NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cenobamate for focal onset seizures in epilepsy [ID1553]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cenobamate for focal onset seizures in epilepsy [ID1553]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document** from Arvelle Therapeutics

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Eisai
   b. ILAE British Chapter

4. **Comments on the Appraisal Consultation Document received through the NICE website**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Cenobamate for treating focal onset epilepsy

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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 number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	NICE	Medicines and Prescribing Team, Centre for Guidelines, NICE	Recommendations What is meant by 'managed in tertiary care'? Does this mean that tertiary care will need to continue to prescribe and supply cenobamate after it has been started or does it mean that tertiary care will need to continue to monitor cenobamate treatment but they could transfer the prescribing to primary or secondary care once the person is stabilised? This is something that may cause some confusion in practice regarding who takes responsibility for continued prescribing and could lead to differences in practices across the NHS. Could it be clarified what is meant by managed. Marketing authorisation indication Regarding the marketing authorisation for cenobamate. The marketing authorisation state's 'treatment with at least 2 anti-epileptic medicines' not 'a history of treatment with at least 2 anti-epileptic medicines.' See the SPC on the MHRA website here: https://products.mhra.gov.uk/search/?search=cenobamate&page=1&doc=Spc&rerouteType=0 People with drug-resistant epilepsy have limited treatment options The NICE guideline gives different recommendations on antiseizure medicines for first-line treatment and adjunctive treatments depending on childbearing potential. So, there are recommendations for women and girls of childbearing potential and recommendations for boys, men and women who are not of childbearing potential. In section 3.2 on current clinical management and treatment options can something be added to highlight this.	Please see the updated recommendations in section 1.1 of the final appraisal document. Please see the updated marketing authorisation in section 2.1 of the final appraisal document. Additional guidance on use of sodium valproate has been referenced in section 3.2 of the final appraisal document.

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			Cenobamate should be used as a third-line add-on therapy in tertiary care to establish evidence about its long-term effectiveness and safety With regards to the point raised in section 3.3 on the marketing authorisation and that it could be open to interpretation to perceive to mean it could be used first-line if 2 initial drugs are not tolerated; the marketing authorisation includes the wording 'for the adjunctive treatment' (i.e. it is licensed as an 'add on' treatment). It is not licensed to be used as monotherapy.	The committee noted that the original wording of the marketing authorisation could be interpreted as being used as a 'first-line' adjunctive treatment.
2	Professional group	ILAE British Chapter	We are concerned about the statement that intends to limit the initiation and monitoring of cenobamate to "tertiary epilepsy specialists"". It is not clear, on a UK basis how a tertiary epilepsy specialist is defined It does not take a super-specialist to identify that a patient meets ILAE criteria for drug refractory epilepsy, this is a common competence, seen in all neurologists and other epilepsy specialists who care for people with epilepsy. There are big differences in the structure of care across the UK which means that it is harder for some people to be referred to a tertiary epilepsy specialist. We fear that barriers to care, such as this will disproportionately affect people from under privileged areas, people who do not have English as a first language, and people with intellectual disability. We agree that correct supervision of patients starting cenobamate is laudable and that people prescribing this should have access to sufficient training and peer-support that they are working at the level of an epilepsy specialist.	Please see the updated recommendations in section 1.1 of the final appraisal document. In its updated recommendation, the committee considered that its recommendation of requiring referral to a tertiary epilepsy service would not constitute a barrier that would lead to a disproportionate effect on people protected by the equality legislation than on the wider population. The Committee had due regard for the impact of the guidance on patients from under privileged areas, people who do not have English as a first language, and people with intellectual disability.
3	Comparator company	Eisai Limited	Eisai (marketing authorisation holders of perampanel) would like to make the following clarifications on the description of perampanel within the cenobamate appraisal consultation document.	Please see the updated description in section 3.2 of the final appraisal document. Please note that NICE CG137

