**National Institute for Health and Care Excellence**

**Solriamfetol for treating excessive daytime sleepiness caused obstructive sleep apnoea (STA)**

**Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)**

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

**Comment 1: the draft remit**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Appropriateness | Association of British Neurologists | Excessive daytime sleepiness (EDS) is usually the most disabling symptom in narcolepsy and frequently is not fully treated by available drug therapy. A new agent is therefore appropriate and welcome to patients and their treating physicians.<br>The EDS caused by sleep apnoea is thought to stem from disrupted or poor quality overnight sleep. A minority of patients remain sleepy despite best available therapy (usually CPAP masks). However, treating residual EDS with stimulant therapy is controversial in the UK and not widely considered appropriate. | Thank you for your comment. |
| | Bioprojet Europe | We are aware that Narcolepsy has not, to date, been evaluated as a therapeutic area by NICE so would propose that this needs to be done separately to OSA. Even though both have EDS as a key symptom, they are very different types of sleep disorder<br>Narcolepsy is a central hypersomnia (neurological sleep disorder) and OSA is a respiratory sleep disorder | Thank you for your comment. The appraisal has been split into two separate Single Technology Appraisals: ID1602 for treating excessive sleepiness caused by narcolepsy and ID1499 for treating |

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| | | | excessive sleepiness caused by obstructive sleep apnoea. |
| | British Thoracic Society | To our knowledge, the marketing authorisation application (MAA) has only just been submitted to the EMA, which means that it will be several months before a decision is available.<br>We note that clinicians would not considering applying for this to be on the formulary until it has a license and had been launched in the UK.<br>This is unlicensed, non-formulary and therefore not available for clinicians to use except upon special approval for its use from the DTC (usually only for up to 2 people). | Thank you for your comment. NICE's topic selection process accounts for the marketing authorisation process with the aim of producing timely guidance. |
| | Jazz Pharmaceuticals UK | Jazz Pharmaceuticals believes that it is appropriate to refer this topic to NICE for appraisal | Thank you for your comment. |
| Wording | Association of British Neurologists | The draft remit combines the treatment of EDS in two separate conditions with very different aetiologies. Comparing these two populations and having similar treatment guidelines might be problematic. | Thank you for your comment. The appraisal has been split into two separate Single Technology Appraisals: ID1602 for treating excessive sleepiness caused by narcolepsy and ID1499 for treating excessive sleepiness caused by obstructive sleep apnoea. |

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| | British Thoracic Society | No concerns | Thank you for your comment. |
| | Jazz Pharmaceuticals UK | The remit should state that the proposed indication of Solriamfetol is "indicated to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy) or obstructive sleep apnoea" | Thank you for your comment. To maintain flexibility, the remit has been kept broad. |
| Timing Issues | Association of British Neurologists | There is no immediate urgency given the availability of conventional therapies. | Thank you for your comment. |
| | British Thoracic Society | Not urgent | Thank you for your comment. |
| | Jazz Pharmaceuticals UK | Jazz Pharmaceuticals expects that NHS stakeholders will prefer to have NICE recommendations available within 6 months of marketing authorisation, to support reimbursement decision making. | Thank you for your comment. |

