

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Solriamfetol for treating excessive daytime
sleepiness caused by narcolepsy**

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using solriamfetol in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

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 recommendations sound and 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?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using solriamfetol in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: Friday 26 March 2021

Second appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 5

1 Recommendations

- 1.1 Solriamfetol is not recommended, within its marketing authorisation, for treating excessive daytime sleepiness in adults with narcolepsy with or without cataplexy.
- 1.2 This recommendation is not intended to affect treatment with solriamfetol that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Excessive daytime sleepiness caused by narcolepsy is usually first treated with modafinil then dexamfetamine or methylphenidate. There is limited availability of other treatments such as sodium oxybate and pitolisant in clinics across England, which means they cannot be considered routine practice.

Clinical trial evidence shows that solriamfetol reduces excessive daytime sleepiness compared with placebo. It does not show a difference in quality of life but this is not certain because of the way that quality of life was assessed in the trial. There are no data comparing solriamfetol with dexamfetamine or methylphenidate. Therefore, the clinical effectiveness of solriamfetol compared with dexamfetamine or methylphenidate is uncertain.

There are also concerns about how the treatment pathway and quality of life are modelled, and uncertainty about the assumptions around stopping treatment and dose. Therefore the cost-effectiveness estimates for solriamfetol compared with dexamfetamine or methylphenidate are uncertain. They are also very likely to be higher than what NICE normally considers an acceptable use of NHS resources. So solriamfetol is not recommended.

2 Information about solriamfetol

Marketing authorisation indication

- 2.1 Solriamfetol (Sunosi, Jazz Pharmaceuticals) has a marketing authorisation ‘to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy)’.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.3 The list price for solriamfetol is £177.52 for a 75 mg 28-day pack and £248.64 for a 150 mg 28-day pack (BNF online accessed February 2021). Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The [appraisal committee](#) considered evidence submitted by Jazz Pharmaceuticals, a review of this submission by the evidence review group (ERG), NICE’s technical report, and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

It recognised that there were remaining areas of uncertainty associated with the analyses presented and took these into account in its decision making. It discussed the following issues: treatment pathway, comparators, generalisability of clinical trial evidence, indirect treatment comparison, subgroup analysis, dosing splits, treatment discontinuation and healthcare resource use (see the technical report issues 1 to 9), which were outstanding after the technical engagement stage.

The condition

Narcolepsy substantially affects many aspects of daily life and people with narcolepsy would welcome a new treatment option

3.1 Excessive daytime sleepiness and other symptoms of narcolepsy can significantly affect the quality of life of people with the condition. According to the patient experts, as well as excessive daytime sleepiness, symptoms include cataplexy, sleep paralysis and poor sleep quality. As a result people with the condition often feel extremely tired throughout the day. The patient experts said their narcolepsy affects their physical and mental wellbeing and every aspect of daily life, including education, employment, maintaining a social life, carrying out everyday activities and the ability to drive. They said it can also affect family members. The patient experts said that narcolepsy can be unpredictable, because symptoms and treatment effectiveness can differ significantly from person to person. They also said that the condition was difficult to manage with current treatments and that a new treatment option would be welcomed. The clinical and patient experts highlighted that diagnosis can be delayed in clinical practice because it is not always easy to identify. The committee concluded 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.

Treatment pathway and comparators

Dexamfetamine and methylphenidate are standard treatments after modafinil and there are no established treatments after this

3.2 The clinical experts said that narcolepsy symptoms vary widely, and the characteristics and comorbidities of each person need to be considered when making treatment decisions (see section 3.1). This means that treatments for narcolepsy vary depending on the person. They explained that modafinil is currently the established first-line treatment for excessive daytime sleepiness caused by narcolepsy in NHS clinical practice in

