

Resolution

of the Federal Joint Committee on an Amendment of the
Pharmaceuticals Directive:

Annex XII – Benefit Assessment of Medicinal Products with
New Active Ingredients according to Section 35a SGB V
Cannabidiol (New Therapeutic Indication: seizures associated
with tuberous sclerosis, ≥ 2 years, adjunctive therapy)

of 4 November 2021

At its session on 4 November 2021, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No 49a of 31 March 2009), as last amended by the publication of the resolution of DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

- I. **In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of cannabidiol in accordance with the resolution of 15 April 2021 for the therapeutic indication "Epidyolex is used in addition with clobazam, in patients two years of age and older for the adjuvant treatment of seizures associated with Lennox-Gastaut-Syndrome (LGS).":**

Cannabidiol

Resolution of: 4 November 2021
Entry into force on: 4 November 2021
BAz AT DD.MM.YYYY Bx

New therapeutic indication (according to the marketing authorisation of 16 April 2021):

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

Therapeutic indication of the resolution (resolution of 4 November 2021):

See new therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Cannabidiol is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Patients 2 years and older with seizures associated with tuberous sclerosis, adjunctive therapy

Extent of the additional benefit and significance of the evidence of cannabidiol:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints: ¹

¹ Data from the dossier assessment of the G-BA (published on 16 August 2021) and from the amendment to the dossier assessment, unless otherwise indicated.

Patients 2 years and older with seizures associated with tuberous sclerosis, adjunctive therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	n.a.	The data are not assessable.
Side effects	n.a.	The data are not assessable.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

GWEP1521 study: RCT, cannabidiol (25 mg/kg/d) versus placebo, double-blinded treatment phase of 16 weeks. Inclusion of children and adults treated with other anti-epileptic medicines.

Mortality

Endpoint	Cannabidiol		placebo		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator
Overall survival	75	0 (0)	76	0 (0)	n.c.
Abbreviations used: N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; vs = versus					

Morbidity

Endpoint	Cannabidiol			Placebo ^a			Cannabidiol vs placebo
	N	Baseline [95% CI]	Ratio treatment/baseline [95% CI]	N	Baseline [95% CI]	Ratio treatment/baseline [95% CI]	Ratio cannabidiol/placebo [95% CI] p-value
Frequency of epileptic seizures							
Frequency of TSC-associated seizures ^b	75	51.6 [40.8; 65.3]	0.51 [0.45; 0.59]	76	54.8 [43.4; 69.3]	0.73 [0.64; 0.84]	0.70 [0.58; 0.85] 0.0003
Total frequency of seizures	75	53.9 [42.4; 68.6]	0.52 [0.45; 0.60]	76	60.7 [47.8; 77.1]	0.73 [0.64; 0.84]	0.71 [0.58; 0.86] 0.0007
Frequency of further seizures ^c	75	11.3 [3.4; 37.0]	0.61 [0.30; 1.22]	76	11.3 [3.4; 37.0]	0.39 [0.21; 0.72]	1.56 [0.61; 3.97] 0.3470
<p>A The two study arms placebo 25 mg/kg/d and placebo 50 mg/kg/d were pooled.</p> <p>B TSC-associated seizures include: focal motor seizures without impairment of consciousness; focal seizures with impairment of consciousness; focal seizures progressing to bilateral generalised convulsive seizures; tonic-clonic, tonic, clonic, or atonic seizures.</p> <p>c Absences, myoclonic seizures, partial sensory seizures, and infantile or epileptic spasms.</p> <p>Abbreviations used: CI = Confidence Interval; N = Number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; TSC = tuberous sclerosis; vs = versus</p>							

