Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2439

solriamfetol 75mg and 150mg film-coated tablets (Sunosi®)

Jazz Pharmaceuticals UK Ltd

10 June 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan equivalent process.

solriamfetol (Sunosi®) is accepted for restricted use within NHSScotland.

Indication under review: to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy).

SMC restriction: for use in patients who have failed modafinil or have a contraindication or intolerance to modafinil**.**

Solriamfetol, compared with placebo, reduced excessive daytime sleepiness in adults with narcolepsy.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Published 11 July 2022

Indication

Solriamfetol is indicated to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy).[1]

Dosing Information

In patients with narcolepsy, the recommended starting dose is solriamfetol 75mg orally once daily with or without food, upon awakening. If clinically indicated in patients with more severe levels of sleepiness, a starting dose of 150mg may be considered. Depending on clinical response, the dose can be titrated to a higher level by doubling the dose at intervals of at least 3 days, with a recommended maximum daily dose of 150mg once daily. Taking solriamfetol less than 9 hours before bedtime should be avoided as it may affect night time sleep. The need for continued treatment and the appropriate dose should be periodically assessed during extended treatment in patients prescribed solriamfetol.

Blood pressure and heart rate should be assessed before initiating solriamfetol and should be monitored periodically during treatment, especially after increasing the dose. Pre-existing hypertension should be controlled before initiating solriamfetol and caution should be exercised in treating patients at higher risk of major adverse cardiovascular (CV) events (MACE), particularly patients with pre-existing hypertension, patients with known CV or cerebrovascular disease and elderly patients. If a patient has increases in blood pressure or heart rate that cannot be managed with dose reduction of solriamfetol or other appropriate medical intervention, discontinuation of solriamfetol should be considered. Caution should be exercised when using other medicinal products that increase blood pressure and heart rate.

Treatment should be initiated by a healthcare professional experienced in the treatment of narcolpesy.[1]

Product availability date

1 September 2020
Solriamfetol meets SMC orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Solriamfetol is a dopamine and norepinephrine reuptake inhibitor; though its mechanism of action to improve wakefulness in patients with excessive daytime sleepiness (EDS) associated with narcolepsy has not been fully characterised.[1]

The submitting company has requested that SMC considers solriamfetol when positioned for use in patients who have failed modafinil or have a contraindication or intolerance to modafinil.

The key evidence supporting the efficacy and safety of solriamfetol comes from TONES 2, a multicentre, randomised, double-blind, parallel group, phase III study in adults (18 to 75 years old)

with a diagnosis of narcolepsy (according to International Classification of Sleep Disorders, 3rd edition or Diagnostic and Statistical Manual of Mental Disorders, 5th edition). Patients were eligible if at baseline they had a mean sleep latency <25 minutes (as documented by the mean of the first four trials of the baseline five trials of the 40-minute Maintenance of Wakefulness Test [MWT]), and an Epworth Sleepiness Scale (ESS) score ≥10. They also had a usual nightly total sleep time of at least 6 hours and body mass index (BMI) from 18 to <45kg/m^2. [2, 3]

Patients were randomised equally to receive oral solriamfetol 75mg, 150mg, 300mg (not a licensed dose, thus results are not presented) or placebo once daily over 12 weeks. Patients who were randomised to the 150mg and 300mg doses received 75mg and 150mg, respectively, on days 1 to 3 of the first week, with the full dose commencing on day 4. Randomisation was stratified according to the presence or absence of cataplexy. [2, 4]

The co-primary outcomes were change from baseline to week 12 in mean sleep latency derived from first four of five trials of 40-minute MWT, and change from baseline to week 12 in ESS score. The three doses of solriamfetol were compared with placebo in a hierarchy that included the key secondary outcome percentage of patients with improvement on Patient Global Impression of Change (PGI-C) commencing at the highest solriamfetol dose. Efficacy was assessed in the modified intention to treat (mITT) population, which comprised all randomised patients who received at least one dose of study drug and had baseline and at least one post-baseline efficacy evaluation of MWT and ESS. [2, 3]

