National Institute for Health and Care Excellence

Health Technology Evaluation

Oveporexton for treating type 1 narcolepsy [ID6622]

Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Association of British Neurologists	Single technology appraisal is the correct evaluation route	Thank you for your comment. The topic will proceed via the single technology appraisal route as proposed.
	Association of Respiratory Nurses	This medication would be appropriate for evaluation in the type 1 Narcolepsy group	Thank you for your comment. The topic will proceed via the single technology appraisal route as proposed.
	Narcolepsy UK	It is appropriate to evaluate oveporexton as a single technology appraisal given that it is the first targeted drug for type 1 narcolepsy. This or future appraisals should address the absence of guidelines for sodium oxybate and pitolisant for type 1 and type 2 narcolepsy.	Thank you for your comment. The topic will proceed via the single technology appraisal route as proposed. Evaluation of other treatments is outside

Section	Stakeholder	Comments [sic]	Action
			the remit of this appraisal.
	Takeda	Single technology appraisal is the appropriate route for evaluation.	Thank you for your comment. The topic will proceed via the single technology appraisal route as proposed.
Wording	Association of British Neurologists	*[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?]* Yes	Thank you for your comment. No change to the scope required.
	Association of Respiratory Nurses	The scope does not provide a cost comparison, but sets out the mechanism for this, which is appropriate.	Thank you for your comment. No change to the scope required.
	Narcolepsy UK	This is appropriate.	Thank you for your comment. No change to the scope required.
	Takeda	*[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?]* Yes.	Thank you for your comment. No change to the scope required.
Timing issues	Association of British Neurologists	Although a relatively rare disease, the impact of narcolepsy (with cataplexy particularly) on the individual is high. Many existing treatments are poorly tolerated and ineffective therefore this first in class disease targeted treatment needs assessing for funding as soon as possible as it represents a major advance in care.	Thank you for your comment. This topic has been scheduled into the work programme.
	Association of Respiratory Nurses	Not urgent	Thank you for your comment. This topic has been scheduled

Section	Stakeholder	Comments [sic]	Action
			into the work programme.
	Narcolepsy UK	Oveporexton is likely to be the first targeted drug approved by the MHRA for narcolepsy. Early adoption would stop people with narcolepsy missing out on, or falling out of education, work and social/family life opportunities (REF: (https://www.narcolepsy.org.uk/narcolepsy-charter/). These opportunities often cannot be recovered and have a life-long impact on people's lives. This evaluation would therefore fulfil the NHS remit to support earlier access to innovative, specialist treatments that preserve long-term social and economic participation and reduce lifelong disability for people with rare conditions (Ref: England Rare Disease Action plan 2026).	Thank you for your comment. This topic has been scheduled into the work programme.
	Takeda	Oveporexton demonstrated superiority over placebo in all primary and secondary endpoints in the phase 3 studies 'FirstLight' (TAK-861-3001) and 'RadiantLight' (TAK-861-3002). When available, oveporexton will be the first treatment for type 1 narcolepsy that addresses the underlying cause of disease and the only treatment that has demonstrated evidence of returning patients to normal function. It will therefore be a step change for patients living with this condition and an important addition to the clinical landscape. UK marketing authorisation is expected between [redacted] and Takeda wish to provide access for patients in the UK at the earliest opportunity.	Thank you for your comment. This topic has been scheduled into the work programme.

Comment 2: the draft scope

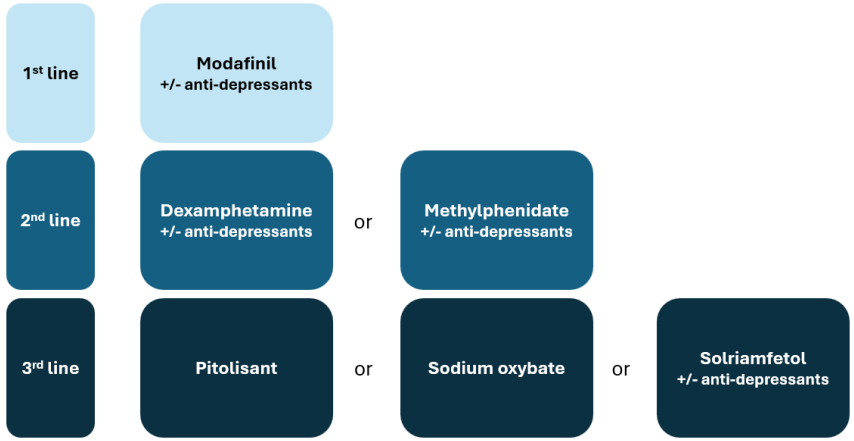
Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Association of British Neurologists	1. In addition to the listed symptoms of narcolepsy, additional symptoms/health issues include • Prominent cognitive dysfunction • Psychiatric issues, particularly anxiety and depression • Autonomic and emotional dysregulation • Substantial social, occupational and educational impairment.	Thank you for your comment. The scope has been updated to reflect the other health issues that people with