Endpoint	Cannabidiol		Placebo ^a		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p-value
Reduction in the frequency of TSC-associated seizures ^b					
Reduction ≥ 25%	75	43 (57.3)	76	33 (43.4)	1.29 [0.93; 1.77] 0.091
Reduction ≥ 50%	75	27 (36.0)	76	17 (22.4)	1.61 [0.96; 2.69]; 0.0692
Reduction ≥ 75%	75	12 (16.0)	76	0	25.33 [1.53; 420.24] 0.0003
100% reduction	75	1 (1.3)	76	0	3.04 [0.13; 73.45] 0.3173
Increase ≥ 0%	75	15 (20.0)	76	20 (26.3)	0.76 [0.43; 1.34] 0.3634

Endpoint	Cannabidiol		Placebo ^a		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p-value
Total reduction in seizure frequency					
Reduction ≥ 25%	75	42 (56.0)	76	34 (44.7)	1.22 [0.89; 1.68] 0.1733
Reduction ≥ 50%	75	26 (34.7)	76	16 (21.1)	1.64 [0.96; 2.79] 0.0655
Reduction ≥ 75%	75	12 (16.0)	76	1 (1.3)	12.07 [1.61; 90.44] 0.0015
100% reduction	75	1 (1.3)	76	0	3.04 [0.13; 73.45] 0.3173
Increase ≥ 0%	75	16 (21.3)	76	22 (29.0)	0.73 [0.42; 1.26] 0.2881
Status epilepticus					
Status epilepticus ^c	75	5 (6.7)	76	7 (9.2)	0.78 [0.25; 2.44] 0.5636
Hospitalisations					
Hospitalisations due to epilepsy	75	8 (10.5)	76	1 (1.3)	n.d.
Global impression of change: Improved ^d					
CGI-C	75 ^e	45 (60.0)	76 ^e	27 (35.5)	1.69 [1.18; 2.41] 0.0027
CGI-C/SGIC (presented additionally)	75 ^e	48 (64.0)	76 ^e	30 (39.5)	1.62 [1.17; 2.25] 0.0027
Global impression of change: deterioration ^f					
CGI-C	75 ^e	7 (9.3)	76 ^e	4 (5.3)	1.77 [0.54; 5.81] 0.3375
CGI-C/SGIC (presented additionally)	75 ^e	8 (10.7)	76 ^e	4 (5.3)	2.03 [0.64; 6.45] 0.2212
<p>a The two study arms placebo 25 mg/kg/d and placebo 50 mg/kg/d were pooled.</p> <p>b TSC-associated seizures include: focal motor seizures without impairment of consciousness; focal seizures with impairment of consciousness; focal seizures progressing to bilateral generalised convulsive seizures; tonic-clonic, tonic, clonic, or atonic seizures.</p> <p>c Any type of seizure (convulsive and non-convulsive) lasting 30 minutes or longer.</p> <p>d An improvement in the global impression of change is defined as (1) very much improved, (2) much improved, (3) slightly improved.</p> <p>e ITT population; subjects with no response are counted as non-responders.</p>					

Endpoint	Cannabidiol		Placebo ^a		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p-value
<p>f A deterioration in the global impression of change is defined as (4) slightly deteriorated, (5) strongly deteriorated, (6) very strongly deteriorated.</p> <p>Abbreviations used: CGI-C = Caregiver Global Impression of Change; n.d. = no data available; CI = Confidence Interval; N = Number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; RR = relative risk; vs = versus</p>					