The co-primary outcomes, change from baseline to week 12 in MWT and ESS score, and the key secondary outcome, percentage of patients with improvement on PGI-C at week 12, were statistically significantly improved with solriamfetol 150mg versus placebo. For solriamfetol 75mg, compared with placebo, there was a statistically significant improvement in ESS at week 12, but not in the MWT, therefore the hierarchical testing strategy was broken and the comparison with placebo for PGI-C is descriptive only. Results are detailed in Table 1 for the licensed doses. [2, 4]

Table 1: Primary and secondary outcomes at week 12 of TONES 2 study in the mITT. [2, 4]

	Placebo (N= 58)	**Solriamfetol 75mg (N=59)**	**Solriamfetol 150mg (N=55)**
Maintenance of Wakefulness Test, minutes[a]			
Change, LS mean	2.12	4.74	9.77
Difference, LS mean (95% CI) p-value	-	2.62 (-1.04, 6.28) 0.160	7.65 (3.99, 11.3) <0.001
Epworth Sleepiness Scale score[b]			
Change, LS mean	-1.6	-3.8	-5.4
Difference, LS mean (95% CI) p-value	-	-2.2 (-4.0, -0.3) 0.0211	-3.8 (-5.6, -2.0) <0.001

Patient Global Impression of Change			
Improved, n (%)	23 (40%)	40 (68%)	43 (78%)
Difference, % (95% CI) p-value	-	28% (10.8, 45.5) 0.0023[c]	38% (21.9, 55.2) <0.001

Abbreviations: CI = confidence interval; LS = least square; Change = LS mean change from baseline to week 12.
[a] MWT is a measure of an individual's ability to remain awake during the daytime in a darkened, quiet environment. MWT sleep latency range from 0 to 40 minutes, with higher latencies indicating greater ability to stay awake.
[b] ESS is a measure of a person's general level of daytime sleepiness or their average sleep propensity in daily life. Patients completed this self-administered questionnaire (with 8 questions) with regard to the level of sleepiness they experienced over the past 7 days. Total score range of 0 to 24, with higher scores indicating more severe sleepiness.
[c] This is a nominal p-value; 75mg solriamfetol group was below the hierarchical break, therefore the results reported for this outcome are descriptive only and not inferential.

The proposed positioning is in patients who have failed modafinil or have a contraindication or intolerance to modafinil. In TONES 2, almost half of study patients had prior use of modafinil .[5, 6] Thus, the submitting company presented a post-hoc subgroup analysis stratified by prior use of modafinil for change from baseline to week 12 in ESS and upon request for change from baseline to week 12 in MWT and percentage of patients reporting improvement on PGI-C; it generally showed similar trends in patients with or without prior modafinil use.[6]

There were least square mean differences in change from baseline to week 12 that favoured solriamfetol versus placebo in the Functional Outcomes of Sleep Questionnaire 10-item (FOSQ-10) score, the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) in impairment at work, and impairment of activity outside work, and in the Short-Form 36 (SF-36) physical component summary score. However, in general changes with lower doses of solriamfetol were smaller and not significantly different from placebo. Solriamfetol had limited effects on EuroQol 5-dimension 5-level (EQ-5D-5L) with no differences from placebo and no effect on absenteeism on WPAI:SHP. [7]

Supportive evidence came from TONES 1 and 5. TONES 1 was a 12-week, double-blind, phase II, study, in adults with narcolepsy with a baseline ESS score ≥10 and a baseline sleep latency ≤10 minutes (on the 40 minute MWT). Patients received oral solriamfetol 150mg once daily for 4 weeks and then, 300mg (unlicensed) for 8 weeks (N=44) or matching placebo (N=49). The primary outcomes were: change from baseline to end of week 12 in mean sleep latency on the MWT, and percentage of patients reported by clinicians as improved using the Clinician Global Impression of Change (CGI-C) at week 12. At 4 weeks, improvements were greater with solriamfetol 150mg (the licensed dose) versus placebo on the primary efficacy outcomes.[8]

