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 and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V Cannabidiol (reassessment of an orphan drug after exceeding the EUR 30 million turnover limit: tuberous sclerosis, ≥ 2 years)

of 16 May 2024

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 trials 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 benefit,
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 the 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient cannabidiol (Epidyolex) was listed for the first time on 15 October 2019 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Epidyolex for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome (≥ 2 years, in conjunction with clobazam) as well as with tuberous sclerosis (≥ 2 years) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

At its session on 4 November 2021, the G-BA decided on the benefit assessment of cannabidiol in the therapeutic indication "Epidyolex is indicated for use as adjunctive therapy of seizures associated with tuberous sclerosis (TSC) for patients 2 years of age and older" in accordance with Section 35a SGB V. By resolution of 5 October 2023, the G-BA named medicinal products with new active ingredients that are used in a combination therapy with cannabidiol in accordance with Section 35a, paragraph 3, sentence 4 SGB V.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 30 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 17 August 2023, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 December 2023, due to exceeding the € 30 million turnover limit within the period from April 2022 up to and including March 2023.

The pharmaceutical company has 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 6 VerfO on 30 November 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 March 2024 on the G-BA website (www.g-ba.de), 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 cannabidiol 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. 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 cannabidiol.

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 Cannabidiol (Epidyolex) in accordance with the product information

Epidyolex is indicated for use as adjunctive therapy of seizures associated with tuberous sclerosis (TSC) for patients 2 years of age and older.

Therapeutic indication of the resolution (resolution of 16.05.2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Patients 2 years of age and older with seizures associated with tuberous sclerosis

Appropriate comparator therapy for cannabidiol as adjunctive therapy:

- Patient-individual therapy, taking into account the types of seizures occurring, the basic and previous therapy/ therapies and any associated side effects, with selection of

  Brivaracetam, carbamazepine, cenobamate, eslicarbazepine, everolimus, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, topiramate, valproic acid, vigabatrin, zonisamide

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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 patient-relevant benefit has already been determined by the G-BA 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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or

3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. In addition to the active ingredient cannabidiol, the active ingredient everolimus is specifically approved for the treatment of seizures associated with tuberous sclerosis (TSC) for subjects with refractory partial seizures.
The following active ingredients are approved for certain seizure types or generally for the treatment of epileptic seizures: Brivaracetam, bromide, carbamazepine, cenobamate, clobazam, clonazepam, eslicarbazepine, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, mesuximide, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, pregabalin, topiramate, valproic acid, vigabatrin and zonisamide.
The following active ingredients are approved for the treatment of infantile spasms (West syndrome or BNS spasms): Clonazepam, nitrazepam, prednisolone, prednisone, tetracosactide hexaacetate (ACTH) and vigabatrin.

on 2. In the present indication, epilepsy surgery can be considered as non-medicinal treatment.

on 3. For seizures associated with tuberous sclerosis, the resolution on the benefit assessment in accordance with Section 35a SGB V on cannabidiol from 4 November 2021 is available.

The following resolutions have been made in the therapeutic indication of epilepsy in accordance with Section 35a SGB V:

- resolution on cenobamate from 19 November 2021
- resolution on vigabatrin from 19 December 2019
- resolution on brivaracetam from 4 August 2016, 17 January 2019 and 1 September 2022
- resolution on perampanel from 6 November 2014, 17 May 2018 and 3 June 2021
- resolution on retigabine from 3 July 2014

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see “Information on Appropriate Comparator Therapy”).

Overall, the evidence base in the present therapeutic indication must be regarded as limited.

Everolimus is specifically approved for the treatment of refractory partial seizures associated with tuberous sclerosis (TSC) and is recommended according to the available evidence.

The clinical picture of tuberous sclerosis typically includes infantile spasms, which usually manifest themselves in early infancy, but can also persist in children from the age of 2. Due to the decreasing frequency of infantile spasms beyond the age of 2 years, the active ingredients specifically approved for this purpose are not determined as part of the appropriate comparator therapy against the background of the present therapeutic indication (patients 2 years of age and older). However, it is assumed that infantile spasms will be adequately treated in both study arms.

With increasing age, (multi-)focal or secondary generalised seizures come to the fore. Active ingredients that are generally approved (i.e. for epileptic seizures in general or focal seizures in particular) and are recommended for the treatment of focal seizures according to the evidence, provided there are no contraindications in tuberous sclerosis, can therefore also be considered as appropriate comparator therapy. Taking into account the guideline recommendations[2,3,4,5], the active ingredients brivaracetam, carbamazepine, cenobamate, eslicarbazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, topiramate, valproic acid, vigabatrin and zonisamide should therefore be mentioned as therapy options in this therapeutic indication. The evidence for the active ingredients clobazam and clonazepam is considered inadequate.

