NICE National Institute for Health and Care Excellence

NICE guidance

Solriamfetol for treating excessive daytime sleepiness caused by narcolepsy

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Solriamfetol is recommended as an option for treating excessive daytime sleepiness in adults with narcolepsy with or without cataplexy. This is only if modafinil and either dexamfetamine or methylphenidate have not worked well enough or are not suitable.

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. Availability of other treatments such as sodium oxybate and pitolisant varies in clinics across England. If available, they're normally used after modafinil and dexamfetamine or methylphenidate.

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 is no data comparing solriamfetol with dexamfetamine or methylphenidate. And there is no direct data comparing it with sodium oxybate or pitolisant. There is some indirect data but it is from only a small number of short trials. So solriamfetol's clinical effectiveness compared with these treatments is uncertain.

The cost-effectiveness estimates for solriamfetol compared with dexamfetamine or methylphenidate are highly uncertain, because they were based only on assumptions. And they're likely to be higher than what NICE normally considers acceptable. But solriamfetol is cost effective compared with pitolisant and sodium oxybate. So solriamfetol is recommended if modafinil and dexamfetamine or methylphenidate have not worked well enough or are not suitable to control excessive daytime sleepiness caused by narcolepsy.

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 October 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 pointed out 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; access to pitolisant and sodium oxybate varies

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 sodium oxybate and pitolisant are not always available in clinics across England, and access can be restricted. 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 can require 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, no more treatments may be available. At consultation the company provided further information on pitolisant and sodium oxybate's availability, saying that clinical experts had advised them that they are widely used in the NHS. The company also provided NHS formulary data to show that both treatments were used across various regions of England. The ERG agreed that pitolisant and sodium oxybate are used but noted that they are usually subject to

restrictions such as the number of prior treatments. Some regions require individual funding requests. At consultation, the company and other consultees highlighted that a Regional Medicines Optimisation Committee had published a commissioning statement for sodium oxybate and another was planned for pitolisant. The committee noted that the commissioning statement recommended considering sodium oxybate as a third or later line treatment. 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 access to pitolisant and sodium oxybate varies.

The comparators for solriamfetol depend on the treatment pathway

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 is limited data for dexamfetamine and methylphenidate, but concluded that they were the most relevant second-line comparators. It also noted that pitolisant and sodium oxybate are usually given third line or later if available (see section 3.2). The committee agreed that pitolisant and sodium oxybate

could be considered relevant third-line comparators, despite some variability in access. The committee concluded that the relevant comparators for solriamfetol depend on their position in the treatment pathway.

Clinical evidence

TONES 2 results are generalisable to people with excessive daytime sleepiness caused by narcolepsy seen in the NHS

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 3.11). 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, although 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 done 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 anticataplexy 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 explained that narcolepsy can involve other symptoms, for example cataplexy, which can also substantially affect 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 noted 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 pointed out 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 between solriamfetol, pitolisant and sodium oxybate 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. 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 g, 6 g and 9 g 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 committee concluded that the indirect treatment comparison between solriamfetol, pitolisant and sodium oxybate is limited by the data available and adds uncertainty to the analysis.

Comparisons with dexamfetamine or methylphenidate are highly uncertain because there is no clinical trial data for them

3.7 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 at this part of the pathway (see section 3.2 and section 3.3). At consultation, the company said that the clinical experts they interviewed could not provide estimates for the efficacy of dexamfetamine or methylphenidate. The company therefore presented a cost-effectiveness scenario analysis for solriamfetol compared with dexamfetamine and methylphenidate using a range of assumed ESS reductions. It assumed dexamfetamine and methylphenidate reduced ESS scores by the same amount as 4.5 g sodium oxybate did in the company's NMA (see section 3.6). The ERG noted that 4.5 g sodium oxybate had the lowest ESS reduction in the NMA. The committee also noted that this assumed dexamfetamine and methylphenidate were only marginally more effective than placebo. The company also provided a sensitivity analysis that varied the assumed ESS reductions for dexamfetamine and methylphenidate. 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 concluded that the analysis comparing solriamfetol with dexamfetamine and methylphenidate is limited by the data available and adds a high level of uncertainty to the analysis.