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			Page 6, lines 6-7 of the ACD states “Brivaracetam acetate and perampanel may also be offered at third line.” This interpretation and statement about perampanel in the treatment pathway of focal onset seizures in epilepsy is not factually correct. Perampanel is indicated for adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 4 years and older [1]. Therefore, it can be used earlier in the treatment pathway for focal onset seizures at second-line (adjunctive), as per the terminology on slide 11 of the Public Committee Slides (NICE CG137 treatment pathway and cenobamate positioning). Eisai would kindly request that perampanel is accurately reflected in the treatment pathway for focal onset seizures as outlined in the cenobamate appraisal. The information on the NICE website for perampanel is extremely out of date and is not representative of the current indication and clinical evidence base of perampanel. For context, perampanel received marketing authorisation in August 2012 [1], and is not included in the current NICE Clinical Guideline CG137 for epilepsies: diagnosis and management (dated January 2012) [2]. The NICE evidence summary ESNM7 for partial-onset seizures in epilepsy: perampanel as adjunctive treatment (dated December 2012) is also nine years out of date [3]. For further information, perampanel has a plethora of evidence to support its use as first/early add-on adjunctive therapy for focal onset seizures compared to different anti-seizure drugs [4, 5]. A real-world observational study (PERADON) demonstrated the effectiveness and safety of perampanel as early add-on treatment in patients with epilepsy and focal onset seizures in routine clinical practice [6]. Furthermore, the PERMIT study was the largest global pooled analysis of data from 44 real-world studies from 17 countries, in which people with epilepsy (focal and/or generalised) were treated with perampanel in clinical practice, demonstrating that perampanel is effective and generally well tolerated [7].	guideline is currently being updated and therefore this wording is not designed to provide an accurate representation of the expected treatment pathway.

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			References: [1] European Medicines Agency. EPAR for perampanel (FYCOMPA). https://www.ema.europa.eu/en/medicines/human/EPAR/fycompa Accessed September 2021. [2] NICE CG137. Epilepsies – Diagnosis and Management: https://www.nice.org.uk/guidance/cg137 Accessed September 2021. [3] NICE ESNM7. Partial-onset seizures in epilepsy: perampanel as adjunctive treatment: https://www.nice.org.uk/advice/esnm7/chapter/Overview Accessed September 2021. [4] Kim, Ji Hyun, et al. "First add-on perampanel for focal-onset seizures: An open-label, prospective study." Acta Neurologica Scandinavica 141.2 (2020): 132-140. [5] Santamarina, Estevo, et al. "Efficacy and tolerability of perampanel as a first add-on therapy with different anti-seizure drugs." Seizure 83 (2020): 48-56. [6] Jaramillo, Javier Abril, et al. "Effectiveness and safety of perampanel as early add-on treatment in patients with epilepsy and focal seizures in the routine clinical practice: Spain prospective study (PERADON)." Epilepsy & Behavior 102 (2020): 106655. [7] Villanueva, Vicente, et al. "PERMIT study: a global pooled analysis study of the effectiveness and tolerability of perampanel in routine clinical practice." Journal of Neurology (2021): 1-21.	
4	Company	Arvelle Therapeutics, a Angelini Pharma Group Company	<u>The wording of the recommendation given in Section 1.1 of the ACD is does not align with existing guidance and would unduly restrict the use of cenobamate.</u> In Section 1.1 of the ACD, recommendations state that treatment with cenobamate is recommended only if 'it is used as a third-line add-on treatment, and treatment is started and managed in tertiary care'. We welcome the positive recommendation for cenobamate in the positioning that the Committee have stipulated.[1] However, the specific wording of positioning is unclear and not aligned to existing clinical guidelines. Additionally, the stipulation that treatment should be started and managed in tertiary care will unduly restrict the use of cenobamate.	Please see the updated recommendations in section 1.1 of the final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			With reference to positioning, this is open to confusion as 'third-line add-on' does not align to existing NICE guidance. In NICE clinical guideline 137 (CG137), the term 'adjunctive' is used in preference of 'add-on'; the term adjunctive is known amongst patients with, carers of patients with and clinicians specialising in focal onset seizures (FOS).[2] Therefore, it would be appropriate to refer to adjunctive treatment in the recommendation. Moreover, 'third-line add-on' is not referenced in NICE CG137, so it's use is open to interpretation. The position described in the ACD aligns to the recommendation that 'if adjunctive treatment is ineffective or not tolerated, [patients should] discuss with, or refer to, a tertiary epilepsy specialist'.[1] Other treatments that can then be considered by the tertiary epilepsy specialist are listed in the clinical guidance. For this reason, it would be more appropriate to align to CG137 and explicitly state the requirements of prior treatment to enable a patient to be eligible for treatment with cenobamate (i.e., at least one prior adjunctive anti-seizure medicine [ASM] is ineffective or not tolerated). With reference to the management of patients with FOS, the restriction that treatment should be initiated and managed in tertiary care will reduce uptake of cenobamate and limit the number of patients who would be able to benefit from its recommendation. Additionally, the suggestion that patients treated with cenobamate should be managed in tertiary care is not aligned to existing guidance (NICE CG317) which states that patients should 'discuss with, or refer to, a tertiary epilepsy specialist' in the event that adjunctive therapy is not ineffective or not tolerated.[2]. Requiring patients who are on a stable maintenance dose of cenobamate to frequently return to tertiary care to manage their regular medication would be an unnecessary burden to the tertiary care setting. There are currently long waiting times to access regular appointments in tertiary care and, given the ongoing COVID situation, the burden to tertiary care is growing. It would also pose an additional burden to patients delay their access to treatment. For these reasons, it would be more appropriate to state that treatment should not be initiated in primary care, such that patients can be prescribed cenobamate with tertiary epilepsy specialists either in hospital or an	