**Comment 2: the draft scope**

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| Background information | Association of British Neurologists | The information summarises the 2 conditions but perhaps should emphasise their differences more – narcolepsy causes EDS by virtue of a brain chemical deficiency whereas sleep apnoea disturbs overnight sleep, thereby fuelling subsequent EDS.<br>Anti-depressant therapy is commonly used in narcolepsy, most often to suppress REM sleep problems or cataplexy but not for EDS. | Thank you for your comment. The scope specifies the differences between narcolepsy and OSA. In response to the scoping workshop, anti- |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | | depressant therapy has been removed as a comparator for the population with narcolepsy. |
| | Bioprojet Europe | Narcolepsy has 2 main symptoms EDS and cataplexy. Approx 70% of all patients with narcolepsy have a degree of cataplexy.<br><br>Cataplexy is the term given to sudden muscular weakness triggered by strong emotions such as laughter, anger and surprise. The loss of muscle tone that occurs, may range from a just-perceptible weakening of the facial muscles through weakness at the knees, to total collapse on the floor. Speech may be slurred, and eyesight impaired (double vision, inability to focus) but hearing and awareness remain undisturbed.<br><br>Although EDS is a very important symptom of narcolepsy, cataplexy in its severe form can cause falls, accidents at home, at work or car accidents with significant trauma and complications (Rev Neurol 2000). Some patients need to wear protective clothing such as a helmet at home.<br><br>The burden of cataplexy and impact on patient quality of life can be immense, which is why cataplexy needs to be controlled and very well managed. | Thank you for your comment. The focus of this scope is on the treatment of excessive waketime sleepiness rather than treatments for the underlying disease conditions. Because of this, treatment for cataplexy is not considered in the scope. |
| | British Thoracic Society | Could include more detail on the RCT evidence and side effects of the new drug | Thank you for your comment. The scope aims to provide a brief overview of the disease area. Available evidence and safety profile of the technology |

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| | | | will be considered during the appraisal. |
| | Jazz Pharmaceuticals UK | Jazz Pharmaceuticals wishes to further expand on the disease background, in particular the burden of disease and seriousness of excessive daytime sleepiness (EDS).<br><br>EDS<br>It is important to specify that the symptom of excessive daytime sleepiness (EDS) is distinct from the disorder of hypersomnia.<br>According to ICSD-3, hypersomnia is a condition with specific diagnostic criteria and essential features (e,g, excessive nocturnal sleep). This differs from the symptom of EDS. Patients with EDS do not necessarily sleep for long hours at night – this is a feature of hypersomnia.<br>While mild sleepiness secondary to episodes of insufficient sleep occurs in most individuals, the EDS of sleep disorders is of a far greater magnitude and poses significant burden on both individuals and society. By virtue of the severity, chronicity, pervasiveness, and lack of response to usual countermeasures, EDS profoundly affects those afflicted, and no amount of extra sleep will lessen its debilitating effect. Regardless of the underlying pathophysiology of the EDS, the symptom manifestations and clinical consequences of EDS are similar and consistent across sleep disorders. The most disabling consequences include undesired sleep episodes, reduced attention, cognitive impairment, compromised performance and effects on mood.<br>EDS can affect many aspects of daily life, including education, employment, driving, relationships, emotional health and general health. In participants from the Sleep Heart Health Study, there was a significant association between EDS and poor quality of life, as measured by the Short-Form Health survey (SF-36) physical component summary (Silva et al. 2009) | Thank you for your comment. The scope aims to provide a brief overview of the disease area. Patient perspectives and available evidence about the technology and population will be considered during the appraisal. |

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| | | EDS has also been associated with increased mortality in elderly patients, and contributes to an increased risk of falls, motor vehicle accidents, and work-related injury and fatalities.<br><br>Narcolepsy<br>Narcolepsy is a life-long neurological disease for which no cure has been identified. It affects an estimated 0.02% to 0.067% of the population worldwide, approximately 4.7 of 10,000 (0.047%) individuals in the general population of five European countries (United Kingdom [UK], Germany, Italy, Portugal, and Spain) (Ohayon et al. 2002), and usually presents in young adulthood.<br>There are five core symptoms: EDS is present in 100% of patients, cataplexy in around 40 to 60%, sleep paralysis, sleep-related (hypnagogic and hypnopompic) hallucinations, and disrupted fragmented night-time sleep (DNS). In patients with narcolepsy, EDS is the most prominent symptom and often the most disabling (Thorpy et al. 2017).<br><br>Obstructive Sleep Apnoea (OSA)<br>OSA is associated with decreased health-related quality of life (HRQoL) and an increase in comorbid illnesses including cardiovascular disease and metabolic disorders. A growing number of studies document that EDS imparts an incremental burden of illness beyond that of OSA alone, including increased comorbidities (e.g., coronary artery disease, depression, diabetes), greater negative HRQoL impact, and more substantial deficits in work productivity measures. Compared with OSA patients without EDS, OSA patients with EDS report significantly poorer emotional health and energy levels. Anxiety, as measured by the State-Trait Anxiety Index–State Scale, was significantly associated with EDS in a study of 655 OSA patients (non-standardized coefficient, 0.398; P = 0.015) (Lee SA, et al. J Psychosom Res. 2015;79(1):32-36) | |