England. The clinical experts explained that treatment options after modafinil vary because of different access to some treatments in different centres. Options include dexamfetamine, methylphenidate, sodium oxybate and pitolisant. Only sodium oxybate, pitolisant and dexamfetamine have marketing authorisations in the UK for narcolepsy. The clinical experts said that sodium oxybate is used primarily when cataplexy symptoms are severe in people with narcolepsy. However, they also explained that the availability of sodium oxybate and pitolisant is limited and variable across clinics in England. The committee was aware that sodium oxybate and pitolisant had not been appraised by NICE for treating narcolepsy. The clinical experts said that sodium oxybate is available for children who have narcolepsy with cataplexy through NHS England's National Commissioning policy, but this policy does not include adults. They explained that treatment with pitolisant or sodium oxybate usually requires an individual funding request, which is often rejected. This meant that if someone's condition did not respond to dexamfetamine or methylphenidate, which are widely available treatments after modafinil, usually they had no further treatment options and had to continue on treatment with those drugs. The clinical experts said they can offer a higher dose or combinations of treatments but the response would be limited. 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 agreed 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. The committee therefore concluded that dexamfetamine and methylphenidate were the established treatments for narcolepsy in NHS practice after modafinil, and that there are no established treatments after this.

The most relevant comparators after first-line modafinil are dexamfetamine and methylphenidate

3.3 The NICE scope listed modafinil, dexamfetamine, methylphenidate, pitolisant and sodium oxybate as comparators to solriamfetol. Although the marketing authorisation for solriamfetol does not require previous treatments, the company positioned solriamfetol as a second-line treatment after modafinil. The clinical experts agreed that this was appropriate given that modafinil is the established first-line treatment for excessive daytime sleepiness caused by narcolepsy. They said solriamfetol may also be used third or fourth line depending on baseline characteristics and comorbidities. The committee agreed with the company that modafinil was not an appropriate comparator. The company considered dexamfetamine, methylphenidate, pitolisant and sodium oxybate to be appropriate comparators to solriamfetol. Because of the limited data available for dexamfetamine and methylphenidate, the company focused its clinical and cost effectiveness submission on a comparison with pitolisant and sodium oxybate, and only provided a comparison with dexamfetamine and methylphenidate as scenario analyses. The committee acknowledged that there were limited data available for dexamfetamine and methylphenidate, but concluded that these were the most relevant comparators because it was established NHS practice to offer them after modafinil, unlike pitolisant and sodium oxybate.

Clinical evidence

Results from TONES 2 are generalisable to people with excessive daytime sleepiness caused by narcolepsy seen in NHS clinical practice

3.4 TONES 2 was a randomised 12-week trial comparing solriamfetol against placebo in people with narcolepsy. Results from this trial inform the efficacy of solriamfetol in the network meta-analysis (NMA; see section 3.6) and therefore its cost effectiveness. They showed that solriamfetol significantly reduced excessive daytime sleepiness as measured by the

Epworth Sleepiness Scale (ESS) compared with placebo after 12 weeks (ESS changes of -2.2 and -3.8 compared with placebo for solriamfetol 75 mg and 150 mg doses respectively). However, there was no significant change between trial arms in terms of EQ-5D utilities, functional outcomes of sleep questionnaire score (FOSQ-10; disease-specific measure) or the physical or mental health component scales of the SF-36 (see section 3.10). The trial was primarily carried out in the US and Canada. The proportion of patients in the trial with cataplexy and the proportion of patients whose condition had previously been treated with modafinil were lower than in NHS clinical practice. In addition, small numbers of patients were randomised to each solriamfetol dose (59 patients had 75 mg and 59 had 150 mg). The ERG and clinical experts explained that, while there were some differences between TONES 2 and the narcolepsy population in NHS practice in England, they considered that the results were generalisable. The committee concluded that the results from TONES 2 were generalisable to the population seen in NHS clinical practice.

