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Pentetrazol for idiopathic hypersomnia and narcolepsy type 2

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LAY SUMMARY

Hypersomnia means excessive sleepiness and sleeping, when the person struggles to stay awake during the day and has great difficulty being awakened from sleep. When there is no clear cause, this condition is called idiopathic hypersomnia (IH). Narcolepsy is a rare long-term brain disorder that causes a person to suddenly fall asleep at inappropriate times. Sometimes narcolepsy is associated with temporary loss of muscle control that causes weakness and possible collapse (cataplexy). This type of narcolepsy is called Type 1 narcolepsy. When narcolepsy is not associated with cataplexy is called type 2 narcolepsy. Narcolepsy and IH are very similar conditions.

Pentetrazol is a medicinal product that is being developed for the treatment of IH and narcolepsy type 2. Pentetrazol is administered orally and it acts by blocking the effect of a chemical substance called Gamma-Aminobutyric Acid (GABA). GABA is thought to play a role in promoting sleeping and is believed to be elevated in people with IH. If licensed, Pentetrazol will offer a new treatment option for patients with IH or narcolepsy type 2.

TARGET GROUP

Idiopathic hypersomnia (IH) or narcolepsy type 2

TECHNOLOGY

DESCRIPTION

Pentetrazol (Pentylenetetrazole; BTD-001) is a medicinal product that displays activity as a central nervous system (CNS) and respiratory stimulant. It is considered a non-competitive Gamma-Aminobutyric Acid (GABA) antagonist.[1,2] GABA is thought to play a role in promoting sleep and is believed to be elevated in IH. By blocking GABA's function, the product is expected to reduce excessive daytime sleepiness.[3]

In the phase II clinical trial (NCT02512588), pentetrazol is administered orally in adult patients with IH or Narcolepsy without cataplexy (Type 2).[4] No other information was available at the time of writing the briefing about the dosing and treatment regimen.

Pentetrazol does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

There is currently no satisfactory treatment option for the treatment of IH.[3] The treatment methods adopted for IH are similar to those of narcolepsy.[5] Moreover, the available medicines that are currently used for narcolepsy are not specifically licensed for narcolepsy and there is no robust evidence on its effectiveness in treating the condition.[6] If licensed, pentetrazol will offer a new treatment option for patients with IH or narcolepsy type 2.

DEVELOPER

Balance Therapeutics, Inc.

REGULATORY INFORMATION/ MARKETING PLANS

Pentetrazol was awarded orphan designation in the EU and USA for the treatment of idiopathic hypersomnia in January 2016 and September 2015 respectively.[3, 7]

Pentetrazol was also awarded orphan designation in the USA for the treatment of narcolepsy in March 2017.[8]

PATIENT GROUP

BACKGROUND

Hypersomnia refers to excessive sleepiness and sleeping, when a person struggles to stay awake during the day and has great difficulty being awakened from sleep. When there is no clear cause or origin, this condition is called idiopathic hypersomnia (IH).[9, 10]

Narcolepsy is a rare long-term brain disorder that causes a person to suddenly fall asleep at inappropriate times. Narcolepsy symptoms usually first occur in people between the ages of 15 and 30 years. Symptoms may include excessive daytime sleepiness, sleep attacks (falling asleep suddenly),

sleep paralysis (a temporary inability to move or speak when waking up or falling asleep), excessive dreaming and waking in the night, hallucination, and cataplexy (temporary loss of muscle control resulting in weakness and possible collapse).[6,11]

When narcolepsy is associated with cataplexy it is known as type 1 narcolepsy. Its diagnosis is based on the individual either having low levels of a brain hormone (hypocretin) or reporting cataplexy and having excessive daytime sleepiness on a special nap test. Narcolepsy without cataplexy is known as type 2 narcolepsy. People with type 2 narcolepsy experience excessive daytime sleepiness but usually do not have muscle weakness triggered by emotions. They usually also have less severe symptoms and have normal levels of the brain hormone hypocretin.[6,12]

It is not yet clear whether idiopathic hypersomnia and narcolepsy type 2 are the same condition.[5]

