National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Cenobamate for focal onset seizures in epilepsy [ID1553]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Arvelle Therapeutics UK	It is appropriate to refer cenobamate to NICE for appraisal.	Thank you for your comment. No action required.
	Association of British Neurologists	Yes.	Thank you for your comment. No action required.
	Epilepsy Action	Cenobamate is intended to be used for adjunctive treatment of focal onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least two epilepsy medicines. We would therefore welcome this topic being referred to NICE for appraisal, and possible inclusion as an adjunctive treatment option for uncontrolled focal onset epilepsy	Thank you for your comment. No action required.

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Wording	Arvelle Therapeutics UK	Generally, the remit is adequate but should be amended to reflect the indication more accurately: *"To appraise the clinical and cost effectiveness of adjunctive cenobamate within its marketing authorisation for treating focal onset seizures with or without secondary generalisation in adults."* It is worth nothing that wording of the remit does not reflect the anticipated use of cenobamate within clinical practice in England and Wales. The anticipated marketing authorisation also states that: [redacted] This is further discussed in the 'Population' section below.	Thank you for your comment. The remit has been revised accordingly.
	Association of British Neurologists	Yes.	Thank you for your comment. No action required.
	Epilepsy Action	Yes.	Thank you for your comment. No action required.
Timing Issues	Arvelle Therapeutics UK	This appraisal should be done as soon as possible. As reported in the background information, more than a third of patients are treatment resistant with the probability of achieving seizure freedom diminishing substantially with each additional attempt at an ASM regimen. This demonstrates a	Thank you for your comment. NICE schedules technology appraisals so that

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		significant unmet within focal-onset epilepsy and the urgent need for further treatment options.	guidance to the NHS is timely. No action required.
	Association of British Neurologists	What is the timeline of this consultation?	Thank you for your comment. The consultation period closed July 2020.
	Epilepsy Action	As this treatment is intended to treat people with current uncontrolled seizures, we would welcome an urgent appraisal in order to assess this potential treatment.	Thank you for your comment. NICE schedules technology appraisals so that guidance to the NHS is timely.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Arvelle Therapeutics UK	We agree that the background summary gives a reasonable summary of clinical practice for epilepsy. However, it should be noted that this section does not reference perampanel which, like briviaracetam acetate, has become available for the treatment of focal onset seizures since CG137 was published. Additionally, note should be taken that perampanel has been assessed in an evidence summary, where NICE stated that perampanel was indicated at a	Thank you for your comment. The background section has been revised accordingly.

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		"point in the care pathway [where treatment decisions] should be made after advice from a tertiary epilepsy specialist" has been sought.	
	Association of British Neurologists	No comments	Thank you for your comment. No action required.
	Epilepsy Action	We would suggest including a link to further information regarding the use of sodium valproate, given the established teratogenic risks of taking that AED during pregnancy. In addition, reference to the updated MHRA advice on pregabalin and gabapentin would be useful and welcome.	Thank you for your comment. This section of the scope is intended to be a brief overview. No action required.
The technology/ intervention	Arvelle Therapeutics UK	The draft scope does not adequately capture the detail of the mechanism of action for cenobamate. Cenobamate is thought to: • Efficiently enhances tonic Gamma-Amino-Butyric Acid-A ($GABA_A$) inhibition via non-benzodiazepine binding sites in the principal neuron of the hippocampus. • Decrease excitatory currents by both inhibiting the persistent sodium current and enhancing the inactivated state of voltage-gated sodium channels. Therefore, the wording on the mechanism of action should be changed to: *"Cenobamate works through a unique, dual, complementary mechanism of action: enhancing inhibitory currents through positive modulation of $GABA_A$ receptors at a non-benzodiazepine binding site, and decreasing excitatory currents by both inhibiting the persistent sodium current and enhancing the inactivated state of voltage-gated sodium channels."*	Thank you for your comment. This section of the scope is intended to be easily accessible to a wide audience. Further details of the technology can be presented in the submission. No action required.

