FDA Approves Oveporexton for Narcolepsy Type 1

Key Takeaways

- FDA approval introduces the first NT1 therapy intended to treat the disorder as a unified syndrome, using an orexin receptor 2 agonist mechanism to restore wake-promoting signaling.
- Phase 3 FirstLight and RadiantLight (n=273; 12 weeks; 19 countries) met the primary endpoint of improved MWT with twice-daily oveporexton versus placebo.
- Beyond wakefulness, reported outcomes showed improvements in functional impact and cognitive domains, with higher rates of absent hallucinations and sleep paralysis and REM architecture shifting toward healthy patterns.
- Common adverse events included insomnia, urinary frequency/urgency, and hypersalivation; discontinuations were low, long-term extension uptake exceeded 95% among completers, and safety/efficacy remain unestablished <18 years.
- Dispensing requires attention to drug–drug interactions, as concomitant strong CYP3A inhibitors are contraindicated, and Controlled Substances Act scheduling awaits DEA determination affecting launch logistics.

Orzeyful is the first orexin-restoring therapy for NT1, backed by the phase 3 FirstLight and RadiantLight trials.

The FDA has approved oveporexton (Orzeyful; Takeda Pharmaceuticals) tablets for the treatment of patients with narcolepsy type 1 (NT1), marking the first medicine to address the condition as a complete disorder and the first to work by directly targeting the loss of orexin signaling that drives the disease. For pharmacists, the approval introduces a twice-daily oral agent with a mechanism unlike existing stimulants and sedatives, along with a CYP3A drug interaction and a pending controlled-substance scheduling decision that will shape dispensing.[1]

A First-in-Class Mechanism

NT1 is a rare, lifelong neuropsychiatric sleep disorder that affects an estimated 1 in 2000 people in the United States. It is caused by the loss of brain cells that produce orexin, a chemical messenger that regulates wakefulness, sleep, and muscle tone. The deficit produces a cluster of disabling symptoms, including excessive daytime sleepiness, cataplexy (sudden muscle weakness triggered by strong emotions such as laughter), sleep paralysis, hallucinations at the edge of sleep or waking, and disrupted nighttime sleep. Until this action, there was no medicine FDA-approved for NT1 as a unified disorder, and none acted on the orexin system.[1]

Oveporexton is an oral orexin receptor 2-selective agonist. Rather than masking symptoms with stimulants or sedatives, it selectively stimulates the same receptor the body's own orexin would normally activate, restoring the missing signal to promote wakefulness and reduce abnormal rapid eye movement (REM)-sleep phenomena, including cataplexy. The medicine is taken as an oral tablet twice daily.[1,2]

Efficacy Across the Symptom Spectrum

Approval was supported by the phase 3 FirstLight (NCT06470828) and RadiantLight (NCT06505031) trials, which were global, multicenter, placebo-controlled studies conducted across 19 countries that collectively enrolled 273 adults with NT1 over 12 weeks. FirstLight randomly assigned 168 participants to twice-daily oveporexton 2 mg, 1 mg, or placebo, and RadiantLight randomly assigned 105 participants to twice-daily 2 mg or placebo, with change in Maintenance of Wakefulness Test (MWT) as the primary end point.[1-5]

Patients taking oveporexton 2 mg showed improvements in their ability to stay awake during the day compared with placebo, along with substantially less daytime sleepiness, a significant reduction in cataplexy episodes, and meaningful improvement across the full spectrum of symptoms (eg, sleep paralysis, hallucinations, and disrupted nighttime sleep).[1,2]

Secondary and exploratory data presented at SLEEP 2026 extended the picture beyond wakefulness. Across all doses, oveporexton significantly improved daily functioning at week 12 versus placebo on the Functional Impacts of Narcolepsy Instrument. On its cognitive function domain, approximately 70% of patients across doses reported no significant cognitive

difficulties, compared with approximately 15% in the placebo arm. Most patients also reported no hallucinations or sleep paralysis, and the timing and pattern of REM sleep shifted toward that seen in healthy controls.[2]

Safety and Dispensing Considerations

The most common adverse effects (AEs) were insomnia, increased urinary frequency, urgency to urinate, and increased saliva production. The rate of participants stopping treatment because of AEs was low, and more than 95% of those who completed the trials enrolled in the ongoing long-term extension. Pharmacists should counsel patients to report all medicines they are taking, as oveporexton should not be used at the same time as strong CYP3A inhibitors. The safety and effectiveness of the drug have not been established in patients younger than 18 years.[1,2]

Oveporexton has been recommended for scheduling under the Controlled Substances Act and will be lawful to market following the scheduling decision issued by the Drug Enforcement Administration—a step pharmacists will want to track, as it determines record-keeping and dispensing requirements at launch.[1]

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