Epilepsy surgical resective measures can also be used in this therapeutic indication, but these are generally a secondary option compared to medicinal therapies. It is therefore assumed that epilepsy surgery is not indicated for patients with TSC who are eligible for treatment with cannabidiol in the present treatment setting.

In the overall assessment of the evidence, a patient-individual therapy is determined as the appropriate comparator therapy for cannabidiol for patients 2 years of age and older with seizures associated with tuberous sclerosis, taking into account the seizure types occurring, the basic therapy and previous therapy/ therapies as well as any associated side effects, selecting brivaracetam, carbamazepine, cenobamate, eslicarbazepine, everolimus, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, topiramate, valproic acid and zonisamide.

Even if all the above-mentioned active ingredients are named as appropriate comparator therapy as part of a patient-individual therapy, not all active ingredients have to be offered and used in a study in order to implement the appropriate comparator therapy.

As a rule, combination therapies are used in this therapeutic indication. On the contrary, monotherapies are exceptions; their use in the comparator arm of a study should be justified.

The unchanged continuation of an inadequate therapy does not correspond to the implementation of the appropriate comparator therapy if there is still the option of optimisation. Adjusting the dosage of a previously stable, inadequate anti-epileptic therapy also does not correspond to the appropriate comparator therapy, as a rule.

2 Holtkamp M, May TW, Berkenfeld R, Bien CG, Coban I, Knake S, Michaelis R, Rémi J, Seeck M, Surges R, Weber Y, et al., First epileptic seizure and epilepsy in adulthood, S2k guideline, 2023; in: German Society of Neurology (ed.), Guidelines for Diagnosis and Therapy in Neurology. Online: www.dgn.org/leitlinien

3 National Institute for Health and Care Excellence (NICE). Epilepsies in children, young people and adults [online]. 2022. [Accessed: 28.07.2022]. URL: https://www.nice.org.uk/guidance/ng217/resources/epilepsies-in-children-young-people-and-adults-pdf-66143780239813

4 Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults: a national guideline [online]. 2018. URL: https://www.sign.ac.uk/media/1079/sign143_2018.pdf

5 Scottish Intercollegiate Guidelines Network (SIGN). Epilepsies in children and young people: investigative procedures and management: a national guideline [online]. 2021. URL: https://www.sign.ac.uk/media/1844/sign-159-epilepsy-in-children-final.pdf

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

A ketogenic diet can also be considered as a therapy option in this therapeutic indication. Against this background, patients in both study arms should have the opportunity to take advantage of appropriate nutritional counselling or to continue a ketogenic diet (already started before the start of study) during the study.

Change of the appropriate comparator therapy

To date, a patient-individual therapy was determined for patients 2 years of age and older with seizures associated with tuberous sclerosis, taking into account the seizure types occurring, the basic therapy and previous therapy/ therapies as well as any associated side effects, selecting brivaracetam, carbamazepine, cenobamate, clonazepam, eslicarbazepine, everolimus, gabapentin, lacosamide, lamotrigine, levetiracetam, nitrazepam, oxcarbazepine, perampanel, pregabalin, topiramate, valproic acid, vigabatrin, zonisamide, glucocorticoids (prednisone or prednisolone) and tetracosactide (ACTH).

The active ingredients or product classes vigabatrin, tetracosactide (ACTH), glucocorticoids (prednisone or prednisolone), nitrazepam and clonazepam are approved for the treatment of infantile spasms. In view of the decreasing frequency of infantile spasms beyond the age of 2 years, the active ingredients mentioned are not to be classified as standard therapy for patients affected by tuberous sclerosis from the age of 2 years. The significance of the active ingredients mentioned in this therapeutic indication was also described as subordinate overall during the written statement procedure. Against this background, it is considered appropriate not to designate the active ingredients ACTH, prednisone, prednisolone, nitrazepam and clonazepam as part of the appropriate comparator therapy.

Vigabatrin, on the contrary, is recommended in guidelines in the same way as the active ingredients phenobarbital and phenytoin as part of adjuvant anti-epileptic therapy for focal-onset seizures if other anti-epileptic medicines have not previously achieved any effect ("third line" options). Against the background of the written statement procedure, which emphasised the treatment refractoriness of epileptic seizures in this therapeutic indication, it is considered appropriate to name phenobarbital, phenytoin and vigabatrin as options in the context of patient-individual therapy and thus as part of the appropriate comparator therapy.