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			epilepsy clinic, and that initiation of treatment is overseen by these specialists. Given the above, we kindly request that Section 1.1 of the ACD is revised to read: "Cenobamate is recommended as an option for adjunctive treatment of focal onset seizures with or without secondary generalised seizures in adults with epilepsy that has not been adequately controlled with at least 2 antiseizure medicines. It is recommended only if: • At least one prior adjunctive treatment (see NICE CG 137 recommendation 1.9.3.4) is ineffective or not tolerated. Treatment is initiated after discussion with, or after referral to, a tertiary epilepsy specialist or a neurologist with a subspecialised interest in epilepsy."	
5	Company	Arvelle Therapeutics, a Angelini Pharma Group Company	The existing NICE CG137 is not appropriately reflected in the appraisal consultation document (ACD) There are a number of references to NICE CG137 in the ACD. However, the terminology used in the ACD is different to the terminology used in NICE CG137. For example, the term 'add-on' is not used in NICE CG137, with 'adjunctive' used instead.2 Therefore, we kindly ask that the ACD is aligned to NICE CG137 and, more specifically, that: 1. The text "if add-on treatment is ineffective, the guideline recommends referral to a tertiary epilepsy specialist and third-line add-on therapy (addition of a third drug) with eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin or zonisamide" in Section 3.2 of the ACD is changed to the following: "If adjunctive treatment is ineffective, the guideline recommends discussion with, or referral to, a tertiary epilepsy specialist who may consider treatment with eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin or zonisamide."	Please note that the term 'adjunctive' has been replaced with 'add-on' after consultation with all stakeholders as part of the CG137 guideline update in line with NICE's commitment for accessible terminology. Please note that all references to lines of treatment have been minimised to allow for more accuracy in alignment with the anticipated CG137 guideline update wording and treatment pathway.