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| | | Despite optimized treatment of the upper airway abnormality, EDS can continue to be a problem for patients with OSA and may necessitate independent, direct management. The worldwide prevalence of EDS caused by OSA is between 2-7% (Garvey et al. 2015), with little significant difference between prevalence estimates worldwide. The prevalence of residual EDS in OSA patients without major comorbidities who are compliant on CPAP as a primary therapy has been estimated to be 6% to 13% based on data from a multicenter study in France (6%; Pépin et al. 2009) and from the French National Sleep Registry (13%; Gasa et al. 2013).<br>Currently there are no available pharmacological therapies indicated for the treatment of EDS in patients with OSA in the UK. The challenges with current treatments for EDS associated with narcolepsy and EDS associated with OSA coupled with the significant morbidity and impact on patient quality of life supports the need for additional therapeutic options for these patient populations. | |
| The technology/ intervention | Association of British Neurologists | Yes | Thank you for your comment. |
| | British Thoracic Society | Yes | Thank you for your comment. |
| | Jazz Pharmaceuticals UK | The proposed brand name of solriamfetol is Sunosi (commercial in confidence) – this is not yet approved although the trademark is registered.<br>Administration of solriamfetol is oral, once daily, with or without food.<br>Solriamfetol has been studied in randomized, placebo-controlled clinical trials. Separate phase 3 trials were conducted in people with EDS associated with narcolepsy (with or without cataplexy) and people with EDS associated with OSA | Thank you for your comment. This information has been noted. We note that the brand name is now in the public domain and no longer commercial in confidence. |

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| Population | Association of British Neurologists | It is not clear whether the population of sleep apnoea patients refers to those resistant to conventional therapy who display residual EDS | Thank you for your comment. The population description has been updated to specify 'people with obstructive sleep apnoea who have received treatment for the underlying condition and experience residual excessive waketime sleepiness'. The appraisal has been split into two separate Single Technology Appraisals: ID1602 for treating excessive sleepiness caused by narcolepsy and ID1499 for treating excessive sleepiness caused by obstructive sleep apnoea. The final scope for ID1499 will be made available in due course. |
| | Bioprojet Europe | Populations need further definition: e.g Narcolepsy Type I & 2 and OSA with / without use of CPAP | Thank you for your comment. Following the scoping workshop, the |

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| | | | population description has been updated to:<br>'People with excessive waketime sleepiness caused by narcolepsy<br>People with obstructive sleep apnoea who have received treatment for the underlying condition and experience residual excessive waketime sleepiness'.<br>The appraisal has been split into two separate Single Technology Appraisals: ID1602 for treating excessive sleepiness caused by narcolepsy and ID1499 for treating excessive sleepiness caused by obstructive sleep apnoea. The final scope for ID1499 will be made available in due course. |

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| | British Thoracic Society | OSA and narcolepsy should be considered separately as they are different disease processes. | Thank you for your comment. Following the scoping workshop, the population description has been updated to:<br>'People with excessive waketime sleepiness caused by narcolepsy<br>'People with obstructive sleep apnoea who have received treatment for the underlying condition and experience residual excessive waketime sleepiness'.<br>The appraisal has been split into two separate Single Technology Appraisals: ID1602 for treating excessive sleepiness caused by narcolepsy and ID1499 for treating excessive sleepiness caused by obstructive sleep apnoea. The final scope for ID1499 will be made available in due course. |

