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: Lennox-Gastaut syndrome, ≥ 2 years, combination with clobazam)

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 sessions on 2 April 2020 and 15 April 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 Lennox-Gastaut syndrome (LGS), in conjunction with clobazam, 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 Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.

Therapeutic indication of the resolution (resolution of 16.05.2024):

Epidyolex is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS), in conjunction with clobazam, for patients 2 years of age and older.

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome

Appropriate comparator therapy for cannabidiol in combination with clobazam 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, bromide, carbamazepine, cenobamate, clobazam, clonazepam, eslicarbazepine, ethosuximide, felbamate, fenfluramine, gabapentin, lacosamide, lamotrigine, levetiracetam, mesuximide, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, 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 ingredients clonazepam, felbamate, fenfluramine, lamotrigine, rufinamide and topiramate are approved for the therapeutic indication of Lennox-Gastaut syndrome (LGS).

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 are approved for certain types of seizures or generally for the treatment of epileptic seizures.

on 2. In the present therapeutic indication, no non-medicinal treatment is considered as an appropriate comparator therapy.

on 3. In the present therapeutic indication, there are resolutions on the benefit assessment according to Section 35a SGB V for the active ingredient cannabidiol from 2 April 2020 and 15 April 2021 and on the active ingredient fenfluramine from 3 August 2023.

In the therapeutic indication of epilepsy, the following resolutions on the benefit assessment according to Section 35a SGB V are available:

- 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 therapeutic indication according to Section 35a, paragraph 7 SGB V.

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

The clinical picture of Lennox-Gastaut syndrome typically includes a variety of seizure types (including tonic, tonic-clonic, myoclonic and atonic seizures). Therefore, in addition to the

active ingredients clonazepam, felbamate, fenfluramine, lamotrigine, rufinamide and topiramate that are specifically approved for the therapeutic indication, active ingredients that are approved for the various seizure types or generally for the treatment of epileptic seizures can also be considered as part of the appropriate comparator therapy, provided there are no contraindications for the Lennox-Gastaut syndrome.

Although some of the active ingredients are specifically recommended in the guidelines[2,3], all approved anti-epileptic active ingredients that are suitable for the predominant seizure type can be used. The widest possible selection of active ingredients is considered to be sensible, particularly in view of the fact that the disease is severe and refractory to treatment. Consequently, all active ingredients approved for the treatment of epileptic seizures in general or specifically for Lennox-Gastaut syndrome can be considered as appropriate therapy options in this therapeutic indication.

Therefore, a patient-individual therapy is determined as appropriate comparator therapy for cannabidiol in combination with clobazam for patients aged 2 years of age and older with seizures associated with Lennox-Gastaut syndrome, taking into account the seizure types occurring, the basic and previous therapy/ therapies and any associated side effects, with the selection of brivaracetam, bromide, carbamazepine, cenobamate, clobazam, clonazepam, eslicarbazepine, ethosuximide, felbamate, fenfluramine, gabapentin, lacosamide, lamotrigine, levetiracetam, mesuximide, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, topiramate, valproic acid, vigabatrin 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 alone also does not correspond to the appropriate comparator therapy, as a rule.

The active ingredient 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

The active ingredient fenfluramine has been approved since 24 January 2023 for the treatment of seizures associated with Lennox-Gastaut syndrome in patients ≥ 2 years of age.

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

The benefit assessment according to Section 35a SGB V showed a hint for a considerable additional benefit of fenfluramine as adjunctive therapy to other anti-epileptic medicines in this therapeutic indication. The S2k guideline recommends the use of fenfluramine for seizures associated with Lennox-Gastaut syndrome.

The marketing authorisation for the active ingredient carbamazepine generally relates to the treatment of various forms of epileptic seizures. Even if carbamazepine should preferably be administered as monotherapy according to the product information, guidelines recommend the treatment of focal-onset seizures.

