Cenobamate for treating focal onset seizures in epilepsy

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1   Recommendations

1.1   Cenobamate is recommended as an option for treating focal onset seizures with or without secondary generalised seizures in adults with drug-resistant epilepsy that has not been adequately controlled with at least 2 antiseizure medicines. It is recommended only if:

- it is used as an add-on treatment, after at least 1 other add-on treatment has not controlled seizures, and

- treatment is started in a tertiary epilepsy service.

1.2   This recommendation is not intended to affect treatment with cenobamate that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Treatment for focal onset seizures includes many antiseizure medicines used on their own and in combination. Treatment options for focal onset seizures after at least 2 antiseizure medicines are not very effective.

Short-term clinical evidence shows that cenobamate reduces the number of seizures. It also increases how many people stop having any seizures. It is uncertain how this compares with other antiseizure medicines because cenobamate has not been directly compared with them. The results of an indirect comparison are uncertain because the clinical trials included are short and have different designs. Because it is unclear how the benefit of cenobamate compares with its risks, it should only be started in a tertiary epilepsy service.

Taking into account uncertainties with the clinical evidence, the most likely cost-effectiveness estimates for cenobamate are within what NICE normally considers an acceptable use of NHS resources. So, it is recommended for drug-resistant epilepsy as an add-on treatment in a tertiary epilepsy service, after at least 1 add-on treatment has not

controlled symptoms.

2   Information about cenobamate

Marketing authorisation indication

2.1   Cenobamate (Ontozry, Arvelle Therapeutics) is indicated for the 'adjunctive treatment of focal onset seizures with or without secondary generalisation in adults with epilepsy who have not been adequately controlled despite treatment with at least 2 anti-epileptic medicinal products'.

Dosage in the marketing authorisation

2.2   The dosage schedule for cenobamate is available in the summary of product characteristics.

Price

2.3   Titration packs of 14 to 28 tablets are available in different doses ranging from 12.5 mg to 200 mg and costing between £85.54 to £165.62 per pack. Maintenance packs of 28 tablets are available in doses ranging from 50 mg to 200 mg costing £91 to £182 per pack. Estimated cost for the maintenance phase of treatment is £206 per person every 28 days (£7.37 per day).

3   Committee discussion

The appraisal committee considered evidence submitted by Arvelle Therapeutics, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Drug-resistant epilepsy has a substantial physical and psychological burden on patients and their families and caregivers

3.1   Epilepsy is a neurological disorder characterised by recurrent spontaneous focal or generalised seizures. They happen because of a disruption in the normal balance between excitation and inhibition in the brain. Focal onset seizures start in 1 side of the brain and affect over 60% of people with epilepsy. There are 3 types of focal onset seizures: focal aware, focal impaired awareness and focal-to-bilateral tonic-clonic seizures. Focal-to-bilateral tonic-clonic seizures are the most severe form with the highest risk of morbidity and mortality. The patient experts explained that having epilepsy may be overwhelming and distressing, especially because of the inability to do some activities such as driving. This can cause loss of independence and social isolation. While physical effects vary, they can be debilitating, affecting people's ability to concentrate and work. Psychological stress, anxiety and fear of having seizures in public can affect people's confidence to do even simple daily tasks. Behavioural changes, psychological and physical symptoms resulting from seizures can negatively affect daily life and quality of life. Epilepsy also increases the risk of death and is associated with comorbidities such as stroke. The patient and clinical experts explained that people with drug-resistant epilepsy (epilepsy that has not been controlled by 2 antiseizure medicines) usually need some help from families or caregivers. The committee concluded that there is a substantial physical and psychological burden associated with having uncontrolled seizures in drug-resistant epilepsy that affects both

patients and their families or caregivers.

