NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Solriamfetol for treating excessive daytime sleepiness caused by obstructive sleep apnoea

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: Wednesday 28th of April 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, to improve wakefulness and reduce excessive daytime sleepiness in adults with obstructive sleep apnoea whose sleepiness has not been satisfactorily treated by primary obstructive sleep apnoea therapy, such as continuous positive airway pressure (CPAP).

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 obstructive sleep apnoea is usually first treated with a primary obstructive sleep apnoea therapy such as CPAP.

Clinical trial evidence shows that solriamfetol added to a primary obstructive sleep apnoea therapy (standard care) reduces excessive daytime sleepiness compared with standard care alone. The evidence does not show a difference in quality of life, but this is uncertain because of the way that quality of life was assessed in the trial. No evidence has been presented on solriamfetol alone, although it is an option in the full marketing authorisation for people who cannot use CPAP.

There are concerns about how the trial data have been modelled to take account of a potential placebo effect in the standard care group, and uncertainty about the assumptions around the doses used in clinical practice. Therefore, the cost-effectiveness estimates for solriamfetol with standard care compared with standard care alone are uncertain. They are also 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 obstructive sleep apnoea whose excessive daytime sleepiness has not been satisfactorily treated by primary obstructive sleep apnoea therapy such as continuous positive airway pressure (CPAP).

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.

The appraisal committee was aware that 1 issue was resolved during the technical engagement stage. It agreed that a subgroup of people with a baseline Epworth Sleepiness Scale (ESS) score of 12 should be used in the modelling (see technical report issue 2).

The committee 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: primary therapy adherence, treatment response, placebo effect adjustment, health utility values, partner utilities, treatment discontinuation, adverse events, and dosing splits (see the technical report issues 1 to 9), which were outstanding after the technical engagement stage.

The condition

Excessive daytime sleepiness caused by obstructive sleep apnoea affects quality of life

3.1 The patient expert explained that obstructive sleep apnoea can negatively affect people's physical and mental wellbeing. Because of excessive daytime sleepiness aspects of daily life, such as education, employment, maintaining a social life and the ability to drive, are all negatively affected. Symptoms of sleep apnoea such as snoring can disrupt partners' sleep, which can affect their quality of life as well. The clinical experts noted that obstructive sleep apnoea can also be associated with an increased risk of high blood pressure or stroke. The committee concluded that excessive daytime sleepiness caused by obstructive sleep apnoea affects quality of life.

CPAP is an appropriate comparator, but some people cannot tolerate it

3.2 The clinical experts said that most people with excessive daytime sleepiness caused by obstructive sleep apnoea are referred to sleep clinics. Initial treatment includes lifestyle advice about weight loss. For people with mild symptomatic obstructive sleep apnoea mandibular devices are considered. NICE's guidance on continuous positive airway pressure (CPAP) for obstructive sleep apnoea/hypopnoea syndrome recommends CPAP for adults with moderate or severe obstructive sleep apnoea. The patient expert explained that CPAP is usually well tolerated, although some people struggle to use it regularly because of its size, the amount of noise it makes, and because it can affect sleep. The clinical experts also said CPAP is not well tolerated by some people with mental health issues because they can feel claustrophobic wearing a mask.

People with neurodegenerative conditions may also not tolerate CPAP. The clinical and patient experts said some people using CPAP will still have residual excessive daytime sleepiness. They noted that solriamfetol as another potential treatment option for this group would be welcome. The committee concluded CPAP is an appropriate comparator, but some people cannot tolerate it.

The clinical and cost-effectiveness evidence submitted by the company does not cover the full marketing authorisation

3.3 According to the marketing authorisation (see section 2.1), solriamfetol can be offered alone or in combination with a primary obstructive sleep apnoea therapy. However, the company positioned solriamfetol as an add-on to primary therapy such as CPAP for obstructive sleep apnoea (defined by the company as standard care). This is a smaller population than specified in the marketing authorisation. The committee concluded that the clinical and cost-effectiveness evidence submitted by the company does not cover the full marketing authorisation.