Given the treatment refractoriness of the clinical picture, all approved anti-epileptic active ingredients suitable for the respective seizure type are generally considered appropriate options as part of patient-individual therapy in this therapeutic indication. Against this background, it is considered appropriate to determine fenfluramine and carbamazepine as appropriate comparator therapy as part of patient-individual therapy.

In addition, for patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome, a patient-individual adjuvant anti-epileptic therapy has been determined as appropriate comparator therapy, provided that it is medically indicated and if no pharmacoresistance (in the sense of an inadequate response), intolerance or contraindication is known, by selecting the active ingredients mentioned, taking into account the seizure types occurring, the basic and previous therapy/ therapies and any associated side effects.

For reasons of clarity and for better understanding, the formulation of the appropriate comparator therapy is adapted and changed to a patient-individual therapy, taking into account the occurring seizure types, the basic and previous therapy/ therapies as well as any associated side effects, with selection of the active ingredients mentioned.

When selecting an active ingredient as part of patient-individual therapy, it is also assumed that it is medically indicated and that there is no known inadequate response (drug-related pharmacoresistance), intolerance or contraindication with regard to the respective active ingredient. Thus, the adjustment of the formulation does not result in any change in the content 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 Lennox-Gastaut syndrome, the additional benefit is not proven.

Justification:

For the assessment of the additional benefit, the pharmaceutical company submits evaluations of the GWEP1414 and GWEP1423 studies.

These are two randomised, controlled, double-blind studies in which cannabidiol was compared with placebo, in each case in addition to continued anti-epileptic treatment. The results of both studies were already the basis for the resolutions on the benefit assessment of the active ingredient cannabidiol according to Section 35a SGB V from 2 April 2020 and 15 April 2021.

Patients 2 to 55 years of age with Lennox-Gastaut syndrome who had been taking one or more anti-epileptic medicines at an unchanged dose for at least 4 weeks were enrolled. Patients had to have a documented history of failure on more than one anti-epileptic medicine and at least 2 falls per week during the 4-week baseline phase.

The study population was randomised in a ratio of 2:2:1:1 to the study arms cannabidiol 10 mg/kg/day, cannabidiol 20 mg/kg/day or a respective placebo equivalent (GWEP1414) or in a ratio of 1:1 to the study arms cannabidiol 20 mg/kg/day and placebo (GWEP1423).

The treatment duration in both studies was 14 weeks (including a 2-week 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 Lennox-Gastaut syndrome 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 studies for the present benefit assessment, no optimisation of anti-epileptic treatment was planned for 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 GWEP1414 and GWEP1423 studies.

For patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome, 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 Lennox-Gastaut syndrome 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 Lennox-Gastaut syndrome.

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 Lennox-Gastaut syndrome (LGS), in conjunction with clobazam, 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 Lennox-Gastaut syndrome, taking into account the seizure types occurring, the basic and previous therapy/ therapies and any associated side effects, with the selection of brivaracetam, bromide, carbamazepine, cenobamate, clobazam, clonazepam, eslicarbazepine, ethosuximide, felbamate, fenfluramine, gabapentin, lacosamide, lamotrigine, levetiracetam, mesuximide, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, topiramate, valproic acid, vigabatrin and zonisamide.

For the assessment of the additional benefit, the pharmaceutical company presented the GWEP1414 and GWEP1423 studies, in which cannabidiol was compared with placebo, in each case in addition to anti-epileptic treatment continued without change.

In the studies, 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 studies 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 Lennox-Gastaut syndrome 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 for the lower limit and the information on the number of patients in the resolutions on cannabidiol from 15 April 2021 and on fenfluramine from 3 August 2023, which are relevant for this therapeutic indication, for the upper limit.

The pharmaceutical company's assessment is based, among other things, on the determination of a range for the prevalence of Lennox-Gastaut syndrome using a retrospective cohort study and a SHI routine data analysis. In addition, the percentage of patients for whom treatment with clobazam is suitable is determined on the basis of the approval studies on cannabidiol and fenfluramine.

