

**NIHR Innovation Observatory
Evidence Briefing: June 2018**

Cenobamate for partial focal epilepsy – adjunctive therapy

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LAY SUMMARY

Epilepsy is a common condition that affects the brain and causes frequent seizures; abnormal electrical activity in the brain that occurs suddenly and can temporarily affect how the brain functions. Epilepsy can start in any age, but usually either in childhood or in people over 60 years. In most cases, it is not clear why this happens. However, it may be caused by several factors including brain injury, infection or oxygen deprivation, scarring of brain tissue, brain tumours, and/or chemical/hormonal imbalances. In epilepsy there are two main types of seizures: generalised seizures which affect the whole brain and focal (or partial) seizures, which occur when the electrical disturbance in the brain is focussed in just one part of the brain. The symptoms associated with focal seizures depend on the part of the brain that is affected. The symptoms may vary from language and speech disturbances, having strange feelings, impaired consciousness, seeing patterns, and flashing lights or colours.

Cenobamate is a medicinal product that is being developed as a therapy for patients with partial focal epilepsy that would be taken in addition to other anti-epileptic medicine (adjunctive therapy). It is given as capsules. Cenobamate is considered a new generation antiepileptic therapy and clinical trials have shown that it may be more effective and safer than existing drugs. If licensed, cenobamate will offer a new adjunctive treatment option for patients with partial focal epilepsy.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Partial focal epilepsy – adjunctive therapy

TECHNOLOGY

DESCRIPTION

Cenobamate (YKP3089) is a novel medicinal product for the treatment of epilepsy. Its exact mechanism of action remains under active investigation; it is a sodium channel blocker, although its binding site is different from that of classical sodium channel blocking drugs and it enhances GABAergic transmission by increasing presynaptic GABA release. This agent displays a broad-spectrum of anticonvulsant activity in rodent seizure and epilepsy models and is also active in models of anxiety and neuropathic pain.¹

In the phase II (NCT01397968) clinical trial in subjects with treatment resistant partial onset seizures, cenobamate was given in a titrated dose as capsules. No further details about the treatment schedule are reported.² In the phase III (NCT02535091) clinical trial in subjects with partial onset seizures, cenobamate is given as an adjunctive therapy, initially to subjects taking phenytoin or phenobarbital, followed by additional subjects taking anti-epileptic drugs other than phenytoin and phenobarbital to further investigate long-term safety.³

Cenobamate does not currently have Marketing Authorisation in the EU for any indication.^{4,5}

INNOVATION and/or ADVANTAGES

According to SK Bio-Pharmaceuticals, cenobamate is a next generation antiepileptic drug candidate which showed superior efficacy (seizure frequency reduction, seizure free rate) and safety compared to existing drugs through recent phase II studies.⁶ If licensed, Cenobamate will offer a new adjunctive treatment option for patients with partial focal epilepsy.

DEVELOPER

SK Bio-Pharmaceuticals

PATIENT GROUP

BACKGROUND

Epilepsy is a common condition that affects the brain and causes frequent seizures. Seizures are bursts of electrical activity in the brain that temporarily affect how it works. Epilepsy can start in any age, but usually either in childhood or in people over 60 years. It is a lifelong condition, although it may slowly improve over time.⁷ Epilepsy may be caused by several factors including brain injury due to trauma, infection or oxygen deprivation, scarring of brain tissue, brain tumours, and/or chemical/hormonal imbalances. However, these factors are believed to only explain 30% of epilepsy diagnoses. In cases where the cause is not known, the disease is called idiopathic epilepsy.⁸

In epilepsy there are two main types of seizures: 1) Generalised seizures: including tonic clonic, absence, myoclonic or atonic seizures and 2) Focal (or partial) seizures.⁹ Generalized seizures affect the whole brain by an abnormal electrical disturbance. In these seizures, the person affected becomes

unconscious. Before a seizure, the person might experience unusual symptoms that will alert them to a seizure starting.¹⁰

Focal (partial) seizures occur when the electrical disturbance in the brain is focussed in just one part of the brain. Therefore, the type of seizure will depend on exactly where in the brain it comes from and what functions that area of the brain is responsible for.¹¹ Temporal lobe epilepsy is the most common form, occurring in the temporal lobe in the brain which is responsible for language, feelings, emotions and memory.¹² Frontal lobe epilepsy is the second most common focal seizure and these seizures usually start and end suddenly. They may produce weakness in certain muscles, including those used to speak.¹³ Parietal lobe epilepsy is rare and originates in the parietal area usually resulting in strange sensations. They are also known as sensory seizures.¹⁴ Occipital lobe epilepsy is not common. It affects the sight. Symptoms might include seeing patterns, flashing lights or colours, or images that appear to repeat before the eyes.¹⁵