The change in the appropriate comparator therapy has no impact on the present benefit assessment.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

For patients 2 years of age and older with seizures associated with tuberous sclerosis, the additional benefit is not proven.

Justification:

For the assessment of the additional benefit, the pharmaceutical company submits evaluations of the GWEP1521 study.

This is a randomised, controlled, double-blind study in which cannabidiol was compared with placebo, in each case in addition to continued anti-epileptic treatment. The results of the study were already the basis for the resolution on the benefit assessment in accordance with Section 35a SGB V for the active ingredient cannabidiol on 4 November 2021.

Patients aged 1 to 65 years with tuberous sclerosis who were taking one or more anti-epileptic medicines at an unchanged dose for at least 4 weeks and who had 8 or more convulsive seizures during the four-week baseline phase (including at least one seizure in the last week) were enrolled.

The study population was randomised in a ratio of 2:2:1:1 to the study arms cannabidiol 25 mg/kg/day, cannabidiol 50 mg/kg/day or a respective placebo equivalent. No data are available on the likewise approved dose of 10 mg/kg/day.

The treatment duration was 16 weeks (including a 9-day titration phase).

Pre-existing anti-epileptic pharmacotherapy was to be continued throughout the duration of the study; anticonvulsant doses had to have been stable for at least 4 weeks prior to screening and remain stable throughout the study period. The use of emergency medication was possible if required. The initiation of a new seizure suppressive therapy (anticonvulsants, ketogenic diet or vagus nerve stimulation) during the course of the study was not permitted.

The appropriate comparator therapy for patients 2 years of age and older with seizures associated with tuberous sclerosis will be a patient-individual therapy, taking into account the seizure type occurring, the basic therapy and previous therapy/ therapies as well as any associated side effects, by selecting the above-mentioned active ingredients.

In the relevant study for the present benefit assessment, no optimisation of anti-epileptic treatment was planned for the patients in the comparator arm. Although epileptic seizures occurred regularly in the enrolled patients, the existing anti-epileptic medication in the comparator arm was only supplemented with placebo and thus continued unchanged.

As part of patient-individual therapy, the unchanged continuation of inadequate treatment does not correspond to the implementation of the appropriate comparator therapy if there is still the option of optimisation.

Also taking into account the assessment of the clinical experts involved in the written statement procedure, it can be assumed that an adjustment of the anti-epileptic medication is indicated in the present therapeutic indication, despite a history of multiple inadequate responses to anticonvulsants. The data submitted by the pharmaceutical company do not sufficiently justify that there is no further possibility of optimisation of the existing anti-epileptic medication for the patients enrolled in the studies.

In summary, the appropriate comparator therapy was not implemented in the GWEP1521 study.

For patients 2 years of age and older with seizures associated with tuberous sclerosis, no data are therefore available comparing cannabidiol with the appropriate comparator therapy. Accordingly, there are no relevant data for the benefit assessment of cannabidiol.

The additional benefit of cannabidiol over the appropriate comparator therapy for patients 2 years of age and older with seizures associated with tuberous sclerosis is therefore not proven.

Taking into account the severity of the disease and the statements of scientific-medical societies as well as clinical experts on the current reality of care, cannabidiol may represent a relevant therapy option in individual cases for patients 2 years of age and older with seizures associated with tuberous sclerosis.

2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient cannabidiol due to the exceeding of the € 30 million turnover limit.

The therapeutic indication assessed here is as follows: Epidyolex is indicated for use as adjunctive therapy of seizures associated with tuberous sclerosis (TSC) for patients 2 years of age and older.

The G-BA determined a patient-individual therapy as appropriate comparator therapy for patients aged 2 years of age and older with seizures associated with tuberous sclerosis, taking into account the seizure types occurring, the basic and previous therapy/ therapies and any associated side effects, with the selection of brivaracetam, carbamazepine, cenobamate, eslicarbazepine, everolimus, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, topiramate, valproic acid, vigabatrin and zonisamide.

For the assessment of the additional benefit, the pharmaceutical company presented the GWEP1521 study, in which cannabidiol was compared with placebo, in each case in addition to anti-epileptic treatment continued without change.

In the study, no optimisation of anti-epileptic medication was planned in the comparator arm, although the patients included had epileptic seizures and it could not be adequately justified on the basis of the data presented that there was no possibility of optimising treatment in the comparator arm.

The appropriate comparator therapy was therefore not implemented in the study submitted for the benefit assessment.

