NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Cenobamate as an adjunctive therapy for primary generalised tonic-clonic seizures

Company/Developer	Arvelle Therapeutics

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 26930	NICE ID: 10214	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III/II trials

Summary

Cenobamate is in clinical development as an adjunctive therapy for adults with primary generalized tonic-clonic (PGTC) seizures. A generalised tonic-clonic seizure is the type of epileptic seizure which is defined as a seizure that has a tonic phase (stiffening of the muscles) followed by clonic muscle contractions (rhythmical jerking). They are usually associated with impaired awareness or complete loss of consciousness. Some of the more severe conditions that can cause this type of seizure include a brain tumour or a ruptured blood vessel in the brain, which can cause a stroke. PGTC are sometimes resistant to some existing treatments, therefore, there is a need for more effective adjunctive ('ad-on') treatments of this condition.

The exact way in which cenobamate works is unclear but it affects the activity of channels that allow electrical impulses to be transmitted between nerve cells. This may prevent abnormal electrical activity in the brain, reducing the chance of an epileptic fit. Cenobamate is administered orally. Evidence shows that cenobamate has a potential for a high degree of efficacy in reducing seizures. Cenobamate is already approved as an adjunctive therapy option for another type of seizure called focal-onset seizures. Thus, if licensed, cenobamate will offer an additional adjunctive therapy option for patients with PGTC seizures.

Proposed Indication

Adjunctive therapy in adults with primary generalised tonic-clonic (PGTC) seizures.[1]

Technology

Description

Cenobamate (Ontozry, YKP3089C025, XCOPRI) is a small molecule with a dual mechanism of action. It is a positive allosteric modulator of subtypes of the γ-aminobutyric acid ($GABA_A$) ion channel, that does not bind to the benzodiazepine binding site. Cenobamate has also been shown to reduce repetitive neuronal firing by enhancing the inactivation of sodium channels and by inhibiting the persistent component of the sodium current. However, the precise mechanism of action by which cenobamate exercises its therapeutic effects is unknown.[1,2]

Cenobamate is in clinical development for the treatment of PGTC seizures. In the phase III clinical trials (NCT03961568, NCT03678753), cenobamate is administered orally as 12.5 mg tablet, 25 mg tablet, 50 mg tablet, 100 mg tablet, 150 mg tablet and 200 mg tablet once a day for 12 weeks.[1,3]

Key Innovation

A narrative review on available cenobamate study results from pre-clinical animal models through to phase 3 clinical studies suggests that cenobamate is effective. It showed potential for a high degree of efficacy in reducing seizures with an unprecedented seizure-free rate of up to 28%. Rare cases of hypersensitivity reactions seen in early trials seem to be avoided by the current recommended titration schedule.[4] Therefore, if licensed, cenobamate will offer an additional adjunctive treatment option for subjects with PGTC seizures, particularly those that are uncontrolled on other antiepileptic drugs.

Regulatory & Development Status

Cenobamate is already licensed in the EU/UK for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite treatment with at least 2 anti-epileptic medicinal products..[2]

Cenobamate is in phase II/III clinical development for other epilepsy subtypes:[5]

- Focal seizures
- Partial seizures
- Epilepsy

Patient Group

Disease Area and Clinical Need

A generalised tonic-clonic seizure, formerly known as grand mal seizure, is the type of epileptic seizure which is defined as a seizure that has a tonic phase followed by clonic muscle contractions. Among patients, families, and observers, they are most feared of seizure types. They are usually associated with impaired awareness or complete loss of consciousness. According to the recent classification from the International League Against Epilepsy (ILAE), they are categorised under seizures belonging to generalised in onset.

Generalised onset seizures are further categorised into motor and non-motor (absence) seizures. A generalised tonic-clonic seizure is a motor seizure and the most common type seen in patients with epilepsy. Generalised tonic-clonic seizures arise within and rapidly involve bilateral cortical, subcortical, and brainstem networks of the brain.[6,7] All seizures are caused by unusual electrical activity in the brain. The onset of tonic-clonic seizures could be related to a variety of health conditions. Some of the more severe conditions include a brain tumour or a ruptured blood vessel in the brain, which can cause a stroke. Other potential causes of a tonic-clonic seizures include: injury, such as a head injury, infection, low levels of sodium, calcium, glucose, or magnesium, drug or alcohol misuse or withdrawal.[8]

Epilepsy has been estimated to affect between 362,000 and 415,000 people in England (published 2021)[9] and approximately 60% of them result in tonic-clonic seizures.[10] In addition, it is it is estimated that misdiagnosis rates of epilepsy range between 5–30%. Incidence is estimated to be 50 per 100,000 per year and the prevalence of active epilepsy in the UK is estimated to be 5–10 cases per 1000.[9] In England 2020-2021, there were 417 admissions of which 10 were day cases, 648 finished consultant episodes (FCE) for Grand mal seizures (with or without petit mal) (ICD-10: G40.6).[11] It is estimated that in 2019 there were 743 deaths caused by epilepsy.[12] The disability employment gap in the UK affects people with epilepsy acutely. Two thirds (66%) of working-age people with epilepsy are unemployed, far lower than for those with most other disabilities. Disabled workers are paid on average 19.6% less than their non-disabled peers.[13]

