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 (Dravet syndrome, ≥ 2 years, combination with clobazam))

of 16 May 2024

Contents

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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 Dravet syndrome (DS), 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

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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), therefore 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 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 Dravet syndrome (DS) in conjunction with clobazam, for patients 2 years of age and older.

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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 Dravet syndrome

Appropriate comparator therapy for cannabidiol in combination with clobazam as adjunctive therapy:

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

  Brivaracetam, bromide, clobazam, fenfluramine, levetiracetam, stiripentol, topiramate, valproic acid

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,

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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 cannabidiol, the active ingredients bromide, fenfluramine and stiripentol are approved for the therapeutic indication of Dravet syndrome.

The following active ingredients are approved for certain seizure types or generally for the treatment of epileptic seizures: Brivaracetam, carbamazepine, cenobamate, clobazam, clonazepam, eslicarbazepine, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, mesuximide, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, pregabalin, topiramate, valproic acid, vigabatrin, zonisamide.

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 15 July 2021.

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.

In addition to the active ingredient cannabidiol, the active ingredients stiripentol, fenfluramine and bromide are approved specifically for the treatment of seizures associated

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with Dravet syndrome. For the present therapeutic indication the guidelines[1,2] also recommend the active ingredients valproic acid, clobazam, levetiracetam and topiramate, which are generally approved for the treatment of various epileptic seizures. In addition, brivaracetam, which has similar properties to levetiracetam, can also be considered as an appropriate comparator therapy.

The decision as to which of the active ingredients mentioned is suitable for the subject to be treated is made on a patient-individual basis in medical care. This takes into account the therapies carried out to date, medications currently being used for treatment, the seizure types the subject suffers from and which side effects may occur.

In the overall assessment of the evidence, a patient-individual therapy is recommended for patients 2 years of age and older with seizures associated with Dravet syndrome, taking into account the seizure type occurring, the basic and previous therapy/ therapies and any associated side effects, selecting the active ingredients brivaracetam, bromide, clobazam, fenfluramine, levetiracetam, stiripentol, topiramate and valproic acid as the appropriate comparator therapy for cannabidiol in combination with clobazam.

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 therapy 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, for patients 2 years of age and older with seizures associated with Dravet syndrome, a patient-individual adjunctive 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, and 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

1 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

2 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

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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 Dravet syndrome, the additional benefit is not proven.

Justification:

For the assessment of the additional benefit, the pharmaceutical company submitted evaluations of the GWEP1424 and GWEP1332 (Part B) 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 aged 2 to 18 years with Dravet syndrome who were taking one or more anti-epileptic medicines at an unchanged dose for at least 4 weeks and who suffered 4 or more convulsive seizures during the 4-week baseline phase were enrolled.

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 (GWEP1424) or in a ratio of 1:1 to the study arms cannabidiol 20 mg/kg/day and placebo (GWEP1332 Part B).

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 Dravet syndrome will be a patient-individual therapy, taking into account the

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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 GWEP1424 and GWEP1332 (Part B) studies.

For patients aged 2 years and older with seizures associated with Dravet 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 Dravet 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 Dravet 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 Dravet syndrome (DS) in conjunction with clobazam, for patients 2 years of age and older.

The G-BA determined the appropriate comparator therapy for patients 2 years of age and older with seizures associated with Dravet syndrome to be a patient-individual therapy, taking into account the seizure types occurring, the basic therapy and previous therapy/ therapies as well as any associated side effects, selecting brivaracetam, bromide, clobazam, fenfluramine, levetiracetam, stiripentol, topiramate and valproic acid.

For the assessment of the additional benefit, the pharmaceutical company presented the GWEP1424 and GWEP1332 (Part B) 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

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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 Dravet 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.

The pharmaceutical company's assessment is based, among other things, on the determination of a range for the prevalence of the Dravet syndrome using two studies, which are based on a US-American analysis of insured persons and a SHI routine data analysis. In addition, the percentage of patients for whom treatment with clobazam is suitable will be determined using a European cross-sectional study based on an anonymous survey of caregivers and the approval studies on cannabidiol.

Limitations of this approach include the unclear transferability of the data on prevalence to the SHI population and uncertainties in the limitation to patients treated with clobazam. Overall, the information is subject to 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).

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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 Dravet syndrome. The calculation of the annual treatment costs for the lowest (children 2 years of age) and highest maintenance dose (adults) is shown below for each active ingredient.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics of the Microcensus[3] 2017 to 2021 were used as a basis (average body weight of a two-year-old child: 14.1 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.

Stiripentol is only administered in combination with clobazam and valproate in accordance with the marketing authorisation.