Section	Consultee/ Commentator	Comments [sic]	Action
		• Weight gain (and consequent co-morbidities) Although there are symptomatic treatments available, they are often relatively ineffective, have very significant side effect profiles, are teratogenic come with significant addiction and abuse risk and are difficult to use (particularly sodium oxybate which has a night time dosing regime). Oveporexton in contrasts targets the underlying neurochemical deficiency. The European guidelines are not fully reflective of UK practice, partly due to the relative lack of availability of sodium oxybate and pitolisant due to commissioning guidelines and specialist expertise placing them second or third line agents in treatment algorithms, whereas they are listed as first line for patients with cataplexy in the European guidelines.	narcolepsy can experience. The scope has also been updated to remove the European guidelines given that they do not reflect UK clinical practice.
	Association of Respiratory Nurses	This is accurate and correct	Thank you for your comment. No change to the scope required.
	Narcolepsy UK	Narcolepsy symptoms extend beyond those listed in the background, especially in people who have had narcolepsy for a long time. The following references provides a good description of under-recognised symptoms including psychiatric, cognitive and metabolic problems (DOI: 10.3389/fpsyt.2026.1799520, 10.1177/13591053231221373). The prevalence estimates provided in this section include people with narcolepsy whether or not they have received a diagnosis; diagnosis rates are considerably lower than this as estimated in a recent study (DOI: 10.1136/thorax-2025-223863). The European guidelines do not appear to recommend methylphenidate or dexamfetamine due to limited evidence base. Please check this.	Thank you for your comment. The scope has been updated to reflect the other health issues that people with narcolepsy can experience. The scope has also been updated to remove the European guidelines given that they do not fully reflect UK clinical practice.

Section	Consultee/ Commentator	Comments [sic]	Action
	Takeda	Disease background: Takeda consider the characterisation of narcolepsy in the draft scope to be inadequate. The description does not fully encapsulate the disease, and the distinction between type 1 and type 2 narcolepsy is inappropriately defined. Takeda propose to include information on the pentad of symptoms (excessive daytime sleepiness, cataplexy, disrupted nighttime sleep, sleep paralysis and hypnagogic/hypnopompic hallucinations), as well as the cognitive, physical and psychological impacts experienced by those with narcolepsy. The background section states: "*Type 1 narcolepsy (previously known as narcolepsy with cataplexy). People with type 1 narcolepsy have cataplexy and usually have low orexin levels.*" This is an inadequate description of type 1 narcolepsy, given that people with type 1 narcolepsy experience a variety of other symptoms associated with excessive daytime sleepiness, as well as cataplexy. Takeda proposes the alternative wording: ***"Type 1 narcolepsy (previously known as narcolepsy with cataplexy). People with type 1 narcolepsy typically experience excessive daytime sleepiness, cataplexy, disrupted nighttime sleep, sleep paralysis and hypnagogic/hypnopompic hallucinations. People with type 1 narcolepsy usually have low orexin levels."*** The background section states: "*Type 2 narcolepsy (previously known as narcolepsy without cataplexy). People with type 2 narcolepsy do not have cataplexy, typically have less severe symptoms, and have normal orexin levels*." This is an inaccurate description of the disease. People with type 2 narcolepsy do not have less severe symptoms, rather they typically have fewer than seen with type 1 narcolepsy. Studies show that people with type 2 narcolepsy have symptoms that can evolve over time into a type 1 narcolepsy or idiopathic hypersomnia presentation, or even remit. Furthermore, whilst	Thank you for your comment. The scope has been updated to reflect that: • Cataplexy is a symptom that distinguishes type 1 narcolepsy from type 2 and occurs alongside other symptoms. • A 2026 study suggests the UK prevalence of narcolepsy is 0.02%. • NHS treatment pathways do not follow the European 2021 guidelines and instead follow a stepwise switching approach beginning with modafinil with or without antidepressants, and reserving sodium oxybate, pitolisant, and solriamfetol for later lines.