Subgroup analysis by prior modafinil and cataplexy status is informative but limited by the data available

3.5 The company provided a TONES 2 analysis that was stratified by 2 subgroups: prior modafinil and cataplexy status. The ERG said that the prior modafinil subgroup reflected the company's positioning of solriamfetol as a post-modafinil treatment. But it was based on small numbers of patients (exact numbers are academic in confidence and cannot be reported here) and therefore the subgroups may be underpowered. The clinical experts said that the lower proportion of modafinil use in TONES 2 may be because the trial was primarily in the US and Canada. The company pointed out that the results showed solriamfetol effectiveness did not differ significantly depending on whether modafinil had been taken previously. But the trial was not powered to detect differences in effectiveness by this subgroup. The clinical experts said that there were fewer people in TONES 2 with cataplexy than in NHS practice. The company explained that this was likely to be because of the

small numbers in the trial or because the trial excluded people who did not stop their anti-cataplexy treatment. It also explained that solriamfetol was not thought to affect cataplexy symptoms, and the main aim was to improve wakefulness and reduce excessive daytime sleepiness. The committee recalled that the patient experts outlined that narcolepsy can involve other symptoms, for example cataplexy, which can also have a substantial impact on quality of life (see section 3.1). The ERG said that the subgroup analysis from TONES 2 showed no clear difference in outcomes between people with narcolepsy with cataplexy and without it in terms of ESS reduction. It highlighted however that effectiveness could still differ between these groups. The company said that it was not possible to include subgroups in the indirect comparison because the comparator treatment trials did not report results by these groups (see section 3.6) and highlighted that neither of the subgroup analyses changed the cost-effectiveness conclusions. The committee agreed that the subgroup analysis by prior modafinil use and cataplexy status was informative because it added some certainty to solriamfetol's clinical effectiveness after modafinil and for narcolepsy with cataplexy. But it concluded that it was limited by the data available.

Indirect treatment comparison

The indirect treatment comparison is limited by the data available and adds uncertainty to the analysis

3.6 Because TONES 2 only included a placebo comparator, the company used an NMA to indirectly compare solriamfetol with pitolisant and sodium oxybate. Only one NMA (which estimated mean change in the ESS) was used in the cost-effectiveness analysis to compare solriamfetol with comparators through a common placebo comparator (see section 3.10). The results from the random effects model showed that the mean ESS change 95% credible intervals had a wide range and crossed 0 for comparisons between solriamfetol 150 mg and pitolisant (at a dose of less than 40 mg), sodium oxybate (4.5 mg, 6 mg and 9 mg doses), solriamfetol

75 mg and placebo. This meant that ESS change comparisons between solriamfetol 150 mg and comparators were not considered to be statistically different using the random effects model. The ERG noted that the NMA was limited to a small number of trials and that there were high levels of heterogeneity between the included trials, which meant there was substantial uncertainty in its results. The clinical experts said that it was difficult to say if any treatment in the NMA was more effective than another in treating excessive daytime sleepiness caused by narcolepsy. The indirect treatment comparison was also limited by the inability to compare potentially important subgroups, such as previous modafinil use or cataplexy status (see section 3.5). The NMA was further limited to an 8-week timepoint because of the maximum length of comparator trials. The ERG's clinical experts explained that this may underestimate the effectiveness of sodium oxybate, which can take up to 12 weeks to show a response. The company explained that it found no clinical trial evidence to estimate the effectiveness of dexamfetamine or methylphenidate and therefore these treatments could not be included in the indirect treatment comparison. The committee considered that the lack of trial evidence to inform comparisons between dexamfetamine and methylphenidate was a key uncertainty in the analysis. This is because these treatments are commonly used after modafinil as second-line options and therefore are the most relevant comparators (see sections 3.2 and 3.3). The company presented cost-effectiveness comparisons between solriamfetol, dexamfetamine and methylphenidate using a range of assumed ESS reductions for these treatments. The ERG provided comparisons based on assuming these treatments reduced ESS scores by 3 points less than solriamfetol 150 mg. The ERG also provided additional scenarios in which dexamfetamine and methylphenidate were assumed to reduce ESS by the same amount as placebo and the lower 95% confidence interval for placebo (relative to 150 mg solriamfetol) as reported in the NMA (the exact ESS reductions are academic in confidence and cannot be reported here). The committee noted that this limited any comparison between solriamfetol and dexamfetamine and methylphenidate to one based on

assumed differences in ESS reduction between these treatments, which made results highly uncertain. The committee said it would have liked to see other sources of evidence for the efficacy of these treatments and more clinical expert input into the assumptions used in the scenario analysis comparing them with solriamfetol. The committee concluded that the indirect treatment comparison between solriamfetol and other comparators is limited by the data available and adds uncertainty to the analysis.