In the overall assessment, there are no suitable data for the comparison of cannabidiol with the appropriate comparator therapy. Thus, an additional benefit of cannabidiol for patients 2 years of age and older with seizures associated with tuberous sclerosis 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 provided by the pharmaceutical company in the dossier. These are based, among other things, on the determination of a range for the prevalence of tuberous sclerosis using two studies based on a database of the Taiwanese national health insurance organisation and the Swedish national patient register. Furthermore, a restriction is applied to patients with an additional diagnosis of epilepsy who are eligible for adjunctive therapy of seizures associated with tuberous sclerosis.

Limitations of this approach include the unclear transferability of the data on prevalence to the German healthcare context and to the target population aged ≥ 2 years.

Overall, it must be assumed that the lower limit is an underestimate while the upper limit is fraught with uncertainty.

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 Epidyolex (active ingredient: cannabidiol) at the following publicly accessible link (last access: 15 April 2024):

https://www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf

Treatment with cannabidiol should only be initiated and monitored by doctors experienced in treating patients with epilepsy.

A combination of cannabidiol with other anti-epileptic medicines can lead to pharmacokinetic interactions that can lead to an increase in adverse drug reactions. The patient should be closely monitored for adverse drug reactions. If somnolence or sedation occurs in combination with clobazam, a reduction in the clobazam dosage should be considered.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2024).

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.

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 varies from patient to patient 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.

The present therapeutic indication includes patients 2 years of age and older with seizures associated with tuberous sclerosis. For each active ingredient, the calculation of the annual treatment costs is shown below for the least maintenance dose (children 2 years of age or the lowest age approved for the respective active ingredient) and the highest maintenance dose (adults). If an active ingredient is approved exclusively for adults, the minimum and maximum recommended maintenance doses are stated in the product information.

The active ingredient perampanel is approved for patients 4 years of age and older according to the product information. The active ingredients oxcarbazepine, gabapentin and zonisamide, on the contrary, are only approved for patients 6 years of age and older. Eslicarbazepine is approved for children over the age of six. The active ingredients cenobamate and pregabalin are only approved for adults.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics of the Microcensus[6] 2017 to 2021 were used as a basis

6 Federal Health Reporting. Average body measurements of the population (2017 and 2021: both, aged 1 year and 15 years and over), www.gbe-bund.de

(average body weight of a two-year-old child: 14.1 kg; average body weight of a four-year-old child: 18.5 kg; average body weight of a six-year-old child: 23.6 kg; average body weight of a seven-year-old child: 26.6 kg; average body weight of an adult: 77.7 kg).

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form. According to the product information for cannabidiol, the calculated dose should always be rounded up to the next possible scalable dose.

In this particular patient population, it is up to the physician to decide which is the most appropriate dosage form for the respective child < 6 years of age, depending on body weight and dose. For this reason, where available, the dosages of both a solid (tablet or hard capsule) and a liquid formulation (solution, suspension or syrup) are shown for each active ingredient, if no limitations are described in the product information.

In the present therapeutic indication, both cannabidiol and the appropriate comparator therapy are administered as adjunctive therapy to an anti-epileptic medication. The annual treatment costs are shown for the individual active ingredients administered as part of an adjunctive therapy and not for possible combinations.

The shelf life of the medicinal products was taken into account in the calculation.
According to the product information, the dosage of everolimus is different from patient to patient and depends on the trough concentrations of everolimus in the whole blood sample. The costs can therefore not be quantified at this point.

According to the product information, the dosage of phenytoin is different from patient to patient and depends, among other things, on the plasma concentration. The costs can therefore not be quantified at this point.

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				
Cannabidiol	Continuously, 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
Patient-individual therapy, taking into account the types of seizures occurring, the basic and previous therapy/ therapies and any associated side effects, with selection of the following active ingredients:				
Brivaracetam	Continuously, 2 x daily	365.0	1	365.0
Carbamazepine	Continuously, 1 - 2 x daily	365.0	1	365.0
Cenobamate	Continuously, 1 x daily	365.0	1	365.0
Eslicarbazepine	Continuously, 1 x daily	365.0	1	365.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Everolimus	Continuously, 1 x daily	365.0	1	365.0
Gabapentin	Continuously, 3 x daily	365.0	1	365.0
Lacosamide	Continuously, 2 x daily	365.0	1	365.0
Lamotrigine	Continuously, 2 x daily	365.0	1	365.0
Levetiracetam	Continuously, 2 x daily	365.0	1	365.0
Oxcarbazepine	Continuously, 2 x daily	365.0	1	365.0
Perampanel	Continuously, 1 x daily	365.0	1	365.0
Phenobarbital	Continuously, 1 - 2 x daily	365.0	1	365.0
Phenytoin	Continuously, 1 - 2 x daily	365.0	1	365.0
Pregabalin	Continuously, 2 - 3 x daily	365.0	1	365.0
Topiramate	Continuously, 2 x daily	365.0	1	365.0
Valproic acid	Continuously, 2 - 4 x daily	365.0	1	365.0
Vigabatrin	Continuously, 1 - 2 x daily	365.0	1	365.0
Zonisamide	Continuously, 1 – 2 x daily	365.0	1	365.0