Current clinical management

People with drug-resistant epilepsy have limited treatment options

3.2   Epilepsy is primarily managed with a range of antiseizure medicines. If they do not control the seizures, non-pharmacological, invasive options are considered. This includes resective surgery and vagal nerve stimulation. The NICE guideline on the diagnosis and management of epilepsies recommends that people with focal onset seizures start on monotherapy with carbamazepine or lamotrigine. If these are not suitable or not tolerated, levetiracetam, oxcarbazepine or sodium valproate may be offered (sodium valproate is subject to additional safety advice, see NICE's implementation support on valproate in children, young people and adults: summary of NICE guidance and safety advice). If treatment does not control seizures, the guideline recommends add-on (combination) therapy with lamotrigine, levetiracetam, carbamazepine, clobazam, gabapentin, oxcarbazepine, topiramate or sodium valproate. If add-on treatment is ineffective, the guideline recommends referral to a tertiary epilepsy specialist who can consider other add-on therapy options such as eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin or zonisamide. Brivaracetam acetate and perampanel may also be offered. This guideline is currently being updated. The clinical experts explained that the pharmacological management of epilepsy is highly individualised and different medicines may be trialled, combined or sequenced depending on a person's circumstances, tolerability, drug interactions, biological targets and mechanisms of action. This means the treatment pathway is complex and not clearly defined and some or all medicines may be used depending on patient and clinician preference. Most antiseizure medicines are taken more than once daily. Cenobamate is taken once a day which is more convenient and so people are more likely to take the treatment as intended. The clinical experts agreed that while the treatment pathway does not wholly represent clinical practice, it is broadly accurate. They explained that medicines are applied using a

'start low, go slow' approach, with a small starting dose and slow dose increments. Usually, it may take 1 year to confirm whether a medicine is ineffective. Despite treatments with 2 appropriate and tolerated antiseizure medicines, up to 30% of people have drug-resistant epilepsy and do not become and stay seizure free. A patient expert explained that they had tried 9 medicines and their seizures were still not controlled. They highlighted the important balance of seizure control, tolerability and interactions when taking more than 1 medicine. The clinical experts explained that for people with drug-resistant epilepsy the options available have limited effectiveness. Also, the chance of having a year free from seizures decreases with each medicine trialled.

Cenobamate should be used as an add-on therapy in specialist epilepsy centres after at least 1 add-on therapy does not control symptoms to establish evidence about its long-term effectiveness and safety

3.3   The marketing authorisation for cenobamate is for adjunctive treatment of adults 'who have not been adequately controlled despite treatment with at least 2 anti-epileptic medicinal products'. The committee considered that this wording could be open to interpretation. In its submission, the company positioned cenobamate as an add-on option after at least 1 add-on treatment had failed to control seizures. The clinical experts explained that cenobamate is likely to be first used in specialist epilepsy centres for people with drug-resistant epilepsy, because of concerns about potential long-term adverse effects of treatment. One clinical expert advised that cenobamate is not currently an attractive option as an initial add-on treatment because of its moderate risk of adverse effects. However, if cenobamate has been shown to be effective in controlling seizures in a clinical setting with a good tolerability and safety profile, clinicians are likely to consider using it earlier in the pathway. The clinical experts explained that clinicians are likely to be overly cautious at first, because experience from previous antiseizure medicines suggest that efficacy of some medicines reported in trials may not be reflected in clinical practice. The committee considered that cenobamate would likely be used later in the pathway as long-term evidence of its efficacy and adverse effect profile is established. Therefore, it concluded that positioning cenobamate as an

add-on treatment after at least 1 other add-on treatment has not controlled seizures was appropriate. These add-on treatments are currently started in tertiary epilepsy services (see section 3.2).

Comparator treatments

The relevant comparators are add-on options offered by epilepsy specialists after at least 1 add-on treatment does not control symptoms