Section	Consultee/ Commentator	Comments [sic]	Action
		most people with type 2 narcolepsy have normal orexin levels, some do not (Cavalli et al. 2025). Takeda proposes the alternative wording: ***"Type 2 narcolepsy (previously known as narcolepsy without cataplexy). People with type 2 narcolepsy experience excessive daytime sleepiness, alongside other symptoms that may include disrupted nighttime sleep, sleep paralysis and hypnagogic/hypnopompic hallucinations. People with type 2 narcolepsy do not have cataplexy and typically have normal orexin levels. Over time, symptoms may evolve into a presentation consistent with type 1 narcolepsy or idiopathic hypersomnia presentation or may remit."*** <u>Prevalence</u> The background section states: "*Approximately 30,000 people (1 in 2,500) have narcolepsy in the UK, this may be an underestimate due to underdiagnosis*." However, a recent published study in England found the prevalence of narcolepsy to be 0.02% (Strongman et al. 2026). Based on projected 2026 population estimates for people aged ≥ 16 years in England from mid-2024, and growth estimates from mid-2023 to mid-2024 from the Office for National Statistics (ONS 2025), this equates to approximately 10,000 people with narcolepsy (type 1 and type 2) in England today. Strongman et al. 2026 is the most recent evidence directly applicable to England and therefore serves as the most reliable source for estimating the patient population. Takeda proposes the alternative wording: ***"The prevalence of narcolepsy in England is estimated to be 0.02%, this equates to approximately 10,000 people. This may be an underestimate due to underdiagnosis"*** <u>Treatment</u>	

Section	Consultee/ Commentator	Comments [sic]	Action
		The background section details the 2021 joint European guideline and states: "*There are no UK-specific treatment guidelines for narcolepsy… …or switching from venlafaxine or clomipramine to a different anti-depressant*." Takeda considers this wholly inappropriate because the 2021 joint European guideline does not reflect current standard treatment practice of type 1 narcolepsy in the UK. While there are currently no UK-wide treatment guidelines, there is evidence to show that the treatment pathway of type 1 narcolepsy is broadly in line with the pathway described and agreed by the committee in TA758, with the addition of anti-depressants for the treatment of cataplexy in combination with therapies that only target excessive daytime sleepiness. This is supported by an analysis of trust-level guidelines from the nine highest-prescribing centres for branded narcolepsy treatments in England (Takeda internal research). Of the nine centres, Takeda identified five published local treatment guidelines, and formulary information was available for the remaining four centres. The identified sources are outlined in the list of trust-level guidelines that Takeda have added at the end of this form. While some geographic variation in practice was observed, Takeda has amalgamated these local approaches into an overarching treatment pathway (Figure 1) intended to reflect routine UK clinical practice for type 1 narcolepsy.	

		Figure 1: Proposed UK Type 1 Narcolepsy Treatment Pathway  The analysis shows modafinil with or without anti-depressants as first line therapy; dexamphetamine or methylphenidate, with or without antidepressants, as second line therapy; and solriamfetol with or without antidepressants, or sodium oxybate, or pitolisant as subsequent therapy options. The sequencing of the subsequent therapy options varies by local practice, reflecting that they can be considered to represent the same line of therapy in an amalgamated UK pathway. Across local trust guidelines, combination therapy besides the aforementioned addition of anti-depressants is generally discouraged as routine practice but may be used selectively under specialist supervision where monotherapy is ineffective or not tolerated. This selective use of combination therapy with treatments targeting excessive daytime sleepiness is seen in refractory patients, after the expected positioning of oveporexton, so it is not considered a relevant comparator for this appraisal. The proposed pathway has also been validated with UK healthcare professionals.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Takeda proposes that NICE applies the same treatment pathway as used in TA758, with the addition that treatments not indicated for cataplexy may be used in combination with anti-depressants. Takeda proposes the alternative wording: ***"There are no UK-specific treatment guidelines for narcolepsy. Whilst there is slight variation in local practice, routine UK clinical practice for type 1 narcolepsy treatment typically follows a stepwise switching pathway. First line treatment is modafinil, with or without anti-depressants. Second-line options include dexamphetamine or methylphenidate, with or without antidepressants. Subsequent treatment options include solriamfetol with or without antidepressants, or sodium oxybate, or pitolisant. The sequencing of these subsequent options varies by local practice, reflecting that they are generally considered to represent the same line of therapy."*** The identified sources are outlined in the list of trust-level guidelines that Takeda have added at the end of this form. <u>NICE-recommended treatments:</u> The background section states: "*There are no NICE-recommended treatments specifically for cataplexy symptoms caused by narcolepsy*." Takeda considers this an inappropriate statement given that type 1 narcolepsy typically presents as a variety of symptoms including excessive daytime sleepiness, cataplexy, disrupted nighttime sleep, sleep paralysis and hypnagogic/hypnopompic hallucinations. Takeda proposes the alternative wording: ***"There are no NICE-recommended treatments for type 1 narcolepsy."***	

Section	Consultee/ Commentator	Comments [sic]	Action
Population	Association of British Neurologists	*[Is the population defined appropriately?]* Yes	Thank you for your comment. No change to the scope required.
	Association of Respiratory Nurses	*[Is the population defined appropriately?]* yes	Thank you for your comment. No change to the scope required.
	Narcolepsy UK	*[Is the population defined appropriately?]* Yes although should note clinical challenges with differentiating between type 1 and type 2 narcolepsy as cataplexy may develop over time (DOI: 10.3389/fpsyt.2026.1799520)	Thank you for your comment. The background section of the scope has been updated to reflect the difficulty of distinguishing between type 1 and type 2 narcolepsy.
	Takeda	*[Is the population defined appropriately?]* No. Based on the expected marketing authorisation for oveporexton, Takeda proposes the alternative wording: ***"People aged ≥ 16 with type 1 narcolepsy"***	Thank you for your comment. The population has been updated to align with the anticipated marketing authorisation.
Subgroups	Association of British Neurologists	Patients with type I narcolepsy (with cataplexy) will be the main recipients rather than type II (without cataplexy) who are more difficult to diagnose accurately and do not always have the orexin deficiency almost uniformly detected in type I narcolepsy.	Thank you for your comment. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Oveporexton works as an orexin receptor agonist and therefore is a highly targeted treatment for those with type I narcolepsy which should be viewed as an orexin-deficiency syndrome. There are no subgroups within this group that would definitely benefit more or less well from the treatment with current available data.	
	Association of Respiratory Nurses	*[Are there groups within the population that should be considered separately?]* No	Thank you for your comment. No change to the scope required.
	Narcolepsy UK	We haven't seen the clinical trial results which makes it difficult to comment on this.	Thank you for your comment. No change to the scope required.
	Takeda	Takeda does not consider there to be any subgroups within the population that should be considered separately. The expected positioning of oveporexton in clinical practice is third line following modafinil with or without anti-depressants (first line), and following dexamphetamine or methylphenidate with or without anti-depressants (second line). The oveporexton phase 3 clinical trials FirstLight (TAK-861-3001) and RadiantLight (TAK-861-3002) demonstrate that clinical efficacy is consistent irrespective of prior therapies.	Thank you for your comment. No change to the scope required.
Comparators	Association of British Neurologists	All relevant drugs have been included although additional anti-depressants are used as anti-cataplexic agents in addition to clomipramine and venlafaxine in UK practice, particularly SSRIs such as fluoxetine as anti-cataplexic agents. The availability of some of the medications and restrictions on prescribing mean that generally the UK does not use pitolisant or sodium oxybate ever as a first line medication, even in patients with cataplexy (see above), usually trialling stimulant medication first.	Thank you for your comment. The scope has been updated to include fluoxetine and to reflect that sodium oxybate and pitolisant are typically reserved for later lines of treatment. The

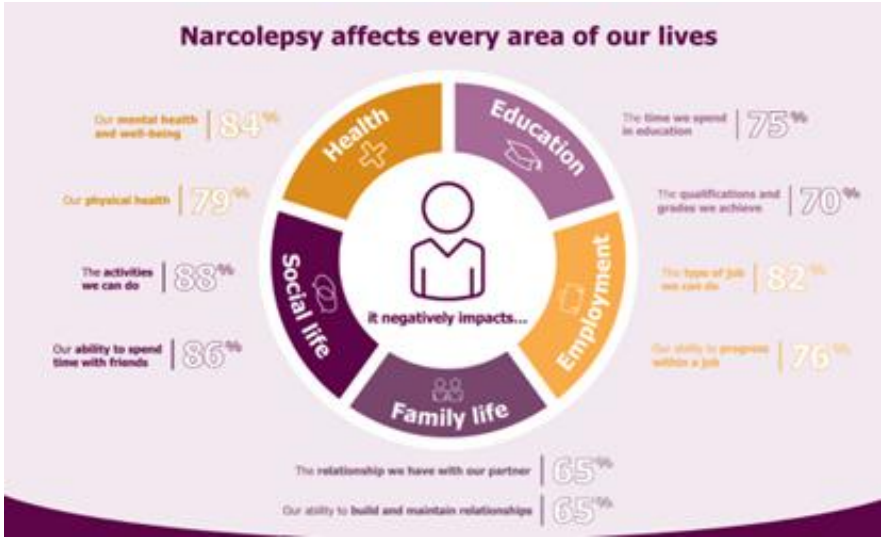
Section	Consultee/ Commentator	Comments [sic]	Action
			committee will decide which are the relevant comparators based on the evidence presented to it.
	Association of Respiratory Nurses	*[Have all relevant comparators been included?]* Yes	Thank you for your comment. No change to the scope required.
	Narcolepsy UK	The comparators listed are based on the European recommendations for narcolepsy with cataplexy. People with type 1 narcolepsy who have mild cataplexy symptoms may be treated with a single wake-promoting agent. Oveporexton may improve treatment of excessive daytime sleepiness and other narcolepsy symptoms in this group, given that it is a targeted treatment.	Thank you for your comment. No change to the scope required.
	Takeda	No. Takeda disagrees with the comparators described in the draft scope, they do not reflect the standard treatments with which oveporexton should be compared. The expected positioning for oveporexton will be in third line after modafinil with or without anti-depressants (first line), and dexamphetamine or methylphenidate with or without anti-depressants (second line). As such, the relevant comparators for oveporexton should be current third line therapies. Anti-depressants should not be considered as standalone comparators. Takeda proposes the following as the only relevant comparators: • ***Solriamfetol (with or without anti-depressants)*** • ***Pitolisant*** • ***Sodium oxybate***	Thank you for your comment. The scope has been updated to reflect that sodium oxybate, pitolisant, and solriamfetol are typically reserved for later lines of treatment. The committee will decide which are the relevant comparators based on the evidence presented to it.