3 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

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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 to 3 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
Clobazam	Continuously, 1 to 3 x daily	365.0	1	365.0
Fenfluramine	Continuously, 2 x daily	365.0	1	365.0
Potassium bromide	Continuously, 2 - 3 x daily	365.0	1	365.0
Levetiracetam	Continuously, 2 x daily	365.0	1	365.0
Stiripentol	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

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)

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Clobazam[4] 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)[5]
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:					
Brivaracetam					
Minimum maintenance dose for 2-year-olds					
Brivaracetam[6] OS (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
Clobazam					
Minimum maintenance dose for 2-year-olds					
Clobazam[4] 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)[5]
Maximum maintenance dose for adults					
Clobazam TAB	80 mg	80 mg	8 x 10 mg	365.0	2,920 x 10 mg
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[7]					
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)
Potassium bromide					

4 According to the product information, a liquid dosage form should be used for children under 6 years of age.
5 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.
6 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.
7 The recommended maximum dose is for patients who do not receive additional stiripentol.

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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 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
Levetiracetam					
Minimum maintenance dose for 2-year-olds					
Levetiracetam[8] OS (100mg/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[8] FCT	1,500 mg	3,000 mg	2 x 1,500 mg	365.0	730 x 1,500 mg
Stiripentol					
Minimum maintenance dose for 2-year-olds					
Stiripentol POS	500 mg/ 250 mg	705 mg (= 50 mg/kg BW)	1 x 500 mg + 1 x 250 mg	365.0	365 x 500 mg + 365 x 250 mg
Maximum maintenance dose for adults					
Stiripentol HC	1,942.5 mg	3,885 mg (= 50 mg/kg BW)	8 x 500 mg	365.0	2,920 x 500 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[9]	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					

8 According to the product information, the film-coated tablets are unsuitable for children under 6 years of age.
9 The tablets are divisible into four parts (6.25 mg topiramate each) at the same dose.

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Valproic acid OS[10,11] (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 EFCT[11]	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
Abbreviations: FCT = film-coated tablets; EFCT = enteric film-coated tablets; HC = hard capsules; OS = oral solution; POS = powder for oral suspension; OSUS = oral suspension; TAB = tablets					

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
Clobazam OSUS (2 mg/ml)	150 ml	€ 177.14	€ 2.00	€ 20.99	€ 154.15
Clobazam FCT 10 mg[12]	50 FCT	€ 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:					

10 According to the product information, a liquid dosage form should preferably be used for children up to 3 years of age.
11 The dosage information refers to sodium valproate.

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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
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
Clobazam OSUS (2 mg/ml)	150 ml	€ 177.14	€ 2.00	€ 20.99	€ 154.15
Clobazam FCT 10 mg[12]	50 FCT	€ 19.22	€ 2.00	€ 0.00	€ 17.22
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
Potassium bromide TAB 850 mg	60 TAB	€ 694.32	€ 2.00	€ 80.18	€ 612.14
Levetiracetam OS (100 mg/ml)	150 ml	€ 49.04	€ 2.00	€ 1.79	€ 45.25
Levetiracetam FCT 1,500 mg[12]	200 FCT	€ 106.47	€ 2.00	€ 7.53	€ 96.94
Stiripentol POS 250 mg	60 POS	€ 294.51	€ 2.00	€ 15.68	€ 276.83
Stiripentol POS 500 mg	60 POS	€ 543.94	€ 2.00	€ 29.49	€ 512.45
Stiripentol HC 500 mg	60 HC	€ 543.94	€ 2.00	€ 29.49	€ 512.45
Topiramate FCT 25 mg[12]	200 FCT	€ 49.75	€ 2.00	€ 3.04	€ 44.71
Topiramate FCT 200 mg[12]	200 FCT	€ 267.83	€ 2.00	€ 20.29	€ 245.54
Valproate sodium OS (300 mg/ml)[12]	100 ml	€ 23.10	€ 2.00	€ 0.93	€ 20.17
Valproate sodium EFCT 300 mg[12]	200 EFCT	€ 34.19	€ 2.00	€ 1.81	€ 30.38
Valproate sodium EFCT 600 mg[12]	200 EFCT	€ 50.09	€ 2.00	€ 3.07	€ 45.02
Abbreviations: FCT = film-coated tablets; EFCT = enteric film-coated tablets; HC = hard capsules; OS = oral solution; POS = powder for oral suspension; OSUS = oral suspension; TAB = tablets					

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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

12 Fixed reimbursement rate

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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.

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
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

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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.

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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.

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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 Dravet 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 Dravet 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 15 July 2021 (Federal Gazette, BAnz AT 28.09.2021 B1):

Fenfluramine (Fintempla)

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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 20 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.

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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	8 April 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

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