3.4   The NICE scope specified relevant comparators as established add-on treatments. This included, but is not limited to, brivaracetam acetate, carbamazepine, eslicarbazepine acetate, lacosamide, levetiracetam and perampanel. In its submission, the company included only 'third generation' medicines used as add-on options after at least 1 add-on treatment had not controlled seizures in its network meta-analyses (brivaracetam acetate, eslicarbazepine acetate, lacosamide and perampanel). It stated that most drug-resistant epilepsy is likely to be treated with 'third generation' medicines because of fewer drug interactions, milder adverse events and novel mechanisms of action. It also stated that the other medicines are not relevant to UK clinical practice. The ERG disagreed, noting that there is no consensus that cenobamate should only be compared with 'third generation' medicines, and that published evidence from systematic reviews suggest that older medicines are as efficacious as newer medicines. The ERG noted that some of the treatments in the NICE guideline are no longer used. But some, such as zonisamide, clobazam and topiramate are still used for different purposes as add-on medicines. For example, clobazam is used as a short-term treatment. The company did not provide any relevant comparative evidence for cenobamate compared with these comparators or with any treatments that would be used earlier in the treatment pathway. Therefore, the committee concluded that it would be appropriate to appraise cenobamate for drug-resistant epilepsy only as an add-on option after at least 1 add-on treatment has not controlled seizures. The appropriate comparators would be most of those listed at this point in the NICE treatment pathway. That is, eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine,

vigabatrin, zonisamide, brivaracetam acetate and perampanel (see section 3.2).

Clinical evidence

Key short-term clinical evidence for cenobamate comes from 2 randomised controlled trials

3.5   The main evidence for cenobamate came from 2 registrational trials, C013 and C017. These are multinational, multicentre, double-blind trials. They compared cenobamate with placebo in a total of 659 adults (aged 18 to 70) with drug-resistant focal seizures despite treatment with at least 1 antiseizure medicine in the last 1 or 2 years, who had 1 to 3 concomitant medicines at baseline that continued during the trial (background therapy). People with progressive central nervous system disease or 'psychiatric illness, psychological, or behavioural problems' were excluded from the trials. C017 had a higher threshold for inclusion for seizure frequency at baseline (at least 8 focal onset seizures over the 8-week phase before randomisation) compared with C013 (at least 3 seizures over 28 days). C013 included 1 cenobamate arm (200 mg once daily) whereas C017, a dose finding study, included 3 arms (100 mg, 200 mg and 400 mg, all once daily). Both trials had 6-week titration periods, but C013 had a 6-week maintenance phase, compared with 12 weeks in C017. The primary end point of C013 was the percentage change from baseline in seizure frequency per 28 days in the treatment period. In C017, it was at least a 50% reduction in seizures from baseline during the maintenance period. The results showed that for this outcome, 25.5% of people in the placebo arm had at least a 50% reduction in seizure frequency compared with 40.2%, 56.1% and 64.2% in the 100 mg, 200 mg and 400 mg arms, respectively.

Clinically meaningful outcomes to patients are seizure freedom (100% reduction in seizures) or near seizure freedom (at least 90% reduction)

3.6   The clinical experts explained that the regulatory end point used in epilepsy trials of at least 50% reduction in seizures compared with

baseline may not be as meaningful to patients as seizure freedom. This is because a 50% reduction may not change a person's level of independence or ability to do daily activities, and its impact may depend on the starting seizure frequency. The main aim of treatment is to retain or regain independence by prolonged and reliable periods of seizure freedom or near seizure freedom. The clinical experts suggested that 'near seizure freedom' may also be a good outcome as relapses most commonly happen when people forget to take their medicine, resulting in a seizure, rather than being because of lack of efficacy of the medicine. The clinical experts noted that a reduction in particular types of seizure may also represent meaningful clinical outcomes, such as reducing more severe seizures or seizures that happen at night. The committee considered that at least 1 year of follow up is needed to ascertain whether a person is seizure free. This is the same length of time needed for other potential benefits of seizure freedom to happen, such as the ability to re-apply for a driving license.

Longer-term effectiveness and safety evidence of cenobamate comes from 2 open-label single-arm observational studies (C017-OLE and C021)

3.7　　Two open-label extension, single-arm studies provided longer-term effectiveness and safety data. C017-OLE used 300 mg of cenobamate for 355 people who had completed the C017 trial. C021 is an ongoing phase 3, single-arm, open-label, multinational, multicentre study including 1,347 people with drug-resistant focal onset seizures. Cenobamate doses from 200 mg to 400 mg were titrated over 12 weeks (starting from 12.5 mg), followed by a 40-week maintenance period. The results showed that 23.2% of people were seizure free for at least 1 year during the C017-OLE study. The ERG noted that long-term evidence was at risk of attrition bias because many people left the study during follow up and there was no comparative evidence in the open-label extension arm of the study.