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| | Jazz Pharmaceuticals UK | The population should be defined as people with EDS caused by narcolepsy and people with EDS caused by OSA. It should be noted that the pathophysiology and patient characteristics of the underlying conditions differ in certain respects. | Thank you for your comment. Following the scoping workshop, the population description has been updated to:<br>'People with excessive waketime sleepiness caused by narcolepsy<br>'People with obstructive sleep apnoea who have received treatment for the underlying condition and experience residual excessive waketime sleepiness'.<br>The appraisal has been split into two separate Single Technology Appraisals: ID1602 for treating excessive sleepiness caused by narcolepsy and ID1499 for treating excessive sleepiness caused by obstructive sleep apnoea. The final scope for ID1499 will be made available in due course. |

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| Comparators | Association of British Neurologists | Anti-depressants are not used as primary treatment for EDS in narcolepsy; OSA patients are rarely also on stimulant therapy in the UK (with or without CPAP) | Thank you for your comments. Following the scoping workshop, antidepressants have been removed as comparators for the population with narcolepsy. Dexamphetamine, methylphenidate, pitolisant and sodium oxybate have been removed as comparators for the OSA population.<br><br>The appraisal has been split into two separate Single Technology Appraisals: ID1602 for treating excessive sleepiness caused by narcolepsy and ID1499 for treating excessive sleepiness caused by obstructive sleep apnoea. The final scope for ID1499 will be made available in due course. |

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| | Bioprojet Europe | Again, there needs to be clear differentiation between Narcolepsy comparators and OSA comparators. Narcolepsy is a central hypersomnia (neurological sleep disorder) and OSA is a respiratory sleep disorder | Thank you for your comment. The comparators in the scope. The appraisal has been split into two separate Single Technology Appraisals: ID1602 for treating excessive sleepiness caused by narcolepsy and ID1499 for treating excessive sleepiness caused by obstructive sleep apnoea. The final scope for ID1499 will be made available in due course. |
| | British Thoracic Society | Not routinely used in care of OSA patients. More relevant in narcolepsy and could be compared with other stimulants. | Thank you for your comments. Following the scoping workshop, antidepressants have been removed as comparators for the population with narcolepsy. Dexamphetamine, methylphenidate, pitolisant and sodium oxybate have been removed as |

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| | | | comparators for the OSA population.<br><br>The appraisal has been split into two separate Single Technology Appraisals: ID1602 for treating excessive sleepiness caused by narcolepsy and ID1499 for treating excessive sleepiness caused by obstructive sleep apnoea. The final scope for ID1499 will be made available in due course. |
| | Jazz Pharmaceuticals UK | OSA and Narcolepsy are different diseases with different populations, and distinct treatment pathways exist for management of EDS. Accordingly, the appropriateness of comparators differs markedly between the two populations.<br>EDS associated with Narcolepsy:<br>Modafinil is indicated and widely used for the treatment of EDS in narcolepsy patients and is an appropriate clinical comparator for 1st line therapeutic treatment<br>Dexamfetamine and methylphenidate are traditional stimulants, and both products are indicated as a treatment programme for attention-deficit/hyperactivity disorder (ADHD). Neither stimulant is indicated for treatment of EDS.<br>There is some evidence that dexamfetamine and methylphenidate are sometimes used off-label to treat EDS in narcolepsy patients after failure of the sole indicated option, modafinil. Physicians use dexamfetamine and | Thank you for your comment. The comparators in the scope have been updated and described separately for each condition. Following the scoping workshop, antidepressants have been removed as comparators for the population with narcolepsy. Dexamphetamine, methylphenidate, |

