REPORT AT A GLANCE: **NARCOLEPSY**

KEY FINDINGS

Intervention	Comparators	Evidence Rating	US Price	Health-Benefit Price Benchmark
Oveporexton	No pharmacological treatment	B+	PDUFA Date: Q3 2026	$50,400 to $59,400 per year
	Modafinil/armodafinil with venlafaxine	C++		
	Sodium oxybate	C++		
	Pitolisant	C++		

"The narcolepsy treatment landscape includes several pricey medications that do not provide complete relief for patients. ICER's analyses found that oveporexton, the first medication for narcolepsy type 1 that directly addresses the underlying cause of the condition, is effective in promoting wakefulness, improving quality of life, and appears to offer better health benefits than current options. The manufacturer choosing a value-based price for oveporexton would help de-escalate the cycle of high prices being met with onerous access challenges. Our independent analysis can offer a roadmap for improving affordability and access for patients and the health system."

– ICER's Senior Vice President of Research Foluso Agboola, MBBS, MPH

THEMES AND RECOMMENDATIONS

- Manufacturers have a responsibility to set prices at levels that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments.
- If oveporexton is priced in line with its value, because it has a novel mechanism of action that directly addresses the underlying cause of NT1, it would not be appropriate for payers to restrict access to oveporexton using step therapy.
- Patient organizations have a powerful voice to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Narcolepsy is a rare, chronic neurological disorder characterized by disruptions in the sleep-wake cycle. It affects approximately one in 2,000 people in the United States (US), and the onset is usually in adolescence or young adulthood. The main symptoms of narcolepsy are excessive daytime sleepiness (EDS), disrupted nighttime sleep, hallucinations while falling asleep or waking up, and sleep paralysis. People living with narcolepsy type 1 (NT1) also experience cataplexy - the sudden loss of muscle tone triggered by strong emotions - and have low levels of the neurotransmitter orexin.

Narcolepsy symptoms can severely impact all aspects of a person's daily life, including work, education, social activities, travel, family planning, as well as everyday activities such as driving, grocery shopping, and exercise. We heard that there is also a large caregiver impact, including financial, as people living with NT1 may have difficulty finishing their education or working enough to support themselves. Additionally, people living with NT1 are also more likely to have comorbid conditions such as sleep apnea, obesity, high blood pressure, depression, anxiety, and heart disease. Consequently, annual direct medical costs are approximately twice as much as those without the disorder; and studies also show higher short-term disability rates.

Treatment of NT1 focuses on increasing wakefulness and preventing cataplexy episodes. Daytime naps and a consistent sleep schedule can help people manage narcolepsy symptoms. Pharmacological treatment focuses on improving wakefulness and preventing cataplexy. Wake-promoting agents such as modafinil, methylphenidate, and solriamfetol are used to treat EDS, but have no direct effect on cataplexy symptoms. Antidepressants are often used off-label to prevent cataplexy, and sodium oxybates and pitolisant treat both EDS and cataplexy. We heard from persons living with NT1 that polypharmacy is commonly required to address symptoms; however, the efficacy of current treatments can wear off over time, do not restore normal function, and can have substantial side effects. Oveporexton is a first-in-class oral orexin receptor 2 agonist that addresses the orexin deficiency that underlies NT1. It is under consideration for approval by the US Food and Drug Administration (FDA), with a decision expected in the third quarter of 2026.

Oveporexton was compared with no pharmacological treatment in two Phase III and one Phase II randomized, controlled trials of participants with NT1. Participants in the trials were, on average, in their 30s, and over half were female. Baseline narcolepsy symptom measures (Epworth Sleepiness Scale [ESS] and Maintenance of Wakefulness Test [MWT]) were indicative of severe excessive daytime sleepiness, and participants experienced a median of over 20 weekly cataplexy attacks. A meta-analysis of the trials demonstrated that participants in the oveporexton arm saw statistically significant and clinically meaningful improvements on the MWT (mean difference 19.59 minutes; 95% CI: 17.3 to 21.88) and ESS (mean difference -9.84; 95% CI: -11.58 to -8.10) compared with those on no pharmacological treatment. Additionally, participants in the oveporexton group were nearly six times as likely to have a treatment response, defined as an ESS ≤10 (relative risk 5.64; 95% CI: 3.45 to 9.23). Oveporexton also decreased weekly cataplexy rates by 62-75%, appeared to decrease symptoms such as sleep paralysis, hallucinations, and disrupted nighttime sleep, and improved health-related quality of life measures. A pooled safety review showed that oveporexton was tolerable, with low rates of serious adverse events and discontinuations.

