Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2408

cenobamate 12.5mg, 25mg, 50mg, 100mg, 150mg, and 200mg film-coated tablets (Ontozry®)

Arvelle Therapeutics

14 January 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

cenobamate (Ontozry®) is accepted for restricted use within NHSScotland.

Indication under review: 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.

SMC restriction: in patients with drug-resistant epilepsy as a second-line adjunctive anti-seizure medicine, after the failure of the first adjunctive anti-seizure medicine

In patients with uncontrolled focal seizures, despite treatment with anti-epileptic medicines, cenobamate was superior to placebo in terms of the proportion of patients experiencing a ≥50% reduction in focal seizure frequency.

Chairman
Scottish Medicines Consortium

Indication

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.[1]

Dosing Information

The recommended starting dose of cenobamate is 12.5mg per day, titrated gradually to the recommended target dose of 200mg per day. Based on clinical response, dose may be increased to a maximum of 400mg per day. Cenobamate should typically be taken once daily as single oral dose at any time. However, it should preferably be taken at the same time each day.

For more information on posology and method of administration, including the recommended titration schedule, see Summary of Product Characteristics (SPC).[1]

Product availability date

15 December 2021.

Summary of evidence on comparative efficacy

Cenobamate has a dual mechanism of action. It is a positive allosteric modulator of the γ-aminobutyric acid ($GABA_A$) ion channel (via a different binding site than benzodiazepines), and 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.[1, 2]

The submitting company has requested that SMC considers cenobamate when positioned for use in patients with drug-resistant epilepsy as a second-line adjunctive anti-seizure medicine, after the failure of the first adjunctive anti-seizure medicine.

Study C017 is a multinational, randomised, double-blind, phase II study which evaluated the efficacy and safety of cenobamate compared with placebo in 437 patients with uncontrolled focal (partial)-onset epilepsy. Patients had epilepsy with focal onset seizures according to International League Against Epilepsy (ILAE) criteria, uncontrolled focal onset seizures despite treatment with at least one anti-seizure medication within the last 2 years, and at screening were on stable doses of one to three anti-seizure medications for ≥4 weeks. Patients were randomised equally to receive cenobamate orally 100mg/day (n=108), 200mg/day (n=110), 400mg/day (n=111) or placebo (n=108). All patients underwent a 6-week titration period followed by a 12-week maintenance period where patients received their maximum tolerated dose of the medicine (up to the maximum dose of their respective randomised group). Patients continued taking their concomitant anti-epileptic medicines at the same doses throughout the double-blind period. After the double-blind treatment period, patients who continued to meet study eligibility criteria

(except for seizure frequency) could opt to enrol in the open-label extension study. Cenobamate 100mg/day is not a target dose and will not be discussed further.[1, 3]

The primary outcome was responder rate, defined as the percentage of patients achieving ≥50% reduction from baseline in focal seizure frequency during the 12-week maintenance phase. Efficacy analyses were primarily performed in a modified intention-to-treat population, which included patients who completed the 6-week titration phase, took at least one dose of study drug in the maintenance phase, and had maintenance phase seizure data. A step-down procedure was used to ensure the overall type I error rate was controlled at the 5% level, allowing the formal testing of the primary outcome in cenobamate 100mg, 200mg, and 400mg treatment groups versus placebo.[3]

In Study C017, 56% of the cenobamate 200mg group and 64% of the cenobamate 400mg group had a ≥50% reduction in focal seizure frequency per 28 days compared with 25% of patients in the placebo group.[3] See Table 1 for more details.

Table 1. Efficacy results of Study C017 (mITT population).[2, 3]

	Cenobamate 200mg	Cenobamate 400mg	Placebo
Primary outcome: ≥50% reduction from baseline in focal seizure frequency during the 12-week maintenance phase			
n	98	95	102
Responder rate	56%	64%	25%
Odds ratio (95% CI) versus placebo	3.74 (2.06 to 6.80)	5.24 (2.84 to 9.67)	-
p-value versus placebo	<0.001	<0.001	-
Secondary outcomes			
≥50% reduction from baseline in seizure frequency during the 18-week double-blind period (titration + maintenance periods)			
n	109	111	106
Responder rate	58%	60%	22%
≥75% reduction from baseline in seizure frequency during the 12-week maintenance phase			
n	98	95	102
Responder rate	31%	46%	9.8%
≥90% reduction from baseline in seizure frequency during the 12-week maintenance phase			
n	98	95	102
Responder rate	17%	28%	2.9%
≥100% reduction from baseline in seizure frequency during the 12-week maintenance phase			
n	98	95	102
Responder rate	11%	21%	1.0%
Percent change from baseline in seizure frequency in the 12-week maintenance phase			
n	98	95	102
Median change*	-56%	-63%	-27%

*Negative numbers means a reduction in seizure frequency from baseline.

mITT = modified intention-to-treat; CI = confidence interval.