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					
Minimum maintenance dose for 2-year-olds					
Cannabidiol OS (100 mg/ml)	70.5 mg (= 5 mg/kg BW)	141 mg (= 10 mg/kg BW)	2 x 75 mg (= 2 x 0.75 ml)	365.0	730 x 75 mg (= 730 x 0.75 ml)
Maximum maintenance dose for adults					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Cannabidiol OS (100 mg/ml)	971.3 mg (= 12.5 mg/kg BW)	1,942.5 mg (= 25 mg/kg BW)	2 x 980 mg (= 2 x 9.8 ml)	365.0	730 x 980 mg (= 730 x 9.8 ml)
Appropriate comparator therapy					
Patient-individual therapy, taking into account the types of seizures occurring, the basic and previous therapy/ therapies and any associated side effects, with selection of the following active ingredients:					
Brivaracetam					
Minimum maintenance dose for 2-year-olds					
Brivaracetam OS[7] (10 mg/ml)	7.1 mg	14.1 mg (= 1 mg/kg BW)	2 x 7 mg (= 2 x 0.7 ml)	365.0	730 x 7 mg (= 730 x 0.7 ml)
Maximum maintenance dose for adults					
Brivaracetam FCT	100 mg	200 mg	2 x 100 mg	365.0	730 x 100 mg
Carbamazepine					
Minimum maintenance dose for 2-year-olds					
Carbamazepine SUS (20 mg/ml)	100 mg	200 mg	2 x 100 mg (= 2 x 5 ml)	365.0	730 x 100 mg (= 730 x 5 ml)
Carbamazepine TAB	200 mg	200 mg	1 x 200 mg	365.0	365 x 200 mg
Maximum maintenance dose for adults					
Carbamazepine SRT	600 mg	1,200 mg	2 x 600 mg	365.0	730 x 600 mg
Cenobamate (from the age of 18)					
Minimum maintenance dose for adults					
Cenobamate FCT	200 mg	200 mg	1 x 200 mg	365.0	365 x 200 mg
Maximum maintenance dose for adults					
Cenobamate FCT	400 mg	400 mg	2 x 200 mg	365.0	730 x 200 mg
Eslicarbazepine (from the age of 7)					
Minimum maintenance dose for 7-year-olds					
Eslicarbazepine TAB	266 mg (= 10 mg/kg BW)	266 mg (= 10 mg/kg BW)	1.5 x 200 mg	365.0	547.5 x 200 mg
Maximum maintenance dose for adults					

7 According to the product information for brivaracetam, patients for whom the appropriate dose cannot be made up using whole tablets should use the oral solution. Therefore, only the liquid dosage form for 2-year-olds is calculated here.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Eslicarbazepine TAB	1,200 mg	1,200 mg	1 x 800 mg + 2 x 200 mg	365.0	365 x 800 mg + 730 x 200 mg
Everolimus					
Everolimus[8]	Different from patient to patient				
Gabapentin (from the age of 6)					
Minimum maintenance dose for 6-year-olds					
Gabapentin HC	197 mg	590 mg (= 25 mg/kg BW)	6 x 100 mg	365.0	2,190 x 100 mg
Maximum maintenance dose for adults					
Gabapentin FCT	1,200 mg	3,600 mg	6 x 600 mg	365.0	2,190 x 600 mg
Lacosamide					
Minimum maintenance dose for 2-year-olds					
Lacosamide SYR (10 mg/ml)	28.2 mg (= 2 mg/kg BW)	56.4 mg (= 4 mg/kg BW)	2 x 27.5 mg (= 2 x 2.75 ml)	365.0	730 x 27.5 mg (= 730 x 2.75 ml)
Lacosamide FCT	28.2 mg (= 2 mg/kg BW)	56.4 mg (= 4 mg/kg BW)	1 x 50 mg[9] (= 2 x 25 mg)	365.0	365 x 50 mg (= 730 x 25 mg)
Maximum maintenance dose for adults					
Lacosamide FCT	200 mg	400 mg	2 x 200 mg	365.0	730 x 200 mg
Lamotrigine					
Minimum maintenance dose for 2-year-olds					
Lamotrigine[10] TOS	7.1 mg	14.1 mg (= 1 mg/kg BW)	2 x 5 mg + 2 x 2 mg	365.0	730 x 5 mg + 730 x 2 mg
Lamotrigine[10] TAB	7.1 mg	14.1 mg[11] (= 1 mg/kg BW)	2 x 5 mg	365.0	730 x 5 mg
Maximum maintenance dose for adults					