TONES 5 was an open-label extension study, which recruited patients with narcolepsy or obstructive sleep apnoea (OSA) who had completed a previous solriamfetol study (N=643). All patients entered a two-week titration phase where they commenced once daily solriamfetol 75mg, which was increased to 150mg, then 300mg until the maximum tolerated dose was achieved. Patients continued on this dose for up to 40 weeks (Group A) or 52 weeks (group B). The

study enrolled 226 patients with narcolepsy (186 and 40 in Group A and B, respectively). After approximately 6 months of treatment a subgroup of patients (including 79 with narcolepsy) were randomised (stratified by condition) equally to double-blind continuation of their solriamfetol dose or placebo for 2 weeks. At the end of this randomised withdrawal phase, patients continued to receive solriamfetol. The most frequently received dose during open-label treatment was 75mg, 150mg and 300mg (unlicensed) for 10%, 32% and 58% of patients, respectively. In the subgroup of patients with narcolepsy after the initial two-week titration, LS mean ESS decreased from baseline of 17.3 to 10.0 in Group A and from 17.9 to 10.2 in Group B; the proportions reporting improvement in PGI-C was 94% in Group A and 95% in Group B. These benefits in both outcomes were generally maintained in patients who continued treatment over the 40 and 52 week treatment periods. In the overall population of the 2-week withdrawal phase, patients treated with solriamfetol generally maintained their improvement while those who received placebo worsened. Over this 2-week phase, the LS mean change in ESS was significantly less with solriamfetol than placebo (1.6 versus 5.3, respectively) with a LS mean difference of -3.7 (95% CI: -4.8 to -2.6). Similar results were observed in the narcolepsy subgroup. [2, 9-10]

A Bayesian indirect treatment comparison (ITC) was conducted to compare the efficacy and safety of solriamfetol 150mg and solriamfetol 75mg daily with pitolisant ≤40mg daily and sodium oxybate 3 to 9 grams daily, with placebo as a common comparator in adult patients with narcolepsy (with or without cataplexy) and EDS. The ITC included eight studies (including TONES 1 and 2 for solriamfetol). Efficacy outcomes included ESS at weeks 4 and 8 and MWT40 at week 8. Safety outcomes included incidence of any treatment emergent adverse event (TEAE), incidence of serious adverse events (AEs) and incidence of discontinuations as a result of AEs. The submitting company concluded that solriamfetol is at least as effective, and in some cases more effective than pitolisant and sodium oxybate. In terms of the safety outcomes they noted that incidence of AEs was similar across all treatments analysed with the exception of the 150mg dose of solriamfetol; however, there were no differences (credible intervals for relative effectiveness crossed zero) in the incidence of discontinuations resulting from AEs nor for overall rates of serious AEs. The submitting company considered that the results of the ITC justified the use of a cost-minimisation analysis. They noted that there is no evidence of suitable quality to allow dexamfetamine or methylphenidate to be incorporated into the ITC.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

The European Medicines Agency (EMA) review noted that the overall safety data for solriamfetol was mainly characterised by psychiatric disorders (symptom complex of anxiety, feeling jittery and irritability), nervous system disorders (headache, dry mouth and dizziness), gastrointestinal disorders (nausea, decreased appetite and diarrhoea) and effects on vital signs (blood pressure and heart rate increase). In most cases a clear dose-response or tendency towards higher incidence with increasing doses was observed.[2]

In the TONES 2 study within the placebo, solriamfetol 75mg and 150mg groups, adverse events were reported by 46% (27/59), 58% (34/59) and 80% (47/59), respectively. These were serious in only one patient in the 150mg group. They led to study drug discontinuation in 1.7%, 1.7% and 5.1% of patients, respectively. In the respective groups, the most common adverse events (reported by >6% of patients in any group) included headache (5.1%, 10% and 24%), nausea (1.7%, 5.1% and 10%), decreased appetite (1.7%, 8.5% and 8.5%), nasopharyngitis (5.1%, 8.5% and 14%), dry mouth (3.4%, 5.1% and 6.8%), anxiety (1.7%, 1.7% and 5.1%), upper respiratory tract infection (1.7%, 1.7% and 6.8%). [4]