Recommended Treatment Options

NICE recommends three categories of antiepileptic drugs:[14]

- Category 1 - for these drugs, doctors are advised to ensure that their patient is maintained on a specific manufacturer's product. The medicinal products include:
  - Carbamazepine
  - Phenobarbital
  - Phenytoin
- Category 2 - for these drugs, the need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient and/or carer and taking into account factors such as seizure frequency, treatment history, and potential implications to the patient of having a breakthrough seizure. The medicinal products include:
  - Clobazam
  - Clonazepam
  - Eslicarbazepine acetate
  - Lamotrigine
  - Oxcarbazepine
  - Perampanel
  - Rufinamide
  - Topiramate
  - Valproate
  - Zonisamide
- Category 3 - for these medicinal products, it is usually unnecessary to ensure that patients are maintained on a specific manufacturer's product as therapeutic equivalence can be assumed, however, other factors are important when considering whether switching is appropriate. Differences between alternative products (e.g., product name, packaging, appearance, and taste) may be perceived negatively by patients and/or carers, and may lead to dissatisfaction, anxiety, confusion, dosing errors, and reduced adherence. In addition, difficulties for patients with co-

morbid autism, mental health problems, or learning disability should also be considered. These medicinal products include:

- Brivaracetam
- Ethosuximide
- Gabapentin
- Lacosamide
- Levetiracetam
- Pregabalin
- Tiagabine
- Vigabatrin

Clinical Trial Information	
Trial	NCT03678753; A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Cenobamate Adjunctive Therapy in Subjects With PGTC Seizures **Phase III –** Recruiting **Location(s):** five EU countries, USA and Ukraine **Primary completion date:** June 2023
Trial Design	Randomised, parallel assignment, quadruple-blinded, placebo-controlled
Population	N=152 (estimated); adults (≥18 years) who have a clinical diagnosis of PGTC seizures (with or without other subtypes of generalized seizures) in the setting of idiopathic generalised epilepsy
Intervention(s)	Oral cenobamate administered as 12.5 mg tablet, 25 mg tablet, 50 mg tablet, 100 mg tablet, 150 mg tablet and 200 mg tablet
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: seizure diary [time frame: 28 days]
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT03961568; A Multicenter Open-Label Extension Study to Evaluate the Long-Term Safety of Cenobamate Adjunctive Therapy in Subjects With Primary Generalized Tonic-Clonic Seizures **Phase III –** Enrolling by invitation **Location(s):** five EU countries, USA and Ukraine **Primary completion date:** May 2023
Trial Design	Single group assignment, open-label
Population	N=130 (estimated); adults (≥18 years) who have successfully completed the Double-blind Treatment Period in the Core study.

Intervention(s)	Oral cenobamate administered as 150 mg or 200mg tablets (only for those who received cenobamate in the Core study)
Comparator(s)	Oral cenobamate administered as 12.5 mg tablet, 25 mg tablet, 50 mg tablet, 100 mg tablets, 150 mg tablets and 200 mg tablets (only for those who did not receive Cenobamate in the Core Study)
Outcome(s)	Primary outcome measure: incidence of adverse events and serious adverse events (SAEs) [time frame: 386 +/- 2 days]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Cenobamate is already marketed in the UK as an adjunctive treatment of focal seizures with or without secondary generalisation by Arvelle Therapeutics UK; NHS indicative prices of cenobamate are as follows:[15]

- 50mg tablets
  - 14 tablets - £85.54
  - 28 tablets - £91.00
- 100mg tablets
  - 14 tablets - £87.36
  - 28 tablets - £136.50
- 150mg tablets
  - 14 tablets - £89.18
  - 28 tablets - £182.00
- 200mg tablets
  - 14 tablets - £91.00
  - 28 tablets - £182.00

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Epilepsies: diagnosis and management (CG137). January 2012 (updated: May 2021).
- NICE clinical guideline in development. Epilepsies in adults: diagnosis and management (GID-NG10110). Expected publication: TBC.
- NICE quality standard. Epilepsy in adults (QS26). February 2013.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. Clinical Commissioning Policy: Deep Brain Stimulation for Refractory Epilepsy (all ages). 170036P. March 2018.
- NHS England. Clinical Commissioning Policy: Vagal Nerve Stimulation for Epilepsy. NHSCB/D04/P/d. April 2013.

Other Guidance

- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults (SIGN 143). May 2015 (revised: 2018).[16]
- American Epilepsy Society Guideline. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. 2016.[17]
- American Academy of Neurology and the American Epilepsy Society. Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. 2015.[18]
- American Academy of Neurology. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. 2013.[19]

Additional Information

Arvelle Therapeutics 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.

References

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