CLINICAL NEED and BURDEN OF DISEASE

The exact prevalence of IH remains unknown due to uncertainties in the diagnostic criteria resulting in an absence of robust epidemiological studies. Ratios of IH to narcolepsy (with and without cataplexy), and to narcolepsy (without affiliation status) in cohorts of patients have been published by different sleep disorders centres. These ratios range from 5.0% to 47.2% which are thought to reflect referral and reporting biases.[5]

Since there is not a uniform standard for the diagnosis of narcolepsy, assessing epidemiologic estimates of narcolepsy is challenging.[13] Narcolepsy is estimated to affect about 1 person in 2,500.[14] It is estimated that it affects at least 25,000 people in the UK, and is usually diagnosed between 20 and 40 years of age, although the symptoms often begin during adolescence. [15]

Narcolepsy can have an effect on almost all aspects of daily life including education, employment, and the ability to drive, and also relationships and emotional health. Narcolepsy can also have a major indirect impact on concentration, attention span and short term memory, but it does not affect cognition or intelligence directly.[16,17]

The population likely to be eligible to receive pentetrazole could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Evidence summary. Narcolepsy with or without cataplexy in adults: pitolisant (ES8). March 2017

NHS ENGLAND and POLICY GUIDANCE

No relevant guidelines could be identified.

OTHER GUIDANCE

- European Federation of Neurological Societies (EFNS) Task Force. EFNS guidelines on management of narcolepsy. 2006[18]

CURRENT TREATMENT OPTIONS

Until recently, the treatment of IH has mirrored that of the sleepiness of narcolepsy type 1 or 2.[5] There are currently no medicines specifically designed to treat IH, but medications used for narcolepsy can be helpful.[19]

There is no specific cure for narcolepsy, but it is sometimes possible to manage the symptoms and minimise their impact on the daily life. In mild cases, making some simple changes to the sleeping habits can help. If the symptoms are more severe, the patient will usually need to take medication. A number of different medications are used to treat the symptoms of narcolepsy, although they are not all licensed for narcolepsy and the evidence for their effectiveness in treating the condition is not always strong. The availability of some of these medications on the NHS can also differ, depending on the policy of the local NHS authority.

Stimulants such as modafinil, dexamphetamine or methylphenidate may be prescribed, when necessary, by the patient's GP or specialist.

Sodium oxybate can improve cataplexy and help the patient sleep at night, which can also reduce daytime sleepiness. However, it is not yet funded by the NHS in many areas.

Antidepressants: although there is some uncertainty about how effective antidepressants are at treating narcolepsy, they are sometimes used to treat symptoms such as cataplexy, hallucinations and sleep paralysis.[6]

EFFICACY and SAFETY

Trial	**NCT02512588; pentylenetetrazole vs placebo; phase II**
Sponsor	Balance Therapeutics
Status	Ongoing
Source of Information	Trial registry.[4]
Location	USA
Design	Randomized, Placebo-Controlled
Participants	n= 120 (planned); aged 18-65 years; males and females; meets International Classification of Sleep Disorders (ICSD)-3 criteria for IH or Narcolepsy Type 2 and not undergoing pharmacologic treatment for the condition; usual nightly total sleep at least 6 hours as single major rest period without naps; Epworth Sleepiness Scale of 10 or greater.
Schedule	Randomised to pentylenetetrazole or placebo. No further information could be identified about the schedule.
Follow-up	Active treatment period: not reported. Follow-up period: ranges from 1 day to 56 days depending on the type of outcome (see below)
Primary Outcomes	Efficacy Epworth Sleepiness Scale [Time Frame: After 14 days per treatment]
Secondary Outcomes	Secondary Outcomes: Efficacy Maintenance of Wakefulness Test [Time Frame: After 14 days per treatment] Other outcomes: Time Frame: Selected Days 14, 35, and 56 • Pharmacokinetics (after multiple doses): Maximum serum concentration (Cmax) • Pharmacokinetics(after multiple doses): Time of maximum plasma concentration (Tmax) Time Frame: Selected Days 1, 14, 31, 35, 42, and 56 • Pharmacokinetics (after multiple doses): Elimination half-life (T½) • Pharmacokinetics (after multiple doses): Area under the concentration time curve (AUC)
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date reported as Jan 2018.

ESTIMATED COST and IMPACT

COST

The cost of pentetrazol is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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