People in cenobamate trials are representative of people likely to have treatment in clinical practice

3.8   The committee considered that the baseline rates of seizures were extremely high and variable across the groups in the cenobamate trials. The ERG noted that these baseline rates may not reflect the experience of people likely to be seen in clinical practice, and importantly may confound outcomes of the trial through regression to the mean. This is because there are natural variations in the number of seizures over time. So, inclusion criteria requiring a high baseline seizure rate would mean more people would be recruited during a period of high seizure frequency that would naturally reduce over time. The committee considered whether the high baseline seizure frequency rate could be a treatment effect modifier. The company explained that it had done subgroup analyses based on number of seizures at baseline (with a threshold of 6 seizures) and seizure types and the results were consistent. The clinical experts emphasised that the absolute number of seizures in a trial is not important, as long as it represents a person's typical rate. The clinical experts agreed that the high number of seizures in the trials is representative of people with drug-resistant epilepsy likely to have treatment with cenobamate in tertiary centres in clinical practice. They noted that high seizure frequency at baseline is common in regulatory trials because it allows outcomes to be reached sooner. This decreases trial duration and minimises the risk of unnecessary drug exposure. The committee considered that excluding people with psychiatric comorbidities and other exclusion criteria in the trial would limit generalisability of the outcomes, but that this is typical of regulatory trials. It concluded that people in cenobamate trials have a high baseline seizure rate but are likely to be representative of people likely to have cenobamate in clinical practice.

C013 should be included in the company's clinical and cost-effectiveness analyses

3.9   The company excluded C013 from its clinical and cost-effectiveness analyses. This was because it did not consider that its use reflected clinical practice, because the 6-week maintenance period was too short and it did not include a 400 mg dose cenobamate arm. The ERG

highlighted that the mean dose of 200 mg used in C013 was more representative of the mean dose used in C021, which would likely reflect clinical practice. It also noted that the short maintenance period was similar to that of comparator trials, notably brivaracetam acetate. One clinical expert considered that a 6-week maintenance period in a trial setting is acceptable. The clinical experts explained that brivaracetam is often used without a titration phase and noted that most medicines are used differently in clinical practice compared with trials. The company highlighted that the shorter maintenance period for brivaracetam acetate reflected the treatment period because titration periods are not used in clinical practice. The committee concluded that data from C013 should be included the analyses. This is because the dose used was relevant to clinical practice and the duration of the maintenance phase was similar to other trials included in the network meta-analysis.

Network meta-analyses

Modified intention-to-treat (mITT) data for the entire treatment period should be used in the network meta-analyses

3.10   The company used mITT data for the maintenance phase only from C017 in its network meta-analyses, whereas comparator trials used mITT data for the entire treatment period (both titration and maintenance phases). The committee noted that higher levels of seizure reduction were seen in C017 using mITT data over the maintenance period compared with using data over the entire treatment period. The clinical experts explained that until the medicine is titrated to an effective dose, seizures can continue to happen, so it may be more appropriate to consider seizure reduction after the titration phase. The committee appreciated that seizures may happen during the titration phase. But it agreed that for consistency with other comparator trials, mITT data for the treatment phase of cenobamate trials should be used in analyses. Because of slower titration in clinical practice this may represent a substantial proportion of time on treatment.

