unit (Section 3.2.2)
- In-depth clinician interviews with expert prescribers of these medicines (Section 3.2.3)

- In addition, the scenario analysis for methylphenidate and dexamfetamine (Section 3.3.4) includes a contingent resource use for special storage, prescription, dispensing and auditing of Schedule 2 drugs, as per Schedule 2 of The Misuse of Drugs Regulations 2001.

3.2.1. A comparison of the Summary of Product Characteristics for methylphenidate, dexamfetamine and solriamfetol

The Summary of Product Characteristics (SmPC) forms a key part of the marketing authorisation of all medicines and is scrutinised by Regulators to ensure that the information is of high quality (43). The generation of an SmPC is a standardised procedure, associated with a rigorous and independent review of the data. Safety data within the SmPC is tabulated in a common format, often reporting the anticipated frequency of adverse events, thus allowing side-by-side comparison of the frequency rates and types of adverse events occurring for different treatments.

- All of the adverse reactions listed in Section 4.8 "Undesirable effects" of the solriamfetol SmPC were also mentioned in one or both of the equivalent sections of the methylphenidate and

dexamfetamine SmPCs; this indicates that none of the anticipated adverse events are unique to solriamfetol.

- Adverse events distinct and/or common to methylphenidate and dexamfetamine were:
  - For methylphenidate, "arrhythmia" is cited as being common (expected to occur in 1-10% of patients)
  - For dexamfetamine, "cardiomyopathy" is part of the expected adverse events, but not quantified
  - For both methylphenidate and dexamfetamine, "psychosis" is described as an expected adverse event; for methylphenidate psychosis is quantified as being uncommonly expected (expected to occur in 0.1–1% of patients)

- These AEs were also consistent with the screening and monitoring requirements for prescribing listed in the SmPCs:
  - Methylphenidate and dexamfetamine both require pre-treatment evaluation of cardiovascular status and assessment for a family history of sudden cardiac/unexplained death. Subsequent to prescribing psychiatric and cardiovascular status should be *continuously* monitored

3.2.2. Pharmacovigilance data for methylphenidate, dexamfetamine, and solriamfetol

Pharmacovigilance data for methylphenidate, dexamfetamine and solriamfetol are available in the form of a report from the Drug Safety Research Unit. Pharmacovigilance reporting is associated with a minimal information standard, allowing an analysis on what adverse drug reactions occur specifically in real-world setting in the UK.

- The data source used for this analysis was the UK's Medicines and Healthcare products Regulatory Agency (MHRA) Yellow Card scheme's Interactive Drug Analysis Profile with a data lock point of 31 March 2021
- Descriptive statistics were produced for each drug. The raw data are not categorised by indication. Given that prescription of methylphenidate in the narcolepsy indication is not licensed, and dexamfetamine has other indications (attention-deficit hyperactivity disorder), the data are taken as indicative of the types of adverse events that are experienced in general in a real-world setting
- Overall, there were 270 adverse drug reactions from 102 patients for dexamfetamine and 3,947 adverse drug reactions from 1,730 patients for methylphenidate, submitted to the UK's Yellow Card scheme between 1964 and 31 March 2021
- Events were stratified by age, as adult patients are the focus of healthcare resource utilisation in ID1602
- The majority of adverse drug reactions reported to the Yellow Card scheme are consistent with the existing safety knowledge of methylphenidate and dexamfetamine
- The two reported events for solriamfetol were both classified as non-serious. The lower counts are consistent with the more recent authorisation of this medicine
- 9.8% of reports in the Interactive Drug Analysis Profile for dexamfetamine, and 1.6% of those for methylphenidate, described a fatal adverse drug reaction
- For both methylphenidate and dexamfetamine, the top ten adverse drug reactions (as a proportion of total reported events) are presented in Table 7. The adverse drug reactions formatted in **bold** are those described in the respective SmPC.

Table 7. Top ten adverse drug reactions reported in Interactive Drug Analysis Profile (adults only)

Dexamfetamine, n (%)	**Methylphenidate, n (%)**
Anxiety (4, 2.6%)	Anxiety (12, 2.1%)
Drug ineffective (4, 2.6%)	Aggression (11, 1.9%)
Fatigue (4, 2.6%)	Palpitations (10, 1.7%)
Product substitution issue (4, 2.6%)	Overdose (10, 1.7%)
Palpitations (3, 1.9%)	Nausea (7, 1.2%)
Psychotic disorder (3, 1.9%)	Headache (7, 1.2%)
Amnesia (2, 1.3%)	Loss of consciousness (7, 1.2%)
Chest pain (2, 1.3%)	Paranoia (6, 1.0%)
Condition aggravated (2, 1.3%)	**Psychotic disorder (6, 1.0%)**
Congestive cardiomyopathy (2, 1.3%)	Exposure during pregnancy (5, 0.9%)

The adverse drug reactions formatted in **bold** are those described in the respective SmPC.

3.2.3. Additional in-depth clinician interviews with expert prescribers of these medicines

Within the interview programme conducted post-ACD stage, the Company sought additional clinical input to further understand the relative safety and healthcare resource utilisation of methylphenidate and dexamfetamine (based on the clinicians' clinical experience of these treatments), as compared with that of solriamfetol (based on the trial data); the methods of these interviews are described in Appendix A.

- Advisors generally considered that methylphenidate and dexamfetamine would be associated with more healthcare resource use than solriamfetol. This use would not be large compared with the amount of healthcare resource use due to untreated narcolepsy (which was said to be a larger burden on system resource than the resource use as a consequence of treatment).
- On anticipated adverse events: 3 out of 5 advisors described concern about cardiovascular side effects; 2 out of 5 describing a concern about psychiatric side effects for methylphenidate and dexamfetamine.
- Discontinuation rates due to these adverse events were anticipated to be higher for methylphenidate and dexamfetamine (based on clinical experience) than for solriamfetol (based on the available clinical trial data).
- Due to the nature of prescribing dexamfetamine as an adjunctive, or last line therapy:
  - One advisor described that patients "find a way to tolerate it", rather than discontinue
  - Another advisor said that in using dexamfetamine as last line, patients "are so desperate that they grin and bear it" with respect to side effects.
- One advisor described the "cost and hassle factor" of prescribing controlled drugs
- Another said that "people don't want to try dexamfetamine because it's a controlled drug."

3.3. Comment 3. On the Committee's conclusion that the costs of healthcare resource use should be appropriately included in the analysis for comparisons against dexamfetamine and methylphenidate (ACD 3.13)

3.3.1. Estimated healthcare resource use for adverse events associated with methylphenidate and dexamfetamine

Based on the information provided in Section 3.2, the costs of healthcare resource use associated with hospital admission due to adverse events were calculated. This additional healthcare resource use included the anticipated hospital admissions related to arrhythmia, cardiomyopathy, and psychosis for dexamfetamine and methylphenidate, as identified in Section 3.2:

- The frequency of adverse events was based on the midpoint value where available (e.g., a reported frequency of 1–10% used the midpoint of 5%)
- For each of the NHS Reference Costs 2019/20 applied, the lowest bracket for Complication and Comorbidities (CC) score was assumed (44)

Table 8. Healthcare resource use associated with adverse drug reactions to methylphenidate or dexamfetamine and requiring hospital admissions

	Methylphenidate	Dexamfetamine	Reference cost (44)
Arrhythmia	5.0%	0.0%	£600*
Cardiomyopathy	0.0%	0.5%	£824†
Psychosis	0.5%	0.5%	£1208‡

* EB07E Arrhythmia or Conduction Disorders, with CC Score 0-3
† EB14E Other Acquired Cardiac Conditions with CC Score 0-2
‡ WD08Z Mental and Behavioural Disorders Due to Drug or Alcohol Use, treated by a Non-Specialist Mental Health Service Provider

3.3.2. Estimated healthcare resource use associated with the prescription of Schedule 2 drugs including methylphenidate and dexamfetamine

In addition to the estimated costs associated with adverse events, the analysis includes an additional healthcare resource use associated with the burden of prescribing a Schedule 2 medication, calculated to be £1.28 for each prescription (Table 9). Methylphenidate and dexamfetamine are both Schedule 2 drugs (37, 38), therefore the prescribing fee was added to their treatment costs (see Section 3.3.3).

Table 9. Tangible healthcare resource use associated with Schedule 2 drugs

Direct system costs for prescribing Schedule 2 medications	**General requirements for managing Schedule 2 medication resulting in personnel-related resource utilisation (45)** *Not an exhaustive list.*
£1.28 fee per prescription to dispense (paid to Business Services Authority to community pharmacists)	Governance arrangements and accountability
	Policies, processes, and procedures
	Processes and procedures for storage, stock checks and audits
	Processes and procedures for transportation

	Nominated person not involved in handling of controlled drugs to be appointed to oversee the management and governance of activities related to controlled drugs
	Providing information and advice to people taking or carers administering controlled drugs
	Identifying and reporting trends and barriers

3.3.3. Estimated daily cost for each of the four comparator treatments, including the prescribing fee associated with the prescription of Schedule 2 drugs

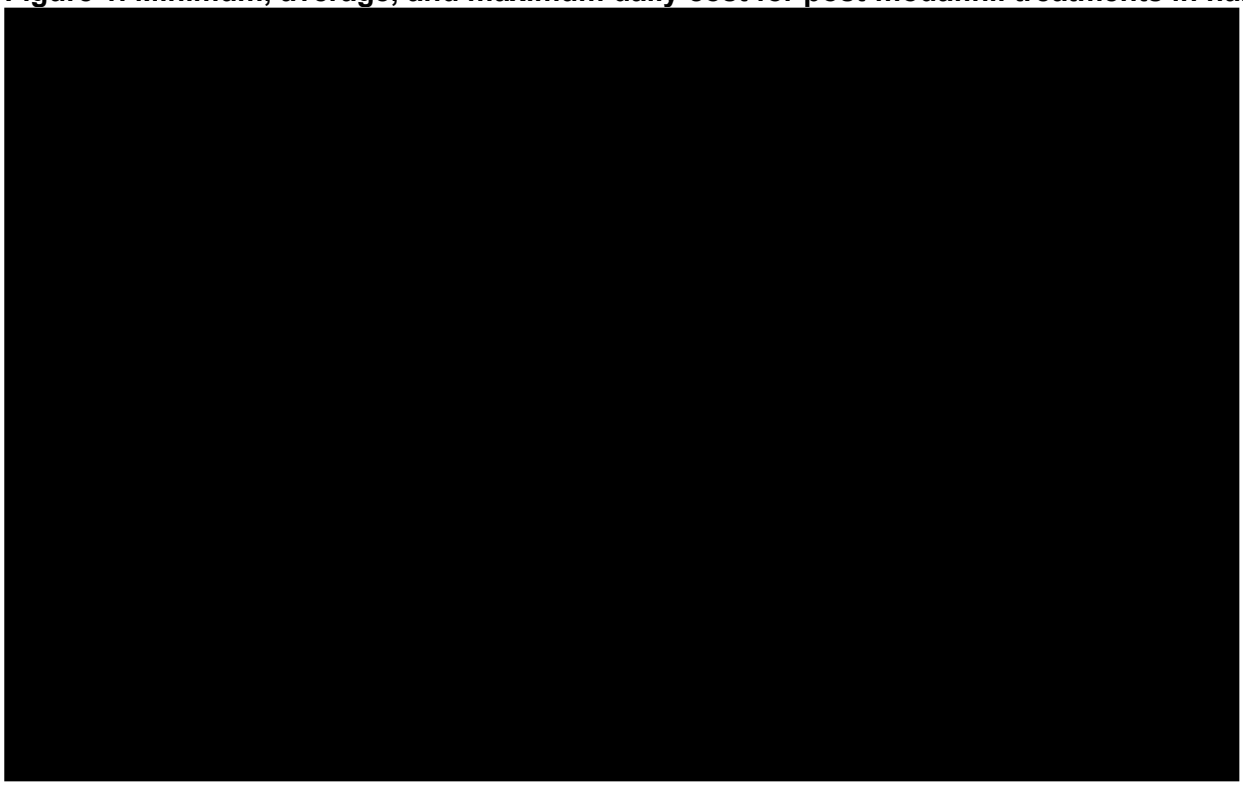
Given the absence of available data to compare solriamfetol with dexamfetamine and methylphenidate from a cost-effectiveness perspective, the Company investigated the maximum and minimum cost of each drug including any prescribing fees (for controlled substances) and made a direct price comparison between all post-modafinil therapies (Figure 1).