Limitations to this approach include uncertainties in the disease definitions used in the prevalence studies and in the limitation to patients treated with clobazam. With regard to the upper limit, it is assumed that the corresponding figure from the above-mentioned resolutions is a better approximation, although an overestimation can also be assumed in this respect.

Overall, the figures are subject to uncertainties; the upper limit is likely to be an overestimate.

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 Lennox-Gastaut syndrome. 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 ingredients felbamate and perampanel are only approved for patients 4 years of age and older according to the product information. The active ingredients oxcarbazepine,

gabapentin and zonisamide are 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[4] 2017 to 2021 were used as a basis (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.

The shelf life of the medicinal products was taken into account, and, if applicable, the discard due to expiry of the shelf life was included.

Cannabidiol is given in combination with clobazam in accordance with the marketing authorisation. Therefore, the annual treatment costs of both active ingredients and the resulting total are shown.

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

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
Clobazam	Continuously, 1 – 3 x daily	365.0	1	365.0
Appropriate comparator therapy				

4 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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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
Clobazam	Continuously, 1 – 3 x daily	365.0	1	365
Cenobamate	Continuously, 1 x daily	365.0	1	365.0
Clonazepam	Continuously, 3 - 4 x daily	365.0	1	365.0
Eslicarbazepine	Continuously, 1 x daily	365.0	1	365.0
Ethosuximide	Continuously, 1-3 x daily	365.0	1	365.0
Felbamate	Continuously, 2 - 3 x daily	365.0	1	365.0
Fenfluramine	Continuously, 2 x daily	365.0	1	365.0
Gabapentin	Continuously, 3 x daily	365.0	1	365.0
Potassium bromide	Continuously, 2 – 3 x daily	365.0	1	365.0
Lacosamide	Continuously, 2 x daily	365.0	1	365.0
Lamotrigine	Continuously, 1-2 x daily	365.0	1	365.0
Levetiracetam	Continuously, 2 x daily	365.0	1	365.0
Mesuximide	Continuously, 1 - 3 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,	365.0	1	365.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	2 - 3 x daily			
Primidone	Continuously, 2 - 3 x daily	365.0	1	365.0
Rufinamide	Continuously, 2 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)
Clobazam[5] OSUS (2 mg/ml)	4.2 mg	4.2 mg (= 0.3 mg/kg BW)	1 x 4.2 mg (1 x 2.1 ml)	365.0	365 x 4.2 mg (6.1 x 150 ml)[6]
Maximum maintenance dose for adults					
Cannabidiol OS (100 mg/ml)	777 mg (= 10 mg/kg BW)	1,554 mg (= 20 mg/kg BW)	2 x 780 mg (= 2 x 7.8 ml)	365.0	730 x 780 mg (= 730 x 7.8 ml)
Clobazam TAB	80 mg	80 mg	8 x 10 mg	365.0	2,920 x 10 mg
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:					

5 According to the product information, a liquid dosage form should be used for children under 6 years of age.
6 The shelf life of an opened bottle is 60 days according to the product information, so that discard must be taken into account in this case.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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 7.1 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
Clobazam					
Minimum maintenance dose for 2-year-olds					
Clobazam[5] OSUS (2 mg/ml)	4.2 mg	4.2 mg (= 0.3 mg/kg BW)	1 x 4.2 mg (= 1 x 2.1 ml)	365.0	365 x 4.2 mg (6.1 x 150 ml)[6]
Maximum maintenance dose for adults					
Clobazam TAB	80 mg	80 mg	8 x 10 mg	365.0	2,920 x 10 mg
Clonazepam					
Minimum maintenance dose for 2-year-olds					
Clonazepam OD (2.5 mg/ml)	0.5 mg (= 5 drops of 0.1 mg each)	1.5 mg (= 15 drops of 0.1 mg each)	15 x 0.1 mg (= 15 drops of 0.1 mg each)	365.0	5,475 x 0.1 mg (= 5,475 drops of 0.1 mg each)