CLINICAL NEED and BURDEN OF DISEASE

Accurate estimates of incidence and prevalence of epilepsy are difficult to achieve because identifying people who may have epilepsy is difficult. There are no direct estimates of the epilepsy prevalence for England. The prevalence of epilepsy was suggested to be between 0.7 to 0.8% for the whole population.¹⁶ Using 2016 mid-year population estimates,¹⁷ it is estimated that epilepsy affects between 386,876 and 442,144 people in England. In addition, it is estimated that misdiagnosis rates of epilepsy range between 5–30%.¹⁶ 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 1,000.¹⁸ It was found that 60% of people with epilepsy have convulsive seizures, of which two-thirds have focal epilepsies with secondary generalised seizures. About one-third of epilepsy cases have less than one seizure a year, one-third have between one and 12 seizures per year and the remainder have more than one seizure per month.¹⁶ Up to 60% of people with active epilepsy have additional neurological or neuropsychological handicaps, e.g. learning disabilities, behavioural disturbances, discrete cognitive impairment, focal neurological deficit.¹⁹

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline in development. Epilepsies in adults: diagnosis and management (GID-NG10110). Expected publication January 2021.
- NICE clinical guideline. Epilepsies: diagnosis and management (CG137). January 2012 (updated: April 2018).
- NICE clinical guideline. Transient loss of consciousness ('blackouts') in over 16s (CG109). August 2010 (updated: September 2014).
- NICE quality standard. Transient loss of consciousness ('blackouts') in over 16s (QS71). October 2014.
- NICE quality standard. Epilepsy in adults (QS26). February 2013.
- NICE interventional procedure guidance. Deep brain stimulation for refractory epilepsy (IPG416). January 2012.
NICE Evidence summary. Partial-onset seizures in epilepsy: zonisamide as monotherapy (ESNM17). April 2013.

NHS ENGLAND and POLICY 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

- 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. 2016.²⁰
- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults (SIGN 143). May 2015.²¹
- 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. 2015²²
- 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. 2013.²³

CURRENT TREATMENT OPTIONS

NICE recommend carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment in children, young people and adults with focal seizures if first-line treatments are ineffective or not tolerated.²⁴

If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other anti-epileptic drugs (AEDs) that may be considered by the tertiary epilepsy specialist are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. NICE recommend to carefully consider the risk–benefit ratio when using vigabatrin because of the risk of an irreversible effect on visual fields.²⁴

EFFICACY and SAFETY

Trial	NCT02535091 ; 18 to 70 yrs; cenobamate as adjunctive therapy to phenytoin or phenobarbital (and later other anti-epileptic drugs); phase III
Sponsor	SK Life Science
Status	Ongoing
Source of Information	Trial registry ³
Location	EU (not UK), USA, and other countries
Design	Open label, single group assignment
Participants	n= 1,200 (planned); aged 18-70 yrs; diagnosis of partial epilepsy; have uncontrolled partial seizures and require additional AED therapy despite having been treated with at least one AED within approximately the last 2 yrs; on stable antiepileptic treatment regimen
Schedule	Participants received cenobamate adjunctive therapy. No further details on treatment schedule are reported. Initially, subjects taking phenytoin or phenobarbital will be enrolled followed by additional subjects taking anti-epileptic drugs other than phenytoin and phenobarbital to further investigate long-term safety.
Follow-up	Active treatment period: not stated Follow up period: 12 mths
Primary Outcomes	Time Frame: 12 mths <ul style="list-style-type: none"> - Evaluate the pharmacokinetics of cenobamate and concomitant AEDs - Number of participants with adverse events (AEs) and serious adverse events (SAEs) - Percentage of participants with laboratory test abnormalities (Hematology) - Percentage of participants with laboratory test abnormalities (Chemistry) - Percentage of participants with laboratory test abnormalities (Urinalysis) - Percentage of participants with vital sign results of potential clinical importance
Secondary Outcomes	None stated
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as June 2018. Study completion date reported as December 2018.