Figure 1 depicts the minimum, average and maximum daily cost for each of the post-modafinil treatments. Note that in addition to these costs, there is a prescribing fee per 30 day prescription of £1.28 for Schedule 2 controlled substances:

- Neither solriamfetol nor pitolisant are Schedule 2 drugs
- Methylphenidate **and** dexamfetamine are both Schedule 2 controlled substances, therefore the associated prescribing fee was applied in the costs
- Sodium oxybate is a Schedule 2 drug however as solriamfetol was cost-effective against sodium oxybate in the base case, the prescribing fee has conservatively been excluded from the analysis

The maximum daily cost of [redacted] to prescribe solriamfetol is comparable with the minimum costs to prescribe pitolisant and lower than the minimum daily cost of sodium oxybate. Note that the wide range of potential doses, combined with availability of different formulations for methylphenidate and dexamfetamine result in a substantial range of daily costs. However, clinicians advise that higher doses are associated with AEs, and that to achieve similar efficacy to solriamfetol, these treatments must be titrated to the higher doses. Further, as previously discussed some patients may continue these treatments despite achieving suboptimal efficacy, in the absence of alternative options. As such, it is likely that the daily costs of solriamfetol are favourable against those of dexamfetamine and methylphenidate. It is also important to note that methylphenidate is a Schedule 2 controlled substance that does not have a license in narcolepsy, and that clinicians have concerns about this treatment (Section 3.1.1).

Figure 1. Minimum, average, and maximum daily cost for post-modafinil treatments in narcolepsy



Costs calculated from the range of potential doses and formulations listed on the BNF (37, 38, 46-48).
Note a wide range of doses and variety of formulations are available for methylphenidate and dexamfetamine, resulting in a wide variation in potential daily doses.

Even if assuming the comparators have clinical equivalence with solriamfetol, solriamfetol is a cost-saving choice for the majority of patient prescriptions. Although this would not be the case for methylphenidate, methylphenidate is unlicensed for use in narcolepsy and as outlined in Section 3.1.1, clinicians have concerns about the use of both methylphenidate and dexamfetamine (9).

3.3.4. Scenario analysis comparing methylphenidate and dexamfetamine with solriamfetol

The data generated through the steps taken in Section 3.2 and 3.3 allowed the Company to conduct a scenario analysis, comparing solriamfetol with all four post-modafinil treatments. The Company acknowledge that the adverse event data underlying this analysis are implicitly weak, however as described previously, there is an absence of clinical data for methylphenidate and dexamfetamine thus the options to conduct such an analysis were limited.

As such, the data supporting this analysis must be considered a crude analysis and the results interpreted as such. Due to the nature of this data, it cannot be considered a replacement for randomised controlled trial data nor a comprehensive description of the safety profile of methylphenidate and dexamfetamine.

The healthcare resource use costs for methylphenidate and dexamfetamine, as estimated in Section 3.3.1 and 3.3.2, may be considered conservative. Given that the costs calculated (i) include only some of the potential adverse events (as identified in Section 3.2), (ii) applied an assumed frequency using a midpoint of reported adverse event rates, (iii) applied the reference cost associated with the lowest CC

score bracket, and (iv) assumed the occurrence of only a single episode of each adverse event, the costs presented likely substantially underestimate the total increase in healthcare resource use that would be associated with methylphenidate and dexamfetamine. The scenario analysis assumes:

- The cost of adverse events (calculated as *cost per adverse event x frequency rate*; Table 8) was:
  - £36.04 per year per patient for methylphenidate (£30.00 for arrhythmia; £6.04 for psychosis)
  - £10.16 per year per patient for dexamfetamine (£4.12 for cardiomyopathy; £6.04 for psychosis)
- The cost associated with prescribing a Schedule 2 drug is:
  - £1.28 per 30 day prescription applied to methylphenidate, dexamfetamine and sodium oxybate
- The efficacy of methylphenidate and dexamfetamine was assumed to be equivalent to that of sodium oxybate 4.5 g as calculated in the indirect treatment comparison (i.e., an efficacy of -2.985 ESS points relative to solriamfetol 150 mg; this was based on the updated indirect treatment comparison used in the Company response to Technical Engagement)

Other than the assumptions outlined above, the scenario analysis makes no changes to the revised base case assumptions outlined in Table 3.

Table 10. Results of a scenario analysis comparing solriamfetol with the four post-modafinil treatments (PAS PRICE)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER vs. methylphenidate	ICER vs. soliramfetol
Methylphenidate	£1,268	14.601	42.445					[redacted]
Dexamfetamine	£3,470	14.601	42.445	[redacted]	0.000	Dominated	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	42.445	[redacted]	0.103	[redacted]	[redacted]	[redacted]
Pitolisant	£19,122	14.717	42.445	[redacted]	0.013	[redacted]	[redacted]	[redacted]
Sodium oxybate	£25,860	14.676	42.445	[redacted]	-0.041	Dominated	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 10A. Results of a scenario analysis comparing solriamfetol with the four post-modafinil treatments (LIST PRICE)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER vs. solriamfetol
Methylphenidate	£1,268	14.601	42.445				£65,648
Dexamfetamine	£3,470	14.601	42.445	£2,202	0.000	Dominated	£44,284
Solriamfetol	£8,034	14.704	42.445	£4,564	0.103	£44,284	NA
Pitolisant	£19,122	14.717	42.445	£11,087	0.013	£886,555	£886,555
Sodium oxybate	£25,860	14.676	42.445	£6,739	-0.041	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

The results of the analysis are unchanged from the base case analysis, in that solriamfetol is a cost-effective treatment compared with pitolisant and sodium oxybate. In the current scenario analysis, with PAS pricing, solriamfetol would be considered cost-effective compared to dexamfetamine with an ICER of £[redacted] per QALY and is just above the £30,000 per QALY threshold when compared to methylphenidate with an ICER of £[redacted].

The initial scenario analysis assumed that the efficacy of dexamfetamine and methylphenidate was equivalent to that of sodium oxybate 4.5 g. As previously noted, there is no published data available to estimate the efficacy of dexamfetamine or methylphenidate, and the clinician interviews were unable to provide any appropriate estimates of their efficacy. Therefore, a sensitivity analysis was conducted to assess the impact of changing the relative difference in ESS compared with solriamfetol 150 mg (excluding costs of treatment in discontinuers) on the ICERs. The results are shown in Table 11. In the base case analysis, solriamfetol 150 mg has an average reduction in ESS of 5 points (based on the TONES 2 individual patient level data) from baseline thus the analysis was limited to this range.

Table 11. Sensitivity analysis to assess the impact of the relative difference in ESS compared with solriamfetol 150 mg on the ICERs (PAS PRICE)

ΔESS relative to solriamfetol 150 mg	ICER vs. methylphenidate	ICER vs. dexamfetamine
-1.00	[redacted]	[redacted]
-2.00	[redacted]	[redacted]
-3.00	[redacted]	[redacted]
-4.00	[redacted]	[redacted]
-5.00	[redacted]	[redacted]

Abbreviations: ΔESS, Difference in ESS; ICER, incremental cost effectiveness ratio; SW, southwest quadrant.

Table 11A. Sensitivity analysis to assess the impact of the relative difference in ESS compared with solriamfetol 150 mg on the ICERs (LIST PRICE)

ΔESS relative to solriamfetol 150 mg	ICER vs. methylphenidate	ICER vs. dexamfetamine
-1.00	Methylphenidate dominates	Dexamfetamine dominates
-2.00	£183,216	£86,406
-3.00	£66,575	£44,234
-4.00	£48,806	£37,694
-5.00	£42,618	£35,230

Abbreviations: ΔESS, Difference in ESS; ICER, incremental cost effectiveness ratio; SW, southwest quadrant.

Note that these results must be interpreted with caution. Solriamfetol 75 mg was less effective than solriamfetol 150 mg in the ITC therefore when methylphenidate or dexamfetamine are considered to be less effective than solriamfetol 150 mg by ≥1 ESS point, the comparison against solriamfetol combined results in counterintuitive ICERs. As such, on average the comparators appear more effective than solriamfetol combined but are not necessarily so against solriamfetol 150 mg.

As the relative efficacy of the comparators versus solriamfetol increase (i.e. the comparators become less effective compared to solriamfetol 150 mg), the utility gain for solriamfetol increases but so does relative cost. Compared with dexamfetamine, solriamfetol is cost-effective at all levels of assumed efficacy; this is due to the small difference in costs between the two products. When compared to methylphenidate the ICER drops below £30,000 per QALY when methylphenidate efficacy is ≥4 lower than that of solriamfetol 150 mg.

Due to the lack of treatment options available and the limitations associated with methylphenidate and dexamfetamine (Section 3.1.1), clinicians suggested that many patients will continue to receive stimulant treatment even when the patient does not perceive a clinical benefit. A threshold analysis was performed to assess the impact of continuing methylphenidate or dexamfetamine treatment in a proportion of non-responding patients. The analysis assumes there are no costs for patients who discontinue solriamfetol, as in contrast to dexamfetamine/methylphenidate, patients are assumed to discontinue solriamfetol if they do not respond to treatment.

AT PAS PRICE:

- For solriamfetol to be cost neutral against methylphenidate, 24.6% of patients need to continue their methylphenidate treatment despite a suboptimal clinical response
- For solriamfetol to be cost-effective at £20,000 per QALY, 10% of patients need to continue their methylphenidate treatment despite a suboptimal clinical response
- For solriamfetol to be cost-neutral against dexamfetamine, 11.4% of patients need to continue their dexamfetamine treatment despite a suboptimal clinical response

AT LIST PRICE:

- For solriamfetol to be cost neutral against methylphenidate, 48.0% of patients need to continue their methylphenidate treatment despite a suboptimal clinical response
- For solriamfetol to be cost-effective at £20,000 per QALY, 31.1% of patients need to continue their methylphenidate treatment despite a suboptimal clinical response
- For solriamfetol to be cost-neutral against dexamfetamine, 11.8% of patients need to continue their dexamfetamine treatment despite a suboptimal clinical response
-

3.3.5. Scenario analysis for an excess mortality associated with use of methylphenidate and dexamfetamine

There is evidence that the use of stimulants is associated with excess mortality (49, 50), thus an analysis investigating the effect of excess mortality on the ICERs was conducted. The analysis assumed a standardised mortality rate of 1.01 applied to dexamfetamine and methylphenidate. As expected, this excess mortality impacted the total QALYs for the stimulant treatments and reduced the ICERs for all treatments vs methylphenidate (Table 12). Note that in order to generate an ICER of £20,000 per QALY for solriamfetol versus methylphenidate, i.e. for solriamfetol to become cost-effective, the excess mortality due to methylphenidate treatment would only need to increase very slightly to 1.04, however, this scenario has the same challenges as all dexamfetamine and methylphenidate scenarios due to a lack of evidence.

Table 12. Scenario analysis outlining the impact of excess mortality associated wtih stimulants on the ICERs (PAS PRICE)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER vs. solriamfetol
Methylphenidate	£1,268	14.585	42.352				[redacted]
Dexamfetamine	£3,470	14.585	42.352	[redacted]	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	42.445	[redacted]	0.120	[redacted]	NA
Pitolisant	£19,122	14.717	42.445	[redacted]	0.013	[redacted]	[redacted]
Sodium oxybate	£25,860	14.676	42.445	[redacted]	-0.041	Dominated	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 13. Scenario analysis outlining the impact of excess mortality associated wtih stimulants on the ICERs (LIST PRICE)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER	ICER vs. solriamfetol
Methylphenidate	£1,268	14.585	42.352				£56,601
Dexamfetamine	£3,470	14.585	42.352	£2,202	0.000	Dominated	£38,183
Solriamfetol	£8,034	14.704	42.445	£4,565	0.120	£38,183	NA
Pitolisant	£19,122	14.717	42.445	£11,087	0.013	£886,555	£886,555
Sodium oxybate	£25,860	14.676	42.445	£6,739	-0.041	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

3.4. Comment 4. On the Committee's consideration that most appropriate dose splits were uncertain (ACD 3.11)

Since the time of response to Technical Engagement (January 2021), the Company have collected further sales data from the French and German markets.

Solriamfetol has been prescribed in France since April 2020 (in the narcolepsy indication only from April 2020 to February 2021, and in both the narcolepsy and OSA indications from February 2021) and in

Germany since May 2020 (in the narcolepsy indication only from May 2020 to July 2021, the OSA indication was approved in July 2021). After the point of initiation of prescribing to patients with OSA in France (February 2021), it is not possible to stratify the sales data by indication and determine whether a sale reflects a prescription for the narcolepsy or OSA indication. As such, the German data (reflecting sales in the narcolepsy indication only) have been used to inform a new dose split for the Company's revised base case.