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
Clonazepam TAB	0.5 mg	1.4 mg (= 0.1 mg/ kg BW)	3 x 0.5 mg	365.0	1,095 x 0.5 mg
Maximum maintenance dose for adults					
Clonazepam TAB	6 / 8 mg	20 mg	10 x 2 mg	365.0	3,650 x 2 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					
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
Ethosuximide					
Minimum maintenance dose for 2-year-olds					
Ethosuximide[8] OS (50 mg/ml)	282 mg (= 20 mg/kg BW)	282 mg (= 20 mg/kg BW)	1 x 275 mg (= 5.5 ml)	365.0	365 x 275 mg (= 365 x 5.5 ml)
Maximum maintenance dose for adults					
Ethosuximide SC	1,500 mg	1,500 mg	6 x 250 mg	365.0	2,190 x 250 mg
Felbamate					
Minimum maintenance dose for 4-year-olds					
Felbamate OSUS (600 mg/5 ml)	69.4 mg	138.8 mg (= 7.5 mg/kg BW)	2 x 72 mg (= 2 x 0.6 ml)	365.0	12 x 230 ml[9]
Maximum maintenance dose for adults					
Felbamate OSUS (600 mg/5 ml)	1,200 mg	3,600 mg	3 x 1,200 mg (= 3 x 10 ml)	365.0	1,095 x 1,200 mg (= 1,095 x 10 ml)
Fenfluramine					
Minimum maintenance dose for 2-year-olds					
Fenfluramine OS (2.2 mg/ml)	2.8 mg (= 0.2 mg/kg BW)	5.6 mg (= 0.4 mg/kg BW)	2 x 2.8 mg (= 2 x 1.3 ml)	365.0	730 x 2.8 mg (= 730 x 1.3 ml)
Maximum maintenance dose for adults[10]					

8 According to the product information, a liquid dosage form should be used for children under 6 years of age.
9 The shelf life of an opened bottle is one month according to the product information, so that discard must be taken into account in this case.
10 The recommended maximum dose is for patients who do not receive additional stiripentol.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Fenfluramine OS (2.2 mg/ml)	13 mg	26 mg	2 x 13 mg (= 2 x 6 ml)	365.0	730 x 13 mg (= 730 x 6.0 ml)
Gabapentin					
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 HC	1,200 mg	3,600 mg	6 x 600 mg	365.0	2,190 x 600 mg
Potassium bromide					
Minimum maintenance dose for 2-year-olds					
Potassium bromide TAB	352.5 mg	705 mg (= 50 mg/kg BW)	2 x 0.5 x 850 mg	365.0	365 x 850 mg
Maximum maintenance dose for adults					
Potassium bromide TAB	1,295 mg	3,885 mg (= 50 mg/kg BW)	3 x 1.5 x 850 mg	365.0	1,642.5 x 850 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[11] (= 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[12] 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

11 The film-coated tablets can be divided equally into 2 x 25 mg lacosamide.
12 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
Lamotrigine[12] TAB	7.1 mg	14.1 mg[13] (= 1 mg/kg BW)	2 x 5 mg	365.0	730 x 5 mg
Maximum maintenance dose for adults					
Lamotrigine[12] TAB	200 mg	400 mg	2 x 200 mg	365.0	730 x 200 mg
Levetiracetam					
Minimum maintenance dose for 2-year-olds					
Levetiracetam OS[14] (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[14] FCT	1,500 mg	3,000 mg	2 x 1,500 mg	365.0	730 x 1,500 mg
Mesuximide					
Minimum maintenance dose for 2-year-olds					
Mesuximide HC	150 mg	150 mg	1 x 150 mg	365.0	365 x 150 mg
Maximum maintenance dose for adults					
Mesuximide HC	600 mg	1,200 mg	4 x 300 mg	365.0	1,460 x 300 mg
Oxcarbazepine					
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[15] (= 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					