Adverse events of special interest included cardiovascular (CV) events.[2] Solriamfetol increases blood pressure and heart rate in a dose-dependent fashion. Epidemiological data show that chronic elevations in blood pressure increase the risk of major adverse CV events, including stroke, heart attack and CV death. [1] Patients with significant CV disease were excluded from the solriamfetol studies. Therefore, solriamfetol is contraindicated in patients with unstable CV disease, serious heart arrhythmias and other serious heart problems.[1, 2] Though it was noted that in the clinical studies, patients with narcolepsy were less prone to CV risks than patients with OSA as they were younger, with lower BMI and a lower rate of comorbidities related to hypertension, hyperlipidaemia, and diabetes mellitus and they had a better medical history. [2]

The solriamfetol studies also excluded patients with a history of psychosis or bipolar disorders and the Summary of product characteristics (SPC) notes that caution should be exercised when treating these patients due to psychiatric adverse reactions that could exacerbate symptoms of pre-existing psychiatric disorders.[1]

Summary of clinical effectiveness issues

Narcolepsy (with or without cataplexy) is a chronic disabling sleep disorder of unknown aetiology, associated with a variety of symptoms including EDS as the most troublesome. EDS presents with different phenotypes including sleep attacks, involuntary napping, excessive need for sleep, difficulty sustaining attention, and cognitive dysfunction; and the degree of EDS is severe in most patients. Narcolepsy usually requires lifelong treatment with non-pharmacological (including with scheduled daytime napping) and pharmacological management tailored to each patient's symptoms, needs and comorbidities. Recent European guidelines recommend solriamfetol, pitolisant (licensed for adults for the treatment of narcolepsy with or without cataplexy; not recommended by SMC [SMC 1229/17]) or modafinil (licensed for adults for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy) monotherapy as first-line pharmacological management when EDS is the only or main symptom. In the second line, combination therapies with pitolisant plus modafinil or solriamfetol, or combination of sodium oxybate (licensed for the treatment of narcolepsy with cataplexy in adult patients; not recommended by SMC [SMC 246/06]; off-label if used in patients without cataplexy) plus any wake promoting agents (solriamfetol, pitolisant, modafinil, methylphenidate [off-label], or

amphetamine derivatives) or another monotherapy with sodium oxybate, methylphenidate or amphetamines are recommended. [2, 11] Solriamfetol meets SMC orphan equivalent criteria for this indication. Clinical experts consulted by SMC considered that solriamfetol fills an unmet need in this therapeutic area, namely by providing an additional treatment option for those who cannot tolerate or do not respond to currently available medications.

In TONES 2, there was a dose-dependent improvement in ESS of approximately 2 to 4 points and in MWT of approximately 3 to 8 minutes (difference with the 75mg dose versus placebo was not statistically significant leading to a hierarchical break) with solriamfetol 75mg and 150mg, compared with placebo. In addition, 28% and 38% more patients reported an improvement on PGI-C with solriamfetol than with placebo (only descriptively assessed for the 75mg dose). Solriamfetol benefits were seen within 1 to 2 weeks of treatment and appeared to be maintained for up to 1 year in the TONES 5 study. This open label extension study included a 2-week placebo-controlled randomised withdrawal phase after 6 months' treatment; results showed that patients treated with solriamfetol generally maintained their improvement while those who received placebo during this withdrawal phase worsened. The EMA considered that solriamfetol clinical benefit was relevant, shown to be robust and that its superiority over placebo in improving EDS was highly significant for solriamfetol 150mg and significant for solriamfetol 75mg. [2, 4, 10]

With regards to quality of life and work impairment, some benefits were observed with the highest licensed solriamfetol dose (150mg [numerical benefit 75mg also seen with a subscale of the SF-36]). The clinical significance of the observed improvements is unclear. For all solriamfetol doses, there were no benefits over placebo in overall quality of life measured using EQ-5D-5L or in absenteeism (on WPAI:SHP).[7]