The Company's original base case analysis (Form B, November 2020) assumed a 50:50 dosing split between 75 mg and 150 mg doses of solriamfetol. At the time of the response to Technical Engagement, the dosing split based on German sales data was calculated as [redacted] for the 75 mg and 150 mg doses, respectively. With the addition of a further 6 months of data, this dosing split has changed slightly to a dose split of [redacted] for the 75 mg to 150 mg doses, respectively.

However, as solriamfetol is a new treatment option, the data are weighted towards the lower dose, new patients are anticipated to start on the 75 mg dosage and depending upon their clinical response, may subsequently titrate up to the higher 150 mg dosage; this is consistent with the solriamfetol SmPC (51). In order to reduce the impact of the initial weighting towards lower doses, the Company has specifically assessed the dosing split for prescriptions made between January 2021 and June 2021. This data cut reflects prescriptions made after 8 months of solriamfetol availability in the narcolepsy indication in Germany, and therefore are assumed to be more representative of a steady state of prescribing in clinicians with first-hand experience with solriamfetol. Based on this representative data cut, the real-world dosing split for solriamfetol was [redacted] for the 75 mg and 150 mg doses, respectively. This dosing split has been applied in the Company's revised base case analysis.

3.5. Comment 5. On the Committee's conclusion that mapping from the ESS to the EQ-5D may not adequately capture changes in quality of life (ACD 3.10)

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 (52). In addition, a recent systematic review and meta-analysis highlights this, and confirms the lack of an appropriate, validated method to capture health-related quality of life in people with narcolepsy (53). 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 narcolepsy.

Neither the EQ-5D nor the SF-36 data collected in the TONES trials reflected the substantial burden of EDS in narcolepsy on quality of life. Despite the high burden of illness in patients with such a disabling symptom (see Company submission, Form B.1.3), baseline utility scores collected in the trials were inconsistent with the widely accepted negative impact of EDS and narcolepsy. The reasons why these health questionnaires were incapable of capturing changes in quality of life in the trials are discussed at length in the Company submission Form B and Technical Engagement response (e.g., a lack of a sleep domain, inability to capture impact on relationships, high baseline utility scores, patient adaptation to sleepiness over time). Furthermore, the 12-week trial duration was likely insufficient to capture the effect of solriamfetol on quality of life.

Therefore, in the absence of appropriate health-related quality of life trial data, the Company maintain that the best method for describing the quality of life improvement for patients with narcolepsy is the use

of the EQ-5D from the NHWS mapping formula in the base case, with an analysis using the McDaid algorithm provided in a scenario.

The Committee commented that changes in quality of life may not be adequately captured by mapping the Epworth Sleepiness Scale to the EQ-5D. The Committee also commented that the results from the mapping algorithm estimated a high valuation of quality of life even at extremely high ESS scores (higher ESS scores equal higher levels of excessive daytime sleepiness), which did not appear to be valid. The Committee concluded that mapping from the ESS to the EQ-5D may not adequately capture changes in quality of life. The Company agrees that the improvement in quality of life is likely to be an underestimate, and it is likely that the analyses underestimate the cost-effectiveness of solriamfetol.

Following the ACD, the Company discussed with clinicians the topic of using generic health questionnaires to measure changes in quality of life associated with changes in EDS (9). Please see the Discussion Guide (provided in the reference pack) for details. Based on these discussions, the Company's resolve to the use of the mapping approach was strengthened. Clinicians described a very substantial burden on quality of life for patients with EDS. Statements from the clinicians include:

- "If you're not dealing with these patients day to day you don't understand the severity and impact on life. The patient could get an A grade in the morning and an E grade in the afternoon, due to their narcolepsy."
- "Even at their very best, [patients with narcolepsy] perform as someone who hasn't slept for 22 hours, but they think they're doing OK. The tools are so crude for measuring this – how do you measure that a patient doesn't fall asleep at the cinema?"

The Company discussed the mapping with clinicians (see the interview 'Pre Read' in the reference pack for details). Clinicians confirmed they expected to see a correlating decrease in quality of life as a patient's sleepiness increased. In general, clinicians agreed that the shape of the NHWS and McDaid graphs were an appropriate reflection of the impact of EDS on quality of life but believed the graphs to underestimate the detrimental impact of EDS on the patient. For example:

- "Quality of life increases as ESS decreases. I'm surprised it's not more steep. The trend is correct, but it should be more steep"
- "The inflection point looks at the right place, but it doesn't sit right in that the QoL is as high as it is when they patients are so sleepy – these QoL scores are high for such sleepy patients"

Clinicians highlighted that these (EQ-5D, SF-36) are generic scales and not tailored for EDS, and the clinicians felt that these generic scales underestimate the true burden of EDS on quality of life, thus the QALY gain with solriamfetol is likely an underestimate of the true cost-effectiveness of solriamfetol, as supported by the scenario using the time trade off study utility values.

3.6. Comment 6. Other issues

3.6.1. On the clinical experts' statement that if someone's condition did not respond to dexamfetamine or methylphenidate, usually they had no further treatment options and had to continue on treatment with those drugs (ACD 3.2)

The company acknowledges the limitation arising from the lack of head-to-head comparisons between solriamfetol and other medications used in the treatment of narcolepsy. This limitation is particularly acute for dexamfetamine and methylphenidate, for which two systematic literature reviews failed to identify any studies reporting methods and sufficient quality data to include in an indirect treatment comparison (see Company submission, Form B.2.9.1).

This absence of data for methylphenidate and dexamfetamine is acknowledged in the evidence-based recommendations of the recent European guideline and expert statements on the management of narcolepsy in adults and children (a joint guideline from the European Academy of Neurology, European Sleep Research Society, and European Narcolepsy Network (54)). In this comprehensive expert statement, the quality of data for both methylphenidate and amphetamine derivatives (which encompasses dexamfetamine) are deemed "weak."

The Company acknowledge the limitations associated with drawing conclusions about the relative clinical effectiveness of the treatment options given the absence of relevant and valid data. Consistent with NICE guidance, the Company has not presented a naïve analysis and has instead restricted to a narrative overview (55).

As such, in order to contribute further clinical expert input to understand relative efficacy of solriamfetol compared with methylphenidate and dexamfetamine, the company conducted a series of in-depth interviews (9), the methods of which are described in Appendix A. This is in addition to clinical expert opinion previously submitted (2, 8).

In this interview programme, Clinicians consistently described the practice of titrating both methylphenidate and dexamfetamine not just to clinical effect, as measured by ESS, but also to the emergence of adverse events. The dose-response relationship was described as "not a linear relationship" and "[not] predictable at all." In addition, the patient experience was described as "incredibly variable."

Where possible, clinicians gave an estimate of the treatment effect for each of methylphenidate and dexamfetamine with respect to ESS. A reduction in ESS in the range of 3-5 points was reported for methylphenidate and 3-6 points was reported for dexamfetamine. In one of these interviews, a clinician who is a current prescriber of solriamfetol estimated the reduction of ESS to be 5–6 points and when describing the relative effect of solriamfetol stated:

- "I don't think it's inferior to dexamfetamine or methylphenidate"

Clinical expert opinion was that an adequate therapeutic response to methylphenidate and dexamfetamine occurs in only 50-60% of patients at the maximum tolerated dose. A direct quote from this set of expert interviews was:

- "Solriamfetol is likely to be better tolerated… than dexamfetamine or methylphenidate"

This clinician input supports the assumption in the Company's revised model that methylphenidate and dexamfetamine may achieve similar efficacy as solriamfetol, with the added context that in order to achieve this level of efficacy, patients may experience adverse events due to titrating to a sufficiently high dose to achieve therapeutic response.

3.6.2. Solriamfetol will be confined to secondary care prescribing

Solriamfetol prescribing will be limited to secondary care. The summary of product characteristics for solriamfetol states that treatment with solriamfetol requires specialist initiation (51). Further, it is common for patients with narcolepsy to remain within secondary and sometimes tertiary care, given the nature of the disease.

In addition, as a newly licensed medication, solriamfetol carries a black triangle, severely limiting (in many cases precluding) its use in primary care at this time.

The restriction of solriamfetol to secondary care is also consistent with the anticipated prescribing of pitolisant hydrochloride in secondary care per the ACD for NICE ID1065 (56). Discussions with NHS stakeholders (clinicians and pharmacists) revealed the preferred route for continuation of prescribing of solriamfetol is outsourced outpatient pharmacy from secondary care; however, some areas will prefer to adopt NHS contracted homecare medicines services.

The NHS England Specialist Pharmacy Service has published clear principles on routes of supply for medicines to outpatients, ratified by the Regional Medicines Optimisation Committee (57). The document uses sodium oxybate as an example of a drug that is suitable for Outsourced Outpatient Dispensing or Homecare Delivery for continuation of prescribing to outpatients. During the COVID-19 pandemic, many Outsourced Outpatient Dispensing services have been couriering drugs to patients. In discussions with NHS customers, these routes have been validated as well-suited for solriamfetol. In addition, in areas where early access has been approved, solriamfetol is listed as a restricted 'Red' drug in formularies, meaning its prescription is limited to hospital only (14, 15, 17, 19-21, 23-26).

Clinical expert statements further support the expectation that ongoing prescribing will remain with sleep physicians.

- Dr Martin Allen's clinical expert statement in the Committee meeting stated that "Patients should be under the regular review of a specialist sleep centre where the treatment can be both initiated, observed for effect and then stopped if necessary" (58).
- Dr Sonya Craig's clinical expert statement, representing the British Thoracic Society, for NIC TA ID1499 (Solriamfetol for treating excessive daytime sleepiness caused by OSA) stated "It is very unlikely that primary care would be willing to take on prescribing of this drug"(59).

There are 14 NHS Hospital Trusts with commissioning agreements for access to pitolisant, and 11 of these have classified pitolisant as a "Red" drug, meaning that it is considered to be a specialist medicine with prescribing responsibility remaining with the consultant or specialist clinician (11-26).

In alignment with its secondary care prescribing, Jazz has listed solriamfetol as 'hospital only' in the British National Formulary (48).

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Appendix A. Additional clinician advice to ensure representative opinions from across England

Appendix A.1 Description of the clinician interview methodology

The Company acknowledge the need for additional clinician expert opinion on the narcolepsy (NHS) treatment pathway, the relative efficacy of solriamfetol compared with methylphenidate or dexamfetamine, the increased healthcare resource use associated with adverse events from treatment with dexamfetamine and methylphenidate, and the applicability of generic health-related quality of life measures to assessing the impact of EDS due to narcolepsy.

The Company therefore presented a new analysis (Section 3.2) using data on the above topics collected through a series of in-depth interviews from UK clinical experts. For clarity, the below section describes the process undertaken to conduct these interviews and collect the relevant information.

- Experts were selected based on the criteria of:
  - >5 years as a consultant physician practising in sleep medicine in the NHS
  - Regular and current management of adult patients with narcolepsy
  - Experience in the prescribing of the full range of medications for narcolepsy and considered by ID1602 (modafinil, methylphenidate, dexamfetamine, sodium oxybate and pitolisant) (10, 58),
    - ◊ And where possible experience of prescribing solriamfetol, and where not possible, familiarity with the data associated with solriamfetol
  - Experts were not from the same clinic, or region as each other
  - Representation from a range of service sizes
  - Representation from the common base specialties for Sleep Medicine (Respiratory Physician, Neurologist, and Anaesthetist)
  - Consent to participate in a paid consultation

- A total of 6 experts were approached and 5 consented to participate
- A pre-read was prepared (provided in the reference pack) and time was allocated for preparation for the interview, including time to read the Appraisal Consultation Document
- Structured, in-depth interviews across four domains were conducted using a video-conferencing platform.
- The interviewing team was consistent across all interviews.
- Verbatim capture of the comments occurred contemporaneously, and were subsequently collated in a spreadsheet to structure comments
- No iteration was used to collate opinions
- Consent to disclose verbatim comments and identify the respondent occurred in 4 out of 5 interviewees. The fifth interviewee consented to disclosure of opinions and requested to remain anonymous.

There was general consistency between this set of interviews, and the initial interviews conducted in 2020 to support the original submission and referenced in the original company submission.