Section	Consultee/ Commentator	Comments [sic]	Action
		Please see Takeda's comments on the background information section, and the trust-level guidelines that Takeda have added at the end of this form for further detail.	
Outcomes	Association of British Neurologists	*[Are the outcomes listed appropriate?]* Yes – we would hope that health-related quality of life would capture cognitive functioning, psychosocial functioning, psychiatric wellbeing, improvement in nocturnal sleep and independence including driving.	Thank you for your comment. No change to the scope required.
	Association of Respiratory Nurses	*[Are the outcomes listed appropriate?]* Yes	Thank you for your comment. No change to the scope required.
	Narcolepsy UK	It will be important to capture the impact of narcolepsy on people's ability to have an active live throughout the day. This is impeded by the full range of daytime and night-time narcolepsy symptoms. Generic health related quality of life scores do measure this meaningfully as people narcolepsy stops people doing things some but not all of the time. Adverse effects of treatment are not specified in the brief. These should include adverse effects of all comparator drugs. It will also be important to consider personal safety implications of taking sodium oxybate, and frequent attendance of A&E settings by people with narcolepsy (Strongman et al, DOI 10.1111/jsr.14290)	Thank you for your comment. The committee will consider how best to capture the quality-of-life impacts of narcolepsy in its deliberations. The committee will consider resource use and the adverse effects of treatment in its deliberations.
	Takeda	To consider the key outcomes for this appraisal, it is important to consider the wider importance of sleep and its impacts when it is not well regulated due to a lack of orexin. Sleep is a vital human process that is essential for human life and impacts multiple aspects of health, both mental and physical (Ohayon 2013). Type 1 narcolepsy prevents this vital process from occurring with sufficient quality and quantity to sustain health and, therefore, results in a multi-faceted disease with potentially debilitating impacts for people who have	Thank you for your comment. The committee will consider the relevant outcomes in its deliberations. Mortality has been

Section	Consultee/ Commentator	Comments [sic]	Action
		it. While the key outcomes of excessive daytime sleepiness and weekly cataplexy rate highlight two of the obvious day-to-day impacts of the disease, there are numerous other factors that have serious consequences for people with type 1 narcolepsy. On the mental component of health, sleep has an important role in preventing serious mental health disorders, thus being prevalent in the type 1 narcolepsy population. These mental health disorders not only have an impact on quality of life but unfortunately can result in suicidality (Barateau 2020, Biscarini 2024, Ruoff 2017) leading to impacts on mortality (Ohayon 2014). Mortality is also impacted by the physical effects of type 1 narcolepsy. Firstly, people with type 1 narcolepsy have a higher risk of both vehicular and non-vehicular accidents (Ohayon 2018, Zheng 2024) partly due to the unpredictable nature of cataplexy, but also as a result of the impact of dysregulated sleep. Secondly, people with type 1 narcolepsy have an increased risk of cardiovascular disease (Ben-Joseph 2023) from the underlying disease. A key aspect of the sleep-wake cycle is that healthy people with well-regulated sleep cycles have a reduction in blood pressure (Dauvilliers 2012, Grimaldi 2012) while asleep; a natural process which is impaired when natural orexin levels are not there to regulate sleep appropriately. Long term periods of elevated blood pressure lead to cardiovascular disease and an increased risk of major acute cardiac events (MACE) such as myocardial infarction and stroke (Ben-Joseph 2023). Thirdly, cardiovascular risk has also been shown to be impacted by some of the currently available narcolepsy treatments, such as sodium oxybate, which is associated with hypertension (Riaz 2025). Hence, people with type 1 narcolepsy may be impacted by both disease-related and treatment-related increased cardiovascular risk. These wider consequences not only have a chronic impact on quality of life but also result in an elevated risk of mortality.	added to the outcome list.

Section	Consultee/ Commentator	Comments [sic]	Action
		Mortality is therefore an important outcome that should be considered for this appraisal. The NICE appraisal for solriamfetol (TA758) included length of life as an outcome, and this appraisal is directly applicable for type 1 narcolepsy patients as they also experience excessive daytime sleepiness. Takeda proposes the following as the outcomes: • ***excessive daytime sleepiness*** • ***number of cataplectic episodes*** • ***adverse effects of treatment*** • ***health-related quality of life*** • ***mortality***	
Equality	Association of British Neurologists	Restricting prescriptions too narrowly may reduce access to treatments in those socially and financially disadvantaged as often people with narcolepsy who have poor disease control may not be able to drive or access geographically remote specialist clinics and there are relatively few specialist sleep clinics in the UK. Ethnic minority groups and people with disabilities are over-represented in this group. Nil other specific	Thank you for your comment. This issue has been added to the Equality Impact Assessment.
	Association of Respiratory Nurses	I do not think this discriminates in any way.	Thank you for your comment. No action required.
	Narcolepsy UK	To consider: - women of child-bearing age (see warnings for the use of modafinil in this population) - the implications of taking sodium oxybate for young people living in shared accommodation or people with caring responsibilities - narcolepsy as a stigmatised disability	Thank you for your comment. These issues have been added to the Equality Impact Assessment.

Section	Consultee/ Commentator	Comments [sic]	Action
	Takeda	Upon review, Takeda does not believe that the draft remit or scope need changing to meet the aims of equality as set out by NICE.	Thank you for your comment. No action required.
Other considerations	Association of British Neurologists	Narcolepsy is a condition which affects every aspect of a person's life and wellbeing; educational, cognitive, social, occupational and mental health. These aspects should be taken into account when reviewing the data.	Thank you for your comment. The committee will consider whether there are any uncaptured benefits of oveporexton in its deliberations.
	Takeda	Additional impacts of narcolepsy In addition to the clinical trial data, Takeda believe it is important for the committee to consider the wider implications of type 1 narcolepsy on the ability of a person to fully function in society. In a survey of 302 people with narcolepsy and 149 supporters, carried out in 2018 by Adelphi with Narcolepsy UK, additional impacts were reported (Narcolepsy UK, 2018). Please see Figure 2 below for details.	Thank you for your comment. The committee will consider whether there are any uncaptured benefits of oveporexton in its deliberations.

Section	Consultee/ Commentator	Comments [sic]	Action
		Figure 2: Narcolepsy UK Charter Survey 2018  <u>NHS priorities</u> It is important to recognise that type 1 narcolepsy aligns directly with the NHS priority of the Optimal Sleep Pathway. Furthermore, given its association with significant co-morbidities such as cardiovascular disease, obesity, obstructive sleep apnoea and ADHD, type 1 narcolepsy intersects with many NHS priority areas. As such, type 1 narcolepsy should not be considered in isolation, but rather within the broader context of these related medical priorities.	
Questions for consultation	Association of British Neurologists	• Which treatments are the preferred first- and second-line options for cataplexy?	Thank you for your comment. The scope has been changed to

Section	Consultee/ Commentator	Comments [sic]	Action
		Venlafaxine, fluoxetine, chlormipramine, then second line, pitolisant, sodium oxybate within specialist centres • Is sodium oxybate routinely available for adults across the NHS? Availability varies across the NHS and treatment is generally initiated and monitored within specialist sleep centres with access to advanced diagnostic testing and experience managing complex narcolepsy therapies • What proportion of people are treated with only an anti-cataplexic agent, and what proportion have both an anti-cataplexic agent and a wake-promoting agent? Almost all patients with narcolepsy with cataplexy will need a wake-promoting medication as well as an anti-cataplexic agent. Sodium oxybate is not a pure anti-cataplexic agent as it improves night time sleep, improving daytime wakefulness but almost always requires some stimulant alongside. • Is modafinil still the preferred first-line wake-promoting agent? Modafinil remains the most commonly used first-line wake-promoting agent in UK practice, however in women of child-bearing potential, it is known to be both teratogenic and potentially interfere with the efficacy of many hormonal contraceptives. Traditional stimulant therapies may also be problematic in patients with cardiovascular disease, hypertension or psychiatric comorbidity • Which treatments are the preferred second- and third-line options in the NHS? Usually stimulants (Modafinil, methylphenidate, dexamphetamine) alongside an anti-cataplexic agent such as venlafaxine are used as first line treatments,	reflect the NHS treatment pathway.

