Oveporexton for the Treatment of Narcolepsy

Draft Background and Scope

OCTOBER 16, 2025

Background

Narcolepsy is a rare, chronic neurological disorder characterized by disruptions in the sleep-wake cycle. It affects approximately 1 in 2000 people in the U.S.,[1] and the onset is usually in adolescence or young adulthood.[2] One of the main symptoms of narcolepsy is excessive daytime sleepiness (EDS), which is described as an overwhelming urge to sleep during the day despite getting sufficient sleep at night. People living with narcolepsy may also experience cataplexy (a sudden loss of muscle tone, often triggered by strong emotions), hypnagogic or hypnopompic hallucinations, sleep paralysis, and nighttime sleep disruptions. Narcolepsy has a substantial impact on quality of life – persons living with narcolepsy report having poorer work performance, education, social interaction, and general health than those without narcolepsy.[3,4] People living with narcolepsy are more likely to have comorbid conditions such as sleep apnea, depression, obesity, high blood pressure, and heart disease, among others.[5] Consequently, annual direct medical costs are approximately twice as much as those without the disease;[6] studies also show higher missed work days and short-term disability rates[7].

Diagnosis of narcolepsy is based on a history of three or more months of EDS plus one of the following: cataplexy, low orexin levels in cerebrospinal fluid, or a mean sleep latency time of eight minutes or less and two or more sleep-onset REM periods on a Multiple Sleep Latency Test (MSLT). There are two types of narcolepsy. Narcolepsy Type 1 (NT1), or narcolepsy with cataplexy, is defined by the presence of cataplexy and by low levels of the neurotransmitter orexin, which regulates sleep and wakefulness. Patients without cataplexy are diagnosed with Narcolepsy Type 2 (NT2); they generally have less severe symptoms and normal orexin levels.[8] However, cataplexy can develop after diagnosis, so patients can shift from being diagnosed with NT2 to NT1. There may also be some racial and ethnic differences in narcolepsy symptoms, with Black persons having earlier onset of symptoms and being less likely to manifest cataplexy despite having low orexin levels.[9] Finally, diagnosis of narcolepsy is often delayed, with studies demonstrating a mean delay of up to 15 years.[10]

Current management of NT1 is mainly symptomatic, with both non-pharmacologic and pharmacologic treatment. Daytime naps can help people with narcolepsy feel more alert, and a consistent sleep schedule is important because sleep deprivation can worsen symptoms. Pharmacologic treatment focuses on improving wakefulness and treating cataplexy in people with NT1. Clinical practice guidelines recommend individualized treatment based on factors such as age, reproductive planning, comorbidities, risk of dependency, history of adverse events, and goals of care,[11] and treatment needs may evolve over time. Pharmacologic treatments can treat EDS, cataplexy, or both. Wake-promoting agents such as modafinil, methylphenidate, and solriamfetol are commonly used to treat EDS, but have no effect on cataplexy symptoms. Antidepressants are often used off-label to treat cataplexy, though evidence for their effectiveness is limited. Sodium oxybate and pitolisant are agents that treat both EDS and cataplexy and can be used as monotherapy; however, more than half of US patients with narcolepsy surveyed were taking combination therapy to treat their symptoms.[3]

Oveporexton is a first-in-class oral orexin receptor-2 agonist that treats both excessive daytime sleepiness and cataplexy and is under US Food and Drug Administration (FDA) consideration for approval for the treatment of NT1. It has been designated a breakthrough drug by the FDA, and the manufacturer is expected to file a new drug application for approval during fiscal year 2025.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

People living with narcolepsy describe fighting to stay awake during the day – e.g., falling asleep frequently during sedentary activities such as lectures, movies, meetings, reading, and driving – as well as having disrupted nighttime sleep. They describe having to carefully plan their day around how long they feel they can stay awake and feel limited in committing to activities because they are not sure how they will feel on any given day. For example, some routine activities, such as grocery shopping, become difficult, as individuals need to pace themselves and may not have enough energy to complete the task. A person living with narcolepsy described that the “brain fog” from narcolepsy makes it difficult to make decisions, resulting in many unfinished tasks. Family members may need to take on more tasks, increasing caregiver burden. Finally, cataplexy episodes can be embarrassing, particularly if those around aren’t aware of the disease.

