Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Cenobamate (epilepsy, focal seizures, after at least 2 previous therapies)

of 19 November 2021

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes, in particular, the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information, in particular:

1. approved therapeutic indications,
2. medical benefits,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the combination of active ingredient cenobamate in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 June 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 28 May 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 September 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of cenobamate compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, and the

addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of cenobamate.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of cenobamate (Ontozry) in accordance with the product information

Ontozry is indicated 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 a history of treatment with at least 2 anti-epileptic medicinal products.

Therapeutic indication of the resolution (resolution from 19.11.2021):

"see approved therapeutic indication"

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with epilepsy and focal-onset seizures with or without secondary generalisation who have not been adequately controlled despite a history of treatment with at least two anti-epileptic medicinal products

Appropriate comparator therapy for cenobamate as adjunctive treatment:

- a patient-individual adjunctive anti-epileptic therapy, if medically indicated and if no pharmacoresistance (in the sense of an insufficient response), intolerance or contraindication is known, under selection of:

brivaracetam, eslicarbazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, valproic acid and zonisamide

taking into account the basic and previous therapy/therapies and considering the reason for the change of therapy and any associated side effects.

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy, for which endpoint studies are available and which has proven its worth in practical application, unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must principally have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. Besides cenobamate, the following active ingredients are approved for the present therapeutic indication:

clobazam, brivaracetam, eslicarbazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, tiagabine[2], topiramate, valproic acid, vigabatrin, zonisamide.

on 2. A non-medicinal treatment cannot be considered an appropriate comparator therapy in this therapeutic indication.

on 3. In the therapeutic indication of adjunctive treatment of focal-onset seizures with or without secondary generalisation, the following resolutions of the G-BA are available:

- resolution on retigabine of 3 July 2014
- resolution on perampanel dated 6 November 2014 and 17 May 2018 and 3 June 2021 (children)
- resolution on brivaracetam dated 4 August 2016 and 17 January 2019 (children and adolescents)
- resolution on vigabatrin of 19 December 2019 (children)

on 4. The generally accepted state of medical knowledge for the indication was established using a search for guidelines and systematic reviews of clinical studies. In accordance with the approved therapeutic indication, the above-mentioned active ingredients are available for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult epilepsy patients. The assessment of the available evidence showed that patient-individual adjunctive anti-epileptic therapy of the doctor's choice

[2] Not in circulation in DE since November 2013.

is appropriate, depending on the basic and previous therapy/therapies and taking into account the reason for the change of therapy and any associated side effects, as long as this is medically indicated and no pharmacoresistance (in the sense of an insufficient response), intolerance and contraindications are known.

In compliance with the marketing authorisation for the therapeutic indication of a combination regimen or adjunctive treatment of focal-onset or partial seizures (with or without generalisation), the active ingredients clobazam, brivaracetam, eslicarbazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, valproic acid, vigabatrin and zonisamide are available, with the exception of the active ingredient tiagabine, which is not available on the German market. In order to specify the appropriate comparator therapy, the eligible active ingredients with a marketing authorisation according to the therapeutic indication of cenobamate are named and listed individually. Evidence does not support the inference of superiority for any of these active ingredients.

Valproic acid is not regularly considered for the adjunctive treatment of focal-onset seizures in women of childbearing age due to teratogenicity. However, in the context of patient-individual therapy, adjunctive treatment with valproic acid may be a possible option.

Clobazam and vigabatrin are not part of the appropriate comparator therapy. There is inadequate evidence for clobazam. The use of vigabatrin is contraindicated due to a high risk of visual field defects, possibly leading to permanent vision loss. In addition, unlike the other active ingredients mentioned above, vigabatrin is only considered as a last-line treatment option according to the marketing authorisation when all other anti-epileptic medicinal products have failed or are not tolerated. Against this background, treatment with vigabatrin appears to be appropriate only in exceptional cases and is not considered a component of patient-individual therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of cenobamate is assessed as follows:

The additional benefit is not proven for adults with epilepsy and focal-onset seizures with or without secondary generalisation who have not been adequately controlled despite a history of treatment with at least two anti-epileptic medicinal products.

Justification:

There are no directly comparative studies of cenobamate versus patient-individual therapy as an appropriate comparator therapy for adults with epilepsy and focal-onset seizures with or without secondary generalisation who have not been adequately controlled despite a history of treatment with at least two anti-epileptic medicinal products. The pharmaceutical company therefore presents an adjusted indirect comparison via the bridge comparator basic therapy + placebo in the dossier. For cenobamate, it draws on the YKP3089C017 (C017 in short) study. On the comparator therapy side, the pharmaceutical company includes ten randomised controlled trials (RCT), comparing brivaracetam, gabapentin, lamotrigine and pregabalin, lacosamide, levetiracetam or perampanel with placebo, each as add-on therapy to an existing basic therapy.