Solriamfetol treatment is likely to be limited to secondary care but more information is needed

3.4 Obstructive sleep apnoea is currently treated in sleep services commissioned by the relevant clinical commissioning group. The clinical experts noted that, if solriamfetol was recommended, the likely requirement for more monitoring of adherence to CPAP (see section 3.6) could put pressure on these services. In its evidence submission and economic model, the company assumed that solriamfetol would be administered in specialist sleep services only. The committee asked the clinical experts if there was a possibility that solriamfetol could be prescribed in primary care. The experts suggested that treatment would have to be started in the specialist sleep clinics but were uncertain if longer-term prescribing could move to primary care. The committee concluded that solriamfetol treatment is likely to be limited to secondary care, but more information is needed.

Clinical evidence

Solriamfetol with standard care improves excessive daytime sleepiness

3.5 TONES 3 was a 12-week, randomised, double-blind, placebo-controlled trial done in multiple centres. The intervention was solriamfetol given in doses of 37.5 mg, 75 mg, and 150 mg (also a 300 mg dose but this was unlicensed). The comparator in the trial was placebo. In both the intervention and comparator groups approximately 70% of patients adhered to a primary obstructive sleep apnoea therapy. This was defined as prior effective surgical intervention or CPAP use. The co-primary outcome of the trial was reduction in the ESS from baseline to week 12. The results showed a significant reduction in ESS from baseline to week 12 across all 3 solriamfetol doses. There was no improvement in quality of life using the EQ-5D-5L from baseline to week 12. The committee concluded that solriamfetol with standard care improves excessive daytime sleepiness.

Adherence to a primary obstructive sleep apnoea therapy like CPAP is unlikely to be affected by solriamfetol treatment, but more data are needed

3.6 The patient expert and ERG said some people with excessive daytime sleepiness may prefer to manage their symptoms with a drug treatment than with a primary therapy such as CPAP. This could lead to them using their CPAP less and therefore a reduction in the combined benefits with CPAP and solriamfetol. The company included patient adherence to a primary obstructive sleep apnoea therapy in its 3 trials as an exploratory end point. It also provided results from a peer-reviewed paper by Schweitzer et al. (2020), which showed no effect on adherence across the 3 trials from baseline up to week 40. The ERG noted that the results of these analyses were highly uncertain because of missing data and poor reporting. It said that the estimates were not reported separately for people classified as ‘compliant’ (adherent) or ‘non-compliant’ at baseline. The clinical experts said that in most sleep clinics CPAP machines can be

monitored remotely and that some people, such as heavy goods vehicle drivers, have their CPAP use monitored remotely regularly. The clinical experts acknowledged that, although people having solriamfetol alongside a primary therapy such as CPAP would have their use monitored, it may have to be more frequent. The committee noted the uncertainty in the trial data around adherence. It noted it would have preferred to see more sensitivity analysis of the impact of missing data across the 3 trials, and a subgroup analysis stratified by adherence at baseline. The committee concluded that adherence to a primary therapy like CPAP is unlikely to be affected by treatment with solriamfetol, but more data are needed.

The economic model

More evidence is needed to establish the clinical and cost-effectiveness evidence of solriamfetol without standard care

3.7 The TONES 3 trial included people who adhered to a primary obstructive sleep apnoea therapy (standard care) and people who did not (see section 3.6. The company's economic model assumed that everyone entering the model had solriamfetol with standard care (for example CPAP) or placebo with standard care. It presented a cost effectiveness scenario analysis that included people from TONES 3 who did not adhere to standard care. The company defined this as only using CPAP a little or not using a device at all. Also defined as non-adherent were people who had a surgical intervention that was no longer effective and who were not using CPAP. The ERG noted that the baseline ESS score was worse for the non-adherent than the adherent group. This meant that the improvement in ESS because of solriamfetol treatment was greater, resulting in a smaller incremental cost-effectiveness ratio (ICER) if the non-adherent group data were used. The committee felt that the company had not properly explained its methods for modelling the non-adherent group. It also noted that the company had not properly explained why people were not using their primary therapy. The committee recalled that the marketing authorisation for solriamfetol includes people who may not

be using a primary obstructive sleep apnoea therapy anymore. It concluded that it would like to see clinical and cost-effectiveness evidence for this group.

