IQWiG Reports – Commission No. A21-78

# Cenobamate (epilepsy) –

## Benefit assessment according to §35a Social Code Book V[1]

**Extract**

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Cenobamat (Epilepsie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 August 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

# Publishing details

**Publisher**
Institute for Quality and Efficiency in Health Care

**Topic**
Cenobamate (epilepsy) – Benefit assessment according to §35a Social Code Book V

**Commissioning agency**
Federal Joint Committee

**Commission awarded on**
31 May 2021

**Internal Commission No.**
A21-78

**Address of publisher**
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**Keywords:** Cenobamate, Epilepsies – Partial, Seizures, Benefit Assessment

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

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**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AED | antiepileptic drug |
| EMA | European Medicines Agency |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SPC | Summary of Product Characteristics |
| SGB | Sozialgesetzbuch (Social Code Book) |

# 2 Benefit assessment

## 2.1 Executive summary of the benefit assessment

### Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug cenobamate. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 May 2021.

### Research question

Aim of the present report is the assessment of the added benefit of cenobamate in comparison with the appropriate comparator therapy (ACT) for the adjunctive treatment of focal-onset seizures with or without secondary generalization in patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 antiepileptic drugs (AEDs).

The research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of cenobamate:

| Therapeutic indication | ACT[a] |
|---|---|
| Adjunctive treatment of focal-onset seizures with or without secondary generalization in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 antiepileptic drugs. | Patient-specific antiepileptic adjunctive treatment, if medically indicated and if no pharmacoresistance (in the sense of an insufficient response), intolerance or contraindication is known, with one of the following drugs:<br>brivaracetam or eslicarbazepine or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or perampanel or pregabalin or topiramate or valproic acid or zonisamide.[b] |
| a. Presentation of the respective ACT specified by the G-BA.<br>b. Treatment is to be chosen by the doctor depending on the basic and prior therapy/therapies under consideration of the reason for treatment switching and any accompanying adverse events.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | |

The company followed the G-BA's specification on the ACT. At the same time, the company stated that in its opinion best supportive care was the ACT in the present therapeutic indication of treatment-resistant epilepsy. This would have been implemented in the placebo-controlled study YKP3089C017 (hereinafter referred to as study C017) conducted by it.

The assessment was conducted in comparison with the G-BA's ACT and by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. A minimum duration of the maintenance therapy of 12 weeks was assumed.

**Results**

Since there are no studies of direct comparison, the company presented an adjusted indirect comparison based on randomized controlled trials (RCTs).

With its information retrieval, the company identified 1 RCT with cenobamate as intervention (C017) and 56 RCTs on drugs specified by the G-BA within the framework of the ACT. From this study pool, it identified 10 studies for the comparator side it considered to be sufficiently similar to the cenobamate study C017. Based on these studies, the company conducted an adjusted indirect comparison using the common comparator "basic therapy + placebo".

The indirect comparison presented by the company is unsuitable for the benefit assessment, i.e. for the following reasons in particular:

- < 2 previous antiepileptic therapies in several of the included studies
- No approval-compliant titration of cenobamate in study C017
- ACT not implemented in the comparator studies
- Insufficient similarity between C017 on cenobamate and most of the studies on the comparator therapy

***Suitability of the C017 study***

Due to the following aspects, the C017 study is unsuitable for the benefit assessment of cenobamate:

*Prior therapies*

Cenobamate is approved for the adjunctive treatment of focal-onset seizures with or without secondary generalization in adult patients whose epilepsy has not been adequately controlled despite a history of treatment with at least 2 AEDs. However, the C017 study also included patients with < 2 previous antiepileptic therapies. As treatment successes in treatment-refractory patients strongly depend on the number of prior therapies, the results of the C017 study might be relevantly influenced by the inclusion of patients who have had only 1 AED in the prior therapy.

*Titration not according to approval*

In study C017, cenobamate was titrated to the target dose much more rapidly than recommended in the Summary of Product Characteristics (SPC). However, titrating cenobamate too quickly may not only lead to an overestimation of side effects, but possibly also to an overestimation of seizure reduction. The transferability of the results of the C017 study to patients in clinical practice who are treated according to the approval is thus considerably limited.