C017 study is a four-arm, blinded, randomised phase II study, justifying the market authorisation. Patients with ongoing uncontrolled focal-onset (partial) seizures were included, although they had been treated with at least one anti-epileptic medicinal product in the last 2 years. The study was divided into a 6-week titration phase and a 12-week maintenance phase in which patients received either 100 mg, 200 mg, 400 mg cenobamate or placebo in addition to existing basic therapy. The dosages of 200 and 400 mg as the target dose are in accordance with the recommendations of the marketing authorisation. In contrast, the titration was much faster than indicated in the product information (6 weeks instead of 10-18 weeks) and started with a significantly higher dosage (50 or 100 mg instead of 12.5 mg). Due to this use that is not compliant with marketing authorisation, the C017 study is considered unsuitable for the indirect comparison presented. Forced titration of cenobamate may not only lead to an overestimation of side effects but is a potential confounder of efficacy. In addition, contrary to the primary study design, the presented assessments of seizure reduction included not only the maintenance phase, but also the titration phase. Therefore, the transferability of the results of the C017 study to patients, who are treated according to the marketing authorisation, is severely limited in clinical practice.

In addition, the results of the C017 study are subject to uncertainties because patients with less than two previous therapies were included – in discrepancy to the present therapeutic indication. According to the experts' statements in the written statement procedure, the success of an epileptic seizure treatment depends, among other things, on the number of previous therapies. The chance of freedom from seizures decreases with each unsuccessful medicinal therapy, so the number of previous therapies is a potentially strong effect modifier that can significantly influence outcomes. Therefore, less than 20% of the study population with only one previous therapy is also viewed critically.

Likewise, four of the comparative studies used by the pharmaceutical company for the indirect comparison included patients who received less than two previous therapies. The percentage of the study population in each case is unknown for three of the studies.

It is also unclear to what extent the study populations of the C017 study and the comparator studies are comparable, particularly with respect to the number of previous therapies and seizure frequency at start of study. Information on the number of previous therapies is not available for most of the comparator studies, and for the C017 study, no further differentiation was made in the study population data after more than 3 previous therapies. However, as explained above, since the chances of success of a treatment depend on the number of previous therapies, sufficient similarity for this effect modifier in the studies to be compared is a necessary prerequisite for a valid indirect comparison in the present therapeutic indication. Complete data on seizure frequency are not available for 4 comparative studies. Thus, the similarity to the C017 study population cannot be estimated appropriately.

Conclusion

In the overall assessment, the adjusted indirect comparison presented is considered unsuitable for the assessment of the additional benefit of cenobamate compared to the appropriate comparator therapy. In the only study included for cenobamate, the C017 study, the titration deviates significantly from the recommendations of the marketing authorisation, so that there is no suitable study on the intervention side for the indirect comparison.

Furthermore, it cannot be assessed from the data presented whether the C017 study has sufficient similarity to the comparative studies, particularly with regard to seizure frequency at start of study and the potentially strong effect modifier "number of previous therapies". Furthermore, both the C017 study and some comparative studies do not adequately represent the indication, as patients with less than two previous therapies were also included.

Therefore, no data relevant for the benefit assessment of cenobamate are available, so an additional benefit is not proven.

Taking into account the available evidence on the medical benefit of cenobamate, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, cenobamate may represent a relevant therapeutic option in specific cases for adults with epilepsy and focal-onset seizures with or without secondary generalisation who have not been adequately controlled despite a history of treatment with at least two anti-epileptic medicinal products.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Ontozry with the active ingredient cenobamate. Cenobamate is approved 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 a history of treatment with at least 2 anti-epileptic medicinal products.

Due to the lack of directly comparative studies, the pharmaceutical company submits an adjusted indirect comparison with placebo + basic therapy as a bridge comparator for the benefit assessment. For cenobamate, it draws on the C017 study. On the comparator therapy side, the pharmaceutical company includes ten randomised controlled trials (RCT) in which individual medicinal products are compared with placebo, in each case as an add-on therapy to an existing basic therapy.