Treatment response defined as an ESS score reduction of 2 points or more is appropriate

3.8 The clinical experts said that the definition of treatment response for obstructive sleep apnoea varies considerably in clinical practice. The company used the ESS in its clinical trials as its primary end point to measure response to treatment (see section 3.5). Its model defined a treatment response as an ESS score reduction of 3 or more points, based on clinical opinion. Advice to the ERG was that a reduction in ESS of 2 or more points was appropriate but clinicians would consider other factors when assessing treatment effectiveness. The clinical experts said that, while an ESS reduction of 2 or more points may be appropriate, there is no consensus on what can be considered a clinically relevant ESS reduction and that it varies by individual. The ERG tested the ESS reduction threshold in a scenario analysis, which showed that changing the threshold did not significantly affect cost-effectiveness results. The committee acknowledged the uncertainty about the ESS but concluded that an ESS score reduction of 2 or more points was an appropriate criterion for treatment response.

The company's adjustment for observation bias in the model is plausible but considerable uncertainty remains

3.9 The company noted that in TONES 3 there was an improvement in ESS score from baseline to week 12 in the placebo plus standard care group. The company suggested this was due to an observation bias – the Hawthorne effect (that is, patients reported an improvement in ESS because they were being observed). The company attempted to adjust for this effect in its economic model by removing the improvement in ESS observed in the placebo arm from both the placebo and solriamfetol groups in the model. The ERG favoured a regression to the mean

approach, in which there is a tendency for extreme values to move closer to the mean when measures are repeated over time. The ERG assumed that the response to treatment in the placebo and solriamfetol groups reported in TONES 3 would be the same in routine practice. It used the raw unadjusted trial data for the placebo with standard care and solriamfetol with standard care groups. During technical engagement, the company presented evidence to suggest there was no regression to the mean. This included evidence from people transitioning from TONES 3 to TONES 5, a 52-week open-label trial assessing solriamfetol's long-term effectiveness. It included a 2-week placebo-controlled randomised withdrawal phase for patients moving from other TONES trials into TONES 5. Transitioning patients already being treated with solriamfetol showed a greater improvement in ESS when treatment with solriamfetol was unblinded. The ERG noted that these people could be susceptible to selection bias and not fully representative of a typical person with obstructive sleep apnoea. The clinical experts advised that a placebo effect is common in trials in this disease area and suggested it could have occurred in the TONES 3 placebo with standard care group. The ERG advised that natural history data on how ESS changes over time would be useful to determine the type of adjustment needed. But the clinical experts suggested these data do not exist. The committee accepted that there was likely to have been some observation bias in the trial. It acknowledged that there may be some regression to the mean, so there was a need to understand its potential impact in sensitivity analyses. The company's method for adjusting for observation bias in the economic model was plausible. But the committee would have preferred to see some threshold analysis assuming a regression to the mean effect or external data to better understand variations in ESS over time, had this existed. The committee concluded that the company's adjustment for observation bias effect in its model was plausible although considerable uncertainty remains.

The ERG's model structure is suitable but has some limitations

3.10 The ERG added a new health state to the company's model to allow for a response to treatment in the standard care alone group. The company's model did not include a response to treatment in the standard care alone group, assuming any response was caused by a Hawthorne effect (see section 3.9). The committee was concerned about the validity of some outputs generated by the ERG's model, including the percentage of people in the standard care group who still have a response to treatment at 3 years and 10 years (the figures are commercial in confidence and cannot be reported here). They noted that the level of response in the standard care alone group and the difference between the 2 groups was implausible. The committee asked the company to explore the regression to the mean effect, as modelled in the ERG's 4-state model (see section 3.9), in threshold analyses. The committee concluded that the ERG's model structure was suitable but with some limitations.

