NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Cenobamate for adjunctive treatment of focal epilepsy

Final scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of adjunctive cenobamate within its marketing authorisation for treating focal onset seizures, with or without secondary generalization, in adults with epilepsy.

Background

Epilepsy is a neurological condition characterised by recurrent seizures unprovoked by any immediately identifiable cause. An epileptic seizure is a sudden episode with changes in movement, sensation, behaviour, emotion, memory or consciousness due to abnormal signalling between the nerve cells in the brain. Epilepsy is not a uniform condition, but comprises many different seizure types and epilepsy syndromes. The severity of the condition and the prognosis vary according to the type of epilepsy.

Epileptic seizures can be broadly categorised into 2 main types: focal and generalised. In focal seizures the abnormal signalling begins in, or is restricted to, a localised part of the brain. Generalised seizures are characterised by more widespread signalling involving both hemispheres of the brain at the same time. Focal seizures may become secondarily generalised seizures if the abnormal signalling spreads to involve the entire brain. The symptoms associated with focal seizures depend on the part of the brain that is affected and may include random bodily behaviour, language and speech disturbances, having strange feelings, impaired consciousness, seeing patterns, and flashing lights or colours. Symptoms of generalised seizures include sudden stiffening or relaxing of the muscles which may mean the person falls over, twitching arms and legs, and loss of consciousness.

Epilepsy is the most common neurological condition in the UK. It has been estimated to affect between 362,000 and 415,000 people in England[1]. Annually, there are approximately 50 new cases of people presenting with epilepsy per 100,000 population. People with epilepsy have a 2 to 3 times higher overall risk of dying than the general population[2]. More than a third of patients with epilepsy are treatment resistant[3], and thus new therapies to achieve seizure freedom are needed.

For focal seizures, NICE clinical guideline 137 (CG137) 'Epilepsies: diagnosis and management' recommends carbamazepine or lamotrigine as first line monotherapy antiepileptic drugs (AED), and levetiracetam, oxcarbazepine or sodium valproate if carbamazepine and lamotrigine are unsuitable or not tolerated. If the first AED tried is ineffective, an alternative from these 5 AEDs is recommended as monotherapy. Adjunctive treatment is considered if a second well-tolerated AED is ineffective. CG137 recommends carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive therapies. If adjunctive treatment is ineffective or not tolerated, other AEDs that may be considered are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide, although not all of these are

indicated in children under 12 years. Brivaracetam acetate and perampanel (ESNM7) have also become available since CG137 was published.

The technology

Cenobamate (brand name unknown, Arvelle Therapeutics) is an anticonvulsant drug for the treatment of epilepsy. Its exact mechanism of action is unknown. It is a sodium channel blocker, although its binding site is different from that of other sodium channel blocking drugs. It increases the principal inhibitory neurotransmitter in the brain, known as presynaptic gamma-aminobutyric acid (GABA), enhancing GABAergic transmission (impairment of which is known to induce epileptic seizures).

Cenobamate does not currently have Marketing Authorisation in the EU for any indication. It has been studied in a multicentre, double-blind, randomised, placebo-controlled phase 3 trial of adults with epilepsy who have uncontrolled focal onset seizures and require additional therapy despite having been treated with at least one AED in the previous 2 years. It is also has been studied in two multicentre, double-blind, randomized, placebo-controlled phase 2 trials of adults with partial onset seizures.

Intervention(s)	Cenobamate
Population(s)	Adults with uncontrolled focal onset seizures with or without secondary generalization in epilepsy in whom adjunctive therapy is needed.
Comparators	Established adjunctive clinical management, including but not limited to: brivaracetam acetate, carbamazepine, eslicarbazepine acetate, lacosamide, levetiracetam and perampanel.
Outcomes	The outcome measures to be considered include: • change in seizure frequency • seizure free rate • time to first seizure • response rate • seizure severity • mortality • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** None **Related Guidelines:** Epilepsies: diagnosis and management (2019) NICE clinical guideline 137. Review date 2021. Partial-onset seizures in epilepsy: perampanel as adjunctive treatment (2012) NICE evidence summary ESNM7. Deep brain stimulation for refractory epilepsy (2012) NICE interventional procedures guidance IPG4216. **Related Quality Standards:** Quality standard for the epilepsies in adults (2013) NICE quality standard 26. Quality standard for the epilepsies in children and young people (2013) NICE Quality Standard 27 **Related NICE Pathways:** Epilepsy (2016) NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1, 2,4 and 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

References

1 NICE guideline CG137 (2012) 'Epilepsies: diagnosis and management'. https://www.nice.org.uk/guidance/cg137/chapter/Introduction

2 Keezer MR, Bell GS, Neligan A et al. (2016) Cause of death and predictors of mortality in a community-based cohort of people with epilepsy. Neurology Feb 2016, 86 (8) 704-712. https://n.neurology.org/content/86/8/704

3 Krauss GL, Klein P, Brandt C, Lee SK, Milanov I, Milovanovic M, Steinhoff BJ, Kamin M. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. The Lancet Neurology. 2020 Jan 1;19(1):38-48. https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(19)30399-0/fulltext