Endpoint	Cannabidiol			Placebo ^a			Cannabidiol vs placebo
	n/N (%)	Baseline, MV (SD)	Change LS-MV (SE)	n/N (%)	Baseline, MV (SD)	Change LS-MV (SE)	LS-MVD [95% CI] p-value
Behaviour (Achenbach Behaviour Checklist)							
CBCL (1.5–5 years)							
Total	14/ 15 (93)	62.3 (25.2)	-9.48 (4.15)	15/ 17 (88)	49.5 (28.1)	-5.49 (4.01)	-3.99 [-16.03; 8.05] 0.5020
CBCL (6–18 years)							
Total	30/ 40 (75)	46.1 (27.1)	-4.02 (3.76)	32/ 39 (82)	46.1 (20.9)	-3.76 (3.86)	-0.27 [-8.04; 7.51] 0.9457
Activities	28/ 40 (70)	5.1 (4.0)	0.45 (0.44)	32/ 39 (82)	4.1 (3.4)	1.06 (0.43)	-0.61 [-1.53; 0.31] 0.1908
Social skills	29/ 40 (73)	2.8 (2.2)	0.01 (0.33)	31/ 39 (79)	3.0 (2.4)	0.07 (0.34)	-0.06 [-0.75; 0.63] 0.8616
School	There are no suitable data. ^b						
Overall competence	There are no suitable data. ^b						
ABCL (18-59 years)							
Total	18/ 20 (90)	44.4 (31.0)	-2.15 (5.01)	15/ 20 (75)	43.0 (21.0)	4.24 (5.49)	-6.39 [-21.56; 8.79] 0.3968

Endpoint	Cannabidiol			Placebo ^a			Cannabidiol vs placebo
	n/N (%)	Baseline, MV (SD)	Change LS-MV (SE)	n/N (%)	Baseline, MV (SD)	Change LS-MV (SE)	LS-MVD [95% CI] p-value
Critical elements	17/20 (85)	4.9 (4.1)	-1.07 (0.54)	15/20 (75)	6.0 (3.1)	-0.05 (0.59)	-1.02 [-2.66; 0.63] 0.2151
Total abnormality	18/20 (90)	5.7 (3.4)	0.39 (0.49)	15/20 (75)	4.9 (4.2)	0.26 (0.53)	0.13 [-1.35; 1.61] 0.8571

a The two study arms placebo 25 mg/kg/d and placebo 50 mg/kg/d were pooled.

b Return rate in both arms < 70%.

Abbreviations used:

ABCL = Adult Behaviour Checklist; CBCL = Child Behaviour Checklist; CI = Confidence Interval; LS-MV = Least Squares Mean Value; LS-MVD = Least Squares Mean Difference; MV = Mean Value; N = Number of patients evaluated; n/N = return rate; SD = Standard Deviation; SE = Standard Error; vs = versus

Health-related quality of life

Endpoint	Cannabidiol			Placebo ^a			Cannabidiol vs placebo
	n/N (%)	Baseline MV (SD)	Change at end of treatment LS-MV (SE)	n/N (%)	Baseline MV (SD)	Change at end of treatment LS-MV (SE)	LS-MVD [95% CI] p-value
Quality of Life in Childhood Epilepsy - Patients ≤ 18 years of age							
QOLCE – Physical activity							
Physical limitations	43/55 (78)	29.6 (16.8)	7.57 (2.42)	51/56 (91)	25.0 (18.5)	1.55 (2.30)	6.03 [0.64; 11.41] 0.0287 <i>Hedges' g:</i> 0.46 [0.05; 0.87]
Energy/fatigue	53/55 (96)	55.4 (20.9)	2.89 (2.87)	54/56 (96)	53.5 (16.4)	1.78 (2.86)	1.11 [-5.16; 7.39] 0.7260
QOLCE – Cognition							
Attention/concentration	36/55 (65)	37.7 (22.4)	0.17 (3.83)	41/56 (73)	37.5 (23.2)	-0.48 (3.67)	0.65 [-8.36; 9.66] 0.8862