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

3.11 The company explained that, because the EQ-5D does not include a sleep domain, it was not sensitive to changes in quality of life for people with excessive daytime sleepiness caused by obstructive sleep apnoea. The company also noted that the trial was not long enough to capture changes in quality of life. It therefore used a mapping algorithm to estimate 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 it may underestimate the impact of treatments on quality of life in this condition. The committee noted that the results from the mapping algorithm estimated a high quality of life value even at extremely high ESS scores, which did not appear to be plausible. Higher ESS scores mean more excessive daytime sleepiness (the data for the mapping algorithm are academic in confidence and cannot be reported here). The committee was concerned that, if EQ-5D is truly insensitive to

changes in quality of life for people with this condition, then mapping ESS scores to it may not be appropriate. SF-36 data were collected by the company in TONES 3, from which SF-6D values can be derived. This can be more sensitive to this condition and potentially provide some insight into the utility valuation in this disease. The company did not provide these data to the committee. The committee wanted to see the SF-6D in the analysis and concluded that mapping from the ESS to the EQ-5D may not adequately capture changes in quality of life.

Partner utility values are an important consideration but there are not enough data to include them in the modelling

3.12 NICE's guide to the methods of technology appraisal paragraph 5.1.7 notes that the perspective on outcomes should include all direct health effects, whether for patients or for other people. The company included partner utility values as a scenario in its modelling. This was because of the substantial impact that symptoms of obstructive sleep apnoea and its treatment can have on partners. The clinical expert agreed that partner utility values should be considered because of the substantial impact on family members (see section 3.1). But the ERG was concerned about the methods the company used to estimate partner utility values because the time trade-off utility estimates may not be comparable to those from the EQ-5D. The impact on partner utilities of displacing treatments such as CPAP was also uncertain. The committee concluded that partner utility values are important to consider but it had not been presented with enough evidence to support its inclusion in the modelling.

Hospitalisation costs for serious adverse events should be included in the modelling

3.13 The company model did not include any costs for serious adverse events. It said this was because most adverse events in TONES 3 were mild or moderate in severity. For adverse events that led to treatment discontinuation, the company's model included the cost of 1 GP consultation. The ERG highlighted that some of the serious adverse

events related to solriamfetol in the 150 mg arm of TONES 5 led to hospitalisation. This included 1 cerebrovascular (stroke) episode. The company argued that to include the cost of stroke would not be appropriate because it can occur in the target patient population in the 'real world'. In its base case the ERG included hospitalisation costs for serious adverse events in patients taking solriamfetol (including stroke). The committee concluded that hospitalisation costs for serious adverse events should be included in the modelling.

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

3.14 Solriamfetol is available in different doses, which vary in cost and effectiveness. Results for these different treatment dose options were weighted, based on dose-splitting assumptions, to inform cost-effectiveness comparisons between solriamfetol and standard care. In the company's base case, it was assumed that the dose splits were 40%, 40% and 20% respectively for 37.5 mg, 75 mg and 150 mg doses of solriamfetol. The ERG noted that this dose split was different to that reported in a US study of prescribing data, in which a greater proportion of patients are on the 75 mg dose (the figures are commercial in confidence and cannot be reported here). In the ERG's base case it was assumed that 50% of people were on the 75 mg dose of solriamfetol. The ERG tested different dosing splits in a sensitivity analysis. The clinical experts explained that it is difficult to estimate the most likely dose split in NHS clinical practice. The ERG highlighted that the cost-effectiveness conclusions were not sensitive to dose split assumptions. The committee concluded that the range of dose split assumptions included in the company's and ERG's analysis is appropriate to account for the variability in clinical practice.