Appendix A.2 Key observations from the post-ACD interview programme

- Modafinil as established first-line therapy was the basis for discussion and was not challenged ("Modafinil is still first line," "modafinil is undoubtedly first line" were typical comments)
- There is variability in subsequent therapy, with no established second-line therapy, and use of all other medicines described by at least one advisor in this position
  - One expert described "I would say that modafinil is first-line and that all other options are second line"
  - Another described "I would position methylphenidate, pitolisant and solriamfetol as second-line."
  - For one advisor, sodium oxybate was described as a "third line option."
  - A Scottish advisor, with experience in prescribing solriamfetol, said "we use solriamfetol second-line after modafinil"
  - Clinician comments on dexamfetamine illustrate the variation in prescribing and episodic rather than regular second-line prescribing:
    - One expert said "I don't use dexamfetamine"
    - Another expert said "I can't remember the last time I prescribed dexamfetamine de novo"
    - In contrast to another, who said "I like the flexibility of dexamfetamine, to be able to take just a little bit before an important activity"

- Access to pitolisant and sodium oxybate was described as through local commissioning arrangements, and being available on formulary by some
  - One expert said "I would take issue with the NICE documents I have seen where they talk about pitolisant and sodium oxybate not being in widespread use"
  - All advisors described the use of pitolisant and sodium oxybate for narcolepsy
  - An advisor said "pitolisant is on our formulary second-line after modafinil. We positioned pitolisant based on evidence."

Adverse event rates were generally described as being higher for methylphenidate and dexamfetamine [than with the other treatments] and associated with higher healthcare resource utilisation.

NICE National Institute for Health and Care Excellence

Solriamfetol for treating excessive daytime sleepiness caused by narcolepsy [ID1602]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 26 March 2021 **email:** 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):	[**Narcolepsy UK**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**No disclosures apply**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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NICE National Institute for Health and Care Excellence

Solriamfetol for treating excessive daytime sleepiness caused by narcolepsy [ID1602]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 26 March 2021 **email:** NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that this recommendation may discriminate against people with narcolepsy compared to people with more common, better researched conditions. Narcolepsy is a disability and people with narcolepsy are protected from discrimination as a result of their condition by legislation enshrined within the Equality Act 2010. This is recognised in the appraisal consultation document, and in Narcolepsy UK's Charter*, both of which describe the chronically debilitating impact of narcolepsy on every aspect of our lives including education, employment, family and social lives. As people with narcolepsy, we suffer disadvantages related to the lack of recognition of our condition, lack of healthcare services and lack of scientific research. This, together with the relative rarity of narcolepsy limits the development of, and access to, new health technologies. These disadvantages are demonstrated in this appraisal consultation document through a recognition of the absence of evidence that would normally be available to NICE to assess the cost effectiveness of new treatments. This includes evidence that could be costly and time consuming to produce such as the development of a method to appropriately capture quality of life changes in this population, other sources of evidence for the efficacy of the comparator drugs (dexamfetamine and methylphenidate), and appropriate estimates of healthcare resource use for treatment with these comparators compared with solriamfetol. Whilst dexamfetamine and methylphenidate have never been subject to a NICE Technical Appraisal and, to our knowledge, have never been trialled in people with narcolepsy, they have been deemed second line by NICE as they represent cheaper alternatives to drugs specifically developed for our condition. In reviewing their decision, the committee should ask themselves what level of evidence would be needed to recommend a new narcolepsy drug, whether it would be possible for a pharmaceutical company to produce this evidence, and whether the company would make sufficient returns to justify generating this evidence. If not, the reports recommendation will have a negative impact on people with narcolepsy compared to people with other more common and well recognised conditions. This will leave us to be treated with high doses of drugs that may well be harmful when taken with the frequency and longitude necessary for our condition, having more side-effects than solriamtetol, including adverse cardiovascular events. *We submitted Narcolepsy UK's Charter as evidence in the consultation. The Charter is a written statement of the rights of people with narcolepsy and their families and friends to have a full and rounded life without having to fight to make this happen. It is based on responses to an externally created, validated online survey of 302 people with narcolepsy and 149 supporters. The Charter and supporting documentation are available here: https://www.narcolepsy.org.uk/resources/narcolepsy-charter
2	We believe that the response provided substantiates the view that a higher % of rare disease patient groups fail to have medicines approved by the standard NICE Technology Appraisal and that there is a pressing need for rare disease treatments to be subject to a specialised appraisal. Failure to do this results in a Catch-22 situation where rare disease patients are unable to access medicines for treatment unless there is evidence to support cost effectiveness. This evidence proving virtually impossible to collect due to the inability to access medicines. We believe this to be discriminatory, based purely on the nature of our

Solriamfetol for treating excessive daytime sleepiness caused by narcolepsy [ID1602]

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	disability.
3	Solriamfetol was granted Orphan Drug Status by the FDA but we understand that this was not sought by Jazz as they are also seeking an appraisal for sleep apnoea by NICE. This has the effect of making the drug available sooner & cheaper than might otherwise occur yet this recognition of potential earlier than normal patient access for a novel medicine has been overlooked. In fact, we believe that this standard method of appraisal does not suit a condition where treatments are both novel & re-purposed & often mixed.
4	NHS England costs are not accurately reflected in the cost models as whilst there is some reference to the legally dubious process of Individual Funding Requests, no account has been taken of their cost per CCG if clinicians and patient groups choose to request treatment. These costs are inevitable if this is the only route open to patients who would benefit from solriamfetol.
5	Various comparisons were made to sodium oxybate & its general lack of availability but this has not been subject to analysis or scrutiny by NICE and neither of the clinicians present at the appraisal committee were representative of an area where sodium oxybate is routinely commissioned and so a more pessimistic view of the availability of treatment was offered The fact that post pubertal children who are refractory to older narcolepsy treatments are now routinely commissioned sodium oxybate is predicated on (as set out in the NHS England commissioning policy 2016) the effectiveness of sodium oxybate as a narcolepsy treatment for adults. It is perverse to have such a treatment for children and apply a different view for adults. You may wish to consider the judgment of Collins J in R (on the application of S (a child) v NHS England [2016] EWHC 1395 (Admin) on the meaning of "exceptional", as it also applied to a refusal of funding of sodium oxybate for narcolepsy with cataplexy within the IFR procedure. An appeal against that decision was refused by the Court of Appeal on 2nd March 2017. We would estimate the total costs associated with this judgement to be c. 20 times the annual cost of treatment of £13,000 per annum.
6	The MHRA has recently issued a warning that modafinil, the first line drug to treat excessive daytime sleepiness in people with narcolepsy, has been linked to increased risk of birth defects and also to reduced effectiveness of oral contraception. Doctors are reluctant to prescribe modafinil to women who are not using alternative methods of birth control. Women who do not want to use alternatives to oral contraception, or do not want or need to use any form of contraception, need access to alternative, safe, treatments for narcolepsy.
7	We would like NICE to consider in what circumstances the following scheme was acceptable in the context of all that has been put forward as part of this appraisal as we believe it shows that patients with narcolepsy are subject to conflicting treatment options by the Department of Health & Social Security. **https://www.narcolepsy.org.uk/resources/sodium-oxybate-xyrem—-ex-gratia-provision-victims-pandemrix** **Ex gratia provision of Xyrem**

NICE National Institute for Health and Care Excellence

Solriamfetol for treating excessive daytime sleepiness caused by narcolepsy [ID1602]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 26 March 2021 **email:** NICE DOCS

	The Government operates a scheme under which the Department of Health will fund, on an ex gratia and time-limited basis, provision of Xyrem to personal injury claimants suffering from narcolepsy with cataplexy, who have made claims against GSK that they developed the condition after immunisation with Pandemrix vaccine. The Government has recently confirmed in Parliament that this scheme will remain in place until all the personal injury claims have been settled. The health departments in Scotland, Wales and Northern Ireland are also participating in the Scheme. Details of this scheme, including an application form for funding under the scheme, can be found here.

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 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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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

1) In relation to the medications used as comparators in the modelling:

a. (3.2) Modafinil may be the first choice of treatment but is typically not potent enough at the maximal dose to treat narcolepsy sufficiently. Additional therapeutic options are therefore required;

b. (3.3) While Dexamphetamine and Methylphenidate are used second line, this is not a satisfactory situation. As the committee recognises, there is limited evidence of effectiveness and safety as they are older drugs. They have known serious cardiovascular and psychiatric side effects. Their potential for habituation is also important to consider. They are used by default for symptomatic patients who do not benefit from or cannot tolerate modafinil, because clinicians lack access to other drugs. As a Society, we do not believe this should be considered a satisfactory state of affairs and does not justify using them as the main comparators.

c. (3.12) The Committee comments that "the adverse effects of Dexamphetamine and Methylphenidate are thought to have been underestimated". We consider it surprising that in this context, an alternative and licensed, and thus safe, alternative treatment is not recommended.

d. (3.2) Sodium Oxybate is not used primarily just for refractory cataplexy. It is effective in, and used for, either sleepiness or cataplexy symptoms that remain debilitating and refractory to first- and second-line medications. In fact, one of the Regional Medicines Optimisation Committees (RMOCs) issued guidance in October 2019 recommending Sodium Oxybate for refractory narcolepsy (https://www.sps.nhs.uk/articles/rmoc-sodium-oxybate-in-adult-patients/). RMOCs are an integral part of NHS England and NHS Improvement. Therefore, Sodium Oxybate should be considered standard of care although the message has been slow to reach all CCGs, possibly due to Covid. The catalyst for this guidance was the approval of funding of sodium oxybate for children with refractory narcolepsy (https://www.england.nhs.uk/publication/clinical-commissioning-policy-sodium-oxybate-for-symptom-control-of-narcolepsy-with-cataplexy-children/). There is more evidence for the effectiveness of Sodium Oxybate in adults and it is a key tool when available. The risk of patients losing access to effective treatment once they reach adulthood was agreed to be unacceptable. As a Society, we believe that the fact that some CCGs have not yet implemented the RMOC guidance should not be used as a reason for adopting the 'deprived' treatment pathway as the basis on which to evaluate Solriamfetol. RMOC guidance for Pitolisant is a work in progress but we suggest NICE also take this into account to future proof the relevance of their recommendations. Sodium Oxybate and Pitolisant are thus already established treatments and in some cases, are first line treatment. In Liverpool, for example, no Individual Funding Request (IFR) is

needed as there is an agreement in place with 13 CCGs for their prescription.
e. As a Society, we therefore respectfully suggest NICE consider using Sodium Oxybate and Pitolisant as comparators in the modelling, rather than Dexamphetamine and Methylphenidate.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
2) In relation to the use of the Epworth Sleepiness Scale to assess efficacy and cost-effectiveness:
a. (3.8) The Epworth Sleepiness Scale (ESS) has not been developed for narcolepsy. It was originally created and validated to assess sleepiness in the context of obstructive sleep apnoea. The minimally clinically important difference (MCID) for the ESS is thought to be more than 2 points (Patel et al, ERJ 2017; Patel et al, Am J Resp Crit Care Med 2018). Although the ESS may have be an easier comparative research tool, it is very difficult to make direct comparisons of "wake promoting" efficacy between the main agents using this scale.
b. (3.8) Sleepiness is a multi-dimensional symptom and the ESS does not seem to capture the entire breadth of the problem. As a Society, we suggest that the cost-effectiveness analysis should include other measures of sleepiness, such as objective outcomes (e.g. Multiple Sleep Latency Tests, Maintenance of Wakefulness Test). This could also help with an adjusted cost-effectiveness, as some of the other medications that have been suggested as comparators have been studied for longer periods and may provide further data for these calculations.
c. (3.8) ESS and current measures of wakefulness underestimate benefit on quality of life in treatment of wakefulness in narcolepsy - patients report this themselves and experience clinicians say this themselves

Are the recommendations sound and a suitable basis for guidance to the NHS?
Based on our other comments, we respectfully request that the Committee review its guidance as we do not believe the current recommendations are sound, or a suitable basis for guidance to the NHS.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
3) In relation to equality of access to treatments:
a. As a Society, we are concerned this recommendation reinforces the already poor availability of licenced treatment options that have been specifically developed for patients with narcolepsy with and without cataplexy. The current recommendation may potentiate geographic inequality of access to treatments as some centres (as indicated above) have special agreement with CCGs for other licenced narcolepsy treatments.

General comments:
We are grateful to the Committee for inviting us to comment on this draft guidance. Our comments are as laid out below.