The submitting company did not present subgroup data for the population described in the proposed positioning. Results from subgroups which may be similar to the proposed population were consistent with the primary efficacy analysis

Health-related quality of life was assessed using the Quality of Life in Epilepsy-Questionnaire (QOLIE-31-P) instrument in English-speaking countries only, which markedly reduced sample size (n=133). No clinically relevant differences were observed.[2]

After the double-blind treatment period, patients who continued to meet study eligibility criteria (except for seizure frequency) in Study C017 could opt to enrol in the open-label extension study. Patients entering the open-label extension underwent a 2-week blinded conversion to a target dose of cenobamate 300mg/day (max dose 400mg/day). Almost all patients that completed the double-blind treatment period entered the open-label extension (99%). At data cut-off April 2018, median duration of cenobamate exposure was 40.1 months. In the open-label extension ITT population (n=354), the median percent seizure frequency reduction during the first 6 months of treatment was 65%; at 25 to 30 months, seizure frequency reductions increased to 76% and 20% of patients were seizure-free.[4] The submitting company provided data from a later data-cut (July 2019) which were consistent.

The submitting company presented Bayesian network-meta-analyses (NMAs) comparing the efficacy and safety of cenobamate versus lacosamide, brivaracetam, eslicarbazepine and perampanel. The NMAs included 19 studies (cenobamate =1 study, Study C017; lacosamide =4; brivaracetam =6; eslicarbazepine =4; perampanel =4). The studies were of adult patients (defined as ≥12 years) receiving adjunctive treatment for uncontrolled focal onset seizures in epilepsy. Efficacy outcomes assessed were ≥50% responder rate (the proportion of patients with at least a 50% reduction in focal seizure frequency or seizure freedom) and seizure freedom (the proportion of patients who achieve seizure-free status for focal onset seizures during the treatment or maintenance period). Safety outcomes reported were the proportion of patients experiencing at least one adverse event and the proportion with adverse events leading to discontinuation. The company concluded that cenobamate was superior to all four comparators for ≥50% responder rate and seizure freedom efficacy outcomes, but there was no evidence of a difference between treatments for safety outcomes.

Summary of evidence on comparative safety

Overall, the safety profile of cenobamate has been extensively studied, with evidence from Study C017, Study C013, Study C021, and two open-label extension studies. The vast majority of adverse events (AEs) were mild to moderate in severity and resolved over time. Common AEs reported were somnolence, dizziness, fatigue and headache. No new safety signals were identified in the longer term open-label studies; there was a slight increase in frequency of AEs believed to be due to the longer treatment duration.[2]

In Study C017 during the double-blind treatment period, any treatment-emergent AE was reported by 76% (84/110) of patients in the cenobamate 200mg group, 90% (100/111) in the cenobamate 400mg group, and 70% (76/108) in the placebo group and these were considered treatment-related in 66%, 83%, and 43% respectively. In the cenobamate 200mg, 400mg and placebo groups respectively, patients with a reported serious AE were 3.6%, 7.2%, and 5.6%; and patients discontinuing therapy due to an AE was 14%, 20% and 4.6%. The most frequently reported treatment-emergent AEs with an incidence >10% (double-blind treatment period) in the cenobamate 200mg, 400mg and placebo groups were: somnolence (21%, 37%, and 8.3%), dizziness (20%, 33%, and 14%), headache (11%, 11%, and 5.6%), fatigue (17%, 24%, and 8.3%) and diplopia (10%, 15%, and 1.9%).[2, 3]

In the open-label extension of Study C017 (data cut-off April 2018), median duration of cenobamate exposure was 40.1 months; 70% (n=247) were treated for ≥24 months. Median modal cenobamate dose was 300mg/day. Treatment-emergent AEs occurred in 88% of patients during the open-label extension; treatment-emergent AEs reported in ≥10% of patients were dizziness, somnolence, headache, diplopia, fatigue, and gait disturbance. Serious treatment-emergent AEs occurred in 18% of patients. Treatment-emergent AEs leading to discontinuation occurred in 7.9% of patients.[4] Updated results provided by the submitting company (data cut-off July 2019) were similar.

