NICE National Institute for Health and Care Excellence

For public observes: Contains no confidential information (noACiC)

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

Chair's presentation

2nd appraisal meeting - Committee C

Chair: Stephen O'Brien

Technical team: Alan Moore, Alex Filby, Jasdeep Hayre

Company: Jazz Pharmaceuticals

ERG: Southampton Health Technology Assessment Centre (SHTAC)

13th October 2021

Excessive daytime sleepiness (Narcolepsy)

Overview of the condition

- Narcolepsy is a rare, disabling long-term brain disorder that causes a person to fall asleep at inappropriate times. Estimated to affect at least 25,000 people in UK, and usually diagnosed between 20 and 40 years of age.
- In narcolepsy, the brain is unable to regulate sleep and waking patterns normally.
- It can result in **excessive sleepiness**: irrepressible need to sleep, struggle to stay awake and alert, likely to fall asleep during the day (often while eating or talking), regularly napping but wake up feeling unrefreshed, and still sleep for long hours at night.
- Excessive sleepiness caused by narcolepsy can affect many aspects of daily life, including education, employment, driving, relationships, emotional and general health.
- Other symptoms of narcolepsy can include sleep paralysis, excessive dreaming, disturbed nocturnal sleep, sleep attacks (falling asleep suddenly and without warning) and cataplexy (temporary loss of muscle control resulting in weakness and possible collapse [type 1 narcolepsy = presence of cataplexy, type 2 = without cataplexy]).
- Narcolepsy diagnosis made through clinical history and a multiple sleep latency test preceded by overnight polysomnography. More difficult to diagnose without cataplexy (type 2).

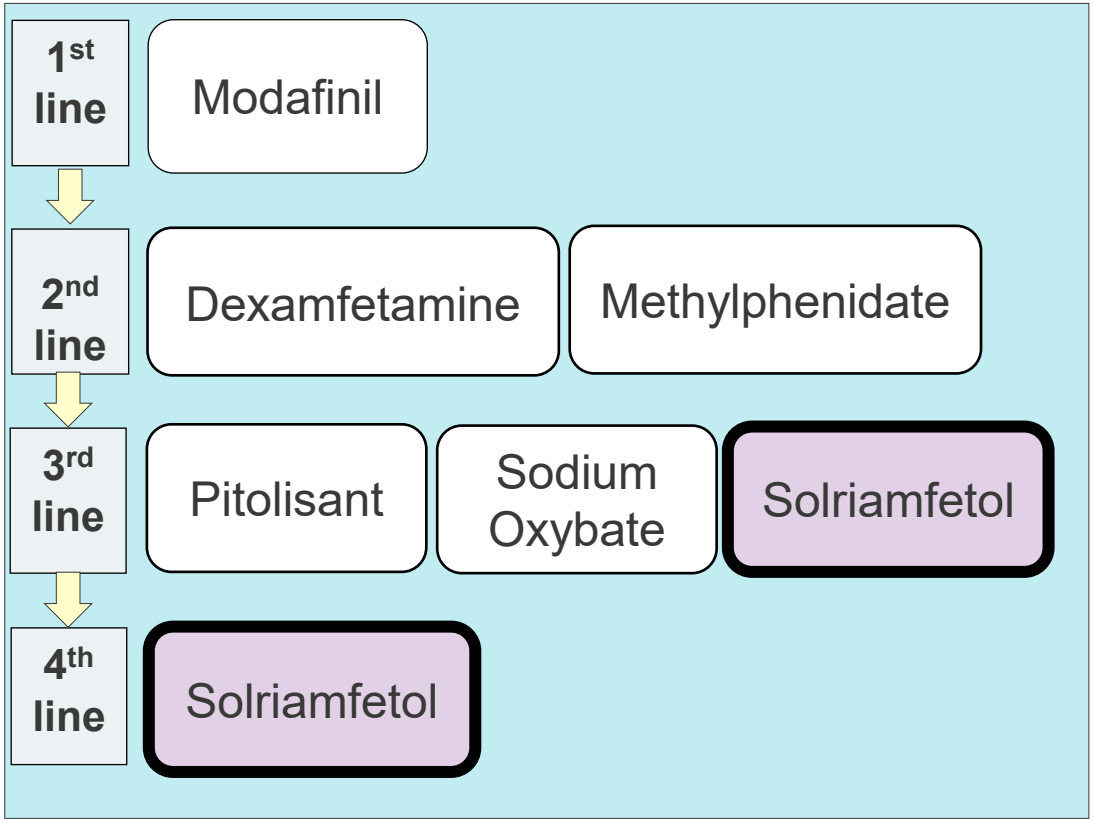
Solriamfetol (Sunosi, Jazz Pharmaceuticals)

Description of technology	Phenylalanine-derived, second-generation wake-promoting agent. Prevents the reuptake of dopamine and noradrenaline, and indirectly enhances dopaminergic and noradrenergic neurotransmission.
UK marketing authorisation (Jan 2020)	Indicated to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy).
Dosage and administration	Available in 2 doses (75mg and 150mg). Recommended starting dose is 75mg. Dose can be titrated up to 150mg after 3-day interval. Administered orally, once daily.
List price	75mg pack (28) = £177.52 (annual cost = £2,314) 150mg pack (28) = £248.64 (annual cost = £3,241)