Treatment discontinuation due to adverse events

Discontinuation due to adverse events for solriamfetol, pitolisant and sodium oxybate are similar but uncertain for dexamfetamine and methylphenidate

3.7 Information on adverse events leading to discontinuation of treatment for solriamfetol comes from the TONES 2 and TONES 5 (long-term follow up) trials. In TONES 2 the incidence of adverse events that led to discontinuation was low at 12 weeks (1.7%, 1.7% and 5.1% for placebo, solriamfetol 75 mg, and solriamfetol 150 mg, respectively). In TONES 5, discontinuation due to adverse events was 10.2% for people with narcolepsy, however 56.8% of these events were in the first 4 weeks of treatment. The company did an NMA estimating the rate of adverse events of solriamfetol, pitolisant and sodium oxybate at 8 weeks using TONES 2 data for solriamfetol (see section 3.6). This showed that all treatments were associated with adverse events, with incidence similar across all treatments except for the higher dose of solriamfetol (150 mg). The company said that the rates of discontinuation due to adverse events were low and there were no significant differences between treatments. The company noted that there was no clinical trial evidence to allow dexamfetamine or methylphenidate to be included in this NMA. The committee accepted that adverse events resulting in discontinuation in the NMA were similar for solriamfetol, pitolisant and sodium oxybate, but the

rates for dexamfetamine and methylphenidate were uncertain because of lack of data.

The economic model

Response to treatment is not based only on the Epworth Sleepiness Scale in clinical practice but there may not be appropriate alternatives

3.8 Improvements in excessive daytime sleepiness and response to treatment were estimated in the company's analysis by the reduction in ESS from baseline. The company explained that it only used the ESS because there was no appropriate alternative measure. The clinical experts explained that a response to treatment is normally defined through consultation with the person taking treatment, not just by ESS reduction. The company assumed that a reduction in the ESS by 3 points or more would equal a response to treatment in the model, and this determined if people remained on treatment beyond an 8-week timepoint. The ERG, in its base case, assumed that reduction in the ESS by 2 points or more would equal a response. The clinical experts said that, while an ESS reduction of 3 may be appropriate, there is no consensus on what can be considered a clinically relevant ESS reduction and that it varies by individual. The ESS reduction threshold was tested in a scenario analysis by the ERG, which noted that the choice of ESS reduction threshold did not significantly affect cost-effectiveness results. The committee concluded that using the ESS alone to determine response to treatment is unlikely to reflect clinical practice but there may not be appropriate alternative measures.

The treatment pathway after modafinil is not fully captured in the company's model

3.9 The company model included a decision tree, which estimated the proportion of people who have a treatment response at 8 weeks (see section 3.6). After this timepoint, the company used a Markov model in which people who have a treatment response were assumed to continue treatment until they stop because of a loss of response or an adverse

event (see section 3.12). People continuing treatment were assumed to have the same level of reduction in mean ESS as measured at 8 weeks. The company did not model any subsequent lines of treatment after treatment discontinuation. The company explained that the modelling approach was limited by the available evidence base. The committee agreed that the lack of evidence made it difficult to model the complexity of the narcolepsy treatment pathway. It noted that treatments for narcolepsy can vary across individuals and can depend on symptoms such as cataplexy severity (see section 3.2). The clinical experts said that if treatment with second-line dexamfetamine or methylphenidate was not effective, people with excessive daytime sleepiness caused by narcolepsy usually do not then have access to pitolisant or sodium oxybate (see sections 3.2 and 3.3). This meant that these people would likely remain on dexamfetamine or methylphenidate, potentially trying a higher dose or a combination of treatments. The clinical experts explained that remaining on these treatments would still provide a small benefit but would not be adequately addressing the excessive daytime sleepiness. The committee noted that these considerations had not been included in the company's model. The committee noted that the company's base case only included comparisons against pitolisant and sodium oxybate. It acknowledged that comparisons of solriamfetol against dexamfetamine and methylphenidate were difficult to do because of a lack of trial evidence (see section 3.6). But it considered that these treatments were the most relevant comparators (see sections 3.2 and 3.3). The committee concluded that the treatment pathway after modafinil is not fully captured in the company's model.