Summary of clinical effectiveness issues

Epilepsy is one of the most prevalent serious neurological conditions, and is associated with significant morbidity and mortality. Antiepileptic medicines are effective in achieving longer-term seizure freedom in a majority of patients, however over 30% of epilepsy cases, particularly those with focal seizures, do not gain seizure freedom on existing therapies. Drug-resistant epilepsy is defined as a failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic medicines (monotherapies or in combination) to achieve sustained seizure freedom. Using these criteria, nearly half (44%) of patients may be considered drug-resistant.[2] Clinical experts consulted by SMC considered that cenobamate fills an unmet need in this therapeutic area since there are many patients who have had an insufficient response with other adjunctive treatment options.

The submitting company has requested that SMC considers the use of cenobamate when positioned for use in patients with drug-resistant epilepsy as a second-line adjunctive anti-seizure medicine, after the failure of the first adjunctive anti-seizure medication.

It is important to note that Study C017 represents a wider patient population than the proposed positioning, and subgroup data for this narrower positioning population were not used to inform the case. Although most patients in the study could be considered as having drug-resistant epilepsy (93% of patients had uncontrolled epilepsy following at least 2 anti-seizure medications),

it is not clear how many patients had previously obtained an insufficient response from a first-line adjunctive anti-seizure medication as this information was not recorded at baseline. The subgroup of patients who had failed ≥3 anti-seizure medications may be the closest representation available, as patients typically receive two anti-seizure medications in monotherapy before the addition of an adjunctive treatment. In the cenobamate 200mg, 400mg, and placebo groups respectively, 65%, 65% and 74% of patients had failed ≥3 anti-seizure medicines. Although subgroup data did not inform the economic case, responder rates and safety outcomes were very similar to the mITT population during the maintenance period of the study. It is not clear if this similarity continues in the long-term.[2, 3]

The primary outcome from Study C017 was statistically significant and can be considered clinically meaningful for a population where the large majority of patients could be classed as being drug-resistant. The responder rate (i.e. having at least 50% reduction in seizures) was 56% and 64% with cenobamate 200mg and 400mg respectively versus 25% in the placebo group. Of particular relevance to patients was the proportions of patients achieving seizure freedom, which was 11% and 21% of the cenobamate 200mg and 400mg groups versus 1.0% in the placebo group.[2]

There were some methodological limitations to the evidence presented. As a placebo-controlled study, the double-blind treatment period is understandably of a limited duration. Consequently, there is some uncertainty with the relative efficacy of cenobamate in the longer-term. Although the open-label extension provides data for up to 5 years, the magnitude of effect with cenobamate cannot be ascertained, due to lack of a control arm. A further limitation was the method for addressing missing data. Days with missing data were assumed to have the same seizure rate as days with non-missing data, and patients that dropped out of the study were similarly treated. Sensitivity analyses using alternative methods for addressing missing data were performed and support the robustness of the primary findings. Lastly, the use of seizure diaries to self-record seizure frequency and type may introduce bias. These limitations are not unique to Study C017 and have been identified in other studies in epilepsy.[2, 3]

There were some potential issues with the generalisability of Study C017 to the relevant population in Scotland. Firstly, there are limited data for use of cenobamate in patients older than 65 years; only nine patients aged ≥65 years were included in the maintenance phase population. Secondly, patients with psychiatric comorbidities were excluded from Study C017. Psychiatric comorbidities are more common in patients with epilepsy than the general public; for example, the prevalence of suicidal thoughts is 2 to 3 times higher. The exclusion of these patients is commonplace in epilepsy studies. Lastly, the 6-week titration period in Study C017 may be quicker than titration schedules used by clinicians in practice. Adverse reactions associated with quick titration may be less frequent in practice.[1, 2, 5]

Study C017 was a placebo-controlled study and did not directly compare cenobamate with relevant comparators in Scotland. The treatment pathway in Scotland for drug-resistant focal epilepsy is not well defined and a number of treatments are available. The choice of adjunctive anti-epilepsy medicine will depend on a number of factors including sex, reproductive potential,

age, concomitant medications, pre-existing or comorbid conditions, other medical or psychiatric conditions and adverse effect profiles. Options for the adjunctive treatment of focal epilepsy include brivaracetam, carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide. Scottish guidelines do not make recommendations for second-line adjunctive anti-epileptic medicines. Clinical experts consulted by SMC considered that cenobamate was most likely to displace use of adjunctive therapies such as perampanel, lacosamide, eslicarbazepine, and brivaracetam, which have been included in the company's NMAs. One expert also considered zonisamide, topiramate, and oxcarbazepine as relevant comparators, which have not been indirectly compared with cenobamate.[5]