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			2. The text "Cenobamate is not currently an attractive option as an early second-line add-on treatment because of its moderate risk of adverse effects" in Section 3.3 of the ACD is changed to the following: "Cenobamate is not currently an attractive option for patients on their first adjunctive treatment because of its moderate risk of adverse effects" 3. The wording throughout the ACD be changed from 'third-line add-on' to 'third-line, adjunctive'.	
6	Company	Arvelle Therapeutics, a Angelini Pharma Group Company	The marketing authorisation is not appropriately described In Section 3.3, the marketing authorisation for cenobamate is described as "people with a history of treatment with at least 2 antiseizure medicines without gaining control of the epilepsy."1 However, this does not correspond to the full marketing authorisation outlined in the NICE scope where cenobamate is specifically indicated for adjunctive treatment.3 Therefore, we ask that the wording is changed to read: "The marketing authorisation for cenobamate is 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."	Please see the updated section 3.3 of the final appraisal document.
7	Company	Arvelle Therapeutics, a Angelini Pharma Group Company	<u>Not all costs considered have been characterised</u> In Section 3.19 of the ACD, it is stated that "*the company categorised resource use based on type of seizures (focal aware, focal awareness impaired, focal-to-bilateral tonic-clonic) and estimated hospitalisations and other costs per seizure*".[1] However, this suggests that fewer costs and resource implications of seizures were considered. The company estimated additional epilepsy event management costs in addition to hospitalisation, such as costs by initial presentation to health care services and acute cost of treatments to ensure all important costs are appropriately captured in the response. To ensure it is accurately characterised which costs were considered by the company, we ask that the wording be amended as follows: "*The company categorised resource use based on type of*	Please see the updated section 3.19 of the final appraisal document.

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			seizures (focal aware, focal awareness impaired, focal-to-bilateral tonic-clonic) and estimated hospitalisations, costs of initial presentation to health care services, acute costs of treatments and other costs per seizure"	
8	Company	Arvelle Therapeutics, a Angelini Pharma Group Company	<u>Improvements in seizure control are described to be only meaningful when patients achieve near seizure freedom</u> In Section 3.6 of the ACD, it is stated that: "*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 meaningful to patients.*"[1] To avoid misinterpretation, we request that Section 3.6 of the ACD is revised as follows: "*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 <u>as</u> meaningful to patients <u>as near seizure freedom or seizure freedom</u>*."	Please see the updated section 3.6 of the final appraisal document.
9	Company	Arvelle Therapeutics, a Angelini Pharma Group Company	In Section 3.15 of the ACD, it is stated that "*transition probabilities for comparators depended on cenobamate transitions and hazard ratios from the ERG network meta-analyses results*."[1] The company believes the original statement is a typographical error, as the output from the Evidence Review Group (ERG) network meta-analysis (NMA) was the relative risk of comparator treatments relative to cenobamate. Therefore, company asks that the above text be changed to the following: "*Transition probabilities for comparators depended on cenobamate transitions and risk ratios from the ERG network meta-analyses results*."[4]	Please see the updated wording of section 3.15 of the final appraisal document.
10	Company	Arvelle Therapeutics,	In Section 3.4 of the ACD, it is stated that: "The NICE scope specified relevant comparators as established add-on treatments (…) It stated	Please note that the committee remit is to appraise

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		a Angelini Pharma Group Company	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."1 In the response to the draft scope and the decision problem section of the company submission, the company provided its reason for the exclusion of ASM therapies from the economic analysis (i.e., comparators were rarely used, already used as a background therapy rather than an adjunctive ASM or that the therapy was already used in an earlier line of treatment). Therefore, the justification for the exclusion of some of the proposed comparators by NICE was that they were not relevant to the third-line, adjunctive setting. Therefore, the company asks that the above text be changed to the following: 'The NICE scope specified relevant comparators as established add-on treatments…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 the third-line, adjunctive setting in UK clinical practice.'	
11	Company	Arvelle Therapeutics, a Angelini Pharma Group Company	In Section 3.5 of the ACD, it is stated that: "*25.5% of people 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." It is not stated that the 25.5% of people achieving at least a 50% reduction in seizure frequency were in the placebo arm of the C017 study*."[1,5] Therefore, the company asks that the above text be changed to the following: "*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 cenobamate arms, respectively*."[5]	Please see the updated section 3.5 of the final appraisal document.

NICE National Institute for Health and Care Excellence

Cenobamate for focal onset seizures in epilepsy [ID1553]

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 September 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Arvelle Therapeutics, a Angelini Pharma Group Company
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links to disclose
Name of commentator person completing form:	[redacted]

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NICE National Institute for Health and Care Excellence

Cenobamate for focal onset seizures in epilepsy [ID1553]

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 September 2021. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Are the provisional recommendations a sound and suitable basis for guidance to the NHS?	
1	<u>The wording of the recommendation given in Section 1.1 of the ACD is does not align with existing guidance and would unduly restrict the use of cenobamate.</u> In Section 1.1 of the ACD, recommendations state that treatment with cenobamate is recommended only if 'it is used as a third-line add-on treatment, and treatment is started and managed in tertiary care'. We welcome the positive recommendation for cenobamate in the positioning that the Committee have stipulated.[1] However, the specific wording of positioning is unclear and not aligned to existing clinical guidelines. Additionally, the stipulation that treatment should be started and managed in tertiary care will unduly restrict the use of cenobamate. With reference to positioning, this is open to confusion as 'third-line add-on' does not align to existing NICE guidance. In NICE clinical guideline 137 (CG137), the term 'adjunctive' is used in preference of 'add-on'; the term adjunctive is known amongst patients with, carers of patients with and clinicians specialising in focal onset seizures (FOS).[2] Therefore, it would be appropriate to refer to adjunctive treatment in the recommendation. Moreover, 'third-line add-on' is not referenced in NICE CG137, so it's use is open to interpretation. The position described in the ACD aligns to the recommendation that 'if adjunctive treatment is ineffective or not tolerated, [patients should] discuss with, or refer to, a tertiary epilepsy specialist'.[1] Other treatments that can then be considered by the tertiary epilepsy specialist are listed in the clinical guidance. For this reason, it would be more appropriate to align to CG137 and explicitly state the requirements of prior treatment to enable a patient to be eligible for treatment with cenobamate (i.e., at least one prior adjunctive anti-seizure medicine [ASM] is ineffective or not tolerated). With reference to the management of patients with FOS, the restriction that treatment should be initiated and managed in tertiary care will reduce uptake of cenobamate and limit the number of patients who would be able to benefit from its recommendation. Additionally, the suggestion that patients treated with cenobamate should be managed in tertiary care is not aligned to existing guidance (NICE CG317) which states that patients should 'discuss with, or refer to, a tertiary epilepsy specialist' in the event that adjunctive therapy is not ineffective or not tolerated.[2]. Requiring patients who are on a stable maintenance dose of cenobamate to frequently return to tertiary care to manage their regular medication would be an unnecessary burden to the tertiary care setting. There are currently long waiting times to access regular appointments in tertiary care and, given the ongoing COVID situation, the burden to tertiary care is growing. It would also pose an additional burden to patients delay their access to treatment. For these reasons, it would be more appropriate to state that treatment should not be initiated in primary care, such that patients can be prescribed cenobamate with tertiary epilepsy specialists either in hospital or an epilepsy clinic, and that initiation of treatment is overseen by these specialists. Given the above, we kindly request that Section 1.1 of the ACD is revised to read: "Cenobamate is recommended as an option for adjunctive treatment of focal onset seizures with or without secondary generalised seizures in adults with epilepsy that has not been adequately controlled with at least 2 antiseizure medicines. It is recommended only if: • At least one prior adjunctive treatment (see NICE CG 137 recommendation 1.9.3.4) is ineffective or not tolerated. • Treatment is initiated after discussion with, or after referral to, a tertiary epilepsy specialist or a neurologist with a subspecialised interest in epilepsy."

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2	<u>The existing NICE CG137 is not appropriately reflected in the appraisal consultation document (ACD)</u> There are a number of references to NICE CG137 in the ACD. However, the terminology used in the ACD is different to the terminology used in NICE CG137. For example, the term 'add-on' is not used in NICE CG137, with 'adjunctive' used instead.[2] Therefore, we kindly ask that the ACD is aligned to NICE CG137 and, more specifically, that: 1. The text "*if add-on treatment is ineffective, the guideline recommends referral to a tertiary epilepsy specialist and third-line add-on therapy (addition of a third drug) with eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin or zonisamide*" in Section 3.2 of the ACD is changed to the following: "*If adjunctive treatment is ineffective, the guideline recommends discussion with, or referral to, a tertiary epilepsy specialist who may consider treatment with eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin or zonisamide.*" 2. The text "*Cenobamate is not currently an attractive option as an early second-line add-on treatment because of its moderate risk of adverse effects*" in Section 3.3 of the ACD is changed to the following: "*Cenobamate is not currently an attractive option for patients on their first adjunctive treatment because of its moderate risk of adverse effects*" 3. The wording throughout the ACD be changed from 'third-line add-on' to 'third-line, adjunctive'.
Has all of the relevant evidence been taken into account?	
3	<u>The marketing authorisation is not appropriately described</u> In Section 3.3, the marketing authorisation for cenobamate is described as "*people with a history of treatment with at least 2 antiseizure medicines without gaining control of the epilepsy*."[1] However, this does not correspond to the full marketing authorisation outlined in the NICE scope where cenobamate is specifically indicated for adjunctive treatment.[3] Therefore, we ask that the wording is changed to read: "*The marketing authorisation for cenobamate is 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.*"
4	<u>Not all costs considered have been characterised</u> In Section 3.19 of the ACD, it is stated that "*the company categorised resource use based on type of seizures (focal aware, focal awareness impaired, focal-to-bilateral tonic-clonic) and estimated hospitalisations and other costs per seizure*".[1] However, this suggests that fewer costs and resource implications of seizures were considered. The company estimated additional epilepsy event management costs in addition to hospitalisation, such as costs by initial presentation to health care services and acute cost of treatments to ensure all important costs are appropriately captured in the response. To ensure it is accurately characterised which costs were considered by the company, we ask that the wording be amended as follows: "*The company categorised resource use based on type of seizures (focal aware, focal awareness impaired, focal-to-bilateral tonic-clonic) and estimated hospitalisations, costs of initial presentation to health care services, acute costs of treatments and other costs per seizure*"

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Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	
5	Improvements in seizure control are described to be only meaningful when patients achieve near seizure freedom In Section 3.6 of the ACD, it is stated that: "*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 meaningful to patients.*"[1] To avoid misinterpretation, we request that Section 3.6 of the ACD is revised as follows: "*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 near seizure freedom or seizure freedom*."
Factual inaccuracies	
7	In Section 3.15 of the ACD, it is stated that "*transition probabilities for comparators depended on cenobamate transitions and hazard ratios from the ERG network meta-analyses results*."[1] The company believes the original statement is a typographical error, as the output from the Evidence Review Group (ERG) network meta-analysis (NMA) was the relative risk of comparator treatments relative to cenobamate. Therefore, company asks that the above text be changed to the following: "*Transition probabilities for comparators depended on cenobamate transitions and risk ratios from the ERG network meta-analyses results*."[4]
8	In Section 3.4 of the ACD, it is stated that: "*The NICE scope specified relevant comparators as established add-on treatments (…) 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*."[1] In the response to the draft scope and the decision problem section of the company submission, the company provided its reason for the exclusion of ASM therapies from the economic analysis (i.e., comparators were rarely used, already used as a background therapy rather than an adjunctive ASM or that the therapy was already used in an earlier line of treatment). Therefore, the justification for the exclusion of some of the proposed comparators by NICE was that they were not relevant to the third-line, adjunctive setting. Therefore, the company asks that the above text be changed to the following: *'The NICE scope specified relevant comparators as established add-on treatments…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 the third-line, adjunctive setting in UK clinical practice*.'
9	In Section 3.5 of the ACD, it is stated that: "*25.5% of people 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." It is not stated that the 25.5% of people achieving at least a 50% reduction in seizure frequency were in the placebo arm of the C017 study*."[1,5] Therefore, the company asks that the above text be changed to the following: "*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 cenobamate arms, respectively*."[5]