The submitting company has requested that SMC considers solriamfetol when positioned for use in patients who have failed modafinil or have a contraindication or intolerance to modafinil. However, the study population in TONES 2 was wider than the proposed positioning as only about half had previously received modafinil , and it is unknown how many had a contraindication or intolerance to modafinil. [5, 6] This may affect the generalisability of the study results to the Scottish population that may receive this treatment in this proposed positioning. Post-hoc subgroup analyses in patients with and without prior use of modafinil were compared and appeared consistent; however this comparison was unpowered. It is uncertain whether other factors may affect the generalisability of the study results, including the over-representation of female patients and patients without cataplexy compared to what is generally seen in practice; in addition most patients were North American. [2, 4]

To enter TONES 2, patients had to discontinue any medications that could affect the evaluation of EDS (including methylphenidate, amphetamines, modafinil, sodium oxybate and benzodiazepines); and these medications were prohibited throughout the study. No clinical data are thus available to support the use of solriamfetol in combination with any of these other narcolepsy treatment options.

In practice, solriamfetol would be dosed in accordance with the SPC, which recommends a starting dose of solriamfetol 75mg once daily that can be increased to a maximum of 150mg depending on clinical response. Dosing in the clinical studies was different. In TONES 2, patients were assigned to fixed once daily doses (75mg, 150mg or 300mg [unlicensed]) and it is possible that some patients may not have received the dose that they would require in practice. In TONES 5, patients commenced on solriamfetol 75mg once daily, increased to the maximum dose (up to 300mg) that they could tolerate in terms of adverse events and it is possible that some had higher doses than they would require in practice. Overall, a large proportion of patients in TONES 5 (58%) received the unlicensed 300mg dose and narcolepsy patients accounted for only 35% of TONES 5 overall study population. Thus, long-term data with the licensed doses are limited for the indication under review, a chronic condition, requiring long-term treatment.[1, 2, 10]

The submitting company considered that sodium oxybate, pitolisant, dexamfetamine, and off-label methylphenidate were relevant comparators in the proposed positioning. These comparators were defined based on clinical experts' feedback received by the submitting company although they noted that there was no consensus on a standard second line therapy (post modafinil). They also stated that the impact of narcolepsy and of its symptoms is highly individual, as is response to available treatments, thus the treatment pathway can vary to accommodate a patient's individual needs or specific requirements. Recent guidelines recommend the use of some combination therapies in second line treatment of EDS in narcolepsy patients; it is uncertain whether combination therapies (such as pitolisant plus modafinil; or sodium oxybate plus a wake promoting agent) are also relevant comparators.[11] Clinical experts consulted by SMC suggested that in the proposed positioning, in Scottish clinical practice, the most used treatments are dexamfetamine and methylphenidate.

To address the lack of direct data against any active comparators, the submitting company conducted an ITC with sodium oxybate and pitolisant. A number of limitations affect the validity of the ITC: the population was broader than the proposed positioning; there was a high level of clinical and methodological heterogeneity across the included studies, including with regards to patients' baseline characteristics and concomitant therapies. Efficacy outcomes were compared at 4 and 8 weeks because the durations of comparative studies were ≤9 weeks. The analyses did not assess health-related quality of life outcomes or patient or clinician reported improvements using the PGI-C (TONES 2 key secondary outcome) or CGI-C. Due to these limitations, the submitting company's conclusions are uncertain. In addition, no comparisons against dexamfetamine and methylphenidate were presented due to an absence of data identified through a systematic literature review and targeted literature search. Uncertainty remains around the relative efficacy and safety of solriamfetol versus dexamfetamine and methylphenidate.