8 According to the product information, the dosage of everolimus is different from patient to patient and depends on the trough concentrations of everolimus in the whole blood sample.
9 The film-coated tablets are divisible into 2 x 25 mg lacosamide at the same dose.
10 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.
11 If the calculated dose of lamotrigine cannot be administered in whole tablets, the next lower dose that can be given in whole tablets should be administered.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Lamotrigine[10] TAB	200 mg	400 mg	2 x 200 mg	365.0	730 x 200 mg
Levetiracetam					
Minimum maintenance dose for 2-year-olds					
Levetiracetam[12] OS (100 mg/ml)	141 mg (= 10 mg/kg BW)	282 mg (= 20 mg/kg BW)	2 x 140 mg (= 2 x 1.4 ml)	365.0	730 x 140 mg (= 730 x 1.4 ml)
Maximum maintenance dose for adults					
Levetiracetam[12] FCT	1,500 mg	3,000 mg	2 x 1,500 mg	365.0	730 x 1,500 mg
Oxcarbazepine (from the age of 6)					
Minimum maintenance dose for 6-year-olds					
Oxcarbazepine MRT	354 mg	708 mg (= 30 mg/kg BW)	2 x 300 mg + 0.5 x 150 mg[13] (= 2 x 37.5 mg)	365.0	730 x 300 mg + 182.5 x 150 mg
Maximum maintenance dose for adults					
Oxcarbazepine FCT	1,200 mg	2,400 mg	4 x 600 mg	365.0	1,460 x 600 mg
Perampanel (from the age of 4)					
Minimum maintenance dose for 4-year-olds					
Perampanel OSUS (0.5 mg/ml)	2 mg	2 mg	1 x 2 mg (= 1 x 4 ml)	365.0	365 x 2 mg (= 365 x 4 ml)
Perampanel FCT	2 mg	2 mg	1 x 2 mg	365.0	365 x 2 mg
Maximum maintenance dose for adults					
Perampanel FCT	8 mg	8 mg	1 x 8 mg	365.0	365 x 8 mg
Phenobarbital					
Minimum maintenance dose for 2-year-olds					
Phenobarbital TAB	42.3 mg	42.3 mg (= 3 mg/kg BW)	3 x 15 mg	365.0	1,095 x 15 mg
Maximum maintenance dose for adults					
Phenobarbital TAB	116.1 mg	233.1 mg (= 3 mg/kg BW)	2 x 100 mg + 2 x 15 mg	365.0	730 x 100 mg + 730 x 15 mg

12 According to the product information, the film-coated tablets are unsuitable for children under 6 years of age.
13 The tablets can be divided equally into 4 x 37.5 mg oxcarbazepine.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Phenytoin					
Phenytoin[14]	Different from patient to patient				
Pregabalin (from the age of 18)					
Minimum maintenance dose for adults					
Pregabalin HC	75 mg	150 mg	2 x 75 mg	365.0	730 x 75 mg
Maximum maintenance dose for adults					
Pregabalin HC	300 mg	600 mg	2 x 300 mg	365.0	730 x 300 mg
Topiramate					
Minimum maintenance dose for 2-year-olds					
Topiramate FCT	35.3 mg	70.5 mg (= 5 mg/kg BW)	2 x 1.5 x 25 mg[15]	365.0	1,095 x 25 mg
Maximum maintenance dose for adults					
Topiramate FCT	200 mg	400 mg	2 x 200 mg	365.0	730 x 200 mg
Valproic acid					
Minimum maintenance dose for 2-year-olds					
Valproic acid[16,17] OS (300 mg/ml)	150 mg	300 mg	2 x 150 mg (= 2 x 0.5 ml)	365.0	730 x 150 mg (= 730 x 0.5 ml)
Maximum maintenance dose for adults					
Valproic acid[17] EFCT	600 mg/ 900 mg	2,100 mg	3 x 600 mg + 1 x 300 mg	365.0	1095 x 600 mg + 365 x 300 mg
Vigabatrin					
Minimum maintenance dose for 2-year-olds					
Vigabatrin GRA	500 mg	500 mg	1 x 500 mg	365.0	365 x 500 mg
Vigabatrin FCT	500 mg	500 mg	1 x 500 mg	365.0	365 x 500 mg
Maximum maintenance dose for adults					
Vigabatrin FCT	1,500 mg	3,000 mg	6 x 500 mg	365.0	2,190 x 500 mg
Zonisamide (from the age of 6)					