1) In relation to the medications used as comparators in the modelling:
a. (3.2) Modafinil may be the first choice of treatment but is typically not potent enough at the maximal dose to treat narcolepsy sufficiently. Additional therapeutic options are therefore required;
b. (3.3) While Dexamphetamine and Methylphenidate are used second line, this is not a satisfactory situation. As the committee recognises, there is limited evidence of effectiveness and safety as they are older drugs. They have known serious cardiovascular and psychiatric side effects. Their potential for habituation is also important to consider. They are used by default for symptomatic patients who do not benefit from or cannot tolerate modafinil, because clinicians lack access to other drugs. As a Society, we do not believe this should be considered a satisfactory state of affairs and does not justify using them as the main comparators.
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In conclusion, we respectfully request that the Committee review its guidance as we do not believe the current recommendations are sound, or a suitable basis for guidance to the NHS.

[redacted]
For and on behalf of the British Sleep Society

Name	[redacted]
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
Nothing to add

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Dear Sir/Madam ,

As a clinician who frequently treats patients with narcolepsy, and as a researcher who has captured the relevant clinical practice in one of the biggest sleep centres in our country, I would like to highlight that using stimulant medications with no RCT data, makes me feel unease. That feeling is heightened when medications with sound scientific and research documentation are available but restricted or limited, on the basis of lack of comparison data with the medications that lacks RCT data anyway (methylphenidate/dexamphetamine).
As a result sleep clinicians feel trapped in their clinical practice, and patients unfairly treated compared to patients in other countries , who enjoy the availability of these extra treatment options.
The treatment of narcolepsy is problematic, hence we should strive to be able to offer all available treatment options to our patients, following proper and agreed clinical decision making.

Are the recommendations sound and a suitable basis for guidance to the NHS?
Please check the answer above

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Nothing to add

Name	[redacted]
Comments on the ACD:	

General Comments:
The document rightly highlights the potentially disabling nature of narcolepsy, a neurological condition that is frequently under-diagnosed and generally affects young populations across the full 24 hour daily period. In section 3.1, the comment "people ... often feel extremely tired" does not capture the situation and I suspect most patients would react adversely to this seemingly trite description. Patients with narcolepsy frequently do not fulfill their potential, partly due to the relative ineffectiveness of currently available drug therapy but also as a result of the patchy nature of neurological sleep services in the UK. In turn, this reflects the relative under-development of sleep medicine as a speciality in the UK compared to the majority of European countries and the USA where treatment protocols have been fully established for some time. It is perhaps surprising that this NICE assessment is the first to fully address any drug treatment in

narcolepsy, a neurological condition with an accepted prevalence of around 0.05%. I suspect this reflects the "cinderalla" status of UK sleep medicine.
In my view, the unwillingness of the committee to compare solriamfetol with pitolisant and sodium oxybate is inappropriate. To comment that these drugs are not "widely available" is disingenuous as this simply reflects the relative lack of NHS facilities and expertise in managing narcolepsy.
Pitolisant has been used in specialist centres fairly routinely for over 3 years and sodium oxybate, widely and rightly recognised as the single most effective drug for narcolepsy, was licenced in 2006 and, again, is widely used whenever commissioning bodies have sanctioned it. It is somewhat ironic that the drug is not formally licenced for use in children yet is easily available to prescribe in this group in contrast to the situation in adults where it is generally deemed not to be cost-effective (as an aside, there are now generic formulations that deserve to be assessed fully in any economic analysis). The data on Pitolisant and especially sodium oxybate are now significant and most authorities in narcolepsy would consider solriamfetol as an alternative to these increasingly established agents.
In section 3.6 there is a clear typo - sodium oxybate doses should be in grams, not milligrams. In this section, it is also commented that beneficial effects of sodium oxybate can take 12 weeks to accrue. However, this applies to reduction of cataplexy attacks, not symptoms of excessive sleepiness or severe sleep maintenance insomnia where positive effects are generally immediate.
In summary, I can state with confidence that there is a desperate need for better services and treatments for those unfortunate enough to suffer from narcolepsy. I do not think this NICE document captures the current best practice for narcolepsy treatment in the UK. This largely reflects the limited and patchy availability of expertise/experience in narcolepsy management. This gap in service provision should not be used as an excuse to ignore the considerable available data on the newer treatments in narcolepsy compared to traditional psycho-stimulant therapy that became available before the era of evidence-based medicine and detailed scrutiny.

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Solriamfetol for treating excessive sleepiness caused by narcolepsy

Evidence Review Group's critique of the company's response to the Appraisal Consultation Document

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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Date completed	22nd September 2021

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1. Introduction

This document is the Evidence Review Group's (ERG's) critique of the response by the company (Jazz Pharmaceuticals) to the NICE appraisal consultation document (ACD) (Issue date: 5th March 2021) for the technology appraisal on Solriamfetol for treating excessive sleepiness caused by narcolepsy [ID1602]. The ERG received the company's ACD response form and revised model on 17th August 2021.

2. ERG validation of cost-effectiveness results

2.1. Revised base case analysis

The company has retained the comparison with pitolisant and sodium oxybate only in their revised base case, omitting methylphenidate and dexamfetamine. The company explain their rationale for this decision in Comment 1 of their ACD response (see ERG discussion in section 3.1 below).

The revised company base case is reported in ACD response Table 5. This includes three changes to the previous base case:

- An adjustment to the dose split for 75 and 150 mg solriamfetol
- NHWS utility mapping algorithm with UK value set
- PAS price discount for solriamfetol

Justification for these revisions and other key modelling assumptions is summarised in ACD response Tables 2 and 3. The company provide further discussion around the dose split and NHWS utility mapping in ACD response Comments 4 and 5 (sections 3.4 and 3.5 below).

The ERG has compared the company's model submitted with their response to the ACD with the previous version submitted at technical engagement (received by the ERG on 17/08/21 and 27/01/21 respectively). In addition to the three changes listed above, we found a difference in the estimated cost of pitolisant in the two models. The previous version of the model had costed induction treatment for 10 weeks, rather than 8 weeks. The company corrected this in the revised post-ACD model. We agree with this correction.

Table 1 below shows the cumulative impact of the ERG correction and company revisions to the previous base case. Overall, the cost-effectiveness results are unchanged. Solriamfetol is estimated to provide similar QALYs to pitolisant and sodium oxybate, at lower cost. This results in a very high ICER for pitolisant versus solriamfetol: £886,555 per QALY gained at solriamfetol list prices and higher with the solriamfetol PAS. Sodium oxybate is dominated by solriamfetol in the previous and revised base cases.

Table 1. Cumulative impact of revisions to company's base case, deterministic

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Fully incremental ICER (£ per QALY)
Company's previous base case (post Technical Engagement)					
Solriamfetol	£8,322	13.368			
Pitolisant	£19,242	13.376	£10,920	0.008	£1,352,843
Sodium oxybate	£25,860	13.336	£6,618	-0.040	Dominated
ERG correction to the cost of Pitolisant (8 week induction)					
Solriamfetol	£8,322	13.368			
Pitolisant	£19,122	13.376	£10,800	0.008	£1,337,909
Sodium oxybate	£25,860	13.336	£6,739	-0.040	Dominated
Revised dose split ([redacted] dose split for solriamfetol 75/150 mg)					
Solriamfetol	£8,034	13.364			-
Pitolisant	£19,122	13.376	£11,087	0.012	£913,221
Sodium oxybate	£25,860	13.336	£6,739	-0.040	Dominated
Revised NHWS utility algorithm with UK value set for EQ-5D					
Solriamfetol	£8,034	14.704			
Pitolisant	£19,122	14.717	£11,087	0.013	£886,555
Sodium oxybate	£25,860	14.676	£6,739	-0.041	Dominated
PAS discount for solriamfetol					
Solriamfetol	[redacted]	14.704			
Pitolisant	£19,122	14.717	[redacted]	0.013	[redacted]
Sodium oxybate	£25,860	14.676	[redacted]	-0.041	[redacted]

Source: Produced by ERG from company model (dated 16/08/21)

2.2. Comparison with dexamfetamine and methylphenidate

Although the company think that pitolisant and sodium oxybate are the appropriate comparators for solriamfetol, they report a scenario analysis and various sensitivity analyses including dexamfetamine and methylphenidate as comparators.

2.2.1. Company scenario including dexamfetamine and methylphenidate

The company's main scenario with dexamfetamine and methylphenidate as comparators alongside pitolisant and sodium oxybate is reported in ACD response Table 10. They explain their approach to costing dexamfetamine and methylphenidate in Comment 3 (see section 3.3 below for ERG comment).

The scenario uses the following assumptions:

- 40 mg daily doses for both dexamfetamine and methylphenidate
- NHS cost of £1.92 per day for methylphenidate and £5.30 for dexamfetamine
- Costs for hospital admissions for serious adverse effects (SAE) associated with dexamfetamine and methylphenidate as listed in ACD response Table 8.
- Inclusion of the Schedule 2 drug dispensing fee for dexamfetamine and methylphenidate

We did find a minor error in this analysis, as the SAE cost for methylphenidate was assigned to dexamfetamine and vice versa (see cells L13 and L14 in the drug_costs sheet of the model). Correcting for this error, the total annual costs after titration in the induction period are estimated at £749 for methylphenidate and £1,956 for dexamfetamine. See section 3.3 below for further detail on what these costs include.

In the absence of comparative evidence of effectiveness for dexamfetamine and methylphenidate, the company assume the same effect as for the 4.5 g daily dose of sodium oxybate, which was the least effective comparator in the indirect treatment comparison: mean difference in ESS reduction between baseline and 8 weeks 2.985 points lower than solriamfetol 150 mg. TONES 2 trial data in the model showed a mean ESS reduction of 5 points for solriamfetol 150 mg, so the mean ESS reduction for dexamfetamine and methylphenidate in the scenario was estimated at 2.015 points (5.0 – 2.985).

Results for this scenario with the ERG's SAE cost correction are shown in Table 2 below, with the PAS price for solriamfetol (list price analyses for this and other analyses are provided in a separate addendum to this ERG critique). The ICER for solriamfetol versus methylphenidate is above £30,000 per QALY. For the pairwise comparison of solriamfetol with dexamfetamine, the ICER is below £20,000 per QALY, but dexamfetamine is dominated by methylphenidate. The ICERs for solriamfetol compared with pitolisant and sodium oxybate are the same as in the base case in Table 1.

Table 2. Company scenario with dexamfetamine and methylphenidate, deterministic (with PAS)

Technologies	Total		Incremental		ICER (£ per QALY)	
	Costs	QALYs	Costs	QALYs	Fully incremental	Sol versus comparator
Methylphenidate	£1,313	14.601				[redacted]
Dexamfetamine	£3,426	14.601	£2,113	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.103	[redacted]	
Pitolisant	£19,122	14.717	[redacted]	0.013	[redacted]	[redacted]
Sodium oxybate	£25,860	14.676	[redacted]	-0.041	Dominated	Dominant

Source: Produced by ERG from company model (dated 16/8/21). Includes correction for the SAE costs for methylphenidate and dexamfetamine.

2.2.2. Sensitivity to treatment effectiveness

The company report a threshold analysis to assess sensitivity of the above scenario to the assumed effectiveness of dexamfetamine and methylphenidate (ACD response Table 11). We repeated this analysis with the ERG correction to SAE costs (Table 3 below). We do not show results for pitolisant or sodium oxybate in this table, as they do not change compared with the company's base case reported above. Table 3 shows that the mean ESS reduction for methylphenidate must be less than 2 points (versus 5 points for solriamfetol 150 mg) before the solriamfetol ICER falls below the £30,000 per QALY threshold.

The ICER remains above £20,000 per QALY even if it is assumed that there is no mean ESS reduction with methylphenidate. This seems counterintuitive but results from the company's model structure and assumptions. In particular, the model uses individual patient data (IPD) from the solriamfetol 150 mg arm of TONES 2. With no *mean* change in ESS there is still a proportion of people (****) who would be classified as responders (ESS reduction of at least 3 points from baseline to 8 weeks). The model assumes that these individuals would continue to benefit from improved sleep and better quality of life for some time (until they lose response or stop treatment because of adverse effects). Non-responders are assumed to stop treatment at 8 weeks and incur no further costs.

Dexamfetamine appears less cost-effective than methylphenidate in these scenarios. This is because it is assumed to cost less and have the same effect as methylphenidate. It is important to remember that the effects for these two drugs (both beneficial and adverse) are highly uncertain, based on assumptions rather than data. The costs are also uncertain, as there is considerable overlap with different doses and formulations (ACD response Figure 1).