Treatment discontinuation due to adverse events

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

3.8 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 these rates were 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 with 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 a 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

3.9 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 by consulting with the person having 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 8 weeks. The clinical experts said that, although an ESS reduction of 3 may be appropriate, there is no consensus on what a clinically relevant ESS reduction is, and it varies from person to person. 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

3.10 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 3.13). People continuing treatment were assumed to have the same level of reduction in mean ESS as measured at 8 weeks. The company positioned solriamfetol as second-line treatment and did not model any later lines of treatment after treatment stops. 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. But it also noted that the model did not include people having treatment after second line, which was a limitation in the analysis. The clinical experts said that if treatment with second-line dexamfetamine or methylphenidate was not effective, people with excessive daytime sleepiness caused by narcolepsy may not have access to pitolisant or sodium oxybate (see section 3.2 and section 3.3). These people may remain on dexamfetamine or methylphenidate, potentially trying a higher dose or a combination of treatments, which could provide a small benefit. At consultation, the company provided a scenario analysis that assumed some people continue these treatments without seeing any ESS reduction. The ERG noted that people may remain on treatment with solriamfetol despite a lack of response if there were no other treatments, so provided a scenario analysis for this. The committee noted that the company's base case only included comparisons against pitolisant and sodium oxybate, which were usually given third line or later in the treatment pathway if available (see sections 3.2 and 3.3). The committee concluded that the treatment pathway after modafinil was 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

3.11 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 the 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 (NHWS). The company also provided an analysis that used the alternative mapping approach published by McDaid et al. (2007). The ERG considered that the company's approach was appropriate given the lack of alternative data. But it noted that mapping from the ESS may underestimate the impact of treatments on quality of life in this condition. At the second meeting the company updated its mapping approach to include only UK EQ-5D tariff values, which the ERG agreed with. The committee noted that the results estimated from both the NHWS and the McDaid mapping were associated with uncertainty. It also acknowledged that the estimated relative differences in quality-adjusted life years (QALYs) between treatments were very similar for each mapping approach. The committee concluded that mapping from the ESS to the EQ-5D may not adequately capture changes in quality of life but the mapping analysis was acceptable for decision-making.

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

3.12 All treatments for narcolepsy are available in different doses, which vary in cost and effectiveness. These different dose options were weighted, based on assumptions, to inform cost-effectiveness comparisons between solriamfetol and other treatments. The company's original base case assumed the proportions of people taking 75 mg and 150 mg doses of solriamfetol were the same as reported in French prescribing data. After consultation the company updated these proportions based on more recent German sales data. (These figures are commercial in

confidence and cannot be reported here.) The ERG noted that the cost-effectiveness conclusions were not sensitive to solriamfetol dose split assumptions. The clinical experts explained that it is also difficult to estimate the most likely dose split in NHS clinical practice for the comparator treatments. At consultation the company presented a scenario analysis using doses of 40 mg for dexamfetamine (instant release tablet) and methylphenidate (modified release capsule). The company explained that it was difficult to determine which dose was the most appropriate, and that its estimate was conservative. The committee considered that the scenario analysis may have overestimated the cost of methylphenidate and dexamfetamine and noted that other formulations and doses with lower costs were available. The committee considered that the most appropriate dose splits were uncertain, particularly for dexamfetamine and methylphenidate, but a range of dosing assumptions in the analysis is appropriate to account for the variability in clinical practice.

The treatment discontinuation due to adverse events assumptions are uncertain for analysis involving dexamfetamine and methylphenidate

3.13 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 3.8). 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 (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 3.8). 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 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. After consultation the company said that clinical experts advised them that adverse event rates were likely to be higher for

dexamfetamine and methylphenidate than solriamfetol, but there was no robust evidence to inform this. The company also provided a scenario analysis in which dexamfetamine and methylphenidate were assumed to increase mortality. The ERG noted that the sources the company provided to support excess mortality with these treatments did not refer to mortality rates. Therefore, it did not consider this scenario to be robust. The ERG did a scenario analysis that assumed higher treatment discontinuation rates for dexamfetamine and methylphenidate. The committee agreed that they may be associated with higher rates of discontinuation due to adverse events. But it noted that it was difficult to determine the appropriate rate to use. The committee concluded that assumptions about treatment discontinuation due to adverse events were uncertain for dexamfetamine and methylphenidate.

It is appropriate to include the costs of healthcare resource use because of adverse events in the analysis for dexamfetamine and methylphenidate

3.14 The company only included the costs of drug acquisition in its original cost-effectiveness analysis. The company pointed out 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 3.8). 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 3.13). 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 dexamfetamine and methylphenidate and likely underestimated the costs of these treatments. After consultation the company updated its scenario analysis to include adverse event costs for dexamfetamine and methylphenidate based on analysis of their summary of product characteristics (SmPC) and the Medicines and Healthcare products Regulatory Agency (MHRA) yellow card scheme data. The ERG agreed with including these costs and noted that, although the analysis was uncertain, it did not believe the company had overestimated these costs.

The committee concluded that including the costs of adverse events for dexamfetamine and methylphenidate was appropriate.

Cost-effectiveness estimates

Solriamfetol is a cost-effective use of NHS resources after modafinil and either dexamfetamine or methylphenidate

3.15 The company's and ERG's base case compared solriamfetol with pitolisant and sodium oxybate. Comparisons with dexamfetamine and methylphenidate were included in a scenario analysis. The company's and ERG's base case assumptions included:

- response defined as an ESS reduction of 3 or more (see section 3.9)
- EQ-5D utility values estimated from using the ESS score using a novel mapping algorithm (see section 3.11)

- 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 3.13).