The ERG placebo-adjusted joint synthesis network meta-analysis

including mITT data for the treatment period for both C013 and C017 is preferred

3.11   In its original submission, the company used network meta-analyses to compare cenobamate using mITT data from the maintenance phase of C017 only with 4 other third generation medicines (brivaracetam acetate, eslicarbazepine acetate, lacosamide and perampanel). It did network meta-analyses on 4 outcomes: at least 50% reduction in seizure frequency, seizure freedom, any treatment-emergent adverse events and stopping because of treatment-emergent adverse events. The ERG highlighted key limitations of the network meta-analyses. These included the absence of trials directly comparing active drugs (all options linked by placebo), comparability of trial populations being unclear because of a lack of reported baseline characteristics, titration periods that are shorter and more intense than would be seen in clinical practice, and the follow-up periods being generally shorter than the recommended 1 year needed to assess treatment success (see section 3.6). In addition, it noted the large variation in placebo response seen across the trials, implying there were different populations studied. It also noted that the company had modelled the different levels of seizure frequency reduction (at least 50% and 100%) as independent outcomes. The ERG corrected for the variable placebo response and correlation between seizure reduction outcomes using a placebo-adjusted joint synthesis model with mITT data from the combined titration and maintenance phases for both C013 and C017. The company accepted the ERG's revised model but still considered including C013 to be inappropriate. The committee concluded that the ERG's network meta-analysis was appropriate but many of the key limitations of the analysis remained.

Compared with placebo and other third generation medicines cenobamate is clinically effective at reducing seizures in the short term, but long-term evidence is uncertain

3.12   The committee acknowledged the methodological limitations of the network meta-analyses (see section 3.11). But, it noted the clinical experts' comments that many of these issues were characteristic of most epilepsy trials. Based on the results of the ERG's placebo-adjusted joint synthesis network meta-analysis for seizure reduction during the

treatment period, the committee agreed that cenobamate was clinically effective at controlling seizures in the short term and probably more so than the other drugs included in the evidence network. It acknowledged the longer-term data for cenobamate that the company had provided from its open-label extension studies. The committee considered that the high baseline seizure frequencies in the studies could result in regression to the mean (see section 3.8). It also noted that the long-term evidence had potential for attrition bias and there was no long-term comparative evidence with other drugs. It concluded that cenobamate's relative long-term effectiveness is still uncertain.

Adverse effects of treatment

The long-term adverse effect profile of cenobamate is uncertain

3.13   The ERG highlighted a potential trend for higher occurrence of treatment-emergent adverse events for cenobamate compared with brivaracetam and lacosamide. It also noted higher rates of stopping treatment because of treatment-emergent adverse events based on evidence from the network meta-analyses. There was evidence of a dose–response relationship for safety and tolerability, with severe reactions seen in the short-term studies if starting doses were high or titration rapid. The most common adverse events were somnolence, dizziness and fatigue. The company considered that these could be explained by the rapid dosing schedule in the trial and would not reflect clinical practice. The clinical experts considered that the adverse event profile was similar to other add-on therapies at this point in the pathway (see section 3.2 and section 3.4). The committee considered the short duration of the trials and the clinical experts' comments that they are likely to use cenobamate cautiously at first to evaluate its safety profile in clinical practice over a longer period. It concluded that the overall balance between efficacy and long-term adverse effect profile of cenobamate is uncertain. More information about this can only be collected in larger head-to-head trials.

The company's economic model

An economic model using only 3 response-based health states is preferred

3.14 The company used a de novo Markov model to compare the cost effectiveness of cenobamate with 4 other third generation medicines over a lifetime. The model has 5 mutually exclusive health states based on level of response defined by degree of reduction in seizure frequency:

- no response (less than 50% reduction in seizure frequency)

- moderate response (50% to less than 75% reduction)

- high response (75% to less than 90% reduction)

- very high response (90% to below 100% reduction)

- seizure freedom (100% reduction).

All patients start in the 'no response' state, then move between the 5 states until they stop treatment or die. Higher levels of response are associated with higher health-related quality of life and lower healthcare resource use. The company assumed that the risk of mortality in the 5 response states was higher than in the general population but that excess mortality was lower in 'seizure freedom' state (hazard ratio 1.6) compared with the other health states (hazard ratio 2.4). People who stop treatment move to the 'subsequent antiseizure medicine' state, comprising other medicines, and can progress to having non-pharmacological treatment with vagal nerve stimulation or surgery. The company assumed that the proportion of people with each level of response is independent of the previous line of treatment. It also modelled adverse drug reactions and carer disutility. The ERG considered that the 5 response state model was inappropriate because most of the comparator trials only reported the proportion achieving a 50% reduction in seizures (see section 3.5). This meant most of the model inputs were based on clinical opinion and 1 cenobamate trial, C017. Therefore, the ERG combined moderate to very high response into a single category to align with evidence available for comparator treatments. This was equivalent to the 3-state model seen in previous appraisals and the NICE guideline. The committee considered that while a more granular 5-state model may capture important differences in health states, there is minimal evidence available in comparator trials to populate the model. It noted that a model structure that is not based on response level but absolute numbers of seizures might be preferable to capture true differences in health-related quality of life and resource use. It concluded that the relative efficacy was the most important outcome to consider and the 3-state model is most appropriate model to evaluate this.

Assumptions in the economic model

Transition probabilities should be estimated using C013 and C017 data and adjusted for placebo response

3.15   The company estimated transition probabilities between the different response states based on time-to-response data between study visits 3 to 5 (titration period) and study visits 6 to 9 (maintenance period)

from C017 only. Transition probabilities for comparators depended on cenobamate transitions and risk ratios from the ERG network meta-analyses results. The company confirmed that the placebo response in C017 had not been adjusted before estimating the transition probabilities. The committee considered that both C013 and C017 data should have been used to inform transition probabilities and would have preferred if the placebo response had been adjusted. The company modelled transition probabilities in cycles 6 to 26 using C017-OLE data (duration of follow up) and in cycles 27 to 462 using average transition probabilities from cycles 6 to 26, leading to continual improvement over time. The ERG considered that the assumption that people will continue to improve over time is highly uncertain. As such, in its base case, the ERG used the probability of at least 50% or 100% response from the network meta-analyses and applied it to the first 20 weeks of the model. In cycle 6, people stay in the same response health state unless the treatment does not work, informed by time to stopping treatment in C017-OLE and C021. The committee considered that there was minimal long-term data to suggest that there would be continued improvement over time. Therefore, it preferred the ERG's base case.

The assumption that all treatments would have the same stopping rate from cycle 6 is appropriate

3.16   The company assumed that people would stop treatments based on naive comparisons of the 4 comparators' open-label extension observational studies that compared the risk ratios from C017-OLE and C021 (cenobamate) with single arms from comparator trials. The ERG considered the naive comparison inappropriate because it does not consider heterogeneity between study design and population and potential confounding from any other trial effects. In addition, it was unclear whether C017-OLE and C021 should be combined because the hazards of stopping treatment did not converge, suggesting that the populations may be different. In the ERG's base case, it used the odds ratios from the network meta-analysis for 'all-cause discontinuation' to inform the probability of stopping treatment in the short term (first 6 cycles), because it provided the best comparative evidence. The company considered this would bias against cenobamate because of the rapid titration periods in trials included in the network meta-analysis,

which would vary for different comparators (brivaracetam is often used without titration). For people continuing treatment, the ERG assumed that the same stopping rates would apply for all options from cycle 6. The committee considered that given the uncertainty in the relative long-term effectiveness of cenobamate compared with other third generation medicines, the ERG's assumption that the same stopping rates after cycle 6 was most appropriate.

Utility values in the economic model

Utility values from the company study and the NICE guideline on epilepsies are highly uncertain but give similar results

3.17   The company did not collect EQ-5D data in its registrational trials. To inform patient utility values for each response health state, the company used a mapping algorithm from a survey of SF-36 and QOLIE-31-P questionnaires (361 people with focal onset seizures in epilepsy). The ERG considered that the company's mapping algorithm did not reflect variability in the observed SF-6D utility index scores and underestimated the range of predicted utilities. The ERG highlighted the need for better utility data and that the utility values were highly uncertain, with some overlap between states. In the probabilistic sensitivity analysis, random utilities in higher response states were often lower than those in lower response states, so the company manually changed them to prevent illogical values. The committee noted that the company's utility values were substantially lower than those used in NICE's guideline on epilepsies (from now, CG137). Also, the differences in utilities between the response states were quite small, suggesting that there is little gain in utility moving from moderate to high response compared with high response to seizure freedom. The ERG noted that the differences between health states were similar for both the utility set derived from the company study and the CG137 utility set. This meant the absolute utility values had a minimal effect on the incremental cost-effectiveness ratio (ICER). The patient experts highlighted that there is a big difference between having seizures and seizure freedom, such as independence and ability to drive or work. The ERG highlighted the difference between health-related quality of life that is reflected in the utility values and

broader quality of life that could include employment and other factors. It considered that the small difference in utility between seizure freedom and no response is seen in published studies such as Selai et al. 2005. The committee considered that both the utility value set from the company study and the utility value set used in CG137 are highly uncertain and could potentially underestimate the benefit of seizure freedom. It concluded that both utility value sets could be considered because of the minimal differences in relative benefit.