The NMAs provided by the submitting company had the following limitations: there were clinical and methodological differences across studies, particularly in terms of prior treatment and outcome definitions, including the length of the evaluation period and populations analysed (mITT in maintenance period versus mITT in titration plus maintenance periods). The population included in the NMAs may not be representative of the proposed positioning in terms of prior adjunctive treatments. The use of last observation carried forward (LOCF) in a minority of included studies to address missing data can bias results. There were no closed loops in the networks, thus limiting the comparisons to indirect evidence and increasing uncertainty in the results. The differences in outcomes for the placebo groups suggest there may be measured or unmeasured differences in patient and study characteristics, which could bias the results. Quality of life outcomes were not included. Due to these limitations, the company's conclusions should be treated with some caution. Results from the indirect comparison have been used to inform the economic case.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of cenobamate compared to the adjunctive anti-seizure medicines (ASMs) brivaracetam, lacosamide, perampanel and eslicarbazepine acetate. The analysis focused on cenobamate when positioned for use in patients with drug-resistant epilepsy as a second-line adjunctive anti-seizure medicine, after the failure of the first adjunctive anti-seizure medicine. SMC clinical experts confirmed there are many ASMs currently used in clinical practice that are relevant comparators, including those used in the economic analysis.

The economic analysis used a Markov cohort model with a total of 11 mutually exclusive health states of which five define initial treatment response followed by five health states representing treatment options following a non-response, and a final health state of death. The model had an initial 28-day cycle for the first five cycles followed by 84-day cycles for the remainder of the time horizon. A lifetime horizon of 60 years was applied, with a starting age of patients of 39.8 years based on baseline patient characteristics from the C017 study.

The primary data source for the clinical efficacy of cenobamate was the double-blind, randomised C017 study and the C017 open label extension study (C017 OLE) whilst the C021 study was used to determine the safety and tolerability of cenobamate.[3, 4, 7] Evidence from C017 and C017 OLE studies was available up to cycle 26 in the economic model. Beyond this, treatment response outcomes were extrapolated over the remaining time horizon using average transition probabilities over cycles 6-26, which comprised the open-label study period. As no head-to-head evidence was available for cenobamate versus the comparators, an indirect treatment comparison was required to estimate comparative efficacy. The results of the NMAs of 19 studies were used to generate relative risks for outcomes of ≥50% reduction in seizures as well as seizure freedom for cenobamate versus each comparator. The relative risks for each comparator were applied to the cenobamate arm to inform relative treatment effects that were applied in the economic analysis.

Treatment duration for cenobamate was based on combined time to treatment discontinuation (TTD) data from Studies C017, C017 OLE and C021, applying parametric distributions fitted to TTD Kaplan-Meier (KM) curves. In the model for the base case, cenobamate TTD was extrapolated using the generalised gamma function based on statistical fit, visual fit and clinical plausibility. TTD extrapolations for the comparators were derived by applying naïve HR estimates generated based on published literature to the cenobamate TTD extrapolation.

Utility values were derived using a mapping algorithm to estimate SF-6D utilities based on patient disease characteristics stratified by response to treatment at the end of the C017 study. A de novo study conducted in Europe in 361 FOS patients (45% UK) was used to derive the mapping algorithm, with estimates applied for no response, moderate response, high response, very high response and seizure freedom states. Base case utility values for subsequent ASM treatment, post-surgery and post-vagal nerve stimulation (VNS) health states were calculated as weighted averages of the response rate utility values and patients' distribution amongst different levels of response to treatment. Carer disutility associated with each heath state was estimated based on a caregiver survey conducted by the company in 86 carers of FOS patients completing the EQ 5D-5L.

Grade ≥3 treatment-emergent adverse events with an incidence of >5% in the cenobamate arms of the C017 study are included in the base case analysis for costs, resource use and quality of life. Adverse event disutility associated with surgery, VNS and subsequent ASM treatment are also included, sourced from published literature.

Costs were included in the economic analysis for medicine acquisition and administration for titration and maintenance phases, subsequent therapies, surgery/VNS, routine monitoring, epilepsy event management in each response health state and adverse event management with additional treatment required due to accidents caused by seizures and societal costs (including carer costs) included in scenario analysis. A clinical expert survey in 14 UK neurology consultants was performed to estimate resource use for response health states associated with routine monitoring and acute management and treatment of seizures, with other resource use estimates and costs from published or other sources.