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Cenobamate for focal onset seizures in epilepsy [ID1553]

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Checklist for submitting comments

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REFERENCES

1. NICE - The National Institute for Health and Care Excellence. Appraisal consultation document: Cenobamate for treating focal onset seizures in epilepsy. Published online 2021. https://www.nice.org.uk/guidance/gid-ta10661/documents/129

2. NICE. Epilepsies: diagnosis and management. Published February 11, 2020. Accessed April 23, 2020. https://www.nice.org.uk/guidance/cg137/

3. NICE - The National Institute for Health and Care Excellence. Health Technology Appraisal: Cenobamate for adjunctive treatment of focal epilepsy Final scope. Published online 2020. https://www.nice.org.uk/guidance/gid-ta10661/documents/final-scope

4. NICE - The National Institute for Health and Care Excellence. Cenobamate for focal onset seizures in epilepsy [ID1553]: Committee Papers. Published online 2021. https://www.nice.org.uk/guidance/gid-ta10661/documents/committee-papers

5. Krauss GL, Klein P, Brandt C, et al. 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;19(1):38-48. doi:10.1016/S1474-4422(19)30399-0

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eisai Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Eisai (marketing authorisation holders of perampanel) would like to make the following clarifications on the description of perampanel within the cenobamate appraisal consultation document. Page 6, lines 6-7 of the ACD states “Brivaracetam acetate and perampanel may also be offered at third line.” This interpretation and statement about perampanel in the treatment pathway of focal onset seizures in epilepsy is not factually correct. Perampanel is indicated for adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 4 years and older [1]. Therefore, it can be used earlier in the treatment pathway for focal onset seizures at second-line (adjunctive), as per the terminology on slide 11 of the Public Committee Slides (NICE CG137 treatment pathway and cenobamate positioning). Eisai would kindly request that perampanel is accurately reflected in the treatment pathway for focal onset seizures as outlined in the cenobamate appraisal. The information on the NICE website for perampanel is extremely out of date and is not representative of the current indication and clinical evidence base of perampanel. For context, perampanel received marketing authorisation in August 2012 [1], and is not included in the current NICE Clinical Guideline CG137 for epilepsies: diagnosis and management (dated January 2012) [2]. The NICE evidence summary ESNM7 for partial-onset seizures in epilepsy: perampanel as adjunctive treatment (dated December 2012) is also nine years out of date [3]. For further information, perampanel has a plethora of evidence to support its use as first/early add-on adjunctive therapy for focal onset seizures compared to different anti-seizure drugs [4, 5]. A real-world observational study (PERADON) demonstrated the effectiveness and safety of perampanel as early add-on treatment in patients with epilepsy and focal onset seizures in routine clinical practice [6]. Furthermore, the PERMIT study was the largest global pooled analysis of data from 44 real-world studies from 17 countries, in which people with epilepsy (focal and/or generalised) were treated with perampanel in clinical practice, demonstrating that perampanel is effective and generally well tolerated [7]. References: [1] European Medicines Agency. EPAR for perampanel (FYCOMPA). https://www.ema.europa.eu/en/medicines/human/EPAR/fycompa Accessed September 2021. [2] NICE CG137. Epilepsies – Diagnosis and Management: https://www.nice.org.uk/guidance/cg137 Accessed September 2021. [3] NICE ESNM7. Partial-onset seizures in epilepsy: perampanel as adjunctive treatment: https://www.nice.org.uk/advice/esnm7/chapter/Overview Accessed September 2021. [4] Kim, Ji Hyun, et al. "First add-on perampanel for focal-onset seizures: An open-label, prospective study." Acta Neurologica Scandinavica 141.2 (2020): 132-140. [5] Santamarina, Estevo, et al. "Efficacy and tolerability of perampanel as a first add-on therapy with different anti-seizure drugs." Seizure 83 (2020): 48-56. [6] Jaramillo, Javier Abril, et al. "Effectiveness and safety of perampanel as early add-on treatment in patients with epilepsy and focal seizures in the routine clinical practice: Spain prospective study (PERADON)." Epilepsy & Behavior 102 (2020): 106655. [7] Villanueva, Vicente, et al. "PERMIT study: a global pooled analysis study of the effectiveness and tolerability of perampanel in routine clinical practice." Journal of Neurology (2021): 1-21.