*Other data were also assessed but remain confidential.**

Patient and Clinician Engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of solriamfetol, as an orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- People with narcolepsy suffer from a range of debilitating symptoms, which have a detrimental impact on daily life, relationships, education and work.
- Current medicines provide variable degrees of management of narcolepsy symptoms and are used to reduce rather than eliminate symptoms. Many patients take a combination of therapies, depending on the need and efficacy for the individual. Current medications have minimal impact on excessive daytime sleepiness in some patients. In addition, some patients do not tolerate the available options.
- Solriamfetol is expected to be reasonably well-tolerated and it will provide an additional licensed option with a convenient once daily dosage.
- Although it is not fully understood how solriamfetol works, benefits are expected for some patients with narcolepsy. Less sleepiness with solriamfetol could result in significantly improved quality of life for some patients.
- If solriamfetol can improve the experience of someone with narcolepsy, there will be a positive impact on the patients' family and carers and on the patients' ability to build and maintain current and future relationships.

Additional Patient and Carer Involvement

We received a patient group submission from Narcolepsy UK, which is a registered charity. Narcolepsy UK has received 20% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Narcolepsy UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing solriamfetol to sodium oxybate, pitolisant, dexamfetamine and methylphenidate for the second-line treatment of patients with EDS due to narcolepsy. The submitting company identified the aforementioned comparator treatments from its clinical expert interviews. However, no consensus over second-line treatments post first-line modafinil was confirmed, although dexamfetamine and methylphenidate were mentioned as being commonly prescribed.

The main source of efficacy and safety data to justify the assumption of clinical equivalence was from the ITC mentioned earlier in the DAD. However, comparative data against dexamfetamine

and methylphenidate were not available in the ITC. The unavailability of data resulted in their safety and efficacy profiles compared with solriamfetol to be assumed similar based on clinician interviews.

The cost-minimisation analysis included only direct medicine costs for solriamfetol, sodium oxybate, pitolisant, dexamfetamine and methylphenidate. These were presented for year 1 and year n (referring to any year beyond year 1). Initiation, administration, monitoring, management and subsequent treatment costs were assumed to be equal and therefore excluded. Potential dose quantities of solriamfetol and the comparators were in-line with those stated in the SPCs. Titrations were incorporated into the year 1 medicine costs for solriamfetol, sodium oxybate and pitolisant. For year 1 and year n, total cost calculations in the base case utilised estimates of the proportion of patients on final doses. For solriamfetol, the final dose proportion split the 75mg and 150mg doses based on German prescribing data. The company assumed an equal split of the possible sodium oxybate final doses of 4.5g, 6g and 9g. Pitolisant's final dose proportion split of the 18mg and 36mg doses was based on manufacturer estimates (1:2). Methylphenidate and dexamfetamine patients were assumed to receive a 40mg dose based on clinical interviews. Medicine costs were obtained from the British National Formulary (BNF).

The base case results are presented in Table 2. Cost savings of using solriamfetol were shown against sodium oxybate and pitolisant, with solriamfetol being cost-increasing compared with dexamfetamine and methylphenidate.

Table 2: Results of the cost-minimisation analysis

	Cost in year 1 (£)	Incremental cost	Cost in a subsequent year (£)	Incremental cost
Solriamfetol	£2,702	-	£2,705	-
Sodium oxybate	£9,380	-£6,678	£9,464	-£6,759
Pitolisant	£6,245	-£3,543	£6,269	-£3,564
Dexamfetamine	£1,931	£771	£1,931	£775
Methylphenidate	£700	£2,002	£700	£2,005

Dexamfetamine and methylphenidate costs based on a 40mg daily dose. Pitolisant costs based on a manufacturer provided final split of 1:2 of the 18mg and 36mg doses post-week 3. Sodium oxybate costs based on an equal final split of the 4.5mg, 6mg and 9mg daily doses. Solriamfetol costs based on a split of the 75mg and 150mg daily doses from German prescribing data. Discrepancies in the year 1 and year n costs for solriamfetol, sodium oxybate and pitolisant are a result of titration. Incremental cost is for solriamfetol relative to comparators, such that a negative value represents a cost-saving with solriamfetol. Year n refers to any year beyond Year 1.

Scenario analyses were performed using a granular comparison of different final doses. These results are presented Table 3. Solriamfetol was cost-saving when compared to sodium oxybate and pitolisant when varying the final doses. Solriamfetol was often cost-increasing when compared to dexamfetamine, and was always cost-increasing when compared to methylphenidate. Adjustment of year 1 titration times did not significantly affect results.

