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.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{13} Parietal lobe epilepsy is rare and originates in the parietal area usually resulting in strange sensations. They are also known as sensory seizures.\textsuperscript{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.\textsuperscript{15}

\begin{center}
\textbf{CLINICAL NEED and BURDEN OF DISEASE}
\end{center}

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.\textsuperscript{16} Using 2016 mid-year population estimates,\textsuperscript{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\%.\textsuperscript{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.\textsuperscript{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 \textsuperscript{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.\textsuperscript{19}

\begin{center}
\textbf{PATIENT PATHWAY}
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\begin{center}
\textbf{RELEVANT GUIDANCE}
\end{center}

\begin{center}
\textbf{NICE GUIDANCE}
\end{center}

NHS ENGLAND and POLICY GUIDANCE


OTHER GUIDANCE

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

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
<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02535091; 18 to 70 yrs; cenobamate as adjunctive therapy to phenytoid or phenobarbital (and later other anti-epileptic drugs); phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>SK Life Science</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Source of Information</td>
<td>Trial registry³</td>
</tr>
<tr>
<td>Location</td>
<td>EU (not UK), USA, and other countries</td>
</tr>
<tr>
<td>Design</td>
<td>Open label, single group assignment</td>
</tr>
<tr>
<td>Participants</td>
<td>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</td>
</tr>
<tr>
<td>Schedule</td>
<td>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.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment period: not stated Follow up period: 12 mths</td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td>Time Frame: 12 mths  - 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</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td>None stated</td>
</tr>
<tr>
<td>Key Results</td>
<td>-</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>-</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Primary completion date reported as June 2018. Study completion date reported as December 2018.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01866111; 18-70 yrs; cenobamate vs placebo; phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
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<td>Trial registry²⁵</td>
</tr>
<tr>
<td>Location</td>
<td>EU (not UK), USA, and other countries</td>
</tr>
</tbody>
</table>
### 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.

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### Trial
NCT01397968; aged 18-65 yrs; cenobamate vs placebo; phase II

### Sponsor
SK Life Science

### Status
Ongoing

### Source of Information
Trial registry

### 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
-
<table>
<thead>
<tr>
<th>Adverse effects (AEs)</th>
<th>-</th>
</tr>
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<tbody>
<tr>
<td>Expected reporting date</td>
<td>Primary completion date reported as June 2013. Study completion date reported as December 2019.</td>
</tr>
</tbody>
</table>

**ESTIMATED COST and IMPACT**

**COST**
The cost of cenobamate 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**
REFERENCES