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| | | methylphenidate only in the absence of more appropriate treatments due to limited evidence of efficacy and the drawbacks of high potential for abuse, misuse or diversion linked to this class. Due to the limited usage in clinical practice and the limited evidence of efficacy and safety, Jazz Pharmaceuticals does not consider dexamfetamine and methylphenidate to be appropriate as clinical comparators for therapeutic treatment of EDS, or solriamfetol, in narcolepsy.<br>Sodium oxybate (Xyrem) is indicated for the treatment of narcolepsy with cataplexy. It is typically used when several symptoms of the disease are present: cataplexy, sleep fragmentation, sleep paralysis, EDS and hallucinations. It is not indicated or used specifically for the treatment of EDS and is only indicated for patients with cataplexy. Xyrem is a CNS depressant, which is administered at night, as opposed to solriamfetol, which is used during the day as a wake promoting agent. Due to the differences in indication, day-time vs night-time dosing and different pharmacology, Xyrem is not an appropriate clinical comparator for therapeutic treatment of EDS, or Solriamfetol.<br>Pitolisant (Wakix) is indicated for the treatment of narcolepsy with or without cataplexy. Pitolisant is not widely used in clinical practice in England and Wales, and its place in therapy is not established. The access and funding for Pitolisant is inconsistent across hospital Trusts and CCGs. Pitolisant showed efficacy in clinical trials in the treatment of EDS and cataplexy. Pitolisant may be an appropriate clinical comparator for the therapeutic treatment of EDS, or solriamfetol. NB: Although pitolisant is indicated in narcolepsy and has clinical data in the treatment of EDS, the lack of clarity in its use in clinical practice in England and Wales, the fragmented access situation, and the lack of inclusion in clinical guidelines or completion of a NICE STA means its appropriateness as a national real world comparator for therapeutic treatment of EDS, or solriamfetol, is extremely subjective and has significant limitations | pitolisant and sodium oxybate have been removed as comparators for the OSA population. The scope has been updated to reflect that modafinil is not recommended by the European Medicines Agency. The scope has been updated to highlight that treatment of excessive sleepiness in OSA usually focuses on the underlying condition.<br>The appraisal has been split into two separate Single Technology Appraisals: ID1602 for treating excessive sleepiness caused by narcolepsy and ID1499 for treating excessive sleepiness caused by obstructive sleep apnoea. The final scope for ID1499 will be made available in due course. |

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| | | Antidepressants (such as selective serotonin reuptake inhibitors (SSRIs), serotonin–noradrenaline reuptake inhibitors (SNRIs) or tricyclic antidepressants) are not indicated or used for the treatment of EDS in narcolepsy. There is evidence of off-label use of antidepressants to treat cataplexy in narcolepsy, but not EDS. As Jazz Pharmaceuticals intends to seek an indication for solriamfetol for the treatment of EDS, and not cataplexy, antidepressants are not an appropriate comparator.<br>EDS associated with OSA<br>Modafinil is not indicated for the treatment of EDS in OSA. In 2011, an Article 31 review by the EMA concluded that treatment of EDS associated with OSA with modafinil resulted in a negative risk/benefit assessment.<br>Research conducted by Jazz Pharmaceuticals in 2018 concluded that there is very low usage of pharmacological treatment for EDS in OSA patients in the UK (c.1% of EDS-diagnosed OSA patients)(NB due to the proprietary nature of this research, this information is commercial in confidence)<br>For these reasons, modafinil is not an appropriate clinical comparator for solriamfetol in EDS associated with OSA.<br>Dexamfetamine, methylphenidate and sodium oxybate are not indicated for or used in clinical practice for the treatment of EDS associated with OSA and are therefore not appropriate comparators for solriamfetol in EDS associated with OSA.<br>CPAP is, according to NICE guidance, a primary treatment option for OSA patients, and is used to treat the underlying airway obstruction in OSA, prior to consideration of any further treatment for residual EDS. CPAP is therefore not an appropriate comparator at the point where solriamfetol use might be considered. | |
| Outcomes | Association of British Neurologists | Sleep latency is a measure of how quickly a subject will fall asleep on command – measures of wakefulness or vigilance would be more useful in clinical assessment | Thank you for your comment. Following the scoping workshop, sleep latency has been removed as a |

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| | | | comparator. Wakefulness is assumed to be captured through 'excessive waketime sleepiness'. |
| | Bioprojet Europe | Separate outcome measures for Narcolepsy and OSA: Narcolepsy outcome measures should include rate / frequency of cataplexy attacks | Thank you for your comment. Following the workshop, the outcomes have been updated to:<br>• excessive waketime sleepiness<br>• adverse effects of treatment<br>• length of life<br>• health-related quality of life<br>These outcomes are considered to be relevant to both populations. |
| | British Thoracic Society | Yes but perhaps be specific for OSA e.g. cardiovascular risks | Thank you for your comment. Cardiovascular risks are assumed to be captured |