13 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.
14 According to the product information, the film-coated tablets are unsuitable for children under 6 years of age.
15 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
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	116.6 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
Phenytoin					
Phenytoin[16]	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
Primidone					
Minimum maintenance dose for 2-year-olds					
Primidone SUS (125 mg/ml)	125 mg	250 mg	2 x 125 mg (= 2 x 5 ml)	365.0	730 x 125 mg (= 730 x 5 ml)
Primidone TAB	125 mg	250 mg	2 x ½ x 250 mg	365.0	365 x 250 mg
Maximum maintenance dose for adults					
Primidone TAB	500 mg	1,500 mg	6 x 250 mg	365.0	2,190 x 250 mg
Rufinamide					
Minimum maintenance dose for 2-year-olds					
Rufinamide SUS (40 mg/ml)	211.5 mg	423 mg (= 30 mg/ kg BW)	2 x 220 mg (= 2 x 5.5 ml)	365.0	730 x 220 mg (= 730 x 5.5 ml)
Rufinamide FCT	211.5 mg	423 mg (= 30 mg/ kg BW)	2 x 200 mg	365.0	730 x 200 mg
Maximum maintenance dose for adults					
Rufinamide FCT	1,600 mg	3,200 mg	8 x 400 mg	365.0	2,920 x 400 mg

16 According to the product information, the dosage of phenytoin is different from patient to patient and depends, among other things, on the plasma concentration.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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[17]	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[18,19] LSE (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[19] EFCT	600 mg/ 900 mg	2,100 mg	3 x 600 mg + 1 x 300 mg	365.0	1,095 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)					
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; OS = oral solution; SRT = sustained release tablet; SYR = syrup; OSUS = oral suspension; SUS = suspension; TAB = tablets; OD = oral drops; TOS = tablets for oral suspension; MRT = modified release tablets; SC = soft capsules					

Costs:

17 The film-coated tablets can be divided equally into 4 x 6.25 mg topiramate.
18 According to the product information, a liquid dosage form should preferably be used for children up to 3 years of age.
19 The dosage information refers to sodium valproate.

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
Clobazam OSUS (2 mg/ml)	150 ml	€ 177.14	€ 2.00	€ 20.99	€ 154.15
Clobazam TAB 10 mg[20]	50 TAB	€ 19.22	€ 2.00	€ 0.00	€ 17.22
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 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
Carbamazepine TAB 200 mg[20]	200 TAB	€ 23.85	€ 2.00	€ 0.99	€ 20.86
Carbamazepine SRT 600 mg[20]	200 SRT	€ 56.03	€ 2.00	€ 3.54	€ 50.49
Cenobamate FCT 200 mg	84 TAB	€ 339.01	€ 2.00	€ 18.14	€ 318.87
Clobazam OSUS (2 mg/ml)	150 ml	€ 177.14	€ 2.00	€ 20.99	€ 154.15
Clobazam TAB 10 mg[20]	50 TAB	€ 19.22	€ 2.00	€ 0.00	€ 17.22
Clonazepam OD (2.5 mg/ml)	50 ml	€ 41.15	€ 2.00	€ 1.42	€ 37.73
Clonazepam TAB 0.5 mg	100 TAB	€ 21.46	€ 2.00	€ 0.48	€ 18.98