The company's estimates of caregiver disutility lack face validity

3.18   The company modelled caregiver disutility based on a caregiver survey (n=86). The ERG considered that this study was small and poorly reported and had concerns about how disutilities from the study were derived. Because of the lack of reporting by the company, the ERG was unable to evaluate the survey's methodology or the validity of the estimates. For its base case, the ERG excluded the carer disutility but agreed that a caregiver disutility was appropriate in principle for a proportion of people. The committee considered that the disutilities from the survey were much higher than those it had seen in other conditions, even when there is significant carer burden. The clinical experts explained that people with uncontrolled epilepsy would need some sort of help and that living alone increases the risk of mortality with epilepsy. The committee considered that for people who become seizure free, carer disutility may not be completely removed because of associated comorbidities needing care. The clinical experts explained that removing the uncertainty of seizure events happening has a large effect on caring. The committee noted that the benefit for carers was of a similar size to the benefit for patients. While the committee recognised that there is some level of carer burden, it considered the company's values disproportionate and preferred to use the ERG's base case. However, it noted that that this would likely underestimate the benefits of cenobamate, because a more effective treatment would be likely to generate some carer benefits.

Resource use

The resource use estimated from clinical experts likely overestimates costs of treatment

3.19   The company explained that there was no UK-specific resource use data for the population with drug-resistant epilepsy and it had not attempted to collect any data. In its base case, it included resource use including costs for drug administration, routine monitoring and epilepsy management (acute management and acute treatment) over a 28-day period. But, in evaluating these it relied heavily on clinical opinion. For people whose epilepsy showed no response to treatment, the company estimated that most would see a GP, neurologist and epilepsy nurse within a 28-day period. The clinical experts explained that typical monitoring would involve 6-monthly follow up with a neurologist and additional contact as needed, whether it is from an epilepsy nurse, GP or the emergency department. They emphasised that the pattern of seizures is important and if the pattern is normal, but high, the person is unlikely to attend the emergency department. The clinical experts noted that people with drug-resistant epilepsy tend to be seen more in hospital rather than in primary care, although most of the monitoring is done in this setting. The patient experts explained that they routinely see a neurologist and would see an epilepsy nurse every 6 months. Because of lack of knowledge by some GPs, they normally contact the epilepsy nurse directly and rarely contact the GP. For epilepsy event management resource use, the company categorised resource use based on type of seizures (focal aware, focal awareness impaired, focal-to-bilateral tonic-clonic) and estimated hospitalisation costs of initial presentation to healthcare services, acute costs of treatment and other costs per seizure. The committee noted that the number of hospitalisations in the model likely did not reflect all patients with drug-resistant epilepsy, but may represent people with more severe disease. The ERG considered that the company estimates of 28-day healthcare costs were high compared with published models. The company also provided a scenario using the resource costs for CG137, from Jacoby et al. 1998. The company highlighted that the data was collected in 1993 in Jacoby and epilepsy management has evolved over that time. The committee had

concerns that there was no new data available since Jacoby. It considered that both the routine monitoring costs and event management costs using company assumptions could be considerably greater than seen in clinical practice. It noted that clinical opinion estimating resource use can be skewed because clinicians do not treat epilepsy in all patients with the condition and see more patients with severe disease. The committee had concerns about both the company's heavy reliance on clinical opinion and the validity of the Jacoby estimates. While it would have preferred for resource use estimates to be based on data, the committee concluded that the true values are likely to be in between the company's estimate and the estimate in the Jacoby study. It considered that the costs derived from clinical opinion would be less relevant for people with epilepsy earlier in the treatment pathway and outside of a tertiary setting, but it had not seen analysis for this population.