Trial	NCT01866111 , 18-70 yrs; cenobamate vs placebo; phase II
Sponsor	SK Life Science
Status	Ongoing
Source of Information	Trial registry ²⁵
Location	EU (not UK), USA, and other countries

Design	Randomised, parallel assignment, double-blind
Participants	n=437; aged 18-70 yrs; a diagnosis of partial epilepsy have uncontrolled partial seizures despite having been treated with at least 1 AED within approximately the last 2 yrs
Schedule	Randomised to cenobamate low dose; cenobamate medium dose; cenobamate high dose; or placebo
Follow-up	Active treatment period: 20 wks Follow-up period: 18 wks
Primary Outcomes	Percent reduction in seizure frequency (average 28-day seizure rate) of complex partial and/or secondarily generalized and/or simple partial motor seizures during the double-blind phase relative to the pre-treatment baseline. [Time Frame: 18 wks]
Secondary Outcomes	The response to treatment, defined as a 50% or greater reduction during the double blind phase in the seizure frequency from baseline for the ITT subjects. [Time Frame: 18 wks]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as July 2015. Study completion date reported as December 2019.

Trial	NCT01397968 ; aged 18-65 yrs; cenobamate vs placebo; phase II
Sponsor	SK Life Science
Status	Ongoing
Source of Information	Trial registry ²
Location	USA, India, Republic of Korea, Poland
Design	Randomised, placebo-controlled, parallel assignment, double-blind
Participants	n=222; aged 18-65 yrs; diagnosis of treatment resistant partial epilepsy; have at least 3 simple partial with motor component, complex partial or secondarily generalised seizures per month with no consecutive 21 day seizure free period; treated on a stable dose of : - 1-3 AEDs for at least 12 wks prior to randomization
Schedule	Randomised to cenobamate given in titrated dose as capsules or placebo capsule.
Follow-up	Active treatment period: 12 wks Follow up period: 12 wks
Primary Outcomes	Percent change in seizure frequency per 28 days in the treatment period compared to the baseline in the intention to treat (ITT) population. [Time Frame: per 28 days during 12 week treatment period]
Secondary Outcomes	Responder rate: An analysis of subjects who experience a 50% or greater reduction in seizure frequency in the treatment period of the double-blind phase. [Time Frame: 12 wks]
Key Results	-

Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as June 2013. Study completion date reported as December 2019.

ESTIMATED COST and IMPACT

COST

The cost of cenobamate is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|---|--|
| <input type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input checked="" type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|---|---|
| <input type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input type="checkbox"/> Other reduction in costs |
| <input type="checkbox"/> Other | <input checked="" type="checkbox"/> None identified |