Changes in quality of life may not be adequately captured by mapping the Epworth Sleepiness Scale to the EQ-5D

3.10 TONES 2 collected data on a range of quality of life measures including the EQ-5D-5L. After 12 weeks there was no significant change in EQ-5D utility values between patients who had solriamfetol (75 mg or 150 mg) or placebo. The committee also recalled that there was no statistical

difference between TONES 2 arms in terms of functional outcomes of sleep questionnaire score (FOSQ-10; disease-specific measure) or the physical or mental health component scales of the SF-36 (see section 3.4). The company explained that the EQ-5D was not sensitive to changes in quality of life in people with excessive daytime sleepiness caused by narcolepsy because the measure does not include a sleep domain. It also noted that the trial was not long enough to capture changes in quality of life. The company therefore developed a mapping algorithm that estimated EQ-5D values based on ESS scores using data from the National Health and Wellness Survey. The ERG considered that the company's approach was appropriate given the lack of alternative data. But it highlighted that mapping from the ESS may underestimate the impact of treatments on quality of life in this condition. The committee 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; the data for the mapping algorithm are academic in confidence and cannot be reported here), 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.

A range of dose split assumptions in the analysis is appropriate to account for the variability in clinical practice

3.11 All treatments for narcolepsy are available in different doses, which vary in cost and effectiveness. These different treatment dose options were weighted, based on assumptions, to inform cost-effectiveness comparisons between solriamfetol and other treatments. In the company's base case, it was assumed the proportions of people taking 75 mg and 150 mg doses of solriamfetol were the same as reported in French prescribing data (these figures are commercial in confidence and cannot be reported here). In the ERG's exploratory base case it was assumed that 90% of people were on the higher dose (150 mg) of solriamfetol. The ERG tested a range of dosing splits across different treatment options in a

sensitivity analysis. The clinical experts explained that it is difficult to estimate the most likely dose split in NHS clinical practice of any treatment in the analysis. The ERG highlighted that the cost-effectiveness conclusions were not sensitive to dose split assumptions. The company presented a scenario analysis for the comparison between solriamfetol and dexamfetamine and methylphenidate using a range of assumed doses for these comparators. The ERG explained that, in its scenario analysis for these comparisons, it assumed a 40 mg dose for both comparator treatments, which may have overestimated their costs. The committee considered that the most appropriate dose splits were uncertain, but a range of dosing split assumptions in the analysis is appropriate to account for the variability in clinical practice.

The company's treatment discontinuation due to adverse events assumptions may not be appropriate for analysis involving dexamfetamine and methylphenidate

3.12 The company assumed that discontinuation due to adverse events at 8 weeks was the same for each treatment, based on the NMA, which did not show a statistical difference in rates between solriamfetol, pitolisant and sodium oxybate (see section 3.7). There was no long-term clinical trial evidence to inform treatment discontinuation due to adverse events for any comparator treatment in the analysis after 8 weeks. So the company assumed in its economic model that all treatments were discontinued because of an adverse event at the same rate from 8 weeks onwards. This rate of discontinuation because of adverse events was estimated from TONES 5 (the company assumed an annual rate of 4.4% which assumes the rate at week 4 in TONES 5 is similar to the rate at week 8; see section 3.7) and was assumed to be the same for each treatment. The ERG agreed that this simplifying assumption was appropriate because there was no robust evidence to inform long-term discontinuation rates due to adverse events. The ERG noted that this rate may be overestimated for solriamfetol, pitolisant and sodium oxybate because TONES 5 included the unlicensed 300 mg solriamfetol dose. The

clinical experts said that dexamfetamine and methylphenidate were associated with higher rates of adverse events, for example cardiovascular adverse events, than other treatments in the analysis. The committee therefore considered that discontinuation rates because of adverse events were likely to be underestimated for dexamfetamine and methylphenidate and would have preferred to see a model that reflected this. The committee concluded that the company's assumptions about treatment discontinuation due to adverse events may not be appropriate for analysis involving dexamfetamine and methylphenidate.