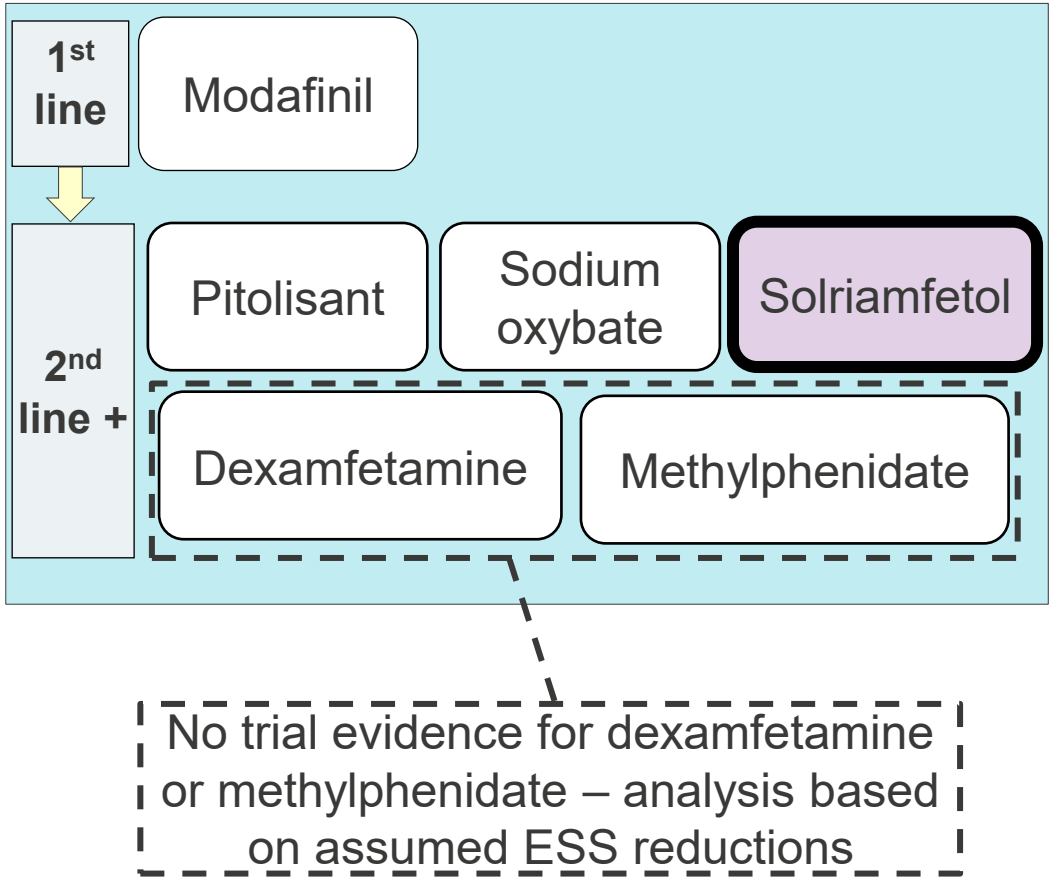
Treatment pathway and comparators

- Marketing authorisation wording does not require previous treatment before solriamfetol
- **Company position solriamfetol after 1st line modafinil**

Association of British Neurologists highlights usual pathway and where solriamfetol likely used



Company pathway - following modafinil, there is no clear pathway (based on clinical advice)



ACD: Committee noted access to pitolisant + sodium oxybate limited (IFRs required) – can not be considered established clinical practice

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Abbreviations: IFR: individual funding request, ACD: appraisal consultation document, ESS Epworth Sleepiness Scale

Costs of treatments for EDS (narcolepsy)

List prices

Treatment		Cost per day (£)	Annual costs (£)
Solriamfetol	75mg	£6.34	£2,314
	150mg	£8.88	£3,241
Pitolisant	18mg	£10.33	£3,770
	36mg	£20.66	£7,540
Sodium oxybate	4.5mg	£18.00	£6,570
	6mg	£24.00	£9,855
	9mg	£36.00	£13,140
Methylphenidate*	40mg	£1.92	£701
Dexamfetamine	40mg	£5.30	£1,935
Modafinil**	100mg	£0.11	£40
	200mg	£0.22	£80

*modified release tablet assumed for methylphenidate

**Modafinil not considered a comparator by company as solriamfetol is positioned after 1st line and not included in analysis

Background

Comparators	NICE scope: modafinil, dexamfetamine, methylphenidate, sodium oxybate and pitolisant • Company position solriamfetol (75mg/150mg) after 1st line modafinil • Comparisons v pitolisant (≤40mg) and sodium oxybate (4.5g/6g/9g) • Comparisons v dexamfetamine, methylphenidate in scenario analysis
Clinical trial	TONES 2 (phase III RCT) informs solriamfetol efficacy (v placebo).
Key results	Solriamfetol significantly reduces ESS scores after 12 weeks: • 75mg: -2.2 relative to placebo • 150mg: -3.8 relative to placebo
Indirect treatment comparison (ITC)	• NMA (random-effects) for ESS reduction (at 8wks): solriamfetol 75mg, pitolisant, and sodium oxybate comparisons vs solriamfetol 150mg show 95% credibility intervals cross zero. • Dexamfetamine, methylphenidate not included in ITC (no trial data)
Model	Decision tree for 1st 8 weeks and 3 state Markov model thereafter

Evidence from TONES 2 trial

Main evidence for solriamfetol comes from TONES 2 which collected data for 12 weeks

Patients enrolled

- 18-75 years of age
- BMI 18-45
- ESS score ≥10
- Narcolepsy (ICSD-3 or DSM 5 criteria)

Key exclusions

- Pregnant women
- Presence/history of significant cardiovascular disease
- Use of medications which could affect excessive sleepiness or cataplexy

TONES 2
Phase III RCT, double blinded

Solriamfetol (75mg n=59, 150mg n=59 and 300mg* n=59)

*300mg solriamfetol dose is unlicensed

Placebo (n=59)

Endpoints

★ Used in economic model

Primary

- Change in Epworth Sleepiness Scale (ESS) ★
- Change in Maintenance of Wakefulness Test (MWT)

