Health Technology Briefing
May 2025

Oveporexton for treating narcolepsy type 1

Company/Developer	Takeda UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 36829	NICE ID: Not available	UKPS ID: 674913

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Oveporexton is in development for the treatment of narcolepsy type 1 (NT1). Narcolepsy is a rare long-term brain condition that can prevent a person from choosing when to wake or sleep. In most cases, it is caused by a lack of a brain chemical known as orexin, which helps keep people awake. NT1 is a type of narcolepsy that includes cataplexy, which is a sudden temporary muscle weakness or loss of muscle control. Other symptoms of NT1 include excessive daytime sleeping, sleep attacks, and sleep paralysis (feeling awake but unable to move). There are currently limited treatment options for people with NT1.

Oveporexton, taken by the mouth, is designed to activate orexin receptors, proteins in the brain that are usually activated by orexin. In people with NT1, who have a lack of orexin, the activation of these receptors by oveporexton may help improve wakefulness and reduce sleep attacks. If licenced, oveporexton could provide a new treatment for patients with NT1.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
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Proposed Indication

Treatment of narcolepsy with cataplexy (narcolepsy type 1 (NT1)).[1]

Technology

Description

Oveporexton (TAK-861) is an ethanesulfonamide compound which is designed as a brain-penetrable OX2R-selective agonist.[2,3] NT1 is associated with severe loss of orexin neurons and studies suggest a pivotal role of orexin receptor 2 (OX2R) in the pathophysiology of NT1.[4-6] OX2R is a post-synaptic G protein-coupled receptor which is activated by orexin peptides produced by orexin neurons in the lateral hypothalamus.[7] Oveporexton is proposed to activate OX2R, leading to wake-promoting effects.[3]

Oveporexton is currently in clinical development for the treatment of NT1. In the phase II and III clinical trials, participants are given oveporexton tablets, orally, for 12 weeks (NCT06470828; NCT06505031),[1,8] or for up to approximately five years (NCT05816382).[9] In the phase II trial (NCT05687903), participants are given oveporexton tablets, orally, twice a day, from days 1 to 56, at 0.5 mg, 2 mg, 2 mg followed by a 5 mg dose, or 7 mg followed by a placebo.[10]

Key Innovation

People with narcolepsy experience a substantially lower health-related quality of life when compared with the general population, and even those with chronic diseases like Multiple Sclerosis, and yet there are limited treatment options available.[11] Current medications often show limited efficacy, not addressing the full spectrum of symptoms, demonstrating a need for novel drugs.[3] No currently approved treatments target the underlying pathophysiology of NT1. Oveporexton is the first oral OX2R agonist to potentially address the underlying pathophysiology.[12] Based on preclinical findings, oveporexton could be expected to produce potent efficacy with a favourable safety profile in individuals with NT1.[3] If licenced, oveporexton will provide a new treatment option for people with NT1.

Regulatory & Development Status

Oveporexton does not currently have Marketing Authorisation in the EU/UK for any indication.

Oveporexton has been awarded a Breakthrough Therapy by the US FDA in April 2024, for the treatment of excessive daytime sleepiness in NT1.[12]

Patient Group

Disease Area and Clinical Need

Narcolepsy is a rare, long-term brain condition that can prevent a person from choosing when to wake or sleep. In most cases, it is caused by a lack of a brain chemical known as orexin, which regulates wakefulness. This lack of orexin is thought to be caused by the immune system attacking the cells or receptors that make it available in the body. But this does not explain all cases of narcolepsy, and the exact cause of the problem is often unclear.[13] When narcolepsy is associated with cataplexy it is known as NT1.[14] Cataplexy is a sudden temporary muscle weakness or loss of muscular control. Other symptoms of NT1 include excessive daytime sleeping, sleep attacks, and sleep paralysis.[15] Factors that may increase the risk of narcolepsy, or cause an autoimmune problem, include hormonal changes in puberty or menopause, an inherited genetic fault, major

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psychological stress, infections like the swine flu, and taking the flu vaccine Pandemrix (which is no longer used in the UK).[16] Men and women are thought to be affected equally by narcolepsy, and the symptoms often begin during adolescence, although it is usually diagnosed between the ages of 20 and 40 years.[13]

In the UK, approximately 30,000 people are estimated to have narcolepsy, and far more undiagnosed. The estimated age and sex standardised 2019 prevalence rate in England was 0.020%.[17] In England, 2023-24, there were 377 finished consultant episodes (FCEs) and 367 admissions for narcolepsy and cataplexy (ICD-10 code G47.4), which resulted in 402 FCE bed days and 133 day cases.[18]

Recommended Treatment Options
The National Institute for Health and Care Excellence (NICE) currently recommends solriamfetol for treating excessive daytime sleepiness caused by narcolepsy.[19]

Clinical Trial Information

Trial	NCT06470828; A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-861 for the Treatment of Narcolepsy With Cataplexy (Narcolepsy Type 1) **Phase III –** active, not recruiting **Locations:** Five EU countries, UK, USA, Canada and other countries **Primary completion date (estimated):** June 2025
Trial Design	Randomised, parallel assignment, placebo-controlled, double masked
Population	N = 168; subjects with NT1 with a greater than or equal to four partial or complete episodes of cataplexy per week; aged 16 to 70 years old.
Intervention(s)	Oveporexton tablet orally, for 12 weeks.
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: change from baseline to week 12 in mean sleep latency from the four Maintenance of Wakefulness Test (MWT) wake trials [Time frame: baseline week 12] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT06505031, 2024-511998-30; A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-861 for the Treatment of Narcolepsy With Cataplexy (Narcolepsy Type 1) **Phase III –** active, not recruiting **Locations:** Five EU countries and other countries **Primary completion date (estimated):** July 2025
Trial Design	Randomised, parallel assignment, placebo-controlled, double masked

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Population	N = 105; subjects with NT1 with a greater than or equal to four partial or complete episodes of cataplexy per week; aged 16 to 70 years old.
Intervention(s)	Oveporexton tablet orally, for 12 weeks.
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: change from baseline to week 12 in mean sleep latency from the four MWT wake trials [Time frame: baseline week 12] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT05687903, 2022-001654-38; A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-861 for the Treatment of Narcolepsy With Cataplexy (Narcolepsy Type 1) **Phase II –** completed **Locations:** Seven EU countries, USA and other countries **Primary completion date:** December 2023	NCT05816382, 2022-002965-13; A Long-term Extension Study to Evaluate the Safety and Tolerability of TAK-861 in Participants With Selected Central Hypersomnia Conditions **Phase II/III –** recruiting **Locations:** Seven EU countries, USA and other countries **Primary completion date (estimated):** Feb 2028
Trial Design	Randomised, parallel assignment, placebo-controlled, double masked	Randomised, parallel assignment, double masked
Population	N = 112; subjects with NT1; aged 18 to 70 years old (16-70 years old in Japan)	N = 500 (estimated); subjects with NT1, who have completed a controlled study with oveporexton; aged 16 to 70 years old
Intervention(s)	• Oveporexton tablet (0.5 mg) orally, twice a day, from days 1 to 56 • Oveporexton tablet (2 mg) orally, twice a day, from days 1 to 56 • Oveporexton tablet (2 mg), followed by a 5 mg dose, orally, twice a day, from days 1 to 56 • Oveporexton tablet (7 mg) orally, twice a day, from days 1 to 56. Placebo was given as the second dose	Oveporexton tablet orally, for up to approximately 5 years
Comparator(s)	Matched placebo tablets orally, twice a day, from days 1 to 56.	-

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Outcome(s)	Primary outcome: Change from baseline in the average sleep latency as determined from the MWT at week 8 [Time frame: baseline week 8] See trial record for full list of other outcomes	Primary outcome: Number of participants with at least one or more treatment-emergent adverse events (TEAEs) [Time frame: from signing the informed consent form up to follow-up of 4 weeks after the last dose (Up to approximately 5 years)] See trial record for full list of other outcomes
Results (efficacy)	See trial record	-
Results (safety)	See trial record	-

Estimated Cost

The cost of oveporexton is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Solriamfetol for treating excessive daytime sleepiness caused by narcolepsy (TA758). January 2022.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Sodium oxybate for symptom control of narcolepsy with cataplexy (children and adolescents aged 7 until 19 years). 210301/P. January 2021.

Other Guidance

- European Journal of Neurology. European guideline and expert statements on the management of narcolepsy in adults and children. 2021.[20]
- NICE evidence summary. Narcolepsy with or without cataplexy in adults: pitolisant (ES8). March 2017.[21]
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