However, the adjusted indirect comparison presented is unsuitable for deriving conclusions on the additional benefit of cenobamate, compared to the appropriate comparator therapy, as in the C017 study on cenobamate, the titration deviates significantly from the recommendations of the marketing authorisation, and thus, there is no suitable study on the intervention side for the indirect comparison.

Furthermore, it cannot be assessed from the data presented whether the C017 study has sufficient similarity to the comparative studies, particularly with regard to seizure frequency at start of study and the potentially strong effect modifier "number of previous therapies". Furthermore, both the C017 study and some comparative studies do not adequately represent the indication, as patients with less than two previous therapies were also included.

Therefore, no data relevant for the benefit assessment of cenobamate are available, so an additional benefit is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on the information from the statement of the pharmaceutical company (lower limit) and the IQWiG addendum (upper limit).

Overall, the estimated number of patients in the SHI target population at the lower limit is subject to uncertainty due to the allocation of patients to the group with focal epilepsies.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Ontozry (active ingredient: cenobamate) at the following publicly accessible link (last access: 4 November 2021):
https://www.ema.europa.eu/documents/product-information/ontozry-epar-product-information_en.pdf

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 November 2021).

The (daily) doses recommended in the product information were used as the calculation basis.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Cenobamate	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
- a patient-individual adjunctive anti-epileptic therapy, if medically indicated and if no pharmacoresistance (in the sense of an insufficient response), intolerance or contraindication is known, under selection of:				
brivaracetam	continuously, 2 x daily	365	1	365
eslicarbazepine	continuously, 1 x daily	365	1	365
gabapentin	continuously, 3 x daily	365	1	365
lacosamide	continuously, 2 x daily	365	1	365
lamotrigine	continuously, 2 x daily	365	1	365
levetiracetam	continuously, 2 x daily	365	1	365
oxcarbazepine	continuously, 2 x daily	365	1	365
perampanel	continuously, 1 x daily	365	1	365
pregabalin	continuously, 2-3 times a day	365	1	365
topiramate	continuously, 2 x daily	365	1	365
valproic acid	continuously, 2 - 4 x daily	365	1	365
zonisamide	continuously, 2 x daily	365	1	365

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Cenobamate	200 mg - 400 mg	200 mg - 400 mg	1 x 200 mg - 2 x 200 mg	365	365 x 200 mg - 730 x 200 mg
Appropriate comparator therapy					
- a patient-individual adjunctive anti-epileptic therapy, if medically indicated and if no pharmacoresistance (in the sense of an insufficient response), intolerance or contraindication is known, under selection of:					
brivaracetam	25 mg - 100 mg	50 mg - 200 mg	2 x 25 mg - 2 x 100 mg	365	730 x 25 mg - 730 x 100 mg
eslicarbazepine	800 mg - 1,200 mg	800 mg - 1,200 mg	1 x 800 mg - 2 x 600 mg	365	365 x 800 mg - 730 x 600 mg
gabapentin	300 mg - 1,200 mg	900 mg - 3600 mg	3 x 300 mg - 6 x 600 mg	365 - 365.0	1,095 x 300 mg - 2192 x 600 mg
lacosamide	100 mg - 200 mg	200 mg - 400 mg	2 x 100 mg - 2 x 200 mg	365	730 x 100 mg - 730 x 200 mg
lamotrigine	50 mg - 200 mg	100 mg - 400 mg	2 x 50 mg - 2 x 200 mg	365	730 x 50 mg - 730 x 200 mg
Levetiracetam[3]	500 mg - 1500 mg	1,000 mg - 3000 mg	2 x 500 mg - 2 x 1500 mg	365	730 x 500 mg - 730 x 1500 mg
oxcarbazepine	300 mg - 1200 mg	600 mg - 2400 mg	2 x 300 mg - 4 x 600 mg	365	730 x 300 mg - 1,460 x 600 mg
perampanel	4 mg - 12 mg	4 mg - 12 mg	1 x 4 mg - 1 x 12 mg	365	365 x 4 mg - 365 x 12 mg