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6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**ILAE British Chapter**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Nil**]
Name of commentator person completing form:	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned about the statement that intends to limit the initiation and monitoring of cenobamate to "tertiary epilepsy specialists". This would have significant resource implications for already over-stretched specialist epilepsy services It is not clear, on a UK basis how a tertiary epilepsy specialist is defined. We do not feel that it requires a super-specialist to identify that a patient meets ILAE criteria for drug refractory epilepsy. This is a common competency, seen in all neurologists and other epilepsy specialists who prescribe and care for people with epilepsy. There are significant differences in the structure of care across the UK which means that it is harder for some people to be referred to a "tertiary epilepsy specialist". We fear that barriers to care, such as this will disproportionately affect people from under-privileged areas, people who do not have English as a first language and people with intellectual disability.
2	We agree that correct supervision of patients starting cenobamate is laudable and that health professionals prescribing cenobamate should have the clinical competency to identify and manage drug resistant epilepsy, access any necessary training and have appropriate peer-support that facilitates safe and appropriate prescribing.
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Insert extra rows as needed

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	Medicines and Prescribing Team, Centre for Guidelines, NICE
Location	
Conflict	
Notes	
Comments on the ACD:	

Recommendations

What is meant by ‘managed in tertiary care’? Does this mean that tertiary care will need to continue to prescribe and supply cenobamate after it has been started or does it mean that tertiary care will need to continue to monitor cenobamate treatment but they could transfer the prescribing to primary or secondary care once the person is stabilised? This is something that may cause some confusion in practice regarding who takes responsibility for continued prescribing and could lead to differences in practices across the NHS. Could it be clarified what is meant by managed.

Marketing authorisation indication

Regarding the marketing authorisation for cenobamate. The marketing authorisation state’s ‘treatment with at least 2 anti-epileptic medicines’ not ‘a history of treatment with at least 2 anti-epileptic medicines.’ See the SPC on the MHRA website here: https://products.mhra.gov.uk/search/?search=cenobamate&page=1&doc=Spc&rerouteType=0

People with drug-resistant epilepsy have limited treatment options

The NICE guideline gives different recommendations on antiseizure medicines for first-line treatment and adjunctive treatments depending on childbearing potential. So, there are recommendations for women and girls of childbearing potential and recommendations for boys, men and women who are not of childbearing potential. In section 3.2 on current clinical management and treatment options can something be added to highlight this.

Cenobamate should be used as a third-line add-on therapy in tertiary care to establish evidence about its long-term effectiveness and safety

With regards to the point raised in section 3.3 on the marketing authorisation and that it could be open to interpretation to perceive to mean it could be used first-line if 2 initial drugs are not tolerated; the marketing authorisation includes the wording 'for the adjunctive treatment’ (i.e. it is licensed as an 'add on' treatment). It is not licensed to be used as monotherapy.