Secondary

- Patient Global Impression of change (PGIc)
- Clinical Global Impression of change (CGIc)

Quality of life data collected

- EQ-5D-5L
- SF-36v2
- FOSQ-10
- WPAI:SHP

Supporting evidence from TONES 1 and TONES 5 trials. Data used to inform some assumptions in model

Abbreviations: ESS: Epworth Sleepiness Scale, BMI: Body Mass Index, ICSD-3:International Classification of Sleep Disorders, DSM: Diagnostic and Statistical Manual of Mental Disorders FOSQ-10 functional outcomes of sleep questionnaire, WPAI:SHP: Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

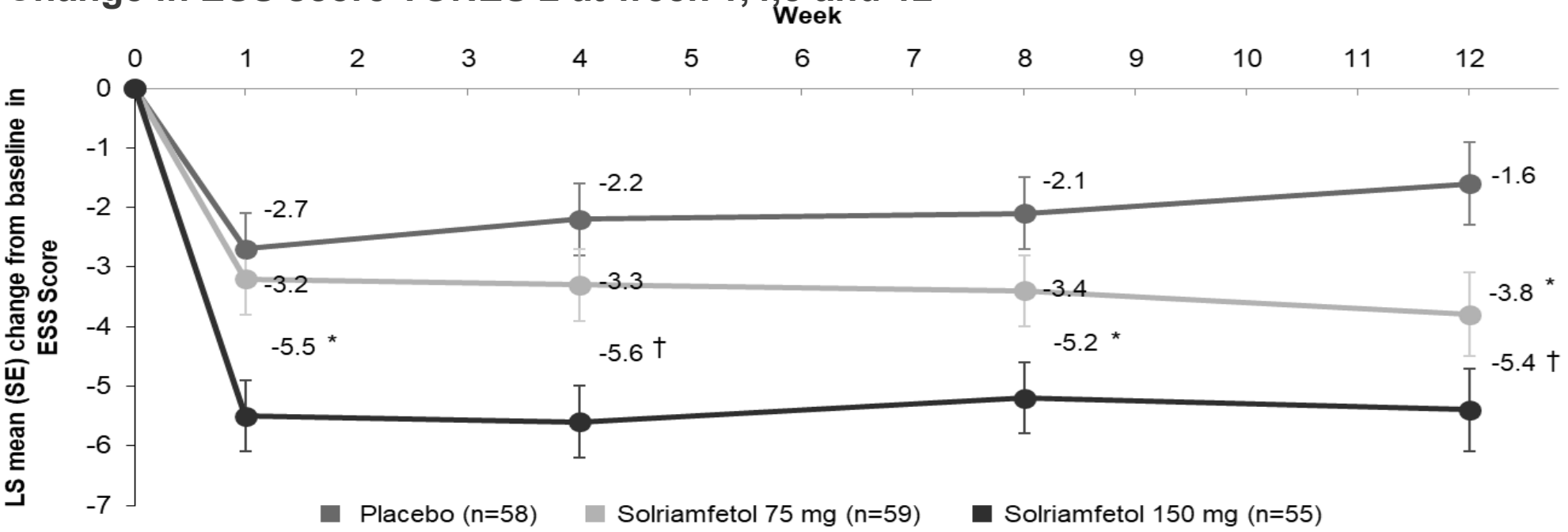
Clinical trial results – TONES 2: ESS

TONES 2 – Phase III RCT ***Solriamfetol compared with placebo (12 week data) – 8 week data used in economic model***			
12-week results	**Solriamfetol 75 mg (n=59)**	**Solriamfetol 150mg (n=55^)**	**Placebo (n=58^)**
Change in ESS score (SE)	-3.8* (0.7)	-5.4** (0.7)	-1.6 (0.7)

- Normal ESS (≤10) scores were achieved by 30.5% and 40.0% of patients in solriamfetol 75 mg and 150 mg groups, compared with 15.5% in the placebo group.

* p ≤ 0.050, ** p ≤ 0.001

Change in ESS score TONES 2 at week 1,4,8 and 12



NICE (number of patients in each trial arm, ^modified intention to treat)

* p<0.05, † p<0.0001 vs. placebo

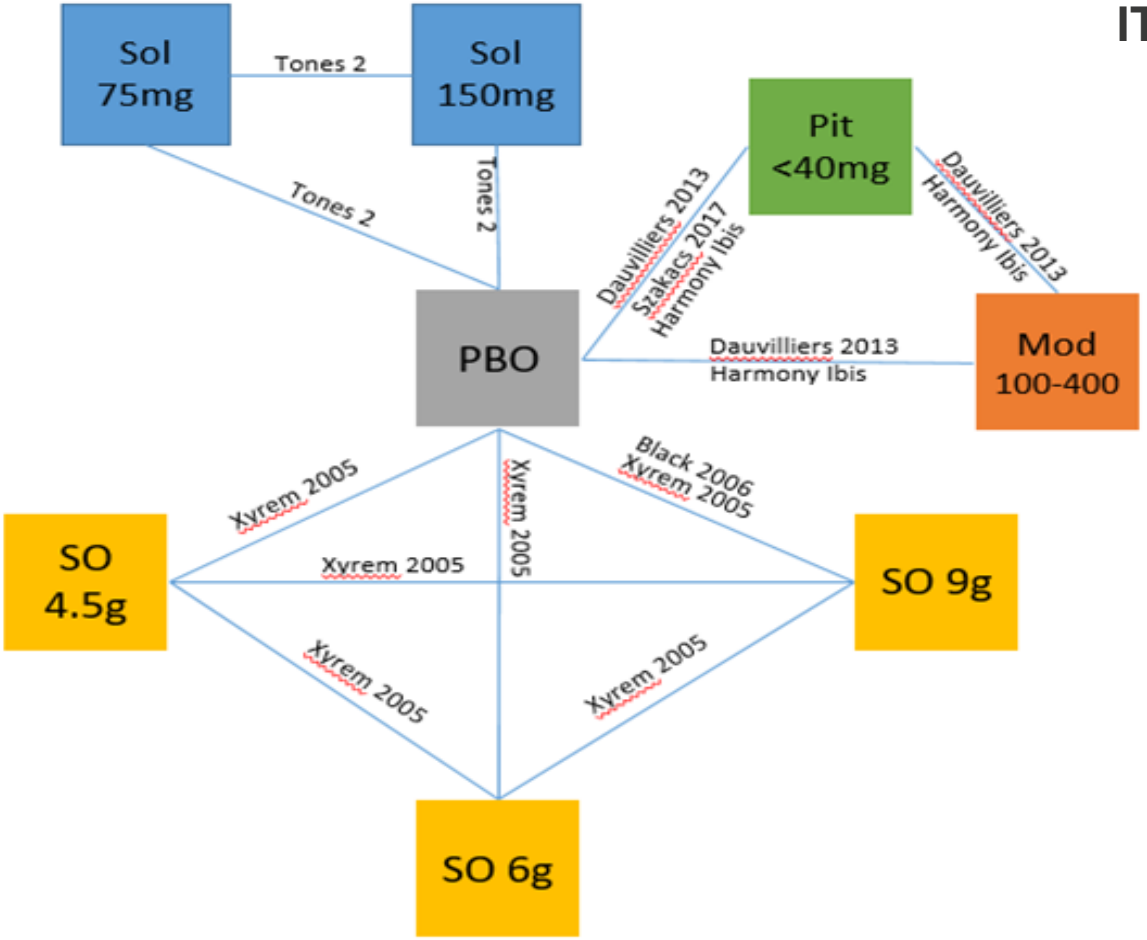
Abbreviations: ESS: Epworth Sleepiness Scale, SE: standard error

Indirect treatment comparison:

Network Meta Analysis (NMA)

- TONES 2 only included a placebo comparator - NMA undertaken to compare against comparator treatments

ERG preferred ESS 8-week NMA (company accept ERG revisions)



ITC results (random effects model) – 8 wks

Relative effects: sol 150mg v treatment	Mean ESS change (95% CrI)
Placebo	-3.098 (-6.907, 0.707)
Solriamfetol 75mg	-1.796 (-5.615, 2.019)
Pitolisant ≤40 mg	-0.714 (-5.224, 3.671)
Sodium oxybate 4.5 g	-2.969 (-8.245, 2.298)
Sodium oxybate 6 g	-1.964 (-7.248, 3.306)
Sodium oxybate 9 g	0.654 (-4.048, 5.353)

Results from 8-week ITC show that 95% credibility intervals cross zero for every comparison

Abbreviations: Sol: Solriamfetol, Pit: Pitolisant, SO: Sodium oxybate, Mod: Modafinil PBO: Placebo, ITC: Indirect treatment comparison

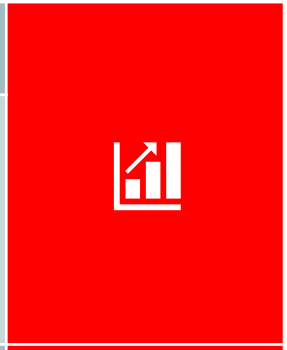
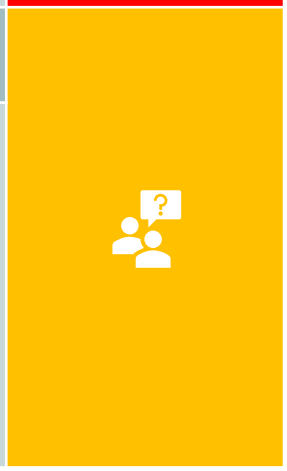
Draft recommendations in appraisal consultation document

Solriamfetol is not recommended, within its marketing authorisation, for treating excessive daytime sleepiness in adults with narcolepsy with or without cataplexy.

Why committee made this decision	Cost-effectiveness estimates for solriamfetol compared with dexamfetamine or methylphenidate are uncertain. They are very likely to be higher than what NICE normally considers an acceptable use of NHS resources
Analyses requested by committee	• Further analyses on impact of ESS caused by narcolepsy on HR-QoL • Other sources of efficacy for dexamfetamine/methylphenidate and clinical expert input on assumptions used • Appropriate estimates of health resource use for dexamfetamine/methylphenidate • Modelling which includes some people remaining on dexamfetamine/methylphenidate despite suboptimal response

Abbreviations: HR-QoL: Health-related quality of life, ESS: Epworth Sleepiness Scale

Key issues

Key issues for ACM2	Impact
Treatment pathway and comparators	
• What is current treatment pathway, when would solriamfetol be used? • What are the relevant comparators? • Are pitolisant and sodium oxybate relevant comparators for solriamfetol?	
Company's updated scenario analysis	
• Are results from the company's updated scenario analyses comparing solriamfetol with dexamfetamine and methylphenidate appropriate?	
Other issues	

• Are dose split assumptions in the analyses appropriate?
• Is quality of life captured appropriately in the analyses?
  • Is the NHWS or McDaid mapping approach the most robust?
• Are there any equalities issues that require consideration?
  • For example, potential issue raised by Narcolepsy UK on modafinil use in women	

NICE  High impact  Unknown impact  Small impact

Abbreviations: NHWS: National Health and Wellness Survey,

Appraisal consultation document (ACD) summary of committee conclusions

Issue	Committee conclusion	Addressed in responses?
Treatment pathway	Modafinil is 1st line treatment. Dexamfetamine, methylphenidate, sodium oxybate and pitolisant are options after modafinil. Availability of sodium oxybate and pitolisant limited/variable and they cannot be considered established clinical practice (usually require individual funding requests)	✓
Comparators	Dexamfetamine and methylphenidate are the most relevant comparators, despite limited clinical evidence, as they are established clinical practice after modafinil	✓
Clinical evidence	TONES 2 results are generalisable to NHS clinical practice	Resolved
Subgroups	Prior modafinil use and cataplexy status subgroup analyses informative. But analyses are limited by the data available	Resolved
Indirect treatment comparison (NMA)	NMAs limited by small number of trials. No data for dexamfetamine/ methylphenidate (assumed ESS reduction, highly uncertain). Committee would like to see other sources/clinical opinion informing efficacy of these treatments	Partially

Appraisal consultation document (ACD) summary of committee conclusions (2)

Issue	Committee conclusion	Addressed in responses?
Treatment discontinuation (adverse events)	Adverse events resulting in discontinuation similar for solriamfetol, pitolisant and sodium oxybate, but dexamfetamine/methylphenidate rates uncertain (no data)	✓
Treatment response and quality of life	Using ESS to determine treatment response unlikely to reflect clinical practice but there may not be appropriate alternative measures. QoL values high in analyses even at high ESS levels – might not capture impact of condition	✓
Company economic model	Many people remain on 2nd line dexamfetamine/ methylphenidate even if not effective as access to pitolisant or sodium oxybate limited (higher dose/treatment combinations). Treatment pathway after modafinil not fully captured in the company's model	✓
Healthcare resource use costs	The economic modelling did not account for the likely increased healthcare resource use from adverse events from treatment with dexamfetamine and methylphenidate	✓
Dose split	A range of dose splits is appropriate to consider to account for variability in clinical practice	Partially

ACD responses

- Company: Jazz Pharmaceuticals
- Narcolepsy UK (Patient group)
- 3 online comments

Patient perspective

ACD response from **Narcolepsy UK**

STA process and rare conditions

- Current recommendation may discriminate against people with narcolepsy (classified as a disability), compared with better researched conditions
- Rarer conditions disadvantaged by STA methods, leading to less access
- Generating data costly and time consuming, e.g. QoL measurement, clinical data for dexamphetamine/ methylphenidate and resource use

Unmet need and equality

- If solriamfetol not approved, people with narcolepsy will be left with high doses of drugs which may be harmful, with more side effects
- MHRA issued warning that modafinil is linked to birth defects and reduced oral contraception efficacy
- Women who do not want to use alternative contraception, or do not want/need contraception, need alternative, safe, narcolepsy treatments

Comparators

- Lack of analysis on availability of sodium oxybate, which is commissioned for children and available in some regions for adults
- Costs of individual funding requests have not been accounted for

Abbreviations: ACD: Appraisal consultation document, STA: Single technology appraisal, QoL: Quality of life, MHRA: Medicines and healthcare products Regulatory Agency

Web comments

ACD comments from the British Sleep Society

Current treatments and unmet need	Comparators	Epworth Sleepiness Scale (ESS)
• Modafinil, 1st line treatment, typically not potent enough – additional treatment options needed • Concerned ACD recommendation reinforces lack of equal access by region • Dexamfetamine and methylphenidate use not a satisfactory situation (limited effectiveness, adverse events e.g. serious cardiovascular and psychiatric side effects)	• Dexamfetamine and methylphenidate used due to lack of access to other drugs – does not justify use as comparators • Sodium oxybate recommended by a Regional Medicines Optimisation Committee (RMOCs) - should be considered standard of care. RMOC guidance for pitolisant in progress • NICE should consider sodium oxybate and pitolisant as comparators, rather than dexamfetamine and methylphenidate	• ESS not developed for narcolepsy and does not capture all relevant information • Cost-effectiveness analyses should include other measures. ESS underestimates benefit to people with narcolepsy

Web comments (2)

Additional ACD online comments

Current treatments and unmet need

- Unease using stimulants with no RCT data, when other treatments with clinical evidence are available
- Sleep clinicians trapped in current practice. Patients unfairly treated - other countries have access to extra treatment options
- ACD does not capture current UK best practice for narcolepsy. There is a desperate need for better services and treatments
- People with narcolepsy frequently do not fulfil their potential, partly due to ineffectiveness of current treatments and patchy nature of UK sleep services

Comparators

- Unwillingness of committee to compare solriamfetol with pitolisant and sodium oxybate inappropriate
- Stating these treatments as not widely available is disingenuous – more reflective of lack of expertise and specialist treatment centres
- Pitolisant and sodium oxybate widely used in specialist centres
- Service provision gaps not a reason to not compare against treatments with clinical evidence (pitolisant and sodium oxybate) instead of older treatments without evidence (dexamfetamine and methylphenidate)

Abbreviations: RCT: Randomised Control Trial

Company's ACD response: summary

Company comments on treatment pathway/comparators, updated base case and additional analyses v dexamfetamine and methylphenidate

Updated company base case

- In company base case, comparisons only provided v pitolisant and sodium oxybate due to no available trial data for dexamfetamine or methylphenidate
- Enhanced scenario analysis including dexamfetamine and methylphenidate provided

Base case updates include:

- Updated dose split for solriamfetol 75/150 mg to reflect recent sales data
- Updated mapping algorithm based on a UK value set (HR-QoL measurement)

Scenario analysis updates include:

- An estimate of additional adverse events costs for dexamfetamine/ methylphenidate
- Sensitivity analysis assuming different efficacy for dexamfetamine/ methylphenidate
- Threshold analysis around people remaining on dexamfetamine/methylphenidate despite suboptimal response and increased risk of mortality of these treatments

