

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Cenobamate for adjunctive treatment of focal epilepsy

Draft scope (pre-referral)

**Draft remit/appraisal objective**

To appraise the clinical and cost effectiveness of adjunctive cenobamate within its marketing authorisation for treating focal onset seizures in 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<sup>1</sup>. 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<sup>2</sup>. More than a third of patients with epilepsy are treatment resistant<sup>3</sup>, 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 has 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 is currently being studied in a multicentre, double-blind, randomised, placebo-controlled 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.

<b>Intervention(s)</b>	Cenobamate
<b>Population(s)</b>	People with uncontrolled focal onset seizures in epilepsy

<b>Comparators</b>	<p>Established adjunctive clinical management, which may include combinations of:</p> <ul style="list-style-type: none"> <li>• Acetazolamide</li> <li>• Brivaracetam</li> <li>• Carbamazepine</li> <li>• Clobazam</li> <li>• Clonazepam</li> <li>• Eslicarbazepine acetate</li> <li>• Gabapentin</li> <li>• Lacosamide</li> <li>• Lamotrigine</li> <li>• Levetiracetam</li> <li>• Oxcarbazepine</li> <li>• Perampanel</li> <li>• Phenobarbital</li> <li>• Phenytoin</li> <li>• Pregabalin</li> <li>• Primidone</li> <li>• Sodium valproate</li> <li>• Tiagabine</li> <li>• Topiramate</li> <li>• Valproic acid</li> <li>• Vigabatrin</li> <li>• Zonisamide</li> </ul>
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• seizure frequency</li> <li>• seizure severity</li> <li>• mortality</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>

<b>Economic analysis</b>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p>
<b>Other considerations</b>	<p>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.</p>
<b>Related NICE recommendations and NICE Pathways</b>	<p><b>Related Technology Appraisals:</b> None</p> <p><b>Related Guidelines:</b>  <a href="#">Epilepsies: diagnosis and management</a> (2019) NICE clinical guideline 137. Review date 2021.  <a href="#">Partial-onset seizures in epilepsy: perampanel as adjunctive treatment</a> (2012) NICE evidence summary ESNM7.  <a href="#">Deep brain stimulation for refractory epilepsy</a> (2012) NICE interventional procedures guidance IPG4216.</p> <p><b>Related Quality Standards:</b>  <a href="#">Quality standard for the epilepsies in adults</a> (2013) NICE quality standard 26.  <a href="#">Quality standard for the epilepsies in children and young people</a> (2013) NICE Quality Standard 27</p> <p><b>Related NICE Pathways:</b>  <a href="#">Epilepsy</a> (2016) NICE pathway</p>
<b>Related National Policy</b>	<p>The NHS Long Term Plan, 2019. <a href="#">NHS Long Term Plan</a>  NHS England (2018/2019) <a href="#">NHS manual for prescribed specialist services (2018/2019)</a>  Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1, 2,4 and 5.</p>

	<a href="https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017">https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017</a>
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### Questions for consultation

Have all relevant comparators for cenobamate been included in the scope? Which treatments are considered to be established clinical practice in the NHS for focal onset seizures in epilepsy?

What is the place in the care pathway of cenobamate in relation to other available adjunctive treatments of focal onset seizures in epilepsy?

Are any of the comparators included in this scope not relevant for this indication?

How should established clinical management be defined?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom cenobamate is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Should NICE consider reviewing this drug within its ongoing update of NICE clinical guideline 137, [Epilepsies: diagnosis and management](#)?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider cenobamate to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of cenobamate can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Draft scope for the proposed appraisal of cenobamate for adjunctive treatment of focal epilepsy

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Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at <http://www.nice.org.uk/article/pmg19/chapter/1-Introduction>).

NICE has published an addendum to its guide to the methods of technology appraisal (available at <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf>), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?
- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?
- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?
- Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?

### 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.

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