20 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
Clonazepam TAB 2 mg	100 TAB	€ 31.96	€ 2.00	€ 0.98	€ 28.98
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
Ethosuximide OS (250 mg/ml)	250 ml	€ 36.51	€ 2.00	€ 11.53	€ 22.98
Ethosuximide SC 250 mg	200 SC	€ 65.00	€ 2.00	€ 2.55	€ 60.45
Felbamate OSUS (600 mg/5 ml)	230 ml	€ 206.88	€ 2.00	€ 10.89	€ 193.99
Fenfluramine OS (2.2 mg/ml)	120 ml	€ 1,031.72	€ 2.00	€ 56.50	€ 973.22
Fenfluramine OS (2.2 mg/ml)	360 ml	€ 3,025.37	€ 2.00	€ 169.49	€ 2,853.88
Gabapentin HC 100 mg[20]	200 HC	€ 24.09	€ 2.00	€ 1.01	€ 21.08
Gabapentin FCT 600 mg[20]	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[20]	50 TAB	€ 11.50	€ 2.00	€ 0.01	€ 9.49
Lamotrigine TAB 5 mg[20]	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[20]	200 FCT	€ 106.47	€ 2.00	€ 7.53	€ 96.94
Mesuximide HC 150 mg	100 HC	€ 70.65	€ 2.00	€ 6.87	€ 61.78
Mesuximide HC 300 mg	100 HC	€ 98.27	€ 2.00	€ 10.03	€ 86.24
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

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
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
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[20]	100 HC	€ 33.64	€ 2.00	€ 1.77	€ 29.87
Pregabalin HC 300 mg[20]	100 HC	€ 71.14	€ 2.00	€ 4.73	€ 64.41
Primidone SUS (125 mg/ml)	250 ml	€ 20.67	€ 2.00	€ 0.52	€ 18.15
Primidone TAB 250 mg[20]	200 TAB	€ 34.28	€ 2.00	€ 1.82	€ 30.46
Rufinamide SUS (40 mg/ml)	460 ml	€ 178.33	€ 2.00	€ 9.25	€ 167.08
Rufinamide FCT 200 mg	50 FCT	€ 86.94	€ 2.00	€ 4.19	€ 80.75
Rufinamide FCT 400 mg	200 FCT	€ 616.56	€ 2.00	€ 33.51	€ 581.05
Topiramate FCT 25 mg[20]	200 FCT	€ 49.75	€ 2.00	€ 3.04	€ 44.71
Topiramate FCT 200 mg[20]	200 FCT	€ 267.83	€ 2.00	€ 20.29	€ 245.54
Valproate sodium OS (300 mg/ml)[20]	100 ml	€ 23.10	€ 2.00	€ 0.93	€ 20.17
Valproate sodium EFCT 600 mg[20]	200 EFCT	€ 50.09	€ 2.00	€ 3.07	€ 45.02
Valproate sodium EFCT 300 mg[20]	200 EFCT	€ 34.19	€ 2.00	€ 1.81	€ 30.38
Vigabatrin FCT 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
Zonisamide HC 50 mg[20]	98 HC	€ 122.18	€ 2.00	€ 8.77	€ 111.41
Zonisamide HC 100 mg[20]	196 HC	€ 315.54	€ 2.00	€ 24.06	€ 289.48

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 HC 200 mg[20]	196 TAB	€ 423.96	€ 2.00	€ 0.00	€ 421.96
Zonisamide HC 300 mg[20]	196 TAB	€ 504.51	€ 2.00	€ 0.00	€ 502.51
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 = tablets for oral suspension; MRT = modified release tablets; SC = soft capsules					

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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.

When using fenfluramine, the heart function must be monitored by echocardiography. Echocardiography must be performed prior to treatment to establish a baseline condition. Monitoring by echocardiography should be performed every 6 months for the first 2 years and annually after that.

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	
Fenfluramine	Duplex-echocardiography (GOP 33022)	1	€ 36.64	€ 36.64

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 Lennox-Gastaut syndrome

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 Lennox-Gastaut syndrome.

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

The following medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product in the therapeutic indication of the present resolution on the basis of the marketing authorisation under Medicinal Products Act are excluded from the designation, as the G-BA has identified at least considerable additional benefit for the combination with the assessed medicinal product in the resolution on the benefit assessment of fenfluramine of 3 August 2023 (Federal Gazette, BAnz AT 24.08.2023 B1):

Fenfluramine (Fintempla)

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 15 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