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	Association of British Neurologists	Brief, more information required including up to date clinical trial evidence.	Thank you for your comment. This section of the scope is intended to be a brief overview. Further details of the clinical trial evidence will be presented in the submission stage of the appraisal. No action required.
	Epilepsy Action	The current description is accurate, although there is further information that could be provided here, including how the drug is administered, its efficacy and currently known side-effects and contraindications.	Thank you for your comment. Further details of the clinical trial evidence will be presented in the submission stage of the appraisal. No action required.
Population	Arvelle Therapeutics UK	The use of cenobamate in clinical practice and its place in therapy is expected to be narrower than both the current remit and the anticipated marketing authorisation and therefore the population within the draft scope is not defined appropriately. According to NICE clinical guideline 137 (CG137), adjunctive therapy is considered following failure of two well-tolerated antiseizure medicines (ASMs) as monotherapy. Therefore, according to NICE CG137 and the anticipated marketing authorisation of cenobamate, the wording suggests that	Thank you for your comment. This section of the scope has been revised to include the distinction made regarding adjunctive treatment being initiated in people for whom seizures remain uncontrolled after treatment with at least

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		cenobamate would be available to epileptic patients with focal onset seizures as a first line adjunctive therapy. However, engagement with clinical experts in England and Wales identified that cenobamate usage would reflect that of other more recently launched medications with **prescribing of cenobamate taking place after discussion with or by a tertiary epilepsy specialist as per NICE CG137 (recommendation 1.9.3.5)**: *1.9.3.5 - If adjunctive treatment (see recommendation 1.9.3.4) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist.* This positioning and population is also in accordance with NICE CG 137 which recommends that referral to tertiary services should be considered when management is unsuccessful after 2 drugs. Therefore, the wording of the population should be amended to: ***'Adult patients with uncontrolled focal onset seizures in epilepsy where treatment decisions are made after discussions with or by a tertiary epilepsy specialist'.***	two prior antiepileptic drugs. At the scoping workshop it was agreed that no mention should be made of tertiary specialists only, in order to include specialists in secondary care also.
	Association of British Neurologists	Consideration of elderly patients, intellectual disability and pregnant women; perhaps also use in children/ adolescents should be considered.	Thank you for your comment. All protected characteristic groups are included within the existing overarching scope population. It is not anticipated that children will be included in the marketing authorisation because

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			the trials for cenobamate were limited to adults. No action required.
	Epilepsy Action	We believe that people with both epilepsy and a learning disability should be given consideration as there is currently research proposed about ways of moving them from Carbamazepine to newer drugs. In addition, the STOMP campaign is about reducing additional drugs in that population.	Thank you for your comment. All protected characteristic groups are included within the existing overarching scope population. No action required.
Comparators	Arvelle Therapeutics UK	There are many individual medicines available to treat focal onset seizures in adults, however these are recommended at different points throughout the treatment pathway as indicated in NICE CG 137 (recommendation 1.9.3.5) and in clinical practice. NICE CG137 also indicates that patients should be referred to a tertiary specialist if management with 2 drugs is unsuccessful. As indicated in the 'Population' section, cenobamate is likely to be used after discussion with or by a tertiary epilepsy specialist and therefore the list of comparators in the scope should be narrowed significantly. According to the anticipated place of cenobamate in the treatment pathway, appropriate comparators are those that are available via tertiary epilepsy specialists as per NICE CG137. That is: eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide.	Thank you for your comment. During the scoping workshop it was agreed that the comparators in the scope should be narrowed down to those most relevant to current NHS practice in the place where cenobamate is likely to be used. The comparator section has been revised accordingly.

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		• Additionally, perampanel has been assessed in an evidence summary, where NICE stated that perampanel was indicated at a "point in the care pathway [where treatment decisions] should be made after advice from a tertiary epilepsy specialist" has been sought. This places perampanel at the same point in the pathway of care as cenobamate. • Furthermore, brivaracetam has become available via tertiary prescribing since the publication of CG137 and has an established place in therapy in a tertiary care setting or after advice from a tertiary epilepsy specialist. However, a number of these treatments are not appropriate comparators: • The following treatments are rarely used as adjunctive treatments for focal onset seizures due to their side effect profiles and/or narrow therapeutic indices and should be excluded from the list of comparators. o Phenobarbital o Phenytoin o Vigabatrin • Expert advice and prescription data from England and Wales indicate that the following medications are rarely used as adjunctive therapy in focal onset seizures and therefore should also be excluded: o Pregabalin o Tiagabine • Zonisamide is also not an appropriate comparator since it is available earlier in the treatment pathway than proposed for cenobamate and is most widely used as a monotherapy in clinical practice.	