Company's ACD response: comparators

The company state that pitolisant and sodium oxybate are relevant comparators

ACD: Dexamfetamine and methylphenidate are most relevant comparators. Pitolisant and sodium oxybate access is limited and not considered established clinical practice

Clinical expert opinion

- The company received clinical expert opinion which stated dexamfetamine, methylphenidate, pitolisant, sodium oxybate are all used post modafinil in the UK
  - Reaffirms company's position that pitolisant and sodium oxybate are comparators: company highlight routine access to these treatments is widespread
- Concerns about dexamfetamine and methylphenidate. Some clinicians may not use these treatments at all

Market data and Regional Medicines Optimisation Committee (RMOC)

- NHS formulary and market share data show all 4 treatments in widespread use
  - 14/19 NHS Trusts in England that treat narcolepsy have routine access to pitolisant and/or sodium oxybate for new adult patients
  - 5 centres gain access through individual funding requests. Sales data show these requests have been successful
- An RMOC commissioning statement for sodium oxybate has been published (2019) and a pitolisant statement will come soon
  - strong indication that these treatments considered established clinical practice

ERG comments: Comparators

ERG comments on company clinical expert interviews

- ERG note from the 5 clinical experts interviewed by the company:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

ERG comments on NHS formulary information and market share sales data

- Agree NHS formulary information shows all 4 2nd-line treatment options are available, but with some restrictions at most centres (e.g. individual funding requests)
- ERG not able to verify sales data for pitolisant/sodium oxybate - not publicly available

ERG comments on Regional Medicines Optimisation Committee (RMOC)

- Note RMOC commissioning statement for sodium oxybate but highlights that it does not state it must be commissioned. It facilitates local commissioning groups decision-making.

ERG conclusions

- Agree with company that clinician interviews show evidence of all 4 potential 2nd-line treatments in use in England
- RMOC commissioning statement for sodium oxybate underpins local decision-making and likely that RMOC work for pitolisant will also influence it's uptake

◉ Are pitolisant and sodium oxybate relevant comparators?

Company's ACD response: scenario analysis

The company provide updated scenario analysis v dexamfetamine / methylphenidate

ACD: Modelling should consider other sources of efficacy, healthcare resource use, adverse events and reflect pathway (some people remaining on treatment despite suboptimal response)

Adverse events (AE): dexamfetamine and methylphenidate

- Using SmPC and MHRA yellow card scheme data, adverse events identified
- Clinical experts: dexamfetamine and methylphenidate associated with higher adverse event rates and resource use (resource use differences not large compared to untreated narcolepsy)
- Clinical expert concerns around cardiovascular and psychiatric side effects
- Costs of arrhythmia, cardiomyopathy, and psychosis included in updated analysis
  - Company state AE costs likely to be underestimated in analysis

Scenario and sensitivity analysis v dexamfetamine and methylphenidate

- Include costs of prescribing schedule 2 controlled drugs
- Assume efficacy of dexamfetamine/methylphenidate equal to 4.5g sodium oxybate – no clinical trial data and clinical opinion unable to estimate efficacy
  - Sensitivity analysis varying assumed efficacy provided
- Threshold analysis provided showing % needing to remain on dexamfetamine/ methylphenidate for solriamfetol to be cost-neutral or cost-effective
- Scenario analysis assuming excess mortality with dexamfetamine/methylphenidate

Abbreviations: SmPC: Summary of product characteristics

ERG comments: scenario analysis

Adverse events (AE): dexamfetamine and methylphenidate

- Most 'undesirable effects' listed in solriamfetol SmPC occur at same or lesser frequency for solriamfetol than for dexamfetamine/methylphenidate
- ERG unclear why company have focused on 3 specific AEs (arrhythmia, cardiomyopathy, and psychosis) but note ACD and clinical interviews highlight concerns with these AEs
- Agree it is challenging to estimate healthcare resource use for AEs of methylphenidate and dexamfetamine and caution that estimates are uncertain

Scenario and sensitivity analysis v dexamfetamine and methylphenidate

- Company estimates of hospitalisation costs for methylphenidate/dexamfetamine are uncertain, but do not seem over-estimated.
- Agree with schedule 2 dispensing fees inclusion
- Provide scenario analyses: estimates of hospitalisation costs for solriamfetol and comparators
- Company's scenario analysis for excess mortality is highly uncertain, due to a lack of evidence
- [redacted] clinicians able to estimate ESS reduction (methylphenidate: 3 to 5 points; dexamfetamine 3 to 6; solriamfetol 5 to 6).
  - In analysis these treatments assumed equal to least effective treatment in ITC (4.5g sodium oxybate) mean ESS reduction is ~2 (compared to ~5 for solriamfetol 150mg)
- ERG notes people may remain on treatment with solriamfetol despite inadequate response if further treatment lines are not available
- Impact of adverse events (costs and disutility) may not be fully captured

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Are the company's scenario analyses appropriate?