OTHER ISSUES

Clinical uncertainty or other research question identified

None identified

REFERENCES

- ¹ Zaccara G, Schmidt D. Do traditional anti-seizure drugs have a future? A review of potential anti-seizure drugs in clinical development. *Pharmacological Research*. 2016 Feb; 104:38-48. Available from: https://ac.els-cdn.com/S1043661815002881/1-s2.0-S1043661815002881-main.pdf?tid=3a2036a5-8577-41bb-aa38-240dbbfca16f&acdnat=1522157425_d0a4ebd0c34461f461731644ad6fa286 [Accessed 27th Mar 2018]
- ² ClinicalTrials.gov. *Efficacy and safety of YKP3089 in subjects with treatment resistant partial onset seizures: NCT01397968*. Available from: <https://clinicaltrials.gov/ct2/show/NCT01397968> [Accessed 27th Mar 2018]
- ³ ClinicalTrials.gov. *Safety and pharmacokinetic study of YKP3089 as adjunctive therapy in subjects with partial onset seizures: NCT02535091*. Available from: <https://clinicaltrials.gov/ct2/show/NCT02535091> [Accessed 4th Jun 2018]
- ⁴ British National Formulary. *Search results*. Available from: <https://bnf.nice.org.uk/#Search?q=Cenobamate> [Accessed 27th Mar 2018]
- ⁵ British National Formulary. *Search results*. Available from: <https://bnf.nice.org.uk/#Search?q=YKP3089> [Accessed 27th Mar 2018]
- ⁶ SK Bio-Pharmaceuticals Co. Ltd. *Cenobamate (YKP3089)*. Available from: http://skbp.com/pipeline/pl_03.asp [Accessed 27th Mar 2018]
- ⁷ NHS Choices. *Epilepsy*. Available from <https://www.nhs.uk/conditions/epilepsy/> [Accessed 4th Jun 2018]
- ⁸ Epilepsy Research UK. *Causes of epilepsy*. Available from <https://www.epilepsyresearch.org.uk/aboutepilepsy/causes-of-epilepsy/> [Accessed 4th Jun 2018]
- ⁹ Young Epilepsy. *Epilepsy seizures*. Available from: <https://www.youngepilepsy.org.uk/about-epilepsy/epilepsy-seizures/> [Accessed 4th Jun 2018]
- ¹⁰ Young Epilepsy. *Generalised seizures*. Available from: <https://www.youngepilepsy.org.uk/about-epilepsy/epilepsy-seizures/generalised-seizures/> [Accessed 4th Jun 2018]
- ¹¹ Young Epilepsy. *Focal (partial) seizures*. Available from: <https://www.youngepilepsy.org.uk/about-epilepsy/epilepsy-seizures/focal-partial-seizures/> [Accessed 4th Jun 2018]
- ¹² Young Epilepsy. *Temporal lobe epilepsy*. Available from: <https://www.youngepilepsy.org.uk/about-epilepsy/seizures/focal-partial-seizures/temporal-lobes.html> [Accessed 4th Jun 2018]
- ¹³ Young Epilepsy. *Frontal lobe epilepsy*. Available from: <https://www.youngepilepsy.org.uk/about-epilepsy/seizures/focal-partial-seizures/front-lobes.html> [Accessed 4th Jun 2018]
- ¹⁴ Young Epilepsy. *Parietal lobe epilepsy*. Available from: <https://www.youngepilepsy.org.uk/about-epilepsy/seizures/focal-partial-seizures/parietal-lobes.html> [Accessed 4th Jun 2018]
- ¹⁵ Young Epilepsy. *Occipital lobe epilepsy*. Available from: <https://www.youngepilepsy.org.uk/about-epilepsy/seizures/focal-partial-seizures/occipital-lobes.html> [Accessed 4th Jun 2018]
- ¹⁶ National Clinical Guideline Centre (UK). *The Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care: Pharmacological Update of Clinical Guideline 20 - NICE Clinical Guidelines, No. 137*. London: *Royal College of Physicians (UK)*; Jan 2012. Available from: <https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0079780/> [Accessed 12th Jun 2018]
- ¹⁷ Office for National Statistics. *Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2016*. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2016#main-points> [Accessed 24th Nov 2017]
- ¹⁸ National Institute for Health and Care Excellence. *Clinical guideline: Epilepsies: diagnosis and management (CG137)*. January 2012 (updated: April 2018). Available from: <https://www.nice.org.uk/guidance/cg137/chapter/Introduction> [Accessed 27th Mar 2018]
- ¹⁹ Brown S, Betts T, Crawford P, Hall B, Shorvon S, Wallace S. Epilepsy needs revisited: a revised epilepsy needs document for the UK. *Seizure*. 1998 Dec; 7(6):435-46. Available from: [https://doi.org/10.1016/S1059-1311\(98\)80001-0](https://doi.org/10.1016/S1059-1311(98)80001-0)
- ²⁰ Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al.

Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Currents*. 2016 Jan-Feb;16 (1):48-61. Available from: <http://www.epilepsycurrents.org/doi/pdf/10.5698/1535-7597-16.1.48> [Accessed 27th Mar 2018]

²¹ Scottish Intercollegiate Guidelines Network (SIGN). *SIGN 143: Diagnosis and management of epilepsy in adults*. Edinburgh: SIGN; 2015. [May 2015]. Available from: <http://www.sign.ac.uk/assets/sign143.pdf> [Accessed 27th Mar 2018]

²² Krumholz A, Wiebe S, Gronseth GS, Gloss DS, Sanchez AM, Kabir AA, et al. 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. *Neurology*. 2015 Apr 21; 84(16):1705-13. Available from: <http://n.neurology.org/content/neurology/84/16/1705.full.pdf> [Accessed 27th Mar 2018]

²³ Morris GL III, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2013 Oct 15; 81(16):1453-9. Available from: https://www.aesnet.org/sites/default/files/file_attach/Guidelines/Neurology-2013-Morris-1453-9.pdf [Accessed 27th Mar 2018]

²⁴ National Institute for Health and Care Excellence. *Clinical guideline: Epilepsies: diagnosis and management*. Available from: <https://www.nice.org.uk/guidance/cg137/resources/epilepsies-diagnosis-and-management-pdf-35109515407813> [Accessed 4th Jun 2018]

²⁵ ClinicalTrials.gov. *A double-blind, randomized, placebo-controlled, phase 2 trial of YKP3089 as adjunctive therapy in subjects with partial onset seizures: NCT01866111*. Available from: <https://clinicaltrials.gov/ct2/show/NCT01866111> [Accessed 5th Jun 2018]