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		○ Expert advice indicates that zonisamide is used most widely as a monotherapy, with low preference as an adjunctive treatment ○ A Survey of neurologists in the UK, identified zonisamide as a background therapy to adjunctive treatment, indicating predominant usage earlier in the treatment pathway. • The following comparators are recommended prior to referral to tertiary epilepsy specialists in the treatment pathway reported in the NICE guideline for epilepsy (CG137). They are therefore not relevant comparators to cenobamate: ○ Acetazolamide ○ Carbamazepine ○ Clobazam ○ Clonazepam ○ Gabapentin ○ Lamotrigine ○ Levetiracetam ○ Oxcarbazepine ○ Primidone ○ Sodium valproate ○ Topiramate ○ Valproic acid Considering the above information and the proposed positioning of cenobamate, the most relevant comparators for the appraisal are **brivaracetam acetate, eslicarbazeline acetate, lacosamide and perampanel**. The relevance of these four key comparators were established through an advisory board which identified cenobamate's place in clinical practice; the	

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		advisory board findings were subsequently verified through a survey of UK neurologists.	
	UCB Pharma	How will the appraisal consider patient demographics and background of the study population in relation to outcomes? Factors such as concomitant antiepileptic drugs, lifetime anti-epileptic drug use, baseline seizure frequency etc, may be relevant when considering effectiveness within the reference anti-epileptic drug framework. Will the appraisal assess trial design factors such as baseline collection, titration schedules and outcomes as measured by mITT/ITT methodologies, when considering outcomes alongside the reference anti-epileptic drug framework?	Thank you for your comment. The main aim of the scoping process is to ensure the population, intervention, comparators and outcomes are correctly specified. No action required.
	Association of British Neurologists	Yes although some of these drugs are used increasingly sparingly and some have significant supply issues e.g. primidone.	Thank you for your comment. Please see response to the comment by Arvelle Therapeutics UK, above. No action required.
	Epilepsy Action	Cenobamate is proposed as an adjunctive treatment and it should be compared to other adjunctive treatments currently recommended by NICE and Brivaracetam.	Thank you for your comment. Please see response to the comment by Arvelle Therapeutics UK, above. No action required.

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Outcomes	Arvelle Therapeutics UK	All of the outcomes listed are appropriate. However, two further outcomes should be considered in order to appropriately capture the benefits of cenobamate: • Seizure freedom (100% reduction in seizure occurrence) • Treatment retention (time to treatment discontinuation) Seizure freedom allows patients to achieve the greatest improvements. Moreover, retention to treatment via a sustained response to treatment adds further quality of life benefits as the patients are satisfied with treatment, rather than cycling through multiple rounds of ineffective treatment.	Thank you for your comment. At the scoping workshop it was agreed that seizure free rate, time to first seizure and response rate would be added to the list of outcomes.
	Association of British Neurologists	The Committee will need to consider the range of outcomes used in trials and how they differ; this should include the duration of trials i.e. the difference between short clinical trials and patients potentially being on long term treatment.	Thank you for your comment. No action required.
	Epilepsy Action	We would also suggest that possible interactions with other medicines should be considered too.	Thank you for your comment. This will be captured under the outcome 'adverse effects of treatment'. No action required.
Economic analysis	Arvelle Therapeutics UK	No comments, no different to reference case.	Thank you for your comment. No action required.
	Association of British Neurologists	No comments (we do not have specific expertise in this).	Thank you for your comment. No action required.