Cost-effectiveness estimates

The ERG's base case includes most of the committee's preferred assumptions

3.20　The committee preferred the following assumptions from the ERG base case:

- using the ERG's placebo-adjusted, joint synthesis network meta-analyses including mITT data for treatment period for both C013 and C017 (see section 3.11)

- using the 3-response health state model (see section 3.14)

- modelling transition probabilities as in the ERG's base case (see section 3.15)

- stopping rates are the same for cenobamate and all comparators after cycle 6 (see section 3.16)

- using patient utility value sets from both available sources (see section 3.17)

- excluding caregiver disutility as in the ERG's base case (see section 3.18).

  The committee considered that the ERG's base case included most of its preferred options. However, the ERG base case also used the same resource use assumptions as the base case. The committee considered that this was a key driver of the cost-effectiveness results and preferred to consider a range using the resource use data from the clinical expert opinion and the Jacoby study (see section 3.19).

Cenobamate is a cost-effective use of NHS resources

3.21   The committee considered the cost effectiveness of cenobamate compared with other third generation medicines (brivaracetam acetate, eslicarbazepine acetate, lacosamide and perampanel). It recognised the limited amount of long-term evidence available (see section 3.12), the uncertainty about cenobamate's adverse effect profile (see section 3.13) and the omission of relevant comparators (see section 3.4). In the company's and ERG's base case, cenobamate dominates all other comparator treatments (that is, it is more effective and less costly than comparators). In the scenario using the Jacoby study for resource use assumptions, cenobamate was more effective and more costly than all other comparator treatments. This resulted in an ICER of £20,522 per quality adjusted life year (QALY) gained. The committee considered that the Jacoby resource use estimates were likely to be an underestimate of costs (see section 3.19) and therefore considered this to be the highest value in the range of probable ICERs. In addition, there were potential uncaptured benefits that were not included in the ICER, such as improvement in carer utility (see section 3.18). Considering this, the committee concluded that cenobamate is a cost-effective use of NHS resources for treating drug-resistant epilepsy despite significant uncertainty in the clinical data and comparisons with other treatments. It recalled the clinical experts' comments that cenobamate may be used earlier in the pathway if shown to be effective and safe in clinical practice. The committee considered that it had not seen any evidence to support its use earlier in the pathway. It agreed that it should only be used as an add-on treatment after at least 1 add-on treatment had not controlled seizures and that treatment should be started in specialist epilepsy centres (see section 3.3).

Other factors

No equality issues were identified

3.22   The patient submission highlighted concerns about the safe use of antiseizure medicines in pregnancy and in people with comorbidities including a learning disability. The committee noted that the summary of product characteristics states that cenobamate is not recommended for women who can have children who are not using contraception. There is also inadequate data about using cenobamate during pregnancy. These issues cannot be addressed in a technology appraisal.

Cenobamate is an innovative medicine

3.23   Patient and clinical experts noted the high seizure freedom rates in clinical trials of cenobamate. The committee noted that the dual mode of action of cenobamate could be innovative as a new dual mechanism. But, it did not consider there was enough evidence that the benefits seen in the trial could be attributed to its mode of action, because of the short-term nature of the evidence and population differences. The committee concluded that cenobamate could be innovative by providing an alternative option for managing focal onset seizures in people with drug-resistant epilepsy. However, it did not hear that there were any additional gains in health-related quality of life that could be attributed to this over those already included in the QALY calculations.

4 Implementation

4.1 [Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has focal onset seizures in drug-resistant epilepsy and the doctor responsible for their care thinks that cenobamate is the right treatment, it should be available for use, in line with NICE's recommendations.

5   Appraisal committee members and NICE project team

Appraisal committee members

This topic was evaluated as a single technology appraisal by the highly specialised technologies evaluation committee. Because of this, some members of the technology appraisal committees were brought in to provide additional expertise to the committee. The highly specialised technologies evaluation committee and the 4 technology appraisal committees are standing advisory committees of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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