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| | | | through ‘adverse effects of treatment’. |
| | Jazz Pharmaceuticals UK | The most appropriate outcome measures for consideration should include:<br>Key Clinical Outcomes<br>• Change in the mean sleep latency time (in minutes) as measured by the Maintenance of Wakefulness Test (MWT)<br>• Change in Epworth Sleepiness Scale (ESS) score<br>• Safety and tolerability, including treatment-emergent adverse events<br><br>Additional Outcome Measures<br>• Patient Global Impression of Change (PGI-C)<br>• Clinician Global Impression of Change (CGI-C)<br>• Functional outcomes and health-related quality of life. | Thank you for your comment. Following the workshop, the outcomes have been updated to:<br>• excessive waketime sleepiness<br>• adverse effects of treatment<br>• length of life<br>• health-related quality of life<br>To maintain flexibility, the outcome measures have not been specified. |
| Economic analysis | Association of British Neurologists | No comment | Noted. |
| | British Thoracic Society | We are unlikely to be able to prescribe this in the OSA population due to constraints of time and cost. | Thank you for your comment. The appraisal committee will consider |

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| | | | the impact on service delivery. |
| | Jazz Pharmaceuticals UK | Jazz Pharmaceuticals does not expect that solriamfetol will have an effect on mortality. Therefore a one-year time horizon is assumed appropriate. A lifetime horizon will be explored. | Thank you for your comment. The assumptions in the economic model will be considered during the appraisal. |
| Equality and Diversity | Association of British Neurologists | No comment | Noted. |
| | Bioprojet Europe | We would like to make the point that Pitolisant (Wakix®, Bioprojet) has already entered the consultation process at NICE, for use in OSA, but has not been included for a scoping workshop. Whilst we accept that such workshops are not always required, we would question why these two potential drug interventions have been treated differently. | Thank you for your comment. A scoping workshop was recently held which discussed issues relating to treating excessive sleepiness caused by obstructive sleep apnoea. Therefore, NICE believes that another workshop is not required at this time. Both pitolisant [ID1065] and solfriamfetol [ID1499] will be assessed through the single technology |

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| | | | appraisals programme for treating excessive sleepiness caused by obstructive sleep apnoea. |
| | British Thoracic Society | None | Noted. |
| | Jazz Pharmaceuticals UK | N/A | Noted. |
| Other considerations | British Thoracic Society | As above. Concern re cost and CV risk in OSA. | Thank you for your comment. The barriers to implementation will be considered in the appraisal. Cardiovascular risks are assumed to be captured through 'adverse effects of treatment'. |
| | Jazz Pharmaceuticals UK | N/A | Noted. |
| Innovation | Association of British Neurologists | With regards to narcolepsy, there is an unmet need for more effective treatment of EDS | Thank you for your comment. The appraisal committee will consider whether there are any |

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| | | | benefits of solriamfetol that are not adequately captured by the QALY estimate. |
| | British Thoracic Society | Not for OSA. Potential for Narcolepsy as current stimulants have limited efficacy.<br>Could be substantial for narcolepsy e.g. able to return to work or drive. | Thank you for your comment. The appraisal committee will consider whether there are any benefits of solriamfetol that are not adequately captured by the QALY estimate. |
| | Jazz Pharmaceuticals UK | The EMA MAA was accepted as a New Active Substance. There are currently no approved drugs for EDS in narcolepsy or OSA with the combined attributes of a low abuse liability, a robust and durable efficacy profile, few drug-drug interactions, and a rapid onset of action which is maintained with chronic administration and that is well tolerated. Solriamfetol meets this need.<br>Residual and unacceptable EDS in CPAP compliant and CPAP exhausted patients (those who, despite efforts to use CPAP or equivalent, are unable to tolerate it or have experienced no benefit) is a symptom that has a considerable negative impact on QoL, in terms of functionality, performance and cognition. This, in turn has a deleterious societal impact in terms of absenteeism, job loss or ability to drive, most importantly in the case of professional drivers.<br>100% of patients suffering from narcolepsy present EDS which is usually severe, based on the ESS and the MSLT (Multiple Sleep Latency Test). The population who have this condition are adults in their active years, resulting in | Thank you for your comment. The appraisal committee will consider whether there are any benefits of solriamfetol that are not adequately captured by the QALY estimate. |