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Equality and Diversity	Arvelle Therapeutics UK	There are no equality issues to comment on.	Thank you for your comment. No action required.
	Association of British Neurologists	Consider: Children/ adolescents Pregnancy Elderly In particular use of this drug in patients with intellectual disability (ID) and impact of such a drug on those with known mental health disorders.	Thank you for your comment. No action required.
Other considerations	Arvelle Therapeutics UK	There are no additional issues to comment on.	Thank you for your comment. No action required.
Innovation	Arvelle Therapeutics UK	Despite a number of currently approved antiepileptic drugs, more than 30% of patients (particularly those with focal seizures) do not achieve seizure freedom despite treatment with multiple ASMs with the probability of achieving seizure freedom diminishing substantially with each additional attempt at an ASM regimen. Cenobamate, with a novel dual mechanism of action, has demonstrated very high responder rates and seizure freedom rates, and has the potential to offer new hope to patients suffering from treatment resistant epilepsy. In clinical trials, cenobamate has demonstrated an ability to achieve seizure freedom in proportions that have not been attained with existing ASMs. Notably, 11.2% and 21.1% of patients treated with cenobamate 200mg and 400mg respectively achieved freedom from seizures compared with 1% for placebo.	Thank you for your comment. No action required.

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		Data from long-term, open-label extension studies demonstrate high retention rates and efficacy with approximately 24% of patient's seizure free for at least 12 months after five years of treatment. These are among the highest reported in the published literature.	
	Association of British Neurologists	Yes although other Na channel blockers exist this does appear to be a step change. Important for committee to do in depth safety profile given at present relatively small volume of data.	Thank you for your comment. No action required.
	Epilepsy Action	Cenobamate has potential as an adjunctive treatment of focal onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least two epilepsy medicines. It would provide an alternate treatment option for patients with uncontrolled epilepsy. Any potential new treatment for people with uncontrolled epilepsy is welcome, and the drug could be a very useful addition where none of the currently licensed drugs have been efficacious. • Krauss G, Klein P, Brandt C et al. Safety and efficacy of adjuvant cenobamate (YKP3089) in patients with uncontrolled focal seizures: A multicentre, double-blind, randomised, placebo-controlled, dose response trials. *Lancet Neurol*. 2020;19(1):38-48. • Arvelle Therapeutics website. Available at: https://www.arvelletx.com/. Accessed January 2020. • Chung SS, Krauss G, French J et al. Efficacy and tolerability of YKP3089 in patients with partial-onset seizures: Results of a phase 2 randomized, double-blind, placebo controlled study. *Epilepsy Curr*. 2014;14(suppl 1):438. Abstract 3.306. Available at: https://journals.sagepub.com/doi/pdf/10.5698/1535-7511-14.s1.1 Accessed January 2020.	Thank you for your comment. No action required.

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		• French JA, Chung SS, Krauss GL et al. Long-term safety of adjunctive cenobamate in patients with uncontrolled focal seizures: open label extension of a randomized clinical study. Presented at the SK life science AES Special Scientific Exhibit and Posters, December 8, 2019 Baltimore MD • Klein P, Krauss GL, Aboumatar S et al. Long-term efficacy and safety of adjunctive cenobamate in patients with uncontrolled focal seizures: open label extension of a randomized clinical study. Abstract presented at the SK life science AES Special Scientific Exhibit and Posters, December 8, 2019 Baltimore MD.	
Questions for consultation	Arvelle Therapeutics UK	NICE should not consider reviewing this drug within its ongoing update of NICE CG137. The update to the guideline is not anticipated to commence until June 2021. This appraisal should be done as soon as possible. As reported in the background information, more than a third of patients are treatment resistant with the probability of achieving seizure freedom diminishing substantially with each additional attempt at an ASM regimen. This demonstrates a significant unmet within focal-onset epilepsy and the urgent need for further treatment options. Due to the additional risk of death and the morbidity associated with uncontrolled seizures, cenobamate could address a large and urgent clinical unmet need and reduce the number of patients with uncontrolled epilepsy. Therefore, the appraisal of cenobamate should be prioritised ahead of the scheduled guideline review. There is no evidence to suggest that cenobamate is more clinically or cost effective in any subgroups.	Thank you for your comment. NICE schedules technology appraisals so that guidance to the NHS is timely.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope:

GSK, Eisai, Pfizer