14 According to the product information, the dosage of phenytoin is different from patient to patient and depends, among other things, on the plasma concentration.
15 The film-coated tablets can be divided equally into 4 x 6.25 mg topiramate.
16 According to the product information, a liquid dosage form should preferably be used for children up to 3 years of age.
17 The dosage information refers to sodium valproate.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Minimum maintenance dose for 6-year-olds					
Zonisamide HC	141.6 mg (= 6 mg/kg BW)	141.6 mg (= 6 mg/kg BW)	1 x 50 mg + 1 x 100 mg	365.0	365 x 50 mg + 365 x 100 mg
Maximum maintenance dose for adults					
Zonisamide TAB	200 mg/ 300 mg	500 mg	1 x 200 mg + 1 x 300 mg	365.0	365 x 200 mg + 365 x 300 mg
Abbreviations: EFCT = enteric film-coated tablets; FCT = film-coated tablets; GRA = granules; HC = hard capsules; SOL = solution; OS = oral solution; SRT = sustained release tablet; SYR = syrup; OSUS = oral suspension; SUS = suspension; TAB = tablets; OD = oral drops; TOS = tablet for oral suspension; MRT = modified release tablet					

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 on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

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					
Cannabidiol OS (100 mg/ml)	300 ml	€ 3,598.70	€ 2.00	€ 0.00	€ 3,596.70
Appropriate comparator therapy					
Patient-individual therapy taking into account the seizure types that occur, the basic and the previous therapy/ therapies and any associated side effects, selecting the following active ingredients:					
Brivaracetam FCT 100 mg	168 FCT	€ 265.22	€ 2.00	€ 14.06	€ 249.16
Brivaracetam OS (10 mg/ml)	300 ml	€ 101.99	€ 2.00	€ 5.02	€ 94.97
Carbamazepine SUS (20 mg/ml)	250 ml	€ 21.00	€ 2.00	€ 0.72	€ 18.28

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
Carbamazepine TAB 200 mg[18]	200 TAB	€ 23.85	€ 2.00	€ 0.99	€ 20.86
Carbamazepine SRT 600 mg[18]	200 SRT	€ 56.03	€ 2.00	€ 3.54	€ 50.49
Cenobamate FCT 200 mg	84 FCT	€ 339.01	€ 2.00	€ 18.14	€ 318.87
Eslicarbazepine TAB 200 mg	60 TAB	€ 72.51	€ 2.00	€ 2.90	€ 67.61
Eslicarbazepine TAB 800 mg	90 TAB	€ 297.35	€ 2.00	€ 13.57	€ 281.78
Everolimus	Not calculable				
Gabapentin HC 100 mg[18]	200 HC	€ 24.09	€ 2.00	€ 1.01	€ 21.08
Gabapentin FCT 600 mg[18]	200 FCT	€ 99.71	€ 2.00	€ 6.99	€ 90.72
Lacosamide SYR (10 mg/ml)	200 ml	€ 50.06	€ 2.00	€ 1.84	€ 46.22
Lacosamide FCT 50 mg	168 FCT	€ 230.05	€ 2.00	€ 10.38	€ 217.67
Lacosamide FCT 200 mg	168 FCT	€ 60.92	€ 2.00	€ 2.35	€ 56.57
Lamotrigine TOS 5 mg	60 TOS	€ 11.69	€ 2.00	€ 0.05	€ 9.64
Lamotrigine TOS 2 mg	30 TOS	€ 11.35	€ 2.00	€ 0.00	€ 9.35
Lamotrigine TAB 5 mg[18]	50 TAB	€ 11.50	€ 2.00	€ 0.01	€ 9.49
Lamotrigine TAB 200 mg[18]	100 TAB	€ 40.27	€ 2.00	€ 2.29	€ 35.98
Levetiracetam OS (100 mg/ml)	150 ml	€ 49.04	€ 2.00	€ 1.79	€ 45.25
Levetiracetam FCT 1,500 mg[18]	200 FCT	€ 106.47	€ 2.00	€ 7.53	€ 96.94
Oxcarbazepine MRT 150 mg	200 MRT	€ 61.19	€ 2.00	€ 2.76	€ 56.43
Oxcarbazepine MRT 300 mg	200 MRT	€ 119.55	€ 2.00	€ 14.26	€ 103.29
Oxcarbazepine FCT 600 mg	200 FCT	€ 142.21	€ 2.00	€ 6.21	€ 134.00
Perampanel OSUS (0.5 mg/ml)	340 ml	€ 84.89	€ 2.00	€ 4.07	€ 78.82
Perampanel FCT 2 mg	28 FCT	€ 102.19	€ 2.00	€ 5.03	€ 95.16