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| | | a dramatic negative societal impact in terms of performance, job loss and accident risk, as well as a decrease in QoL and interpersonal relationships.<br><br>Treatment with solriamfetol leads to a majority of patients with EDS in OSA and narcolepsy reporting meaningful improvements in overall health and QoL. Evidence demonstrates that solriamfetol offers statistically significant improvements on Clinical Outcomes Assessments (COA) such as MWT, ESS, and PGIc compared with placebo. Furthermore, the dose-response profile was similar within and between the narcolepsy and the OSA populations, indicating consistency and generalizability of the treatment effect across populations. In addition, solriamfetol treatment is associated with significant improvements in work productivity as well as activities outside of work. It is worthwhile indicating that the data which supports the impact of solriamfetol on HRQoL is derived from the clinical program where the COAs were included as primary and secondary endpoints. These measures are above and beyond what is possible to capture in a QALY calculation.<br><br>In the context of not having an approved drug to treat EDS in OSA patients, Jazz Pharmaceuticals believes there would be a “step-change” to improve the quality of life in this excessively sleepy population, by providing a once daily dosing with solriamfetol.<br><br>Though it may not be a “step-change” in the management of EDS in narcoleptic patients, solriamfetol would add to and strengthen the therapeutic options available for optimisation of the management and welfare of these patients. | |
| Questions for consultation | Association of British Neurologists | Pitolisant is being increasingly used to treat EDS in narcolepsy as a third-line agent after modafinil and dexamfetamine/methylphenidate;<br><br>I would anticipate solriafemtol would be potentially recommended as add-on therapy in those with residual EDS after treatment with CPAP; | Thank you for your comments. The scope has been updated to reflect that solriamfetol would typically be used in addition to, rather |

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| | | Other treatments for OSA would be suitable comparators;<br>The only routinely used drug treatments to manage EDS in narcolepsy are modafinil, dexamfetamine, methylphenidate, pitolisant and sodium oxybate. | than as an alternative to, treatments for the underlying OSA. The comparators for the narcolepsy population have been updated in line with the suggestions.<br>The appraisal has been split into two separate Single Technology Appraisals: ID1602 for treating excessive sleepiness caused by narcolepsy and ID1499 for treating excessive sleepiness caused by obstructive sleep apnoea. The final scope for ID1499 will be made available in due course. |
| | Bioprojet Europe | Would NICE consider conducting a separate full review on Narcolepsy? | Thank you for your comment. The appraisal has been split into two separate Single Technology Appraisals: ID1602 for treating excessive sleepiness caused by narcolepsy and ID1499 for treating |

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| | | | excessive sleepiness caused by obstructive sleep apnoea. The final scope for ID1499 will be made available in due course. |
| | British Thoracic Society | No comments | Noted. |
| | Jazz Pharmaceuticals UK | Is pitolisant used in clinical practice to treat excessive sleepiness caused by narcolepsy or OSA (outside its marketing authorisation)?<br>Pitolisant is not used in clinical practice to treat EDS caused by OSA. There is inconsistent use of pitolisant to treat EDS caused by narcolepsy.<br>For people with excessive sleepiness caused by OSA, would solriamfetol be considered in addition to, or as an alternative to, continuous positive airway pressure?<br>Enrolment criteria in the solraimafetol OSA clinical studies excluded subjects who had refused to try a primary OSA therapy (e.g. CPAP). Subjects who were currently using CPAP, or had a documented history of attempted use but were not currently treated were accepted for enrolment. Solriamfetol does not treat the underlying airway obstruction and is therefore not suitable as or intended as an alternative to CPAP. There was no evidence in clinical studies of differential efficacy between solriamfetol subjects who were adherent or non-adherent with primary OSA therapy usage. However an attempt to treat the underlying obstruction (such as use of CPAP) is expected to occur (and is the approach intended by Jazz Pharmaceuticals) prior to initiation of | Thank you for your comment.<br>Pitolisant has been removed as a comparator for the OSA population because it is not considered to be established clinical practice.<br>The scope has been updated to reflect that solriamfetol would be typically be used in addition to, rather than as an alternative to, treatments for the underlying OSA.<br>The appraisal has been split into two separate Single Technology |