We heard that narcolepsy can significantly affect a person's work and home life. Narcolepsy symptoms can make completing one's education or maintaining a job more difficult. The disease affects the decision to have children as well, as medications may need to be changed and weaned off for pregnancy and disrupted sleep can worsen symptoms. Since many medications used to treat narcolepsy are controlled substances, timing deliveries to make sure that one has enough medication can be challenging in the context of work, travel or vacation.

People living with narcolepsy describe difficulty getting a diagnosis, in part because the symptoms can be difficult to recognize. For example, many people with narcolepsy initially believe that their fatigue and sleepiness is mainly from life circumstances (being busy with school, work, activities, etc.) and do not necessarily recognize cataplexy symptoms. Even when they go and seek medical care for their symptoms, the symptoms are often brushed off and thus diagnosis can be delayed for years.

We heard from people living with narcolepsy that current treatment usually involves juggling multiple medications. Many people are taking drugs to promote wakefulness, but those do not necessarily treat other symptoms like brain fog – one person described taking such medications as "how much less sleepy does this medication make me", rather than feeling more awake. We also heard that medications constantly need to be adjusted and/or changed due to a change in symptoms, incomplete treatment of symptoms, intolerable side effects, or insurance coverage. For example, the dosing of sodium oxybate requires a dose in the middle of the night, which may be difficult for some people. Additionally, many people struggle to get insurance coverage for newer drugs like Sunosi and often do not have the energy to appeal denials. However, despite being on medication, persons living with narcolepsy did not feel completely satisfied with treatment and wished for drugs that addressed the underlying pathophysiology rather than just treating symptoms.

Clinical experts concurred that diagnosis of narcolepsy is often delayed, and that current treatments allow patients to maintain wakefulness but do not address the fatigue and cognitive slowing that narcolepsy can result in. Clinical experts were excited that there was a new drug in the pipeline that may address the underlying pathophysiology of narcolepsy and thought that if successful, addressing orexin deficiency may change the paradigm of treatment for NT1. Finally, the manufacturer of oveporexton emphasized that since only NT1 patients have orexin deficiency, the drug is only effective in this population and would not be effective in NT2 patient. Thus, accurate diagnosis is important.

Report Aim

This project will evaluate the health and economic outcomes of oveporexton for NT1. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the

clinical evidence, such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider the combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is adults living with NT1. Data permitting, we will evaluate the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors including age, sex, and race/ethnicity

Interventions

Oveporexton (Takeda Development Center Americas)

Comparators

Data permitting, we intend to compare the intervention to the following comparators:

- No pharmacologic treatment (represented as placebo arms in clinical trials)
- Pitolisant (WAKIX®)
- Sodium oxybate (XYREM®/XYWAV®/LUMRYZ®)

- Combination therapy with a wake-promoting agent (e.g., modafinil) and drug to treat cataplexy (e.g., venlafaxine)

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Daytime Symptoms
        - Cataplexy events
        - Excessive Daytime Sleepiness as measured by various tests including Maintenance of Wakefulness Test (MWT), the Epworth Sleepiness Scale (ESS), and the Karolinska Sleepiness Scale (KSS)
        - Cognitive Symptoms
        - Fatigue Symptoms
    - Nighttime Symptoms (e.g., disturbed nighttime sleep, dreams, hallucinations, sleep paralysis)
    - Symptoms and Daily Function
        - Work/school performance/attendance
    - Quality of Life and Treatment Satisfaction (e.g. SF-36, EQ-5D-5L)
    - Adverse events including but not limited to:
        - Insomnia, nausea, anxiety, urinary frequency, cardiovascular or hepatic injury
- Other Outcomes
    - Biomarkers such as levels of orexin (also known as hypocretin) in cerebrospinal fluid

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered.

Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There is substantial unmet need despite currently available treatments.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on 01/23/2026. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of oveporexton relative to no pharmacologic treatment, pitolisant (WAKIX®), sodium oxybate (XYREM®/ Xywav®/Lumryz™), and/or combination therapy with a wake-promoting agent plus drugs for cataplexy. The model structure will be informed by a literature review of prior published models of NT1 treatments and available data. Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Societal impacts (e.g., patient and caregiver productivity) and other indirect costs will be considered in a separate modified societal perspective analysis. This analysis will be considered as a co-base case when (a) direct data on indirect costs are available, (b) the societal costs of care are large relative to direct health care costs, and (c) the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of oveporexton on productivity (patient and caregiver) as well as certain other impacts (e.g., patient time in treatment).

The target population will reflect clinical trial populations, i.e., patients with NT1. The model will likely consist of health states including responders, non-responders, and death. A cohort of patients

will transition between states during predetermined cycles over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness may be estimated for shorter time horizons (e.g., five years) if relevant.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using evidence from clinical trials, and where data allow, from network meta-analyses.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of cataplexy events avoided, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLY). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLY gained, cost per life-year gained, and cost per cataplexy event avoided.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by oveporexton (e.g., emergency care for narcolepsy-related accident injuries), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of NT1 beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

1. Ohayon MM, Duhoux S, Grieco J, Cote ML. Prevalence and incidence of narcolepsy symptoms in the US general population. *Sleep Med X*. Dec 15 2023;6:100095. doi:10.1016/j.sleepx.2023.100095
2. Dauvilliers Y, Montplaisir J, Molinari N, et al. Age at onset of narcolepsy in two large populations of patients in France and Quebec. *Neurology*. Dec 11 2001;57(11):2029-33. doi:10.1212/wnl.57.11.2029
3. Ortiz LE, Morse AM, Krahn L, et al. A Survey of People Living with Narcolepsy in the USA: Path to Diagnosis, Quality of Life, and Treatment Landscape from the Patient's Perspective. *CNS Drugs*. Mar 2025;39(Suppl 1):23-36. doi:10.1007/s40263-024-01142-8
4. Chin WC, Wang CH, Huang YS, et al. Quality of life changes and their predictors in young adult narcolepsy patients after treatment: A real-world cohort study. *Front Psychiatry*. 2022;13:956037. doi:10.3389/fpsyt.2022.956037
5. Cohen A, Mandrekar J, St Louis EK, Silber MH, Kotagal S. Comorbidities in a community sample of narcolepsy. *Sleep Med*. Mar 2018;43:14-18. doi:10.1016/j.sleep.2017.11.1125
6. Thorpy MJ, Hiller G. The Medical and Economic Burden of Narcolepsy: Implications for Managed Care. *Am Health Drug Benefits*. Jul 2017;10(5):233-241.
7. Black J, Reaven NL, Funk SE, et al. The Burden of Narcolepsy Disease (BOND) study: health-care utilization and cost findings. *Sleep Med*. May 2014;15(5):522-9. doi:10.1016/j.sleep.2014.02.001
8. Mahoney CE, Cogswell A, Koralnik IJ, Scammell TE. The neurobiological basis of narcolepsy. *Nat Rev Neurosci*. Feb 2019;20(2):83-93. doi:10.1038/s41583-018-0097-x
9. Kawai M, O'Hara R, Einen M, Lin L, Mignot E. Narcolepsy in African Americans. *Sleep*. Nov 1 2015;38(11):1673-81. doi:10.5665/sleep.5140
10. Thorpy MJ, Krieger AC. Delayed diagnosis of narcolepsy: characterization and impact. *Sleep Med*. May 2014;15(5):502-7. doi:10.1016/j.sleep.2014.01.015
11. Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med*. Sep 1 2021;17(9):1895-1945. doi:10.5664/jcsm.9326