Section	Consultee/ Commentator	Comments [sic]	Action
		Solriamfetol, pitolisant and sodium oxybate are typically used in patients with persistent symptoms, problematic cataplexy, stimulant intolerance or complex disease requiring combination therapy. • Where do you consider oveporexton will fit into the existing care pathway for type 1 narcolepsy? Initially, oveporexton is likely to be used in patients with persistent symptoms despite conventional stimulant therapy, particularly where clinically significant cataplexy is also present. It may also be particularly valuable in patients who: 1. cannot tolerate stimulants 2. have cardiovascular contraindications 3. experience treatment-limiting side effects 4. require complex polypharmacy to control symptoms. 5. Have psychiatric issues such as addiction precluding many treatments If long-term efficacy and safety are confirmed, oveporexton has the potential to reduce reliance on multiple symptomatic medications and may substantially alter future treatment pathways for type 1 narcolepsy. Please select from the following, will oveporexton be: Answer C A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): I would suspect that initially at least, oveporexton would be prescribed and	Thank you for your comment. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		monitored in secondary care within services with expertise in diagnostic sleep physiology and narcolepsy management. • Would oveporexton be a candidate for managed access? The trial evidence so far seems very favourable and it would be ideal if the medication could be used as part of routine NHS care given the significant unmet clinical need in Type I narcolepsy. Managed access data collection adds a considerable burden to overstretched services. However, if NICE considers additional real-world effectiveness or long-term safety data necessary, managed access would still represent an important opportunity to improve patient access to targeted therapy for the disease. • Do you consider that the use of oveporexton can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? The QALY calculation will not include prevention of weight gain and obesity-related comorbidities. In addition it is likely to underestimate the broader benefits of disease control including: • Educational attainment • Employment retention • Reduction in polypharmacy • Social functioning and independence including driving • Cognitive function Relevant evidence may be available from several sources, including: • real-world observational data including registry-based longitudinal follow-up from specialist narcolepsy centres • employment and educational participation data	Thank you for your comment. No change to the scope required. Thank you for your comment. The committee will consider whether there are any uncaptured benefits of oveporexton in its deliberations.

Section	Consultee/ Commentator	Comments [sic]	Action
		• driving and functional independence outcomes • healthcare utilisation data, including medication burden and specialist review requirements • qualitative patient experience evidence	
	Narcolepsy UK	**Questions about current standard of care** There is substantial geographic variability in use of sodium oxybate and pitolisant, with prescribing concentrated in a small number of Integrated Care Boards and variation in preference between these drugs (DOI: 10.1111/jsr.14415). This is due to a lack of national guidelines and the need to submit individual funding requests in some areas. These requests are largely unsuccessful. There is no publicly available data describing use of other drugs. Based on conversations with people with narcolepsy and clinicians, we believe that modafinil is the most common first line drug to treat excessive daytime sleepiness. Methylphenidate and amphetamine derivatives are often used in second, third line treatment despite the limited evidence base. Doses are often escalated much higher than recommended in the summary of product characteristics. This is worrying given potential cardiovascular and psychiatric side effects. There are no research studies that estimate the efficacy and safety implications of this approach. Similarly evidence for the use of antidepressant drugs to treat cataplexy is extremely limited (DOI: 10.1002/14651858.CD003724.pub3). We are not aware of many people who are solely prescribed antidepressants; the exceptions are people who have given up on wake promoting drugs due to side-effects, lack of effectiveness and difficulties obtaining specialist appointments in the NHS.	Thank you for your comment. The scope has been changed to reflect the NHS treatment pathway.

Section	Consultee/ Commentator	Comments [sic]	Action
		Without having seen the clinical trial results, it is difficult to comment on where oveporexton will fit into the existing care pathway. If results are as promising as expected, this is likely to be early to prevent years of experimentation with drugs that have limited evidence of efficacy and safety. **Have all the relevant outcomes been identified?** See above **Prescribing setting** Option D – Other. Ideally, oveporexton would be prescribed in secondary care with routine follow up in secondary care. However, there is a lack of capacity to treat narcolepsy in specialist care and people often have to travel a long way to collect prescriptions from tertiary hospitals. The guidelines should therefore allow shared care agreements that allow prescriptions to be collected from pharmacists in the local community. The setting for prescribing and routine follow-up for comparators differs between ICBs (DOI: 10.1111/jsr.14415). Narcolepsy UK often try to support clinicians and people with narcolepsy to set up shared care agreements for all narcolepsy drugs. **Would oveporexton be a candidate for managed access?** It is difficult to answer this question without knowing more about when oveporexton is going to be assessed by the MHRA. Would this make it more difficult to access oveporexton compared to other treatments with a similar evidence base? **Health related benefits unlikely to be included in QALY calculation** See above	Thank you for your comment. No change to the scope required. Thank you for your comment. The issue around geographical differences in access to specialist sleep centres has been added to the Equality Impact Assessment. No change to the scope required. Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. See above	Thank you for your comment. No change to the scope required.
	Takeda	Have all relevant comparators been identified? No. Takeda disagrees with the comparators described in the draft scope, they do not reflect the standard treatments with which oveporexton should be compared. Please see Takeda's comments on the background information and comparator sections, and the trust-level guidelines that Takeda have added at the end of this form for further detail. Which treatments are the preferred first- and second-line options for cataplexy? Type 1 narcolepsy as a disease causes a pentad of symptoms, one of which is cataplexy. As such, the first- and second-line treatment options solely for cataplexy is inappropriate in this context. The preferred first line treatment for type 1 narcolepsy is modafinil, with or without anti-depressants. Preferred second-line treatments for type 1 narcolepsy include dexamphetamine or methylphenidate, with or without anti-depressants. Please see Takeda's comments on the background information section, and the trust-level guidelines that Takeda have added at the end of this form for further detail. Is sodium oxybate routinely available for adults across the NHS?	Thank you for your comment. The scope has been changed to reflect the NHS treatment pathway.