Company ACD response: other issues

ACD: HR-QoL: commmittee noted high QoL even with high ESS scores using mapping. Concluded that mapping from ESS to EQ-5D may not adequately capture changes in QoL.
Dosing: Range of dose splits appropriate to account for variability in clinical practice

Health-related quality of life

- Acknowledged need for a validated and sensitive measure for sleep disorders
- ED-5D and SF-36 both generic measures without a sleep domain
- These questionnaires not capable of capturing changes in QoL in EDS caused by narcolepsy
- NHWS mapping is the best alternative, with McDaid mapping provided as a scenario
- This mapping likely underestimates cost-effectiveness of solriamfetol
- Clinicians interviewed agreed that ED-5D and SF-36 not tailored for EDS and in general agreed that mapping analysis underestimated impact of EDS on QoL

Dose split used in analysis

- Collected more sales data from France and Germany (OSA and narcolepsy indications)
- Updated German data used in base case (narcolepsy data): 75/150mg dose split = [redacted] reflects data from January to June 2021

Abbreviations: HR-QoL: Health-related quality of life, NHWS: National Health and Wellness Survey

ERG comments: other issues

Health-related quality of life

- TONES 2 did not show a significant EQ-5D effect – possibly due to lack of ED-5D sensitivity, lack of power in trial or short trial duration. [redacted]
- Reasonable to use mapping (no other utility data available) – although adds uncertainty
- On balance, ERG agree with company's NHWS mapping, with McDaid used in a scenario.

ERG comments on alternative mapping approaches

NHWS mapping	McDaid mapping
Well reported and uses a large database	Based on people with obstructive sleep apnoea not narcolepsy, may not be appropriate.
May be subject to recruitment bias (online self-reported)	Used in TA139 (continuous positive airway pressure for OSA)
Includes mostly people with OSA but has small sample of narcolepsy respondents	

Dose split used in analysis

- ERG analysis shows that cost-effectiveness results are not sensitive to dose split assumptions
- Wide variation in costs of dexamfetamine/methylphenidate due to dose and formulation

◉ Is quality of life captured appropriately in the analysis? Is the correct dose split used? Are there any other issues?

Abbreviations: FOSQ-10: functional outcomes of sleep questionnaire, SF-36:Short-Form 36-Item Health Survey, NHWS: National Health and Wellness Survey, OSA: Obstructive Sleep apnoea

Key assumptions in company and ERG analyses

The company and ERG assumptions are described below

Parameter	Base case		Sensitivity/scenario analysis
	Company	ERG	
Treatment pathway + comparators	Comparisons vs pitolisant and sodium oxybate.	Same as company.	Comparison vs dexamfetamine /methylphenidate (assumed ESS reductions and AEs).
Definition of response	≥3 ESS reduction	Same as company	≥2 to ≥4 ESS reduction Scenarios with continued treatment with dexam/methyl
HR-QoL	ESS to EQ-5D mapping: NWHS (UK tariff)	Same as company	McDaid et al mapping (TA139) Scenario with excess mortality
Assumed dose splits	Sol 75/150mg : [redacted] Pit: 18mg 33%, 36mg 66% Sod: 4.5g/6g/9g: 33% each Dexam: 40mg Methly: 40mg Modified release	Same as company	ERG state cost-effectiveness results not sensitive to wide range of solriamfetol dose splits
Model assumptions	Constant ESS reduction over time. Treatment discontinuation rates from TONES 5	Same as company	Alternative discontinuation rates Scenario threshold analysis for continuing dexam/methyl
Resource use	Only drug acquisition costs considered.	Same as company	ERG scenario includes hospitalisation costs

Cost-effectiveness results

Cost-effectiveness results include list prices for all treatments.

Company base case – includes comparisons v pitolisant and sodium oxybate

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

- **ERG Base Case – same as company's**

Company scenario analysis with ERG minor correction for AEs

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER	Solriamfetol Pairwise
Methylphenidate	£1,313	14.601				£65,215
Dexamfetamine	£3,426	14.601	£2,113	0.000	Dominated	£44,717
Solriamfetol	£8,034	14.704	£4,609	0.103	£65,215	
Pitolisant	£19,122	14.717	£11,087	0.013	£886,555	£886,555*
Sodium oxybate	£25,860	14.676	£6,739	-0.041	Dominated	Sol Dominant

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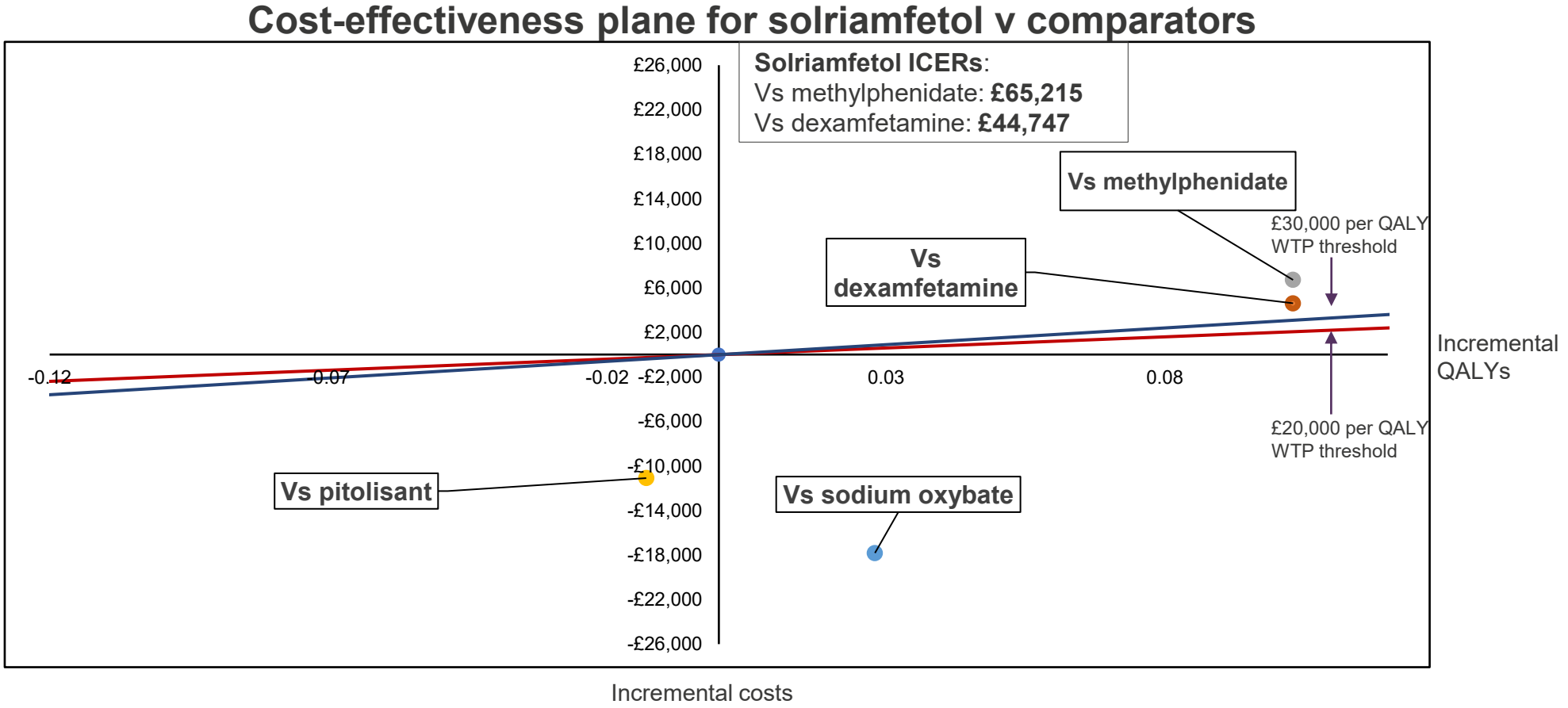
*SW: South West quadrant (solriamfetol less costly and less effective than comparator) - with south west quadrant ICERs, the higher the ICER value the more cost-effective

Cost-effectiveness plane (all treatments)

At list price, base case and scenario analysis shows that:

- solriamfetol produces similar QALYs at lower cost vs pitolisant and sodium oxybate
- solriamfetol produces more QALYs (0.103) at higher costs vs methylphenidate and dexamfetamine



Solriamfetol associated with large southwest ICER of £886,555 v pitolisant (marginally less QALYs and significantly lower cost)

Solriamfetol dominates sodium oxybate – cheaper and produces more QALYs

Cost-effectiveness results: Sensitivity/ scenario analysis

Company scenario/sensitivity analysis: Pairwise

Cost-effectiveness results include list prices for all treatments

Scenario analysis base case ICERs: Sol v Methyl: £65,215 , Sol v Dexam: £44,717

Company sensitivity analysis: varying assumed effectiveness of methyl/dexam

Parameter	ICER sol v methyl	ICER sol v dexam
Varying ESS reduction relative to sol 150mg:		
-1	Methyl dominates	Dexam dominates
-2	£183,216	£86,403
-3 (Similar to base case assumptions)	£66,575	£44,234
-4	£48,806	£37,694
-5	£42,618	£35,230
impact of excess mortality associated with stimulants (rate of 1.01 applied)	£56,601	£38,183

Company provide scenarios assuming some people remain on methyl/dexam without response

Company Threshold analyses: % remaining on methyl/dexam despite suboptimal response

- Solriamfetol cost neutral v methylphenidate if 48% continue methylphenidate treatment
- Solriamfetol cost-effective at £20,000 per QALY if 31.1% continue methylphenidate treatment
- Solriamfetol cost-neutral v dexamfetamine if 11.8% continue dexamfetamine treatment

 sol: solriamfetol, methyl: methylphenidate, dexam: dexamfetamine

ERG sensitivity analysis

ERG analysis assuming higher treatment discontinuation for dexamfetamine and methylphenidate compared to solriamfetol and use of McDaid Mapping

Base case: 4.4% both arms

ERG analysis with treatment related adverse event discontinuation scenarios

Scenario analysis base case ICERs: Sol v Methyl: £65,215 , Sol v Dexam: £44,717

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER	Solriamfetol pairwise
7% per year treatment discontinuation for dexam and methyl (4.4% for solriamfetol)						
Methylphenidate	£1,159	14.584				£57,056
Dexamfetamine	£3,023	14.584	£1,864	0.000	Dominated	£41,590
Solriamfetol	£8,034	14.704	£5,011	0.120	£57,056	
20% per year treatment discontinuation for dexam and methyl (4.4% for solriamfetol)						
Methylphenidate	£719	14.534				£42,912
Dexamfetamine	£1,868	14.534	£1,149	0.000	Dominated	£36,170
Solriamfetol	£8,034	14.704	£6,166	0.170	£42,912	

ERG analysis using McDaid mapping instead of NHWS mapping						
Methylphenidate	£1,313	16.846				£77,332
Dexamfetamine	£3,426	16.846	£2,113	0.000	Dominated	£53,025
Solriamfetol	£8,034	16.933	£4,609	0.087	£77,332	

sol: solriamfetol, methyl: methylphenidate, dexam: dexamfetamine

Key issues

Key issues for ACM2	Impact
Treatment pathway and comparators	
• What is current treatment pathway, when would solriamfetol be used? • What are the relevant comparators? • Are pitolisant and sodium oxybate relevant comparators for solriamfetol?	
Company's updated scenario analysis	
• Are results from the company's updated scenario analyses comparing solriamfetol with dexamfetamine and methylphenidate appropriate?	
Other issues	

• Are dose split assumptions in the analyses appropriate?
• Is quality of life captured appropriately in the analyses?
  • Is the NHWS or McDaid mapping approach the most robust?
• Are there any equalities issues that require consideration?
  • For example, potential issue raised by Narcolepsy UK on modafinil use in women	

 High impact  Unknown impact  Small impact

Abbreviations: NHWS: National Health and Wellness Survey,