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| | | solriamfetol in line with existing clinical practice as recommended by the existing NICE guideline on the treatment of OSA.<br><br>For people with excessive sleepiness caused by OSA, would additional interventions (such as lifestyle changes, mandibular advancement devices or surgery) be relevant comparators?<br>All the above mentioned interventions are recommended as primary therapies for the treatment of OSA, which is the underlying condition. Solriamfetol is intended for the treatment of EDS, which is a symptom of OSA. Evidence shows that, despite adequate, adherent treatment of the underlying obstruction, EDS remains a problem in some patients. Therefore, the named interventions are not appropriate clinical comparators as they form part of a clinical management regime intended for the treatment of the underlying obstruction.<br><br>Have all relevant comparators for solriamfetol been included in the scope?<br>Yes – with some suggested for removal<br><br>Are the outcomes listed appropriate?<br>See outcomes section for edits<br><br>Are the subgroups suggested in 'other considerations' appropriate?<br>OSA and narcolepsy are distinct patient groups and should be treated as such when considering appropriate comparators and place in therapy. | Appraisals: ID1602 for treating excessive sleepiness caused by narcolepsy and ID1499 for treating excessive sleepiness caused by obstructive sleep apnoea. The final scope for ID1499 will be made available in due course. |

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| | | Are there any other subgroups of people in whom solriamfetol is expected to be more clinically effective and cost effective or other groups that should be examined separately?<br><br>Pre-specified study analysis shows that there is little difference in the clinical effectiveness of solriamfetol between subgroups including subjects with or without cataplexy, subjects adherent or non-adherent with primary OSA therapy, by age, by gender, by BMI, or by baseline severity of EDS.<br><br>Is it appropriate to appraise solriamfetol as a single technology appraisal and consider the underlying conditions (narcolepsy and OSA) as subgroups within one population?<br><br>At this point Jazz Pharmaceuticals believes it to be appropriate to appraise solriamfetol as a single technology appraisal, although it must be noted that the underlying conditions, and the populations they represent, have significant and notable differences in epidemiology, treatment landscape and baseline severity of EDS.<br><br>Where do you consider solriamfetol will fit into the existing NICE pathways, Neurological conditions and Respiratory conditions?<br><br>Neurological: Narcolepsy<br><br>Respiratory: Obstructive Sleep Apnoea<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the | |

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| | | proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:<br>• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which solriamfetol will be licensed;<br>• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Jazz Pharmaceuticals does not believe that the proposed remit and scope (with suggested revisions) could exclude or have a negative impact on any clinically appropriate section of the population.<br><br>Do you consider solriamfetol to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?<br>Yes - See "Innovation" section<br><br>Do you consider that the use of solriamfetol can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?<br>Yes - See "Innovation" section | |

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| | | Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. | |
| Additional comments on the draft scope | Association of British Neurologists | A new drug to treat EDS is a welcome development but its potential use in OSA is likely to be controversial. Solriamfetol is likely to carry potential cardiovascular risk and the patient group with severe OSA might be vulnerable. Around 10 years ago, modafinil (a more benign agent from a cardiovascular perspective) briefly had a UK licence for treating residual EDS in OSA but this was overturned by the EMA, largely through safety fears in this patient population. | Thank you for your comment. The scope has been updated to reflect that modafinil is not recommended by the European Medicines Agency. Cardiovascular risks are assumed to be captured through 'adverse effects of treatment'. |

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**