Cost-effectiveness estimates

Because of the uncertainty, an acceptable ICER is below £20,000 per QALY gained

3.15 NICE's guide to the methods of technology appraisal notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted the high level of uncertainty. In particular uncertainties around:

- the effect of solriamfetol on adherence to primary obstructive sleep apnoea therapy (see section 3.6)
- whether changes in quality of life were adequately captured by mapping the ESS to the EQ-5D (see section 3.11)
- the adjustment for the placebo effect (see section 3.9)
- the dose splits that will be used in clinical practice (see section 3.14).

Therefore the committee agreed that, because of the high level of uncertainty in the analyses, an acceptable ICER would be below £20,000 per quality-adjusted life year (QALY) gained.

Solriamfetol with standard care is not a cost-effective use of NHS resources

3.16 The committee considered the cost-effectiveness estimates for solriamfetol plus standard care compared with standard care alone. The committee preferred to use the ERG's base case with the following assumptions:

- treatment response defined as an ESS score reduction of 2 or more points (see section 3.8)
- observation bias (see section 3.9)
- ESS mapped to EQ-5D (see section 3.11)

- hospitalisation costs included for severe adverse events (see section 3.13)
- the ERG's preferred dose split: 50% of people having 75 mg solriamfetol (see section 3.14).

The ICER for solriamfetol with standard care compared with standard care alone was £32,465 per QALY gained. The committee concluded that the cost-effectiveness analysis presented was highly uncertain but the most plausible ICER estimate was likely to be above what NICE considers a cost-effective use of NHS resources.

Other factors

3.17 The clinical expert noted that people with mental health or neurodegenerative conditions struggle to adequately use CPAP regularly, making it difficult to control their excessive daytime sleepiness from obstructive sleep apnoea. The marketing authorisation for solriamfetol includes people with obstructive sleep apnoea whose excessive daytime sleepiness has not been satisfactorily treated by primary obstructive sleep apnoea therapy, such as CPAP. The committee agreed with clinical experts who suggested that people with neurodegenerative conditions or mental health issues with residual excessive daytime sleepiness could be discriminated against if NICE's recommendations restricted solriamfetol for use with CPAP only. The committee has asked the company to provide clinical and cost-effectiveness results for people who cannot tolerate CPAP.

3.18 The model-based QALY estimates may not have fully captured changes in health-related quality of life (see sections 3.11 and 3.12) and the committee took this into account in its decision making.

Conclusion

Solriamfetol is not recommended for treating excessive daytime sleepiness caused by obstructive sleep apnoea

3.19 The committee recognised that excessive daytime sleepiness caused by obstructive sleep apnoea is a debilitating condition that negatively affects many aspects of daily life (see section 3.1). It acknowledged that solriamfetol with standard care was more effective than standard care alone in reducing excessive daytime sleepiness as measured by the ESS (see section 3.5). The committee was not presented with the clinical and cost effectiveness of solriamfetol alone for people who cannot tolerate CPAP. It believed there was substantial uncertainty in the company's analysis, including about:

- adherence to a primary sleep apnoea therapy (see section 3.6)
- how quality of life was measured (see section 3.11)
- the placebo effect adjustment (see section 3.9)
- what an accurate dose split is (see section 3.14).

The committee agreed that it would like to see analyses that include the following:

- sensitivity analysis to assess the impact of missing data on adherence to primary therapy at baseline
- use of SF-6D data from the company's trials to assess quality of life measures
- sensitivity analysis to explore the impact of partner utilities using EQ-5D
- a threshold analysis to assess the potential impact of regression to the mean
- clinical and cost effectiveness of solriamfetol alone compared with standard care.

The committee considered that the most plausible cost-effectiveness

estimate for solriamfetol with standard care compared with standard care alone was 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
March 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.

Tomas Keating
Technical lead

Victoria Kelly
Technical adviser

Gavin Kenny
Project manager

ISBN: [to be added at publication]