18 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
Perampanel FCT 8 mg	98 FCT	€ 350.63	€ 2.00	€ 18.79	€ 329.84
Phenobarbital TAB 15 mg	100 TAB	€ 33.45	€ 2.00	€ 1.05	€ 30.40
Phenobarbital TAB 100 mg	100 TAB	€ 38.15	€ 2.00	€ 1.48	€ 34.67
Phenytoin	Not calculable				
Pregabalin HC 75 mg[18]	100 HC	€ 33.64	€ 2.00	€ 1.77	€ 29.87
Pregabalin HC 300 mg[18]	100 HC	€ 71.14	€ 2.00	€ 4.73	€ 64.41
Topiramate FCT 25 mg[18]	200 FCT	€ 49.75	€ 2.00	€ 3.04	€ 44.71
Topiramate FCT 200 mg[18]	200 FCT	€ 267.83	€ 2.00	€ 20.29	€ 245.54
Valproate sodium OS (300 mg/ml) [18]	100 ml	€ 23.10	€ 2.00	€ 0.93	€ 20.17
Valproate sodium EFCT 600 mg[18]	200 EFCT	€ 50.09	€ 2.00	€ 3.07	€ 45.02
Valproate sodium EFCT 300 mg[18]	200 EFCT	€ 34.19	€ 2.00	€ 1.81	€ 30.38
Zonisamide HC 50 mg[18]	98 HC	€ 122.18	€ 2.00	€ 8.77	€ 111.41
Zonisamide HC 100 mg[18]	196 HC	€ 315.54	€ 2.00	€ 24.06	€ 289.48
Zonisamide HC 200 mg[18]	196 TAB	€ 423.96	€ 2.00	€ 0.00	€ 421.96
Zonisamide HC 300 mg[18]	196 TAB	€ 504.51	€ 2.00	€ 0.00	€ 502.51
Vigabatrin FTA 500 mg	200 FCT	€ 238.38	€ 2.00	€ 12.57	€ 223.81
Vigabatrin GRA 500 mg	100 GRA	€ 202.13	€ 2.00	€ 10.57	€ 189.56

Abbreviations: EFCT = enteric film-coated tablets; FCT = film-coated tablets; GRA = granules; HC = hard capsules; OS = oral solution; SRT = sustained release tablet; SYR = syrup; OSUS = oral suspension; SUS = suspension; TAB = tablets; OD = oral drops; TOS = tablet for oral suspension; MRT = modified release tablet

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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 the standard expenditure in the course of the treatment are not shown.

Due to the risk of visual field defects during treatment with vigabatrin, patients must be examined by an ophthalmologist at regular intervals. Visual field tests (electroretinography or, if possible, perimetry) should be carried out at regular intervals of 6 months during the entire treatment duration. The assessment must be continued for 6 to 12 months after therapy discontinuation. In addition, visual examinations should be carried out at least every 6 weeks.

Designation of the therapy	Designation of the service	Number	Cost per unit	Costs/ patient/ year
Vigabatrin	Ophthalmological examination	Different from patient to patient	Not calculable	

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Patients 2 years of age and older with seizures associated with tuberous sclerosis

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. According to the product information, this therapeutic use is an adjunctive therapy for seizures associated with tuberous sclerosis.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:
Product information on

- Cannabidiol (Epidyolex); Epidyolex 100 mg/ml oral solution; last revised: May 2023
- Brivaracetam (Briviact); Briviact 10 mg/ml oral solution; last revised: February 2023
- Cenobamate (Ontozry); Ontozry tablets; last revised: November 2023
- Vigabatrin (Kigabeq); Sabril 500 mg film-coated tablets, Sabril sachet; last revised: January 2021

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

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.

4. Process sequence

At its session on 28 March 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 30 November 2023, the pharmaceutical company submitted a dossier for the benefit assessment of cannabidiol to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 6 VerfO.

By letter dated 4 December 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 cannabidiol.

The dossier assessment by the IQWiG was submitted to the G-BA on 14 February 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 March 2024. The deadline for submitting statements was 22 March 2024.

The oral hearing was held on 8 April 2024.

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 7 May 2024, and the proposed resolution was approved.

At its session on 16 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 March 2023	Implementation of the appropriate comparator therapy
Working group Section 35a	3 April 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	7 May 2024	Conduct of the oral hearing
Working group Section 35a	16 April 2024 29 April 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure

Subcommittee Medicinal products	7 May 2024	Concluding discussion of the draft resolution
Plenum	16 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 May 2024

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

Prof. Hecken