Table 3: Scenario analyses

		Cost in year 1 (£)	Incremental cost for:		Cost in year n (£)	Incremental cost for:	
			Solriamfetol 75mg	Solriamfetol 150mg		Solriamfetol 75mg	Solriamfetol 150mg
-	Solriamfetol 75mg	£2,308	-	Not applicable	£2,308	-	Not applicable
-	Solriamfetol 150mg	£3,225	Not applicable	-	£3,232	Not applicable	-
1	Pitolisant[a]	£6,245	-£3,937	-£3,020	£6,269	-£3,961	-£3,037
2	Sodium oxybate 4.5g	£6,552	-£4,244	-£3,327	£6,552	-£4,244	-£3,320
3	Sodium oxybate 6g	£8,694	-£6,386	-£5,469	£8,736	-£6,428	-£5,504
4	Sodium oxybate 9g	£12,894	-£10,586	-£9,669	£13,104	-£10,796	-£9,872
5	Dexamfetamine 40mg	£1,931	£377	£1,294	£1,931	£377	£1,302
6	Methylphenidate 40mg	£700	£1,607	£2,524	£700	£1,607	£2,532
7	Pitolisant (All patients receive 18mg from week 3)	£3,834	-£1,526	-£609	£3,761	-£1,454	-£529
8	Dexamfetamine 60mg	£2,896	-£588	£329	£2,896	-£588	£336
9	Dexamfetamine 10mg	£483	£1,825	£2,742	£483	£1,825	£2,750
10	Methylphenidate 60mg	£813	£1,495	£2,412	£813	£1,495	£2,420
11	Methylphenidate 10mg	£292	£2,016	£2,933	£292	£2,016	£2,941

[a] Pitolisant costs based on a manufacturer provided final split of 1:2 of the 18mg and 36mg doses post-week 3.

Incremental cost is for solriamfetol relative to comparators, such that a negative value represents a cost-saving with solriamfetol. Year n refers to any year beyond Year 1.

Key limitations of the analysis were:

- There was uncertainty over which second-line treatments were most relevant and frequently used in NHS Scotland. Dexamfetamine and methylphenidate are likely to be more commonly used than pitolisant and sodium oxybate, and are less costly than solriamfetol, however a systematic review performed by the submitting company highlights the lack of evidence for these treatments.
- It was assumed that dexamfetamine and methylphenidate would have similar safety and efficacy profiles compared with solriamfetol. As these assumed profiles were based on clinician interviews, this increased uncertainty in the appropriateness of these comparators in the cost-minimisation analysis and the obtained cost-increasing results.
- The final dose proportions for solriamfetol, sodium oxybate and pitolisant generated potential uncertainty in the results. However, scenario analyses highlighted solriamfetol was cost-saving for a range of dose scenarios in-line with the base case results.
- The daily dose assumptions of dexamfetamine and methylphenidate were based on clinical opinion, and generated potential uncertainty in the results. However, scenario analyses highlighted solriamfetol was mostly cost-increasing for a range of dose scenarios, which was in line with the base case results.

Although solriamfetol was cost-saving against sodium oxybate and pitolisant, it was generally cost-increasing when compared to dexamfetamine and methylphenidate.

The Committee considered the benefits of solriamfetol in the context of the SMC decision modifiers that can be applied and agreed that as solriamfetol is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted solriamfetol for restricted use in NHSScotland.

Additional information: guidelines and protocols

There are no published guidelines in Scotland or the UK for the management of narcolepsy. The European Academy of Neurology (EAN), European Sleep Research Society (ESRS), and European Narcolepsy Network (EU-NN) published a guideline and expert statements on the management of narcolepsy in adults and children in 2021. [11] The guideline recommends that treatment goals and choice of treatments should take into consideration an individual's pattern of symptoms, preferences and existing comorbidities. They make the following pharmacological recommendations for narcolepsy for adults for whom EDS is the main symptom:

- As first-line therapies, they recommend the use of either solriamfetol, pitolisant or modafinil as monotherapy.