Clinical Analyses

A network meta-analysis comparing oveporexton to modafinil/armodafinil, sodium oxybates, and pitolisant showed that treatment with oveporexton resulted in statistically significant and clinically meaningful differences in MWT scores and ESS scores compared with all other treatments. Additionally, participants in the oveporexton arm were more likely to be treatment responders compared with modafinil/armodafinil and pitolisant. Treatment with oveporexton appeared to result in reductions in cataplexy similar to those with sodium oxybate and pitolisant, although there was greater uncertainty about how it compares on this outcome, due to differences in reporting and data availability across trials.

We have uncertainties about whether some patients treated with oveporexton may also require an additional agent to successfully manage symptoms of NT1. Additionally, we have limited data on long-term efficacy and safety, which may be particularly important for a drug that has a new mechanism of action. There is a lack of head-to-head studies that compare treatments; conclusions about oveporexton compared with active comparators are from indirect comparisons only. Finally, since NT1 is a heterogeneous disease, subgroup data are needed to understand which group of patients may benefit most from treatment; there is also a lack of data on important subgroups such as children and pregnant and lactating persons.

Oveporexton represents the first therapy for NT1 whose mechanism of action directly addresses the orexin pathway. It appears to be both effective in relieving multiple domains of NT1 symptoms and improving quality of life with a relatively benign side effect profile. Therefore, we judged oveporexton to have at least a small but likely substantial net health benefit compared with no pharmacological treatment, an ICER rating of B+. Compared with modafinil/armodafinil + venlafaxine, sodium oxybates, and pitolisant, oveporexton appeared to be more effective and tolerable than all comparators. However, due to the limitations of network meta-analysis and qualitative comparisons, we have more uncertainty for these comparisons and judged oveporexton to have at least comparable but more likely small to substantial net health benefit, an ICER rating of C++.

Economic Analyses

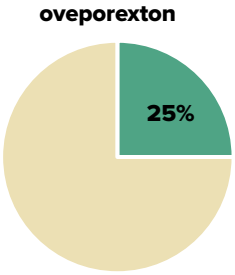
LONG-TERM COST EFFECTIVENESS

For the cost-effectiveness analysis, treatment with oveporexton monotherapy resulted in greater increases in QALYs (quality-adjusted life years) and evLYs (equal value life years) compared with modafinil + venlafaxine, sodium oxybate monotherapy, pitolisant monotherapy, and no pharmacological treatment. However, based on a placeholder price of $250,000, our analysis suggests that oveporexton would not meet traditional cost-effectiveness thresholds when compared to any of these treatment options. The actual cost-effectiveness of oveporexton will depend on its price. The Health Benefit Price Benchmark (HBPB) range for oveporexton was calculated relative to modafinil + venlafaxine, and estimated to be between $50,400 and $59,400 annually.

Economic Analyses

POTENTIAL BUDGET IMPACT

Results showed that 25% of eligible patients could be treated with oveporexton at the annual placeholder price of $250,000 before reaching the potential budget impact threshold of $821 million per year. . Under this assumed placeholder price, ICER is issuing an access and affordability alert for oveporexton. However, if priced within the ICER HBPB range (between $50,400 and $59,400 annually), all potentially eligible patients could be treated, and we would not issue an access and affordability alert.



Percent of eligible patients with narcolepsy that could be treated in a given year before crossing the ICER potential budget impact threshold

Public Meeting Deliberations

VOTING RESULTS

ICER's Virtual Public Meeting: Voting Results on Clinical Effectiveness and Contextual Considerations .

ICER assessed, and the independent appraisal committee voted on the evidence for the net health benefit of oveporexton:

- The panelists unanimously found (13-0) that current evidence is **adequate** to demonstrate a net health benefit for oveporexton when compared to no pharmacological treatment.
- A majority of panelists (8-5) found that current evidence is **adequate** to demonstrate a net health benefit for oveporexton when compared to modafinil with venlafaxine.
- A majority of panelists (10-3) found that current evidence is **adequate** to demonstrate a net health benefit for oveporexton when compared to sodium oxybate.
- A majority of panelists (11-2) found that current evidence is **adequate** to demonstrate a net health benefit for oveporexton when compared to pitolisant.

Panel members also weighed potential benefits and disadvantages beyond the direct health effects and weighed special ethical obligations. Voting highlighted the following as particularly important for payers and other policymakers to note:

- Oveporexton is likely to substantially improve caregivers' quality of life and/or ability to pursue their own education, work, and family life.

ICER's Public Meeting: Voting Results on Long-Term Value for Money

Consistent with ICER's process, because there is no firm estimate yet of a potential launch price for the treatment, the panel did not take a vote on oveporexton's long-term value for money.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit www.icer.org.