The costs of healthcare resource use should be appropriately included in the analysis for comparisons against dexamfetamine and methylphenidate

3.13 The company only included the costs of drug acquisition in its cost-effectiveness analysis. The ERG base case included additional costs including consultant-led appointments (which were assumed to differ in frequency depending on whether a person's condition responded to a treatment) and hospital admissions because of serious adverse events. The company highlighted that the number of serious adverse events in the clinical evidence was low and that adverse events from solriamfetol treatment tended to occur early, be mild in nature and resolve quickly (see section 3.7). The clinical and patient experts explained that treatment with dexamfetamine or methylphenidate would be associated with higher healthcare resource use costs because they are associated with more adverse events (see section 3.12). The committee acknowledged that it was difficult to estimate healthcare resource use because of the lack of available data. But it agreed that the economic modelling did not account fully for the likely increased healthcare resource use from adverse events from treatment with dexamfetamine and methylphenidate. This likely underestimated the costs of these treatments. The committee concluded that the costs of healthcare resource use should be appropriately included in the analysis for comparisons against dexamfetamine and methylphenidate.

Cost-effectiveness estimates

Solriamfetol is not a cost-effective use of NHS resources

3.14 The company's base case compared solriamfetol with pitolisant and sodium oxybate. Comparisons with dexamfetamine and methylphenidate were included in a scenario analysis. Compared with pitolisant, solriamfetol was associated with a high south-west incremental cost-effectiveness ratio (ICER) of £1,352,843 (with a positive net monetary benefit at both £20,000 and £30,000 per quality-adjusted life year [QALY] gained). This meant that solriamfetol was less expensive and only marginally less effective than pitolisant, which leads to high savings in costs in relation to the loss of QALYs. Solriamfetol dominated sodium oxybate (it was less expensive and marginally more effective). The company's scenario analysis showed that solriamfetol was associated with ICERs consistently above £30,000 per QALY gained compared with dexamfetamine or methylphenidate for various efficacy and dose assumptions. The company's cost-effectiveness analysis included the following assumptions:

- response defined as an ESS reduction of 3 or more (see section 3.8)
- EQ-5D utility values estimated from using the ESS score using a novel mapping algorithm (see section 3.10)
- long-term treatment discontinuation rates because of lack of response or adverse events are the same for all treatments and based on TONES 5 data (see section 3.12)
- only drug acquisition costs included (see section 3.13)
- a range of ESS reductions relative to solriamfetol 150 mg for dexamfetamine and methylphenidate assumed because of lack of trial data (see section 3.6).

The committee agreed that after first-line modafinil the most relevant comparators are dexamfetamine and methylphenidate because access to sodium oxybate and pitolisant is limited and variable in clinics across

England and neither of these treatments had previously been appraised by NICE (see sections 3.2 and 3.3). It therefore decided not to consider the ICERs for the comparison with sodium oxybate and pitolisant further in its decision making. The committee also agreed that the company's scenario analysis comparing solriamfetol against dexamfetamine and methylphenidate was highly uncertain because of a lack of trial data (see section 3.6) and because the model did not reflect the clinical pathway appropriately (see section 3.9). The committee also noted that this analysis did not account for the likely higher rate of adverse events associated with dexamfetamine or methylphenidate (see sections 3.12 and 3.13). The committee believed that quality of life changes are not appropriately captured in the analysis (see section 3.10) and that treatment response is not exclusively based on ESS score in NHS clinical practice (see section 3.8).