- In the second line, they recommend the use of either
  - combination therapies with: pitolisant in combination with modafinil or solriamfetol; or sodium oxybate in combination with any wake promoting agents (solriamfetol, pitolisant, modafinil, methylphenidate, or amphetamine derivates)
  - or another monotherapy with: sodium oxybate, methylphenidate or amphetamines.

This guideline notes that the lack of head-to-head studies makes comparisons of efficacy between the different stimulants/wake-promoting treatments options difficult.

Additional information: comparators

Mono- or combination therapies with sodium oxybate, pitolisant, methylphenidate or amphetamine derivates (dexamfetamine).

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Solriamfetol	**75mg to 150mg orally once daily**	**2,308 to 3,232**

Costs from BNF online on 4 March 2022.

Additional information: budget impact

The submitting company estimated there would be an eligible patient population of 152 in year 1 rising to 167 in year 5. The estimated uptake rate was 10% in year 1 and 30% in year 5. This resulted in 15 patients estimated to receive treatment in year 1 rising to 50 patients in year 5.

The gross impact on the medicines budget was estimated to be £41k in year 1 rising to £136k in year 5. Other medicines were assumed to be displaced, however the net budget impact was based on an assumption that a significant proportion of patients would receive solriamfetol in place of sodium oxybate and pitolisant, which were not felt to be the main comparators by SMC clinical experts. The extent of additional costs or savings is dependent on which medicines are likely to be displaced in each health board.

References

1. Jazz Pharmaceuticals Ltd. Solriamfetol film-coated tablets (Sunosi®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 26 October 2021.

2. The European Medicines Agency (EMA) European Public Assessment Report. Solriamfetol film-coated tablets (Sunosi®). 14 November 2019, EMA/686622/2019. www.ema.europa.eu

3. Jazz Pharmaceuticals. Clinical Trial Protocol: 14-002. Study title: A Twelve-week, Double-blind, Placebo-controlled, Randomized, Parallel-group, Multicenter Study of the Safety and Efficacy of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Narcolepsy. February 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02348593

4. Thorpy MJ, Shapiro C, Mayer G, Corser BC, Emsellem H, Plazzi G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. Ann Neurol. 2019;85(3):359-370

5. National Institute for Health and Care Excellence (NICE) Single Technology Appraisal. Solriamfetol for treating excessive daytime sleepiness caused by narcolepsy [ID1602]. Committee Papers. 05 March 2021. Available at https://www.nice.org.uk/guidance/TA758/history

6. Jazz Pharmaceuticals. **CONFIDENTIAL.** TONES 2 Clinical study report. A twelve-week, double-blind, placebo-controlled, randomized, parallel-group, multicenter study of the safety and efficacy of JZP-110 [(r)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy. 2017.

7. Emsellem HA, Thorpy MJ, Lammers GJ, Shapiro CM, Mayer G, Plazzi G, et al. Measures of functional outcomes, work productivity, and quality of life from a randomized, phase 3 study of solriamfetol in participants with narcolepsy. Sleep Med. 2020;67:128-136.

8. Ruoff C, Swick TJ, Doekel R, Emsellem HA, Feldman NT, Rosenberg R, et al. Effect of Oral JZP-110 (ADX-N05) on Wakefulness and Sleepiness in Adults with Narcolepsy: A Phase 2b Study. Sleep. 2016;39(7):1379-1387.

9. Jazz Pharmaceuticals. **CONFIDENTIAL**. TONES 5. Clinical study report. A long-term safety and maintenance of efficacy study of JZP-110 [(r)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy or obstructive sleep apnoea. 2018.

10. Malhotra A, Shapiro C, Pepin JL, Hedner J, Ahmed M, Foldvary-Schaefer N, et al. Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea. Sleep. 2020;43(2).

11. Bassetti CLA, Kallweit U, Vignatelli L, Plazzi G, Lecendreux M, Baldin E, et al. European guideline and expert statements on the management of narcolepsy in adults and children. Eur J Neurol. 2021

This assessment is based on data submitted by the applicant company up to and including 14 April 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.