A Patient Access Scheme (PAS) is in place for the comparator perampanel. The results presented do not take account of the PAS for perampanel but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for perampanel due to commercial confidentiality and competition law issues.

The results of the cost-utility analysis estimated cenobamate to be dominant versus each comparator considered, with lower costs and increased QALYs, over each comparator at list prices (Table 2). There was an incremental medicines acquisition cost for cenobamate which was offset by significant epilepsy event management cost reduction, and lower routine monitoring and subsequent therapy costs vs the comparators and QALY gains associated with short and long term seizure frequency reduction.

Table 2: Base case results for cenobamate versus comparators (list price)

Analysis	Incremental LYG	Incremental QALYs	ICER (cost/QALY)
Cenobamate vs.	-	-	-
Perampanel	0.087	0.503	Cenobamate dominant
Lacosamide	0.091	0.508	Cenobamate dominant
Brivaracetam	0.100	0.569	Cenobamate dominant
Eslicarbazepine acetate	0.124	0.649	Cenobamate dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

The company presented several scenario analyses, for which cenobamate dominated comparators exhibiting the lowest total cost and the highest QALY gain. Key scenario analyses are presented in table 3 for cenobamate versus the comparator perampanel due to perampanel having the lowest total costs and highest QALYs of the comparators. This demonstrated that cenobamate remained dominant with every scenario tested (Table 3).

Table 3: Key scenario analysis results for cenobamate versus comparator perampanel (list price)

	Sensitivity/scenario analysis	Incremental QALYs	ICER (cost/QALY)
1	Base case	0.503	Cenobamate dominant
2.	Time horizon: 15 years	0.349	Cenobamate dominant
3	Costs of epilepsy event maintenance: 25% of base case	0.503	Cenobamate dominant
4	Costs of routine monitoring 50% of base case in the ‘no response’ and ‘moderate response’ health states	0.503	Cenobamate dominant
5	Response health state utilities estimated using clinical expert opinion	0.730	Cenobamate dominant

6.	Utilities from an alternative published source (Phumart et al 2018)	0.373	Cenobamate dominant
7.	Carer disutility applied	0.747	Cenobamate dominant
8	Phumart et al utilities + carer disutility applied	0.617	Cenobamate dominant
9	Mortality HR not applied	0.507	Cenobamate dominant
10	Discontinuation: Gompertz	0.648	Cenobamate dominant
11	Discontinuation: Log-logistic	0.426	Cenobamate dominant
12	Discontinuation equal for cenobamate and comparators	0.699	Cenobamate dominant
13	Societal perspective adopted	0.503	Cenobamate dominant
14	NMA results for first 5 cycles of the model applied corresponding to double blind phase of C017, equivalent efficacy after	0.102	Cenobamate dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; NR, not reported; QALY, quality-adjusted life year

The economic analysis was associated with a number of limitations and uncertainties:

- The analysis was presented against relevant third generation AED comparators, although there are other potential ASMs that appear to be used in clinical practice in the second-line adjunctive positioning that were not included in the economic evaluation (e.g. zonisamide, topiramate, oxcarbazepine as mentioned by one SMC clinical expert). However, SMC felt that the comparators included in the economic analysis were reasonable for the positioning of cenobamate.
- Uncertainty associated with a long lifetime horizon based on short term clinical trial data. However, scenario analyses with much shorter time horizons were performed, with cenobamate remaining dominant in the economic analysis (Table 3).
- Lack of comparative evidence versus each of the comparators, hence an ITC was required which has limitations as described in the comparative clinical effectiveness section above. The NMA estimates a greater treatment response with cenobamate than the comparators but is associated with uncertainty. A scenario analysis assuming equivalent efficacy from cycle 6 in the economic model still resulted in small cost savings and QALY gains for cenobamate vs each comparator (Scenario 14, Table 3).
- The use of average transition probabilities for week 6-26 from cenobamate clinical study data as the base for extrapolation over the long lifetime horizon is associated with uncertainty due to lack of long term data and results in a gradual improvement in outcomes over time, which may not be plausible. Based on additional analysis requested from the company, removing the gradual benefit improvement would reduce the incremental savings and QALYs gained for cenobamate, but not change the overall conclusion of cenobamate being dominant.
- There is uncertainty in the extrapolation of cenobamate and comparators TTD, with the relative estimates based on a naïve comparison using discontinuation hazard rates based on published estimates. However, scenario analysis has shown that varying extrapolations

and assumptions regarding relative TTD does not change the conclusion of cenobamate being dominant versus the comparators (Scenario 12, Table 3).