  Compared with pitolisant, solriamfetol was associated with a high south-west incremental cost-effectiveness ratio (ICER) of £886,555 (with a positive net monetary benefit at both £20,000 and £30,000 per QALY gained). This meant that solriamfetol was less expensive and only marginally less effective than pitolisant, which leads to high cost savings in relation to the loss of QALYs. Solriamfetol dominated sodium oxybate (it was less expensive and marginally more effective). Solriamfetol also dominated sodium oxybate when a confidential discount for sodium oxybate was considered. The committee recalled that access to pitolisant and sodium oxybate varied and, if available, they were usually offered after modafinil and either dexamfetamine or methylphenidate (see section 3.3). The committee considered that quality of life changes were not appropriately captured in the analysis (see section 3.11) and that treatment response is not exclusively based on ESS score in NHS clinical practice (see section 3.9). Despite these uncertainties, the committee concluded that solriamfetol is a cost-effective use of NHS resources after treatment with modafinil and either dexamfetamine or methylphenidate. It therefore recommended solriamfetol as a treatment option at this part of the treatment pathway. The committee was also aware of a potential equalities issue related to the MHRA warning that modafinil use is linked to birth defects and reduced oral contraception efficacy (see section 3.17). It therefore thought it was reasonable to also recommend solriamfetol without prior modafinil and after treatment with either dexamfetamine or methylphenidate if people cannot take modafinil.

Solriamfetol is not a cost-effective use of NHS resources after treatment with only modafinil

3.16 The company's and ERG's scenario analysis showed that solriamfetol was associated with ICERs consistently above £30,000 per QALY gained compared with dexamfetamine or methylphenidate across a range of sensitivity analyses. The scenario and sensitivity analysis included the following changes to the base case:

- Adverse event costs for dexamfetamine and methylphenidate estimated based on SmPC and MHRA yellow card data and a scenario in which these treatments were assumed to increase mortality rates (see section 3.14). The ERG also did a scenario analysis in which discontinuation rates due to adverse events were assumed to be higher for dexamfetamine and methylphenidate (see section 3.14).
- Dexamfetamine and methylphenidate assumed to be equal to 4.5 g sodium oxybate in terms of ESS reduction as estimated by the company's NMA. This was because of a lack of trial data and a sensitivity analysis that varied ESS reduction relative to 150 mg solriamfetol for these treatments (see section 3.6).
- Threshold analysis assuming a proportion of people remain on treatment with dexamfetamine or methylphenidate despite not having an ESS reduction (see section 3.11).

The committee agreed that after first-line modafinil the most relevant second-line comparators are dexamfetamine and methylphenidate (see section 3.2 and section 3.3). 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). The committee considered that the cost-effectiveness scenario analyses presented were highly uncertain and sensitive to various modelling assumptions. It concluded that the most plausible range of ICER estimates was likely to be above what NICE considers a cost-effective use of NHS resources. Therefore, it did not recommend solriamfetol as a treatment option when modafinil is the only previous treatment.

Other factors

3.17 A patient organisation raised a potential equality issue in that the MHRA has issued a warning that modafinil use is linked to birth defects and reduced oral contraception efficacy. It said anyone with narcolepsy affected by this warning needs alternative treatment options. The committee was also aware that treatment with dexamfetamine or methylphenidate may not be suitable for some people. This includes people with certain mental health conditions. The committee concluded that its recommendations would not affect these groups any differently

than other groups because they allow solriamfetol treatment when modafinil, methylphenidate or dexamfetamine cannot be used.

3.18 The QALY may not have captured changes in health-related quality of life in the model and the committee took this into account in its decision-making (see section 3.1 and section 3.11).

Conclusion

Solriamfetol is recommended for treating excessive daytime sleepiness caused by narcolepsy after modafinil and either dexamfetamine or methylphenidate

3.19 The committee concluded that solriamfetol was cost effective compared with pitolisant or sodium oxybate. It also concluded that the most plausible ICERs for solriamfetol compared with dexamfetamine or methylphenidate were substantially above the range that NICE usually considers an acceptable use of NHS resources. Therefore, it recommended solriamfetol for routine commissioning in the NHS only when modafinil and either dexamfetamine or methylphenidate have not worked well enough or are not suitable to control excessive daytime sleepiness caused by narcolepsy.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has excessive daytime sleepiness caused by narcolepsy and the doctor responsible for their care thinks that solriamfetol is the right treatment, it should be available for use, in line with NICE's recommendations.

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 and Alex Filby
Technical advisers

Gavin Kenny
Project manager

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Accreditation