Table 3. Effects of dexamfetamine and methylphenidate, deterministic (with PAS)

Technologies	Total		Incremental		ICER (£ per QALY)	
	Costs	QALYs	Costs	QALYs	Fully Incremental	Sol versus comparator
ESS mean reduction 4 points for dexamfetamine and methylphenidate						
Methylphenidate	£2,290	14.714				Dominated
Dexamfetamine	£5,974	14.714	£3,684	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	-0.009	Dominated	
ESS mean reduction 3 points for dexamfetamine and methylphenidate						
Methylphenidate	£1,941	14.671				[redacted]
Dexamfetamine	£5,064	14.671	£3,123	0.000	Dominated	Dominant
Solriamfetol	[redacted]	14.704	[redacted]	0.034	[redacted]	
ESS mean reduction 2 points for dexamfetamine and methylphenidate						
Methylphenidate	£1,313	14.601				[redacted]
Dexamfetamine	£3,426	14.601	£2,113	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.103	[redacted]	
ESS mean reduction 1 point for dexamfetamine and methylphenidate						
Methylphenidate	£964	14.559				[redacted]
Dexamfetamine	£2,515	14.559	£1,552	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.146	[redacted]	
ESS mean reduction 0 points for dexamfetamine and methylphenidate						
Methylphenidate	£754	14.533				[redacted]
Dexamfetamine	£1,969	14.533	£1,215	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.171	[redacted]	

Source: Produced by ERG from company model (dated 16/8/21). Includes correction for the SAE costs for methylphenidate and dexamfetamine.
SW, southwest quadrant.

To put these hypothetical analyses in context, the company cite clinical opinion on the effectiveness of methylphenidate (ESS reduction of 3-5 points), dexamfetamine (3-6 points) and solriamfetol (5-6 points) (ACD response section 3.6.1). They also report expert opinion that 50-60% of patients would have an adequate therapeutic response to methylphenidate and dexamfetamine at the maximum tolerated dose. This percentage response would be consistent with a mean ESS reduction of 3 to 4 points (based on the IPD in the model). These clinical estimates and the scenario analysis in Table 3 suggest that solriamfetol would not be cost-effective relative to methylphenidate or dexamfetamine at a £30,000 per QALY threshold. Further uncertainties are discussed below.

2.2.3. Sensitivity to treatment continuation for non-responders

The company suggest that due to the lack of alternative treatment options, patients may continue to receive stimulant treatment when they do not perceive clinical benefit. The impact of assuming that a proportion of patients would continue to take dexamfetamine or methylphenidate despite having inadequate clinical results is considered in ACD response section 3.3.4. The company reports that with their base case, if 10% or more of methylphenidate non-responders continue treatment, the ICER for solriamfetol versus methylphenidate falls below £20,000 per QALY. With the ERG SAE cost correction, this threshold value is reached with 9.5% non-responder continuation (Table 4).

The ERG notes that a similar issue might apply to solriamfetol if it were to be recommended in a situation where patients did not have access to further treatment options (e.g., pitolisant and sodium oxybate). For example, if 9.5% of non-responders to solriamfetol were to continue treatment, the ICER for solriamfetol versus methylphenidate would increase to [redacted] per QALY.

Table 4. Scenarios for non-responder treatment continuation, deterministic (with PAS)

Technologies	Total		Incremental		ICER (£ per QALY)	
	Costs	QALYs	Costs	QALYs	Fully incremental	Sol versus comparator
9.5% of non-responders to methylphenidate and dexamfetamine continue treatment						
Methylphenidate	£2,701	14.601				[redacted]
Dexamfetamine	£7,049	14.601	£4,348	0.000	Dominated	Dominant
Solriamfetol	[redacted]	14.704	[redacted]	0.103	[redacted]	
9.5% of non-responders to solriamfetol continue treatment						
Methylphenidate	£1,313	14.601				[redacted]
Dexamfetamine	£3,426	14.601	£2,113	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.103	[redacted]	

Source: Produced by ERG from company model (dated 16/8/21). Includes correction for the SAE costs for methylphenidate and dexamfetamine.

2.2.4. Sensitivity to excess mortality

Finally, the company report a sensitivity analysis for excess mortality associated with dexamfetamine and methylphenidate (ACD response section 3.3.5). They cite two reviews as evidence that the use of stimulants is associated with excess mortality.[1 2] Both reviews focus on dependent and problematic users of amphetamines (and cocaine in the Singleton et al. study), and neither cites excess mortality rates for dexamfetamine or methylphenidate. They are not, therefore, directly relevant to the current decision problem.

In the absence of empirical estimates, the company tests the impact of an assumed standardised mortality rate (SMR) of 1.01 for methylphenidate and dexamfetamine. This reduces the ICER for solriamfetol versus methylphenidate below £30,000 per QALY (ACD response Table 12). The company also report that an SMR of 1.04 is required to reduce this ICER below £20,000 per QALY. Table 5 shows results for these scenarios with the ERG SAE cost correction.

Table 5. Scenarios for excess mortality, deterministic (with PAS)

Technologies	Total		Incremental		ICER (£ per QALY)	
	Costs	QALYs	Costs	QALYs	Fully incremental	Sol versus comparator
Assumed SMR of 1.01 for dexamfetamine and methylphenidate						
Methylphenidate	£1,313	14.585				[redacted]
Dexamfetamine	£3,425	14.585	£2,113	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.120	[redacted]	
Assumed SMR of 1.04 for dexamfetamine and methylphenidate						
Methylphenidate	£1,312	14.536				[redacted]
Dexamfetamine	£3,424	14.536	£2,112	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.168	[redacted]	

Source: Produced by ERG from company model (dated 16/8/21). Includes correction for the SAE costs for methylphenidate and dexamfetamine.

2.3. Additional ERG analysis

2.3.1. Discontinuation rates due to adverse events

The base case uses the same annual rate of discontinuation due to treatment emergent adverse events (TEAEs) for all comparators: 4.4%, estimated from TONES 5. The NICE committee concluded that rates of treatment discontinuation due to adverse events were likely to be underestimated for dexamfetamine and methylphenidate. We conducted an exploratory sensitivity analysis to illustrate the impact of higher TEAE related discontinuation for dexamfetamine and methylphenidate (Table 6). With an assumed rate of 7% or more for methylphenidate, the ICER for solriamfetol compared with methylphenidate falls below the £30,000 per QALY threshold. This ICER remains above £20,000 per QALY unless the TEAE discontinuation rate for methylphenidate is assumed to be very high (80% per year).

Table 6. Sensitivity to TEAE discontinuation, deterministic (with PAS)

Technologies	Total		Incremental		ICER (£ per QALY)	
	Costs	QALYs	Costs	QALYs	Fully incremental	Sol versus comparator
7% per year for dexamfetamine and methylphenidate (4.4% for solriamfetol)						
Methylphenidate	£1,159	14.584				[redacted]
Dexamfetamine	£3,023	14.584	£1,864	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.120	[redacted]	
20% per year for dexamfetamine and methylphenidate (4.4% for solriamfetol)						
Methylphenidate	£719	14.534				[redacted]
Dexamfetamine	£1,868	14.534	£1,149	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.170	[redacted]	

Source: Produced by ERG from company model (dated 16/8/21). Includes correction for the SAE costs for methylphenidate and dexamfetamine.

2.3.2. Cost of adverse events

The company's scenario with dexamfetamine and methylphenidate (Table 2 above) includes additional costs for adverse events: £36.04 per year for methylphenidate and £10.16 per year for dexamfetamine (see section 3.3 below). We illustrate the impact of uncertainty over these estimates in Table 7. This shows, for example, that the ICER for solriamfetol versus methylphenidate is below the £30,000 per QALY threshold if we assume 10 times the company's estimated AE costs for methylphenidate, just over £100 per year.

These scenarios assume no costs for adverse events related to solriamfetol or the other comparators. The ERG report includes a scenario with TEAE related hospitalisation costs for solriamfetol 150 mg estimated from the TONES 5 open label study, adjusted for other treatments with relative risks from an ITC. We adapted this scenario to include additional AE costs for dexamfetamine and methylphenidate (see Table 8 for assumptions). The results in Table 9 are similar to the company's base case.

Table 7. Sensitivity to AE costs, deterministic (with PAS)

Technologies	Total		Incremental		ICER (£ per QALY)	
	Costs	QALYs	Costs	QALYs	Fully incremental	Sol versus comparator
No AE costs for methylphenidate or dexamfetamine						
Methylphenidate	£1,251	14.601				[redacted]
Dexamfetamine	£3,408	14.601	£2,157	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.103	[redacted]	

Technologies	Total		Incremental		ICER (£ per QALY)	
	Costs	QALYs	Costs	QALYs	Fully incremental	Sol versus comparator
10 x scenario: £102 pa for dexamfetamine and £360 pa for methylphenidate						
Methylphenidate	£1,872	14.601				[redacted]
Dexamfetamine	£3,583	14.601	£1,711	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.103	[redacted]	
24 x scenario: £244 pa for dexamfetamine and £865 pa for methylphenidate						
Methylphenidate	£2,742	14.601				[redacted]
Dexamfetamine	£3,829	14.601	£1,086	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.103	[redacted]	

Source: Produced by ERG from company model (dated 16/8/21). Includes correction for the SAE costs for methylphenidate and dexamfetamine.

Table 8 ERG AE cost scenario: assumptions

Treatment	Hospitalisation (per year)		Cost (£ per year) [b]	
	Year 1	Year 2+	Year 1	Year 2+
Solriamfetol 75 mg	[redacted]	[redacted]	£35.13	£15.15
Solriamfetol 150 mg	[redacted]	[redacted]	£105.54	£45.59
Pitolisant ≤40 mg	[redacted]	[redacted]	£34.06	£14.75
Sodium Oxybate 4.5 g	[redacted]	[redacted]	£93.20	£40.23
Sodium Oxybate 6 g	[redacted]	[redacted]	£100.58	£43.45
Sodium Oxybate 9 g	[redacted]	[redacted]	£114.92	£49.62
Dexamfetamine [a]	[redacted]	[redacted]	£115.70 [c]	£55.75 [c]
Methylphenidate [a]	[redacted]	[redacted]	£141.58 [c]	£81.63 [c]

Source: ERG report section 4.2.8.3 and Tables 31 and 32.
[a] Hospitalisation rates assumed equal to those for solriamfetol 150 mg. [b] Mean hospital stay of 1 day at a cost of £1,341. [c] Hospitalisation costs for solriamfetol 150 mg plus £36.04 per year for methylphenidate and £10.16 per year for dexamfetamine.

Table 9. ERG AE cost scenario results, deterministic (with PAS)

Technologies	Total		Incremental		ICER (£ per QALY)	
	Costs	QALYs	Costs	QALYs	Fully incremental	Sol versus comparator
Methylphenidate	£1,403	14.601				[redacted]
Dexamfetamine	£3,516	14.601	£2,113	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.103	[redacted]	[redacted]
Pitolisant	£19,171	14.717	[redacted]	0.013	[redacted]	[redacted]
Sodium oxybate	£25,989	14.676	[redacted]	-0.041	Dominated	Dominant

Source: Produced by ERG from company model (dated 16/8/21). Includes correction for the SAE costs for methylphenidate and dexamfetamine.

2.3.3. Utility estimates

The revised analysis uses utility estimates from the National Health and Wellness Survey (NHWS) ESS to EQ-5D mapping model, with EQ-5D-5L utility scores calculated with the van Hout crosswalk procedure with the UK value set.[3] The previous version of the NHWS mapping used utility scores for EU5 countries. We compare results with the NHWS EU and UK algorithms, as well as the McDaid algorithm, developed for the NICE appraisal of continuous positive airway pressure for obstructive sleep apnoea (TA139).[4 5] Although there are large differences in the absolute QALY estimates between the NHWS mapping with EU and UK value sets, the incremental QALYs, and hence ICERs, are similar. Results are quite different with the McDaid algorithm. See section 3.5 below for ERG comment on the methods.