***Suitability of the comparator studies for the indirect comparison***

The company included 10 studies it considered comparable with study C017 in a study pool for an indirect comparison versus cenobamate. Each of these 10 studies comprised 1 study on brivaracetam (1254), gabapentin (Yamauchi 2006) and lamotrigine and pregabalin (A008112), 2 studies each on lacosamide (0667, 0755) and perampanel (304, 335) and 3 studies on levetiracetam (N01221, N132, Shorvon 2000). The respective drug was compared with placebo in all 10 studies, in each case as adjunctive treatment to ongoing basic therapy.

*Prior therapies*

As in study C017, 4 of the comparator studies (1254 [brivaracetam], Yamauchi 2006 [gabapentin], N01221 and Shorvon 2000 [levetiracetam]) included patients who had been treated with < 2 antiepileptic therapies prior to study entry.

*Similarity of disease severity*

Under the aspect of disease severity, the frequency of seizures at baseline and the duration of the disease were considered as examples. It was shown that data on these aspects were not available for all studies of the comparator side and that some studies were insufficiently similar to study C017.

Complete data on seizure frequency are lacking for 4 studies (N01221, N132 and Shorvon 2000 [levetiracetam]; 335 [perampanel]). Appropriate assessment of the similarity regarding the approval population of C017 is thus impossible. At the same time, the patients in the studies N01221 (levetiracetam) and 335 (perampanel) have notably shorter disease durations compared to the total population of the C017 study. It can be assumed that patients in these two studies had less severe disease than in the other studies. Data on the disease duration are not available for study N132 (levetiracetam).

*Implementation of the ACT*

For the implementation of the ACT, it would have been necessary to prove that in each case, the adjunctive treatment was the individually optimized treatment for the patients included in the studies. However, in none of the studies on the comparator therapy submitted by the company was the therapy chosen according to individual criteria such as prior therapies, side effects and contraindications. Rather, all patients were treated with previously determined doses of the respective drug to be investigated, irrespective of these aspects. Therefore, the ACT was not appropriately implemented in any of the studies identified by the company for the comparator therapy.

Overall, due to the described aspects regarding the similarity of the study populations and the implementation of the ACT, the adjusted indirect comparison of the company is not suitable for deriving conclusions on the added benefit of cenobamate versus the ACT.

**Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]**

Based on the results presented, probability and extent of the added benefit of the drug cenobamate in comparison with the ACT are assessed as follows:

An added benefit of cenobamate is not proven because the company did not present any suitable data.

Table 3 shows a summary of probability and extent of the added benefit of cenobamate.

Table 3: Cenobamate – probability and extent of added benefit

| Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|
| Adjunctive treatment of focal-onset seizures with or without secondary generalization in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 antiepileptic drugs. | Patient-specific antiepileptic adjunctive treatment, if medically indicated and if no pharmacoresistance (in the sense of an insufficient response), intolerance or contraindication is known, with one of the following drugs:<br>brivaracetam or eslicarbazepine or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or perampanel or pregabalin or topiramate or valproic acid or zonisamide.[b] | Added benefit not proven |
| a. Presentation of the respective ACT specified by the G-BA.<br>b. Treatment is to be chosen by the doctor depending on the basic and prior therapy/therapies under consideration of the reason for treatment switching and any accompanying adverse events.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | | |

The G-BA decides on the added benefit.

## 2.2 Research question

Aim of the present report is the assessment of the added benefit of cenobamate in comparison with the ACT for the adjunctive treatment of focal-onset seizures with or without secondary

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

generalization in patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 AEDs.

The research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of cenobamate

| **Therapeutic indication** | **ACT**[a] |
|---|---|
| Adjunctive treatment of focal-onset seizures with or without secondary generalization in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 antiepileptic drugs. | Patient-specific antiepileptic adjunctive treatment, if medically indicated and if no pharmacoresistance (in the sense of an insufficient response), intolerance or contraindication is known, with one of the following drugs:<br>brivaracetam or eslicarbazepine or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or perampanel or pregabalin or topiramate or valproic acid or zonisamide.[b] |
| a. Presentation of the respective ACT specified by the G-BA.<br>b. Treatment is to be chosen by the doctor depending on the basic and prior therapy/therapies under consideration of the reason for treatment switching and any accompanying adverse events.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | |

The company followed the G-BA's specification on the ACT. At the same time, the company stated that in its opinion best supportive care was the ACT in the present therapeutic indication of treatment-resistant epilepsy. This would have been implemented in the placebo-controlled study YKP3089C017 (hereinafter referred to as study C017) conducted by it.

The assessment was conducted in comparison with the G-BA’s ACT and by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. A minimum duration of the maintenance therapy of 12 weeks was assumed. This concurs with the company’s inclusion criteria.

## 2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on erenumab (status: 7 April 2021)
- bibliographical literature search on cenobamate (last search on 7 April 2021)
- search in trial registries/trial results databases for studies on cenobamate (last search on 8 April 2021)
- search on the G-BA website for cenobamate (last search on 8 April 2021)
- bibliographical literature search on ACTs (last search on 7 April 2021)
- search in trial registries/trial results databases for studies on ACTs (last search on 8 April 2021)

- search on the G-BA website for ACTs (last search on 8 April 2021)

To check the completeness of the study pool:

- search in trial registries for studies on cenobamate (last search on 10 June 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

**Direct comparison**

There were no studies of direct comparisons of cenobamate in comparison with the G-BA's ACT. This concurs with the company's assessment.

**Indirect comparison**

Since there are no studies of direct comparison, the company presented an adjusted indirect comparison based on RCTs.

With its information retrieval, the company identified 1 RCT with cenobamate as intervention (C017) and 56 RCTs on drugs specified by the G-BA within the framework of the ACT for the comparator side. In a next step, the company checks the similarity of the comparator studies with study C017 with regard to effect modifiers (patient characteristics, intervention characteristics and study characteristics) and methodological factors (outcome characteristics). In doing so, it classified 10 studies that it considered sufficiently consistent with study C017 in the factors investigated as comparable with study C017; it classified 16 studies as potentially comparable, studies for which, in its opinion, the available information did not allow a conclusive assessment of the comparability, but did not rule this out either. The company assigned the studies it considered comparable to study pool 1 (n = 10), and assigned potentially comparable studies together with the studies it considered comparable to study pool 2 (n = 26).

Based on the studies from study pool 1, the company conducted an adjusted indirect comparison using the common comparator "basic therapy + placebo". It used the corresponding results for the derivation of the added benefit. In addition, the company conducted an indirect comparison with the studies from study pool 2 as sensitivity analysis.

Both indirect comparisons presented by the company are unsuitable for the benefit assessment, i.e. for the following reasons in particular:

- < 2 previous antiepileptic therapies in several of the included studies
- No approval-compliant titration of cenobamate in study C017
- ACT not implemented in the comparator studies
- Insufficient similarity between C017 on cenobamate and most of the studies on the comparator therapy

This is explained below.

***Suitability of the C017 study***

The C017 study [3] is a 4-arm, blinded, randomized phase 2 dose-ranging study, which is also the decisive approval study for cenobamate. Patients with focal-onset seizures whose focal epilepsy had been uncontrolled despite treatment with at least 1 AED within the last 2 years were included and randomly assigned to treatment with 100 mg, 200 mg, 400 mg cenobamate or to the placebo group in a 1:1:1:1 ratio. All patients received additional basic antiepileptic therapy.

Due to the following aspects, the data presented by the company on the C017 study are unsuitable for the benefit assessment of cenobamate:

*Inclusion criterion "number of prior therapies"*

Cenobamate is approved for the adjunctive treatment of focal-onset seizures with or without secondary generalization in adult patients whose epilepsy has not been adequately controlled despite a history of treatment with at least 2 AEDs. However, the inclusion criteria of the C017 study also allowed pretreatment with only 1 AED. According to data in the clinical study report (CSR), 17% of the patients in the 200 g cenobamate arm, 14% in the 400 mg cenobamate arm and 12% in the placebo arm of the C017 study had been pretreated with < 2 AED. As treatment successes in treatment-refractory patients strongly depend on the number of prior therapies [4], the results of the C017 study might be relevantly influenced by the inclusion of patients who have had only 1 AED in the prior therapy. In this case of a verifiable potentially strong effect modifier (number of AED pretreatments), the sole reference by the company to the fact that more than 80% of the total population of study C017 correspond to the approval population is not appropriate in terms of content.

*Titration not according to approval*

According to the SPC [5], cenobamate should be administered at a starting dose of 12.5 mg. The dose should be increased gradually every 2 weeks: at week 3 to 25 mg, at week 5 to 50 mg and thereafter every 2 weeks by 50 mg until the recommended target dose of 200 mg, up to a maximum of 400 mg depending on clinical response (see Figure 1), is reached. The recommended titration plan should not be exceeded due to serious side effects.

At the start of study C017, in contrast, patients were initially treated with a starting dose of 100 mg cenobamate. After 46 (10.5%) patients had been included, the starting dose was reduced to 50 mg, but not to 12.5 mg as described in the SPC, due to a high rate of AEs. The dose was then increased by 50 mg per week up to 200 mg; for patients in the 400 mg cenobamate arm, the dose was further increased in steps of even 100 mg per week from this dose up to the target dose of 400 mg.

The European Medicines Agency (EMA) associated this titration schedule with the occurrence

of severe side effects. A much slower titration schedule was therefore recommended (see Figure 1). The titration schedule of cenobamate in study C017 is therefore neither meaningful in terms of content nor does it comply with the approval. However, titrating cenobamate too quickly may not only lead to an overestimation of side effects, but possibly also to an overestimation of seizure reduction. The transferability of the results of the C017 study to patients in clinical practice who are treated according to the approval is thus considerably limited.

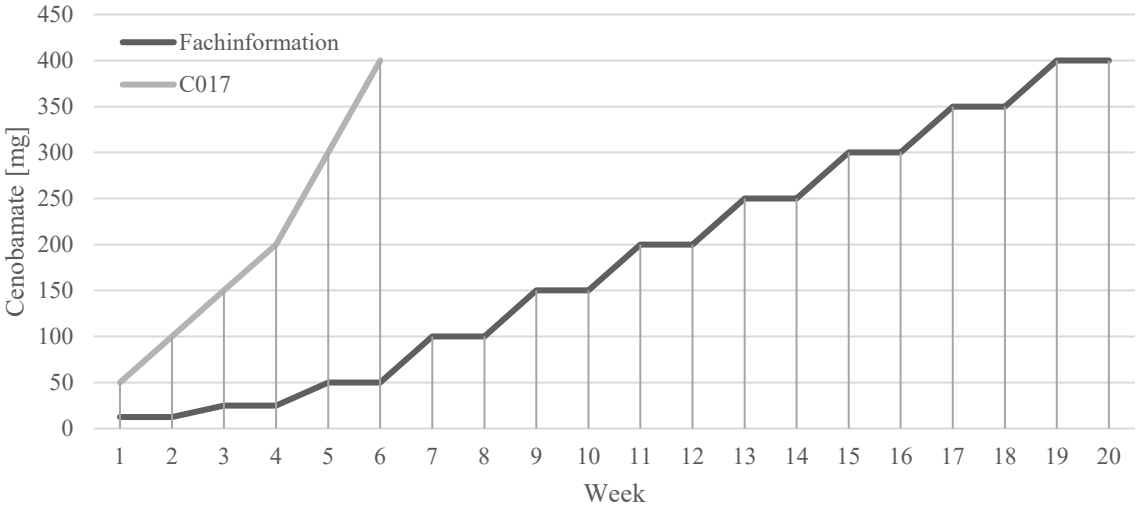


Figure 1: Titration schedule of the C017 study in comparison with the recommended titration schedule according to the SPC of cenobamate.

Fachinformation = Summary of Product Characteristics

***Suitability of the comparator studies for the indirect comparison***

In study pool 1, the company included 10 studies that it considered comparable with study C017 for an adjusted indirect comparison with cenobamate. Each of these 10 studies comprised 1 study on brivaracetam (1254 [6]), gabapentin (Yamauchi 2006 [7]) and lamotrigine and pregabalin (A008112 [8]), 2 studies each on lacosamide (0667 [9], 0755 [10]) and perampanel (304 [11], 335 [12]) and 3 studies on levetiracetam (N01221 [13], N132 [14], Shorvon 2000 [15]). The respective drug was compared with placebo in all 10 studies, in each case as adjunctive treatment to ongoing basic therapy.

This indirect comparison was unsuitable to derive conclusions on the added benefit of cenobamate versus the ACT. One of the reasons for this was that the company included studies also on the comparator side that did not cover the approval population and were thus unsuitable for the benefit assessment (see above). Another reason was that most of the studies included by the company were not sufficiently similar to the C017 study.

The patient characteristics and further parameters at the start of the study were compared to assess the similarity of the study populations. There are one or more aspects to each of the studies that, in addition to the question of general suitability due to the number of previous therapies, result in insufficient similarity to study C017. This is illustrated using characteristics of disease severity, seizure frequency at baseline and duration of the disease as an example.

Table 5 provides an overview of the extent to which these aspects make the comparator studies unsuitable for an indirect comparison to answer the present question. Table 6 also shows the relevant aspects in detail.

Table 5: Reasons for the lack of suitability of the studies presented by the company as study pool 1

| Study | Study design | | Similarity to C017 | |
|---|---|---|---|---|
| | Inclusion criterion ≥ 2 prior therapies | Implementation of the ACT | Seizure frequency at baseline | Duration of disease at baseline |
| **Study with brivaracetam** | | | | |
| 1254 | ○ | ○ | (●) | (●) |
| **Study with gabapentin** | | | | |
| Yamauchi et al. 2006 | ○ | ○ | (●) | (●) |
| **Studies with lacosamide** | | | | |
| 0667 | ● | ○ | (●) | (●) |
| 0755 | ● | ○ | (●) | (●) |
| **Study with lamotrigine and pregabalin** | | | | |
| A008112 | ● | ○ | (●) | (●) |
| **Studies with levetiracetam** | | | | |
| N01221 | ○ | ○ | – | (○) |
| N132 | ● | ○ | – | – |
| Shorvon et al. 2000 | ○ | ○ | – | (●) |
| **Studies with perampanel** | | | | |
| 304 | ● | ○ | (●) | (●) |
| 335 | ● | ○ | – | (○) |

● Criterion fulfilled/comparable to C017
○ Criterion not fulfilled/not comparable to C017
() Similarity with the total study population. Data on the approval population of study C017 and, if applicable, on the approval population from the aforementioned study itself are not available.
- Not assessable due to lack of data

ACT: appropriate comparator therapy

Table 6: Number of previous AEDs, seizure frequency at baseline, duration of the disease at baseline (multipage table)

| Study group | N[a] | Number of previous AEDs % | Seizure frequency per 28 days at baseline mean (SD) [median] | Duration of disease at baseline [years] mean (SD) |
|---|---|---|---|---|
| **Study with cenobamate** | | | | |
| C017 (total population[b]) | | **[1 / 2 / 3 > 3][c]** | | |
| 200 mg | 110 | 17/25/29/29 | 30.6 (60.9) [11] | 22.8 (13.2) |
| 400 mg | 111 | 14/29/26/32 | 24.1 (63.1) [9] | 24.4 (14.2) |
| Placebo | 108 | 12/31/18/40 | 25.3 (71.9) [8.4] | 23.0 (14.2) |
| **Study with brivaracetam** | | | | |
| 1254 | | **[0–1/2–4/≥ 5] (5 years before start of the study)** | | |
| 20-150 mg | 323[d] | 35/54/11 | 20.08 (47.08)[e] [8.8] | 21.8 (12.5) |
| Placebo | 108[d] | 34/53/13 | 20.40 (49.92)e [9.2] | 22.1 (11.7) |
| **Study with gabapentin** | | | | |
| Yamauchi et al. 2006 | | | | |
| 1200 mg | 86 | ND | 31.6 (ND)[f] [11.2] | 19.8 (ND) |
| 1800 mg | 41 | ND | 24.4 (ND)[f] [12.3] | 21.2 (ND) |
| Placebo | 82 | ND | 19.9 (ND)[f] [9.7] | 19.5 (ND) |
| **Studies with lacosamide** | | | | |
| 0667 | | **[1–3/4–6/7+][c]** | | |
| 400 mg | 108 | 22/30/48 [≤ 2: 12[g]] | 26.3 (36.62) [13.0] | 24.7 (13.08) |
| Placebo | 97 | 15/34/51 [≤ 2: 3[g]] | 28.8 (50.34) [11.0] | 24.6 (11.77) |
| 0755 | | **[1–3/4–6/7+/missing][c]** | | |
| 400 mg | 159 | 30/31/39/0 [≤ 2: 16[g]] | 42.0 (203.39) [10.3] | 22.8 (13.2) |
| Placebo | 163 | 31/33/35/1 [≤ 2: 12[g]] | 21.8 (31.18) [9.9] | 21.3 (12.3) |

Table 6: Number of previous AEDs, seizure frequency at baseline, duration of the disease at baseline (multipage table)

| Study group | N[a] | Number of previous AEDs % | Seizure frequency per 28 days at baseline mean (SD) [median] | Duration of disease at baseline [years] mean (SD) |
|---|---|---|---|---|
| **Study with lamotrigine and pregabalin** | | | | |
| A008112 | | | | |
| 300/400 mg lamotrigine | 141 | ND | 21.80 (47.68) 8.67 | 23.1 (13.6) |
| 300/600 mg pregabalin | 152 | ND | 21.32 (38.23) [9.33] | 23.1 (13.5) |
| Placebo | 140 | ND | 16.38 (27.54) [7.33] | 23.4 (12.2) |
| **Studies with levetiracetam** | | | | |
| N01221 | | | | |
| 1000 mg | 70 | ND | ND [11[e]] | 14.5 (8.9) |
| 2000 mg | 70 | ND | ND [12.84[e]] | 13.8 (9.6) |
| 3000 mg | 70 | ND | ND [10.6[e]] | 15.2 (10.3) |
| Placebo | 70 | ND | ND [12[e]] | 16.3 (11.9) |
| N132 | | | | |
| 1000 mg | 98 | ND | ND [10.12[e]] | ND |
| 3000 mg | 101 | ND | ND [8.32[e]] | ND |
| Placebo | 95 | ND | ND [7.08[e]] | ND |
| Shorvon et al. 2000 | | | | |
| 1000 mg | 106 | ND | ND [11.28[e]] | 23.8 (12.3) |
| 2000 mg | 106 | ND | ND [10.32[e]] | 23.6 (13.3) |
| Placebo | 112 | ND | ND [10[e]] | 23.2 (11.0) |
| **Studies with perampanel** | | | | |
| 304 | | | | |
| 8 mg | 133 | ND | 35.5 (94.0) [14.3] | 23.6 (13.5)[g] |
| 12 mg | 134 | ND | 41.4 (109.5) [12] | 23.3 (14.4)[g] |
| Placebo | 121 | ND | 26.8 (32.2) [13.7] | 24.1 (12.9)[g] |

Table 6: Number of previous AEDs, seizure frequency at baseline, duration of the disease at baseline (multipage table)

| Study group | N[a] | Number of previous AEDs % | Seizure frequency per 28 days at baseline mean (SD) [median] | Duration of disease at baseline [years] mean (SD) |
|---|---|---|---|---|
| 335 | | | | |
| 4 mg | 174 | ND | ND | 17.4 (11.1) |
| 8 mg | 175 | ND | ND | 16.9 (11.5) |
| 12 mg | 180 | ND | ND | 17.4 (11.2) |
| Placebo | 175 | ND | ND | 17.5 (10.9) |

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding cell if the deviation is relevant.
b. Data for the approval population are not available.
c. Documentation time not restricted.
d. Patients with focal-onset seizures.
e. Institute's calculation from specified seizure frequency per 7 days.
f. Data refer to per-protocol population.
g. Institute's calculation.

AED: antiepileptic drug; N: number of randomized patients; ND: not data; SD: standard deviation

*Inclusion criterion "number of prior therapies"*

As in study C017, 4 of the comparator studies could also include patients who had received with < 2 antiepileptic therapies before study entry (see Table 5). These were the studies 1254 (brivaracetam), Yamauchi 2006 (gabapentin), N01221 and Shorvon 2000 (levetiracetam). Information on how many prior therapies the patients had actually received at the start of the study is only available for study 1254 and only pertaining to the period of 5 years before the start of the study. According to this information, 35% of the patients in the intervention arm and 34% of the patients in the comparator arm had received < 2 previous antiepileptic therapies in the period of 5 years before the start of the study. Data on previous antiepileptic therapies are not available or the studies Yamauchi 2006, N01221 and Shorvon 2000.