The committee noted that the ERG's analysis included the following assumptions in addition to the company's analysis:

- response defined as an ESS reduction of 2 or more (see section 3.8)
- healthcare resource use based on response to treatment and serious adverse events (see section 3.13)
- a scenario analysis for comparisons with dexamfetamine and methylphenidate assuming a lower ESS reduction of 3 relative to solriamfetol 150 mg for both treatments (see section 3.6)
- further scenario analyses based on the company's base case assumptions and assuming the same ESS reduction for placebo and the lower 95% credible interval ESS response for placebo from the NMA (relative to solriamfetol 150 mg; the exact ESS reductions are academic in confidence and cannot be reported here) for dexamfetamine and methylphenidate (see section 3.6).

The ERG's scenario analysis estimated that the ICER for solriamfetol

compared with dexamfetamine was £141,921 per QALY gained. Compared with methylphenidate it was £159,820 per QALY gained when it was assumed that these treatments reduced the ESS by 3 points less than solriamfetol 150 mg. The committee considered that these ICERs were uncertain and likely to be overestimated because of the assumption that adverse events and discontinuation rates were the same for all treatments (see section 3.12). There were also no data to inform healthcare resource costs with dexamfetamine and methylphenidate (see section 3.13). The ICERs were reduced when dexamfetamine and methylphenidate were assumed to reduce ESS by the same amount as placebo, or the lower 95% credible interval for placebo, from the NMA. But they were still above £30,000 per QALY gained. The ERG explained that these were extreme analyses, which highlighted that solriamfetol was unlikely to be cost effective compared with these treatments even under favourable assumptions. The committee considered that these ICERs were also uncertain and subject to the same limitations as the company's analysis and likely not to be appropriate because of the assumptions used. It concluded that the cost-effectiveness analysis presented was highly uncertain but that the most plausible range of ICER estimates was likely to be above what NICE considers a cost-effective use of NHS resources.

Other factors

- 3.15 No equality or social value judgement issues were identified.
- 3.16 The QALY may not have captured changes in health-related quality of life in the model (see sections 3.1 and 3.10).

Conclusion

Solriamfetol is not recommended for treating excessive daytime sleepiness caused by narcolepsy

- 3.17 The committee recognised that excessive daytime sleepiness caused by narcolepsy is a debilitating condition that negatively impacts many

aspects of daily life (see section 3.1). The committee noted that the treatment pathway after first-line modafinil varied, and that dexamfetamine and methylphenidate were the most relevant comparators after modafinil (see sections 3.2 and 3.3). It acknowledged that solriamfetol was more effective than placebo in reducing excessive daytime sleepiness in people with narcolepsy as measured by the ESS (see section 3.4). However there are concerns that this measure does not reflect how treatment response is defined in NHS practice (see section 3.8). The committee believed there was a high amount of uncertainty in the analysis because of limitations including:

- how quality of life was measured (see section 3.10)
- the indirect treatment comparison (see section 3.6)
- estimates of healthcare resource use (see section 3.13)
- the model not appropriately reflecting clinical practice (see sections 3.2 and 3.9).

The committee agreed that it would like to see analysis that includes the following:

- Further investigation into the impact of excessive daytime sleepiness caused by narcolepsy on quality of life, and a method that appropriately captures quality of life changes in this population (see section 3.10).
- Other sources of evidence for the efficacy of dexamfetamine and methylphenidate and more clinical expert input into the assumptions used in the scenario analyses comparing these treatments with solriamfetol (see section 3.6).
- Appropriate estimates of healthcare resource use for treatment with dexamfetamine and methylphenidate compared with solriamfetol (see 3.13).
- Modelling that reflects the current clinical pathway, in which people with excessive daytime sleepiness whose condition did not respond to dexamfetamine or methylphenidate usually had no further treatment

options and had to continue on treatment with those drugs (see sections 3.2 and 3.9).

All this considered, the ICERs the committee considered most plausible for solriamfetol compared with dexamfetamine or methylphenidate were substantially above the range that NICE usually considers an acceptable use of NHS resources. Therefore, it did not recommend solriamfetol for routine commissioning in the NHS.

4 Proposed date for review of guidance

- 4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee C
February 2021

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Alan Moore

Technical lead

Nicola Hay

Technical adviser

Gavin Kenny

Project manager

ISBN: [to be added at publication]