- There are uncertainties with the face validity of the response health state disutilities associated with the disease characteristics to SF6D mapping study, which appear potentially low. However, the mapping study appears to be robust, and relative utilities for response health states appear reasonable.

Despite the above limitations and uncertainties, the economic case for cenobamate has been demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Epilepsy Scotland and Epilepsy Connections, which are both registered charities.
- Epilepsy Scotland has received less than 1% pharmaceutical company funding in the past two years, including from the submitting company. Epilepsy Connections has not received any pharmaceutical company funding in the past two years.
- Focal onset seizures are the most predominant seizure type and can have a devastating impact on people's wellbeing and quality of life. Ongoing seizure activity can lead to negative outcomes in relation to physical and mental health, education, employment, financial security, personal relationships and independence. Some of the difficulties that people with epilepsy face include stigma and discrimination, transport limitations, cognitive impairment and the side effects of anti-epilepsy medications.
- Current antiseizure medications (ASMs) are not always effective in controlling or even reducing the frequency and severity of seizures. In surveys conducted by the patient groups, many of the respondents said that they continue to experience seizures and have never achieved complete seizure control, despite trying several different medications. Many people also report issues with side effects.
- Cenobamate is potentially of great benefit to people with refractory focal seizures. With improved seizure control, people would be less vulnerable to the recognised negative outcomes associated with epilepsy. There could be substantial psychosocial benefits, notably impacting mental health, relationships, education and employment. Families and carers would also enjoy a better quality of life and the financial burden of epilepsy could be reduced. Any new medications to improve outcomes in people with the condition are welcomed.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published SIGN 143 "Diagnosis and management of epilepsy in adults" in May 2015 and has subsequently been updated in September 2018. The guideline defines drug-resistant epilepsy as failing to achieve sustained seizure freedom after trials of two tolerated and appropriate anti-epilepsy medicine schedules (either as monotherapies or in combination). Following two failed schedules, the guideline recommends the use of adjunctive anti-epilepsy medicines. Options for the adjunctive treatment of focal epilepsy include carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide. The choice of adjunctive anti-epilepsy medicine will depend on a number of factors including sex, reproductive potential, age, concomitant medications, pre-existing or comorbid conditions, other medical or psychiatric conditions and adverse effect profiles. The guideline does not offer advice on second-line adjunctive anti-epileptic medicines.[5]

The National Institute of Health and Care Excellence (NICE) published "Epilepsies: diagnosis and management clinical guideline" (CG137) in January 2012 and was last updated in May 2021. In adjunctive treatment of children, young people, and adults with refractory focal seizures the guideline recommends the use of carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate (not for women or girls of childbearing potential) or topiramate. If adjunctive treatment is ineffective or not tolerated, referral to a tertiary epilepsy specialist is recommended, and the following treatments may be considered: eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide.[6]

Additional information: comparators

Brivaracetam, carbamazepine, eslicarbazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Cenobamate	**12.5mg daily, titrated to 200mg per day. Maximum daily dose 400mg per day. For oral use.**	**Year 1** **200mg daily dose = £2,339** **400mg daily dose = £4,113** **Year 2 onwards** **200mg daily dose = £2,366** **400mg daily dose = £4,732**

Costs from eMC Dictionary of Medicines and Devices Browser on 23 November 2021.

Additional information: budget impact

The submitting company estimated there would be 70 patients treated in year 1 rising to 611 patients in year 5.

SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget impact. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

References

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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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5. Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults (SIGN 143). A national clinical guideline. First published May 2015, updated September 2018. Available from: www.sign.ac.uk

6. National Institute of Health and Care Excellence (NICE). Epilepsies: diagnosis and management clinical guideline (CG137). First published January 2012, last updated in May 2021. Available from www.nice.org.uk

7. Arvelle Therapeutics. Clinical study report: an open-label, multicentre, safety and pharmacokinetic study of cenobamate as adjuctive therapy in subjects with partial onset seizures (Study C021).

8. Phumart P, Limwattananon C, Kitwitee P, et al. EQ-5D-based utilities and healthcare utilization in Thai adults with chronic epilepsy. Epilepsy Behav 2018. 83: 140–146.

This assessment is based on data submitted by the applicant company up to and including 10 December 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.