Table 10. Sensitivity to utility valuation methods, deterministic (with PAS)

Technologies	Total		Incremental		ICER (£ per QALY)	
	Costs	QALYs	Costs	QALYs	Fully incremental	Sol versus comparator
NHWS ESS to EQ-5D mapping, EU value set						
Methylphenidate	£1,313	13.265				[redacted]
Dexamfetamine	£3,426	13.265	£2,113	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	13.364	[redacted]	0.099	[redacted]	[redacted]
Pitolisant	£19,122	13.376	[redacted]	0.012	[redacted]	[redacted]
Sodium oxybate	£25,860	13.336	[redacted]	-0.040	Dominated	Dominant
NHWS ESS to EQ-5D mapping, UK value set						
Methylphenidate	£1,313	14.601				[redacted]
Dexamfetamine	£3,426	14.601	£2,113	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	14.704	[redacted]	0.103	[redacted]	[redacted]
Pitolisant	£19,122	14.717	[redacted]	0.013	[redacted]	[redacted]
Sodium oxybate	£25,860	14.676	[redacted]	-0.041	Dominated	Dominated
McDaid ESS to EQ-5D mapping (OSA)						
Methylphenidate	£1,313	16.846				[redacted]
Dexamfetamine	£3,426	16.846	£2,113	0.000	Dominated	[redacted]
Solriamfetol	[redacted]	16.933	[redacted]	0.087	[redacted]	[redacted]
Pitolisant	£19,122	16.943	[redacted]	0.010	[redacted]	[redacted]
Sodium oxybate	£25,860	16.913	[redacted]	-0.030	Dominated	Dominated

Source: Produced by ERG from company model (dated 16/8/21). Includes correction for the SAE costs for methylphenidate and dexamfetamine.

2.3.4. Definition of response

The cost-effectiveness ranking is not sensitive to the definition of response. Results are very similar to the base case with a more stringent definition (ESS reduction ≥4 points). With a less stringent definition (ESS reduction ≥2), the ICER for solriamfetol versus methylphenidate is higher than in the base case [redacted] per QALY); and although the ICER for solriamfetol versus dexamfetamine is lower [redacted] per QALY), dexamfetamine is dominated by methylphenidate. Relative results for solriamfetol compared with pitolisant and sodium oxybate are unchanged.

2.3.5. Dose split for solriamfetol

The company uses a dose split of [redacted] for 75 mg and 150 mg doses of solriamfetol in their base case analysis, based on recent German data (see discussion in section 3.4 below). The model is insensitive to changes in this ratio – even with extreme ratios of 10:90 or 90:10 the relative cost-effectiveness ranking is maintained.

2.4. ERG conclusions

The results of the company's scenario analysis do not suggest that solriamfetol is a cost-effective alternative to methylphenidate or dexamfetamine. The ICER for solriamfetol versus methylphenidate is above £30,000 per QALY, and although the ICER for solriamfetol versus dexamfetamine is below £20,000, dexamfetamine is dominated by methylphenidate.

A key uncertainty is the relative effectiveness of these treatments, which is based on assumption rather than evidence. The company assume that methylphenidate and dexamfetamine have the same relative effect as the least effective comparator in the ITC (4.5 mg sodium oxybate): with a mean ESS reduction of around 2 compared with a mean reduction of 5 for solriamfetol 150 mg. However, clinical experts consulted by the company have said that the mean ESS reduction with methylphenidate and dexamfetamine would be higher than this: around 3-5 points for methylphenidate and 3-6 points for dexamfetamine. This suggests that the ICERs for solriamfetol relative to these comparators would be less favourable than the company's estimates.

There are some omissions from the analysis that may have biased the results in favour of dexamfetamine and methylphenidate. The impact of adverse effects on patient outcomes and costs with these drugs may not be fully captured: including cost and disutility associated

with adverse events; higher rates of discontinuation; and possibly excess mortality. There is also wide variation in the cost of these drugs, depending on dose and formulation, and it is possible that mean costs in practice are higher than in the model. It has been suggested that in the absence of other treatment options, some patients may continue methylphenidate or dexamfetamine despite an inadequate response (though we note that this could also apply to solriamfetol if it were to be recommended without other treatment options).

An important remaining uncertainty is the utility effect that can be attributed to solriamfetol and the comparators. This is based on a mapping from the ESS to EQ-5D, which is less compelling than direct trial evidence. The revision to the NHWS mapping (UK rather than EU5 value set) is appropriate and gives similar cost-effectiveness results. ICERs are less favourable with the established McDaid. See section 3.5 below for discussion.

In the ACD, the committee concluded that the treatment pathway after modafinil is not fully captured in the company's model. From a cost-effectiveness perspective, and subject to the uncertainties outlined above, the company's cost-effectiveness results suggest that methylphenidate should be considered as a second-line option. The position of dexamfetamine is less clear, due to uncertainty over the relative costs of dexamfetamine and methylphenidate in practice.

Regarding the other comparators included in the scope, through all of the company's and ERG's analyses, solriamfetol is estimated to provide similar QALY gains at lower cost. Pitolisant and sodium oxybate are either dominated by solriamfetol or have very high ICERs.

Ideally the assessment of these options would be based on a sequenced analysis, including only patients after failure of modafinil and methylphenidate/dexamfetamine. The model includes individual patient data, so one could exclude individuals from the analysis who would be expected to have a response to methylphenidate (modelled ESS reduction ≤ 3). However, the dataset is small (n= [redacted]). If we assume a mean ESS reduction of 3 for methylphenidate, there are only [redacted] individuals in the dataset who would not be expected to respond to this treatment. Excluding patients without prior exposure to modafinil would further reduce the sample size. Therefore it is unlikely that further sequenced analysis would be informative.

3. ERG critique of company ACD comments

3.1. Comment 1: On the Committee's conclusions that (ACD 3.2) dexamfetamine and methylphenidate are standard treatments after modafinil and there are no established treatments after this, and (ACD 3.3) the most relevant comparators after first-line modafinil are dexamfetamine and methylphenidate and (ACD 3.9) the treatment pathway after modafinil is not fully captured in the company's model

The company selected and approached six clinicians (based on the criteria presented in Appendix A of the company's response to the ACD) and five consented to participate in interviews so that the company could obtain additional clinical expert opinion on the following topics:

- The treatment pathway for narcolepsy in the NHS
- The relative efficacy of solriamfetol versus methylphenidate or dexamfetamine
- The increase healthcare resource use associated with adverse events from treatment with dexamfetamine and methylphenidate
- The applicability of generic health-related quality of life measures to assess the impact of EDS due to narcolepsy.

The excel spreadsheet containing the transcripts of the interviews[6] shows that the five clinicians were based in different geographical regions [redacted] and represented different specialities for Sleep Medicine ([redacted]. One of the company's selected clinicians was a [redacted] It is not clear whether any of the five clinicians had contributed to either of the company's two previous sets of interviews with clinicians.[7] [8]

3.1.1. Evidence from clinician interviews on the treatment pathway for narcolepsy in the NHS

The ERG has reviewed the additional clinical expert opinion regarding the treatment pathway for narcolepsy that was obtained from the interviews (summarised in Appendix 1).

[redacted]

[redacted]. The ERG agrees with the company conclusion that the clinical experts confirm modafinil as the established first-line therapy, and as Appendix 1 shows, there was variation in the choices made when modafinil treatment was unsuccessful. There is evidence from the interviews that [redacted]

3.1.2. NHS formulary information and market share sales data demonstrate that all four comparators are widely available in the UK

The company have summarised their findings from NHS formulary and market share sales data. The ERG has checked the publicly available NHS formulary information cited by the company and agrees that this shows all four possible second-line treatment options are available, albeit with some restrictions at most centres (e.g. need individual funding requests). The ERG also notes that although dexamfetamine and methylphenidate were listed, there was often no specific mention of their use for people with narcolepsy. The ERG has not been able to independently verify the sales data for pitolisant and sodium oxybate as these data are not publicly available.

3.1.3. The Regional Medicines Optimisation Committee considers sodium oxybate and pitolisant to be relevant treatments for narcolepsy

The ERG agrees that the Regional Medicines Optimisation Committee has published a commissioning statement for sodium oxybate in adult patients with narcolepsy with cataplexy.[9] The statement does not stipulate that sodium oxybate must be commissioned but it aims to facilitate local clinical commissioning groups decision making about whether to commission sodium oxybate for use in all adult patients. The planned commissioning framework for the use of pitolisant in narcolepsy with or without cataplexy[10] does not appear to have been published yet.

3.1.4. ERG conclusion

The ERG agrees with the company's interpretation of data from clinician interviews and NHS formulary information that there is evidence of all four existing potential second-line treatments for narcolepsy being in use across the NHS in England. There is evidence that

some clinicians do not use dexamfetamine or methylphenidate, particularly for new patients, because other options that have been tested in clinical trials are available. The ERG has seen that the Regional medicines Optimisation Committee commissioning statement for sodium oxybate in adult patients with narcolepsy with cataplexy underpins some of the publicly available NHS formulary information recommending sodium oxybate. It seems likely, that when the equivalent framework for the use of pitolisant in narcolepsy with or without cataplexy is published that this would also influence local NHS formulary decisions.

3.2. Comment 2: On the Committee's conclusion that the Company's assumptions about treatment discontinuation due to adverse events may not be appropriate for analysis involving dexamfetamine and methylphenidate (ACD 3.12)

The committee felt that the discontinuation rates due to adverse events were likely to have been underestimated for dexamfetamine and methylphenidate and they would have preferred to see a model that reflected this (ACD 3.12). The company have considered three sources of information, discussed below.

3.2.1. A comparison of the Summary of Product Characteristics for methylphenidate, dexamfetamine and solriamfetol

The company states that all of the 'undesirable effects' listed in section 4.8 of the Summary of Product Characteristics (SmPC) for solriamfetol were also listed in one or both of the SmPCs for dexamfetamine and methylphenidate (note the company did not state which SmPCs they had used and for methylphenidate in particular many different products are available). The ERG agrees this is true and we additionally note that for the majority of the 'undesirable effects' listed for solriamfetol they occur either at the same estimated frequency or a lesser frequency than for dexamfetamine and methylphenidate in the SmPCs that we have used.[11 12] The exception to this is hyperhidrosis (excessive sweating) which is listed as a common 'undesirable effect' of solriamfetol but rare for methylphenidate (and information on sweating is not known for dexamfetamine) in the SmPCs we used.

There are some 'undesirable effects' that are distinct for methylphenidate and/or dexamfetamine. Most distinct events fall under the headings of 'Psychiatric disorders', 'Nervous system disorders' or 'Cardiac disorders' and these are shown in Table 11. In the company's response to the ACD they focus on 'arrhythmia', 'cardiomyopathy' and 'psychosis'. The ERG is unclear why the company have focussed on these events but it may be because they believe these are the events which would be associated with a hospital admission (as described in section 3.3.1 of the company response). Alternatively, the choice

may be a consequence of differences between the SmPCs consulted or perhaps, in the case of 'arrhythmia' and 'cardiomyopathy', because in ACD 3.12 cardiovascular adverse events are provided as an example where higher rates would be expected with dexamfetamine and methylphenidate. The ERG agrees that pre-treatment screening to obtain baseline information on patients' cardiovascular status is required before either dexamfetamine or methylphenidate are prescribed and during treatment cardiovascular status should be monitored regularly.

Table 11 'Undesirable effects' listed in the SmPCs that are distinct for methylphenidate and/or dexamfetamine

Dexamfetamine events[11]	Frequency	Methylphenidate events[12]
Psychiatric disorders		
Nervousness	Very common	Nervousness
Abnormal behaviour, aggression, excitation, depression	Common	Affect lability, Aggression, Agitation, Depression, Abnormal behaviour, Mood swings, Tics, Initial insomnia, Depressed mood, Libido decreased, Tension, Panic attack
	Uncommon	Psychotic disorders, Auditory, visual and tactile hallucination, Anger, Suicidal ideation, Mood altered, Restlessness[a], Tearfulness, Worsening of pre-existing tics of Tourette's syndrome, Logorrhoea, Hypervigilance, Sleep disorder
	Rare	Mania[a], Disorientation, Libido disorder, Confusional state[a]
Hallucinations, psychosis / psychotic reactions, suicidal behaviour (including completed suicide), tics, worsening of pre-existing tics	Very rare	Suicidal attempt (including completed suicide)[a], Transient depressed mood, Abnormal thinking, Apathy[a], Repetitive behaviours, Over-focussing
Confusion, dependence, dysphoria, emotional lability, euphoria, impaired cognitive test performance, altered	Not known	Delusions[a], Thought disturbances, dependence. Cases of abuse and dependence have been described,

Dexamfetamine events[11]	Frequency	Methylphenidate events[12]
libido, night terrors, obsessive-compulsive behaviour, panic states, paranoia, restlessness		more often with immediate release formulations
Nervous system disorders		
Vertigo, dyskinesia, hyperactivity	Common	Dizziness, Dyskinesia, Psychomotor hyperactivity, Somnolence, Paresthaesia, Tension headache
	Uncommon	Sedation, Tremor[a], Lethargy
Fatigue	Rare	
Convulsions, choreoathetoid movements, intracranial haemorrhage	Very rare	Convulsion, Choreo-athetoid movements, Reversible ischaemic neurological deficit, Neuroleptic malignant syndrome (NMS; Reports were poorly documented and in most cases, patients were also receiving other drugs, so the role of methylphenidate is unclear).
Ataxia, dizziness, dysgeusia, concentration difficulties, hyperreflexia, stroke, tremor. Very rarely, cases of neuroleptic malignant syndrome (NMS) were observed. However, these reports were poorly documented and in most cases, patients were also receiving other medicinal products. Thus, the role of dexamfetamine in the development of NMS is unclear.	Not known	Cerebrovascular disorders[a] (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), Grand mal convulsion, Migraine[a], Dysphemia
Cardiac disorders		
Arrhythmia	Common	Arrhythmia
	Uncommon	Chest pain
Angina pectoris	Rare	Angina pectoris
Cardiac arrest	Very rare	Cardiac arrest; Myocardial infarction

Dexamfetamine events[11]	Frequency	Methylphenidate events[12]
Cardiomyopathy, myocardial infarction	Not known	Supraventricular tachycardia, Bradycardia, Ventricular extrasystoles[a], Extrasystoles[a]

[a] Frequency from trials in children and adolescents, frequency reported to be higher in adults.

3.2.2. Pharmacovigilance data for methylphenidate, dexamfetamine, and solriamfetol

The company summarise the top ten adverse drug reactions for adults reported using data from the UK's MHRA Yellow Card scheme's Interactive Drug Analysis Profile (data lock point 31st March 2021) within Table 7 of their response to the ACD. The ERG notes that top 10 reactions are in broad agreement with the information the ERG reported above in Table 11. for those effects that were distinct for methylphenidate and/or dexamfetamine.

3.2.3. Additional in-depth clinician interviews with expert prescribers of these medicines

The company interviews with five clinicians included questions to obtain additional clinical expert opinion on the increase in healthcare resource use associated with adverse events from treatment with dexamfetamine and methylphenidate. Although there were some differences in opinion between the five advisors interviewed, the ERG agrees with the company that:

- [redacted] advisors [redacted] thought health care resource use would be higher with methylphenidate and dexamfetamine than for solriamfetol.
- [redacted] of advisors mentioned a concern about cardiovascular side effects and [redacted] were concerned about possible psychiatric side effects with methylphenidate and dexamfetamine.
- Advisors anticipated that adverse events would be less with solriamfetol that they had observed for methylphenidate and dexamfetamine from their clinical practice.
- Two advisors, who use dexamfetamine as a last-line treatment, stated that patients tend to keep taking dexamfetamine despite any problems with undesirable or adverse effects because they have already tried the alternatives and know there is nothing else available if they come off it.
- there are difficulties in prescribing controlled drugs [redacted] and some patients are unwilling to try a controlled drug.

3.2.4. ERG conclusion

The company sought to identify the healthcare resource use due to adverse events associated with methylphenidate and dexamfetamine. To do this they identified 'undesirable effects' listed in the SmPCs for dexamfetamine and methylphenidate that do not occur with solriamfetol. The ERG would have liked the company to provide some rationale to explain why they have focussed on arrhythmia, cardiomyopathy and psychosis. For example, are these the events most likely to result in a hospital admission? Interviews with clinicians did confirm that cardiovascular side effects and psychiatric side effects of methylphenidate and dexamfetamine were of concern to some prescribers of these drugs. The ERG agrees with the company that it is challenging to estimate healthcare resource use for the adverse events associated with methylphenidate and dexamfetamine and caution that the estimates are uncertain.

3.3. Comment 3: On the Committee's conclusion that the costs of healthcare resource use should be appropriately included in the analysis for comparisons against dexamfetamine and methylphenidate (ACD 3.13)

The company set out the assumptions that they use for costing of methylphenidate and dexamfetamine, including:

- Hospital admissions for specific adverse drug reactions to methylphenidate and dexamfetamine (ACD response Table 8).
- Dispensing fee for Schedule 2 drugs (ACD response Table 9)

We summarise the costs included in the company's model in Table 11 below.

Table 12 Drug costs for the revised base case (PAS prices for solriamfetol)

Drug	Dose	% use	Daily cost	Annual costs (after induction)			
				Drug	Adverse events [a]	Schedule 2 Dispensing	Total
Methylphenidate	40 mg		£1.92	£698	£36.04	£15.53	£749
Dexamfetamine	40 mg		£5.30	£1,931	£10.16	£15.53	£1,956
Solriamfetol	75 mg	[redacted]	[redacted]	[redacted]			[redacted]
	150 mg	[redacted]	[redacted]	[redacted]			
Pitolisant	18 mg	33%	£10.33	£3,761			£6,269
	36 mg	67%	£20.67	£7,523			
Sodium oxybate	4.5 g	33%	£18.00	£6,552			£9,464
	6.0 g	33%	£24.00	£8,736			

	9.0 g	33%	£36.00	£13,104			

Source: Extracted by the ERG from the company's submitted model (dated 16/08/21).

[a] ERG correction for allocation of SAE-related costs for methylphenidate and dexamfetamine

Figure 1 in the company's ACD response illustrates the range of variation in daily drug costs for solriamfetol (with the PAS discount) and comparators according to different doses and formulations in the BNF. The company makes the point that maximum costs for all comparators can be higher than the maximum cost for solriamfetol.

The company report their cost-effectiveness analysis including methylphenidate and dexamfetamine and sensitivity analyses for the assumed effectiveness of methylphenidate and dexamfetamine and excess mortality associated with these drugs in Tables 10, 11 and 12 of their ACD response. We have discussed and critiqued these analyses in section 2.1 and 2.2 above.

3.3.1. ERG conclusion

The company's estimates of hospitalisation costs for adverse drug reactions related to methylphenidate and dexamfetamine are reasonable. They are subject to uncertainty, but do not seem over-estimated. We also agree with the inclusion of the Schedule 2 dispensing fee. We conduct sensitivity analysis over these estimates in section 2.3.2 above, in addition to an ERG scenario including estimates of hospitalisation costs for solriamfetol and other comparators. The scenario analysis for excess mortality associated with dexamfetamine is highly uncertain, due to a lack of relevant evidence.

3.4. Comment 4: On the Committee's consideration that most appropriate dose splits were uncertain (ACD 3.11)

The company present more recent Solriamfetol sales data from Germany because this reflects sales for the narcolepsy indication only. In contrast sales data from France reflects prescriptions for both narcolepsy and OSA indications and the data cannot be separated by indication. The company's information on dose splits is shown in Table 13. The dosing split applied in the company's revised base case analysis comes from German prescription data between January 2021 and June 2021 because the company believe that the prescriptions made after 8 months of solriamfetol availability in the narcolepsy indication in Germany will be less weighted towards the lower dose (which new patients would be anticipated to start on) and more representative of a steady state of prescribing.

Table 13 Company information on dose splits

STA timepoint	75 mg:150 mg dose split	Data source
Original base case (November 2020)	50:50	Assumption
Technical Engagement Response (January 2021)	[redacted]	German sales data
Company response to ACD (September 2021)	[redacted]	Updated German sales data (additional six months of sales)
Company response to ACD (September 2021)	[redacted]	German prescription data between January 2021 and June 2021.

3.4.1. ERG conclusion

Sales data from Germany that are specific for the solriamfetol narcolepsy indication show an overall 75 mg:150 mg dose split of [redacted]. Limiting the data to the period between January 2021 and June 2021 adjusts the dose split estimate slightly to [redacted] This may be a better representation of what the dose split will be in the future because it is expected that some patients who initially start on the 75 mg dose will titrate up to the 150 mg dose. ERG scenario analysis shows that the cost-effectiveness results are not sensitive to a wide range of dose split assumptions.

[redacted]

3.5. Comment 5: On the Committee's conclusion that mapping from the ESS to the EQ-5D may not adequately capture changes in quality of life (ACD 3.10)

The company reiterates arguments that the EQ-5D and SF-6D utility measures and generic SF-36 health profile do not capture the impact of EDS on quality of life for people with narcolepsy. These issues have been discussed in the original company submission, the ERG report and during technical engagement.

The revision to the NHWS mapping to use the UK EQ-5D value set (van Hout crosswalk procedure for EQ-5D-5L) is consistent with the NICE preferred valuation approach. Although it produces higher utility and QALY estimates than the original NHWS version, based on the EU5 EQ-5D value set, utility (and hence QALY) differences between treatments are similar (see Table 10 above).

3.5.1. ERG conclusions

We consider that these conclusions from our original report stand:

- TONES 2 did not detect a significant effect on the EQ-5D Index: possibly because the EQ-5D is insensitive to the effect of daytime sleepiness, a lack of power in the trial and/or study period being too short for changes to ingrained behaviour or expectations to occur. Or possibly because the effect of solriamfetol on quality of life is insufficient. We note that the trial also failed to show a statistically significant effect on other quality of life measures (EQ-5D VAS, SF-36 PCS and MCS and the disease-specific FOSQ-10).
- There is a paucity of other utility data from the literature that could have been used in the model. In this situation, it is reasonable to consider a mapping approach, although this does introduce additional uncertainty.
- The McDaid algorithm found a consistent estimate of the relationship between utility and ESS across EQ-5D and SF-6D datasets. But it is based on data for people with OSA, not narcolepsy, so may not be appropriate.
- The NHWS mapping from ESS to EQ-5D has some advantages. The methods of analysis are well reported and appeared to be thorough. The dataset is large and, though mostly OSA, it does include a small sample of people reporting narcolepsy. The sample may be subject to recruitment bias due to the use of online sample and self-reporting of diagnosis. So, it is not clear whether the estimation sample is sufficiently similar to the target sample of people with narcolepsy in the UK.
- Utilities estimated by applying the NHWS formula to ESS changes in TONES 2 are much lower than UK general population norms, EQ-5D index scores from TONES 2 and 5 and values for narcolepsy reported in the literature: so, may lack face validity. However, as there is no assumed difference in survival between arms, the absolute utility does not drive the cost-effectiveness results and the NHWS estimate of the change in utility associated with a one-unit change in ESS on utility are reasonably consistent with the McDaid estimates.
- On balance, we agree with the company's use of the NHWS mapping algorithm in their base case, with the McDaid formula in a scenario.

The revision of the NHWS mapping to use the UK EQ-5D value set is appropriate.

3.6. Comment 6: Other issues

3.6.1. On the clinical experts' statement that if someone's condition did not respond to dexamfetamine or methylphenidate, usually they had no further treatment options and had to continue on treatment with those drugs (ACD 3.2)

In this section the company state that their revised model assumes that methylphenidate and dexamfetamine achieve similar efficacy as solriamfetol when treating excessive daytime sleepiness associated with narcolepsy, and that in order to achieve this effect patients may experience adverse effects as the dose is titrated. We question this statement, as the model actually assumes a relative treatment effect for methylphenidate and dexamfetamine equal to the least effective comparator in the indirect treatment comparison (sodium oxybate 4.5 g dose).

The company states that these assumptions are based on the additional interviews the company conducted with five clinicians. The ERG agrees some of the clinicians interviewed described the need to titrate the doses of methylphenidate and dexamfetamine with the aim of achieving an acceptable balance between treatment response and side effects. It is also clear from the clinician interviews that only about 50% to 60% of patients achieve an adequate ESS reduction when they are on the maximum tolerated dose and that the maximum tolerated dose varies considerably from patient to patient. [redacted] clinicians were able to estimate what the treatment effect was in terms of ESS which gave the ranges reported by the company (3-5 points for methylphenidate and 3-6 points for dexamfetamine). [redacted]

3.6.2. Solriamfetol will be confined to secondary care prescribing

The company confirms that solriamfetol prescribing will be limited to secondary care.

3.6.3. ERG conclusion

There is a lack of data for dexamfetamine and methylphenidate to inform decisions about the relative clinical effectiveness of these two drugs in comparison to solriamfetol. Clinical expert opinion suggests that an ESS change of 3-5 points for methylphenidate and 3-6 points for dexamfetamine could be possible for 50% to 60% of patients, but to achieve this response some patients would experience adverse events. As noted in section 2.2.2 above, these clinician estimates are not consistent with the company's assumptions about the relative effects of methylphenidate and dexamfetamine.

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Appendix 1 Summary of clinical expert opinion regarding the treatment pathway for narcolepsy

Clinician	1	2	3	4	5
Full access to all options?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Does not use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notes		[redacted]	[redacted]	[redacted]	[redacted]

[redacted]