[3] The dose range depends on whether valproate and/or inducers of glucuronidation of lamotrigine are also being taken. The upper limit of the range can be used with adjunctive therapy WITHOUT valproate and WITH inducers of glucuronidation of lamotrigine.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
pregabalin	75 mg - 300 mg	150 mg - 600 mg	2x 75 mg - 2 x 300 mg	365	730 x 75 mg - 730 x 300 mg
topiramate	100 mg - 200 mg	200 mg - 400 mg	2 x 100 mg - 2 x 200 mg	365	730 x 100 mg - 730 x 200 mg
valproic acid	600 mg - 600 mg/ 900 mg	1,200 mg - 2,100 mg	2 x 600 mg - 3 x 600 mg + 1 x 300 mg	365	730 x 600 mg - 1,095 x 600 mg + 365 x 300 mg
zonisamide	100 mg/200 mg - 200 mg/ 300 mg	300 mg - 500 mg	3 x 100 mg - 5 x 100 mg	365	1,095 x 100 mg - 1,825 x 100 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Cenobamate 200 mg	84 FCT	€ 859.41	€ 1.77	€ 46.97	€ 810.67
Appropriate comparator therapy					
Brivaracetam 25 mg	168 FCT	€ 299.92	€ 1.77	€ 15.99	€ 282.16
Brivaracetam 100 mg	168 FCT	€ 299.92	€ 1.77	€ 15.99	€ 282.16
Eslicarbazepine 600 mg	90 TAB	€ 329.73	€ 1.77	€ 15.12	€ 312.84
Eslicarbazepine 800 mg	90 TAB	€ 419.69	€ 1.77	€ 19.39	€ 398.53
Gabapentin 300 mg[4]	200 HC	€ 52.85	€ 1.77	€ 3.31	€ 47.77
Gabapentin 600 mg[4]	200 FCT	€ 99.42	€ 1.77	€ 6.99	€ 90.66
Lacosamide 100 mg	168 FCT	€ 471.29	€ 1.77	€ 25.48	€ 444.04
Lacosamide 200 mg	168 FCT	€ 774.05	€ 1.77	€ 42.24	€ 730.04
Lamotrigine 50 mg[4]	200 TAB	€ 28.61	€ 1.77	€ 1.39	€ 25.45
Lamotrigine 200 mg[4]	200 TAB	€ 91.87	€ 1.77	€ 6.39	€ 83.71
Levetiracetam 500 mg[4]	200 FCT	€ 61.02	€ 1.77	€ 3.95	€ 55.30
Levetiracetam 1500 mg[4]	200 FCT	€ 180.25	€ 1.77	€ 13.38	€ 165.10
Oxcarbazepine 300 mg	200 FCT	€ 91.86	€ 1.77	€ 3.84	€ 86.25
Oxcarbazepine 600 mg	200 FCT	€ 149.04	€ 1.77	€ 6.55	€ 140.72
Perampanel 4 mg	98 FCT	€ 350.36	€ 1.77	€ 18.79	€ 329.80
Perampanel 12 mg	98 FCT	€ 350.36	€ 1.77	€ 18.79	€ 329.80
Pregabalin 75 mg[4]	100 HC	€ 49.05	€ 1.77	€ 3.01	€ 44.27
Pregabalin 300 mg[4]	100 HC	€ 108.92	€ 1.77	€ 7.74	€ 99.41
Topiramate 100 mg[4]	200 FCT	€ 147.29	€ 1.77	€ 10.78	€ 134.74
Topiramate 200 mg[4]	200 FCT	€ 267.56	€ 1.77	€ 20.29	€ 245.50
Valproic acid 300 mg[4]	200 EFCT	€ 33.92	€ 1.77	€ 1.81	€ 30.34
Valproic acid 600 mg[4]	200 EFCT	€ 49.81	€ 1.77	€ 3.07	€ 44.97

[4] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Zonisamide 100 mg[4]	196 HC	€ 315.27	€ 1.77	€ 24.06	€ 289.44
Abbreviations: EFCT = enteric film-coated tablets; FCT = film-coated tablets; HC = hard capsules; TAB = tablets					

LAUER-TAXE® last revised: 1 November 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs. Process sequence

At its session on 5 May 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 May 2021, the pharmaceutical company submitted a dossier for the benefit assessment of cenobamate to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 31 May 2021, in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient cenobamate.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 August 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 September 2021. The deadline for submitting written statements was 22 September 2021.

The oral hearing was held on 11 October 2021.

By letter dated 12 October 2021, the IQWiG was commissioned with a supplementary assessment. The addenda prepared by IQWiG was submitted to the G-BA on 29 October 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 9 November 2021, and the proposed resolution was approved.

At its session on 19 November 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	5 May 2020	Determination of the appropriate comparator therapy
Working group Section 35a	5 October 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	11 October 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	19 October 2021 2 November 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	9 November 2021	Concluding discussion of the draft resolution
Plenum	19 November 2021	Adoption of the resolution on the amendment of Annex XII AM-RL (Pharmaceuticals Directive)

Berlin, 19 November 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken