Health Technology Briefing
June 2023

Pitolisant for treating narcolepsy in children and adolescents

Company/Developer	Bioprojet SCR

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 36361	NICE TSID: Not Available	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in Phase III clinical trials.

Summary

Pitolisant is currently in clinical development for the treatment of narcolepsy with or without cataplexy in children and adolescents under the age of 18. Narcolepsy is a rare and long-term sleep disorder that affects the brain's ability to regulate the normal sleep-wake cycle. Symptoms include excessive daytime sleepiness, sleep paralysis, hallucinations, and cataplexy – a sudden loss of muscle tone while a person is awake leads to weakness and a loss of voluntary muscle control. Fifty percent of individuals with narcolepsy report experiencing symptoms before the age of 18, yet there is only one medicine licensed in the United Kingdom to manage narcolepsy in people younger than 18.

Pitolisant blocks histamine (an immune system mediator) from attaching to a receptor (target) on nerve cells called 'histamine H3 receptor'. As a result, more histamine is produced in the brain, which attaches to another type of receptor called the 'histamine H1 receptor'. This increases the activity of certain brain cells called histamine neurons, which are important for regulating sleep and wakefulness. If licensed, pitolisant (taken orally) will offer another treatment option for paediatric patients with narcolepsy.

Proposed Indication

Treatment of narcolepsy with or without cataplexy in children aged 6 to less than 18 years.[1]

Technology

Description

Pitolisant (Wakix, BF2.649) is a potent, orally active histamine H3-receptor antagonist/inverse agonist.[2] It blocks histamine (an immune system mediator) from attaching to a receptor (target) on nerve cells called 'histamine H3 receptors'. As a result, more histamine is produced in the brain, which attaches to another type of receptor called the 'histamine H1 receptor'. This increases the activity of certain brain cells called histamine neurons, which are important for regulating sleep and wakefulness.[3] Pitolisant also modulates various neurotransmitter systems, increasing acetylcholine, noradrenaline, and dopamine release in the brain, promoting muscle moment, memory, alertness, etc. [2,4-6]

Pitolisant is currently in clinical development (NCT02611687) for the treatment of narcolepsy with or without cataplexy children aged 6 to less than 18 years.[1] Pitolisant is an orally-administered tablet to be taken once a day by study subjects.[1]

Key Innovation

Fifty percent of individuals with narcolepsy report experiencing the onset of symptoms before the age of 18 years, yet there are no NICE-recommended treatments for narcolepsy in children.[7,8] Childhood and adolescence are crucial periods for physical, emotional, and social development, and narcolepsy can potentially hinder that and impact mental health and quality of life.[9] Therefore, there is a need for approved medications that will help paediatric patients with narcolepsy better manage their debilitating symptoms such as Excessive Daytime Sleepiness (EDS) and cataplexy (which affects 60 – 75% of children).[9,10]

Previous clinical trials in adults with narcolepsy with or without cataplexy have shown positive results in terms of EDS and cataplexy.[11,12] If licensed, pitolisant will be the first approved treatment for narcolepsy with or without cataplexy in children and adolescents under the age of 18.

Regulatory & Development Status

Pitolisant currently has Marketing Authorisation in the UK for the treatment of adults with narcolepsy with or without cataplexy.[2,13]

Pitolisant is currently in phase II and III clinical development for the treatment of:[14]

- Idiopathic hypersomnia
- EDS
- Restless legs syndrome
- Alcohol use disorder
- Myotonic dystrophy 1
- Prader-Willi syndrome
- Pregnancy-related narcolepsy

Pitolisant has the following regulatory designations/awards:

- an EU Orphan Medicine designation on 10 July 2007 for the treatment of Narcolepsy.[15]
- a Fast Track and Breakthrough Therapy by the US FDA in May 2018.[16]

Patient Group

Disease Area and Clinical Need

Narcolepsy is a rare and long-term sleep disorder that affects the brain's ability to regulate the normal sleep-wake cycle.[17] In most cases, it is caused by a lack of hypocretin a brain chemical also known as orexin, which regulates wakefulness. This lack of hypocretin is thought to be caused by the immune system attacking the cells or receptors that make it available in the body. In some cases, it is unclear what exactly causes narcolepsy, but it tends to begin in childhood and affects men and women equally.[18] This leads to symptoms such as excessive daytime sleepiness, sleep paralysis, hallucinations, and cataplexy – a sudden loss of muscle tone while a person is awake which leads to weakness and a loss of voluntary muscle control.[19] 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 psychological stress, infections like the swine flu, and taking the flu vaccine Pandemrix (which is no longer used in the UK).[20] 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.[21]

Narcolepsy affects about 1 person in 2,500. Thus, in the UK, there are approximately 30,000 people who have narcolepsy, though it is believed that the majority have not been diagnosed.[22] The exact prevalence in children is yet to be determined and this could be attributed to delays between the onset of symptoms and diagnosis ranging between 10 to 15 years.[23-25] Information on incidence is limited, with a United States study finding the incidence of narcolepsy with or without cataplexy to be 1.37 per 100,000 person-years.[26] In England, 2021-22, there were 340 finished consultant episodes (FCEs) and 326 admissions for narcolepsy (ICD-10 code G47.4), resulting in 397 FCE bed days and 113 day cases.[27]

Recommended Treatment Options

There is no specific cure for narcolepsy, but medicines can be taken to manage its symptoms and minimise its impact on daily life.[28] NICE does not recommend any treatments for narcolepsy in children or adolescents. In January 2021, NHS England proposed an official plan to commission sodium oxybate for symptom control of narcolepsy with cataplexy in children and adolescents, aged 7 to 19 years who have not responded to current treatments or cannot have current treatments. [29]

Clinical Trial Information

Trial	NCT02611687, EudraCT2013-001506-29; Double Blind, Multicentre, Randomized, Placebo-controlled Trial to Evaluate Safety and Efficacy of Pitolisant in Children From 6 to Less Than 18 Years With Narcolepsy With/Without Cataplexy, Followed by a Prolonged Open-label Period **Phase III** – Active, not recruiting **Location(s)**: Four EU countries and Russia **Primary completion date**: April 2021
Trial Design	Randomised, parallel assignment, double-blind
Population	N=110 (actual); Narcoleptic paediatric subjects with or without cataplexy; aged 6 – 18 years
Intervention(s)	Pitolisant oral tablet once daily
Comparator(s)	Placebo oral tablet once daily

Outcome(s)	Primary outcome measures: • To evaluate the efficacy of pitolisant in reducing residual Excessive Daytime Sleepiness (EDS). [Time frame: 8 weeks]. • To evaluate the efficacy of pitolistant in reducing the number of cataplectic episodes (for patients with cataplexy) [Time frame: 8 weeks] • To determine safety in children and adolescents. Safety assessment will be done on monitoring of adverse events, physical examination, vital signs, ECG (QTc) and blood laboratory tests modifications, and the mood appraisal [Time frame: 8 weeks] See the trial record for a full list of outcomes
Results (efficacy)	The mean adjusted difference in the Ullanlinna Narcolepsy Scale (UNS) total score from baseline to the end of the double-blind period was −6·3 (SE 1·1) in the pitolisant group and −2·6 (1·4) in the placebo group (least squares mean difference −3·7; 95% CI −6·4 to −1·0, p=0·007).[11]
Results (safety)	Treatment-emergent adverse events were reported in 22 (31%) of 72 patients in the pitolisant group and 13 (34%) of 38 patients in the placebo group. The most frequently reported adverse events (affecting ≥5% of patients) in either group were headache (14 [19%] in the pitolisant group and three [8%] in the placebo group) and insomnia (five [7%] in the pitolisant group and one [3%] in the placebo group).[11]

Estimated Cost

The NHS indicative cost of 30 tablets of Pitolisant (4.5mg and 18mg) is £310.[30]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Pitolisant hydrochloride for treating excessive daytime sleepiness caused by obstructive sleep apnoea (TA776). March 2022.
- 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. 15 April 2021.

Other Guidance

- European Academy of Neurology (EAN), European Sleep Research Society (ESRS), and European Narcolepsy Network (EU-NN). European guideline and expert statements on the management of narcolepsy in adults and children. 2021.[31]

Additional Information

Bioprojet SCR did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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