As far as the previous therapies are concerned, the general suitability of the populations of studies 1254 (brivaracetam), Yamauchi 2006 (gabapentin), N01221 and Shorvon 2000 (levetiracetam) cannot be assessed. However, based on the inclusion criteria, it can be assumed that some of the patients had received < 2 previous antiepileptic therapies. The impact on the study results and thus on the indirect comparison cannot be assessed.

The remaining 6 studies should only include patients who had already received ≥ 2 previous antiepileptic therapies. The populations of these studies thus correspond to the target population on cenobamate. However, for all 6 studies, data on the number of AEDs in the pretreatment are not available, so similarity to the approval population in the C017 study cannot be assessed.

*Similarity of disease severity*

Under the aspect of disease severity, the frequency of seizures at baseline and the duration of the disease were considered as examples. It was shown that data on these aspects were not available for all studies of the comparator side and that some studies were insufficiently similar.

Complete data on seizure frequency are lacking for 4 studies (N01221, N132 and Shorvon 2000 [levetiracetam]; 335 [perampanel]). Appropriate assessment of the similarity regarding the approval population of C017 is thus impossible. At the same time, the patients in the studies N01221 (levetiracetam) and 335 (perampanel) have notably shorter disease durations compared to the total population of the C017 study. It can be assumed that patients in these two studies had less severe disease than in the other studies. Data on the disease duration are not available for study N132 (levetiracetam).

*Implementation of the ACT*

The G-BA specified individual antiepileptic adjunctive treatment with brivaracetam or eslicarbazepine or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or perampanel or pregabalin or topiramate or valproic acid or zonisamide as ACT. Treatment is to be chosen by the doctor depending on the basic and prior therapy/therapies under consideration of the reason for treatment switching and any accompanying adverse events. The G-BA also pointed out that in the included studies, it must be ensured that the individual choice of the adjunctive antiepileptic treatment takes place before randomization and is described as concretely as possible by criteria (e.g. by documenting the respective pretreatments, the reasons for treatment discontinuation or treatment switch).

In none of the studies on the comparator therapy submitted by the company was the therapy chosen according to individual criteria such as prior therapies, side effects and contraindications. Rather, all patients were treated with previously determined doses of the respective drug to be investigated, irrespective of these aspects. Therefore, the ACT was not appropriately implemented in any of the studies identified by the company for the comparator therapy.

***Conclusion on the indirect comparison***

Overall, the adjusted indirect comparison of the company based on study pool 1 and study C017 with cenobamate is not suitable for deriving conclusions about the added benefit of cenobamate compared to the ACT due to the described aspects regarding the similarity of the study populations and the implementation of the ACT.

Since study pool 2 corresponds to study pool 1 supplemented with potentially comparable studies, the indirect comparison based on study pool 2 is therefore also unsuitable for the benefit assessment.

## 2.4 Results on added benefit

Sufficient data are not available for the assessment of the added benefit of cenobamate in comparison with the ACT for the adjunctive treatment of focal-onset seizures with or without secondary generalization in patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 AEDs. This resulted in no hint of an added benefit of cenobamate in comparison with the ACT; an added benefit is therefore not proven.

## 2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of cenobamate in comparison with the ACT is summarized in Table 7.

Table 7: Cenobamate – probability and extent of added benefit

| **Therapeutic indication** | **ACT**[a] | **Probability and extent of added benefit** |
|---|---|---|
| Adjunctive treatment of focal-onset seizures with or without secondary generalization in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 antiepileptic drugs. | Patient-specific antiepileptic adjunctive treatment, if medically indicated and if no pharmacoresistance (in the sense of an insufficient response), intolerance or contraindication is known, with one of the following drugs:<br>brivaracetam or eslicarbazepine or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or perampanel or pregabalin or topiramate or valproic acid or zonisamide.[b] | Added benefit not proven |
| a. Presentation of the respective ACT specified by the G-BA.<br>b. Treatment is to be chosen by the doctor depending on the basic and prior therapy/therapies under consideration of the reason for treatment switching and any accompanying adverse events.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | | |

The assessment described above deviates from that of the company, which derived a hint of a considerable added benefit on the basis of the data provided by it.

The G-BA decides on the added benefit.

**References for English extract**

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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