Section	Consultee/ Commentator	Comments [sic]	Action
		Sodium oxybate is generally available across the NHS, however there is some regional variation. Please see Takeda's comments on the background information section, and the trust-level guidelines that Takeda have added at the end of this form for further detail. <u>What proportion of people are treated with only an anti-cataplexic agent, and what proportion have both an anti-cataplexic agent and a wake-promoting agent?</u> Type 1 narcolepsy as a disease causes a pentad of symptoms, one of which is cataplexy. As such, patients with type 1 narcolepsy are treated to address all symptoms simultaneously and are typically not treated solely for their cataplexy symptoms. Please see Takeda's comments on the background information section, and the trust-level guidelines that Takeda have added at the end of this form for further detail. <u>Is modafinil still the preferred first-line wake-promoting agent?</u> Type 1 narcolepsy as a disease causes a pentad of symptoms, one of which is excessive daytime sleepiness. As such, the first-line wake promoting agent is inappropriate in this context. The preferred first line treatment for type 1 narcolepsy is modafinil, with or without anti-depressants. Please see Takeda's comments on the background information section, and the trust-level guidelines that Takeda have added at the end of this form for further detail. <u>Which treatments are the preferred second and third-line options in the NHS?</u> Preferred second-line options for type 1 narcolepsy include dexamphetamine or methylphenidate, with or without antidepressants. Currently, preferred third line options for type 1 narcolepsy include solriamfetol with or without antidepressants, or sodium oxybate, or pitolisant. Please see Takeda's	

Section	Consultee/ Commentator	Comments [sic]	Action
		comments on the background information section, and the trust-level guidelines that Takeda have added at the end of this form for further detail. Where do you consider oveporexton will fit into the existing care pathway for type 1 narcolepsy? Takeda expects oveporexton to be positioned third line, displacing the current third line therapies. Have all the relevant outcomes been identified? No, Takeda consider mortality should also be included as an outcome. Please see Takeda's comments on the outcomes section for further detail. Please select from the following, will oveporexton be: A.Prescribed in primary care with routine follow-up in primary care B.Prescribed in secondary care with routine follow-up in primary care C.Prescribed in secondary care with routine follow-up in secondary care D.Other (please give details): For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. Typically C. However, in some areas such as Leicester, there are shared care agreements in place for primary care prescribing for narcolepsy, with follow up in secondary care. This also applies for all relevant comparators. Would oveporexton be a candidate for managed access? No, Takeda believe the robustness of the RCTs negate the need for managed access for oveporexton.	Thank you for your comment. The committee will decide on the relevant comparators in its deliberations. Thank you for your comment. Length of life has been added to the outcomes list. Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Do you consider that the use of oveporexton can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? As detailed in Takeda's comments on the outcomes section, type 1 narcolepsy is a multi-faceted disease with an array of consequences that can have debilitating impacts on both physical and mental health. The full impact on the health of type 1 narcolepsy patients will not be captured by the outcomes of excessive daytime sleepiness and cataplexy rate alone. Due to the outcomes captured in the clinical trials of oveporexton and the relevant comparators outlined in the comparators section, the economic analyses Takeda are developing will be largely driven by treatment-specific changes in Epworth Sleepiness Scale (ESS) and weekly cataplexy rate. Given the mechanism of action for oveporexton and its ability to address the underlying cause of the disease, the substantial clinical benefits of achieving a normal sleep regulation pattern are therefore wider ranging than that captured by ESS and cataplexy rate alone and are not captured by the model. Societal impacts should also be considered. The debilitating nature of type 1 narcolepsy makes it difficult to maintain a normal working life, having a profound impact on education, productivity and unemployment rates (Bassi 2024). While these are generally wider economic impacts, they are likely to have an impact on quality-of-life and are not captured within the QALYs in the economic analyses. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Published literature will be sourced to provide further justification to these wider benefits not captured within the QALY estimates as modelled. Several	Thank you for your comment. The committee will consider whether there are any uncaptured benefits of oveporexton in its deliberations.

Section	Consultee/ Commentator	Comments [sic]	Action
		references have been provided throughout Takeda's comments on the outcomes section to provide some insight into the wider impacts of narcolepsy that will not be captured within Takeda's QALY estimates. However, Takeda's evidence submission dossier will provide a much more comprehensive overview of the published evidence available to justify this further. <u>Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics.</u> Takeda believe that the relevant comparator treatments indicated for type 1 narcolepsy within the scope of this appraisal (solriamfetol, sodium oxybate, pitolisant) would be used in line with their Summary of Product Characteristics. Anti-depressants are used off label in this setting.	Thank you for your comment. No change to the scope required.