Endpoint	Cannabidiol			Placebo ^a			Cannabidiol vs placebo
	n/N (%)	Baseline MV (SD)	Change at end of treatment LS-MV (SE)	n/N (%)	Baseline MV (SD)	Change at end of treatment LS-MV (SE)	LS-MVD [95% CI] p-value
Recollection	There are no suitable data. ^b						
Language	There are no suitable data. ^b						
Other cognitive abilities	There are no suitable data. ^b						
QOLCE – well-being							
	There are no suitable data. ^b						
QOLCE – Social activities							
Social Interaction	There are no suitable data. ^b						
Social activity	45/55 (82)	44.9 (30.3)	8.64 (3.71)	45/56 (80)	38.3 (27.9)	6.29 (3.72)	2.34 [-6.23; 10.92] 0.5883
Stigma	38/55 (69)	55.3 (34.5)	3.91 (4.91)	40/56 (71)	58.1 (34.6)	11.81 (4.82)	-7.90 [-19.50; 3.70] 0.1788
QOLCE – behaviour							
Behaviour	42/55 (76)	48.9 (16.9)	4.91 (1.84)	47/56 (84)	49.9 (14.9)	2.35 (1.78)	2.57 [-1.62; 6.76] 0.2263
QOLCE – general health							
General health	54/55 (98)	37.5 (24.2)	3.59 (3.29)	56/56 (100)	33.9 (25.0)	5.36 (3.27)	-1.78 [-8.94; 5.39] 0.6238
QOLCE – quality of life							
Quality of life	46/55 (84)	45.7 (24.9)	2.52 (3.57)	49/56 (88)	48.5 (22.5)	5.38 (3.48)	-2.86 [-10.87; 5.15] 0.4799
QOLCE – Overall quality of life							
Overall quality of life	35/55 (64)	52.1 (13.2)	3.50 (1.98)	43/56 (77)	48.2 (13.9)	2.48 (1.84)	1.03 [-3.61; 5.67] 0.6609
<p>a The two study arms placebo 25 mg/kg/d and placebo 50 mg/kg/d were pooled.</p> <p>b Return rate in both arms < 70%.</p> <p>Abbreviations used: CI = Confidence Interval; LS-MV = Least Squares Mean Value; LS-MVD = Least Squares Mean Difference; MV = Mean Value; N = Number of patients evaluated; n = number of patients included in the evaluation; QOLCE: Quality of Life in Childhood Epilepsy; RR = Relative Risk; SD: Standard Deviation; SE: Standard Error; vs = versus</p>							

Side effects

Endpoint	Cannabidiol		Placebo ^a		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p-value
Overall rates					
AE	75	70 (93.3)	76	72 (94.7)	-
SAE	75	16 (21.3)	76	2 (2.6)	8.22 [1.96; 34.45] 0.0004
Therapy discontinuation due to AE	75	8 (10.7)	76	2 (2.6)	4.04 [0.90; 18.20] 0.0484
AEs (SOC/PT) with an incidence of $\geq 10\%$ and statistically significant differences between the treatment groups					
General disorders and administration site conditions	75	21 (28.0)	76	11 (14.5)	2.02 [1.06; 3.85] 0.0404
- Fever	75	14 (18.7)	76	6 (6.7)	2.51 [1.05; 5.99] 0.0428
Investigations	75	30 (40.0)	76	11 (14.5)	2.77 [1.50; 5.12] 0.0005
- Gamma-glutamyltransferase increased	75	12 (16.0)	76	0	25.33 [1.53; 420.24] 0.0003
- Alanine aminotransferase increased	75	9 (12.0)	76	0	19.25 [1.14; 324.93] 0.0021
- Aspartate aminotransferase increased	75	8 (10.7)	76	0	17.22 [1.01; 293.18] 0.0039
^a The two study arms placebo 25 mg/kg/d and placebo 50 mg/kg/d were pooled. Abbreviations used: CI = Confidence Interval; N = Number of patients evaluated; n = number of patients with (at least one) event; RR = Relative Risk; vs = versus					

2. Number of patients or demarcation of patient groups eligible for treatment

Patients 2 years and older with seizures associated with tuberous sclerosis, adjunctive therapy

approx. 500 – 2,700 patients

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 acid at the following publicly accessible link (last access: 29 September 2021):

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 causes pharmacokinetic interactions that can lead to an increase in adverse drug reactions. The patient should be closely monitored for adverse drug reactions. In the case of somnolence or sedation in combination with clobazam, a reduction in the dose of clobazam should be considered.

4. Treatment costs

Annual treatment costs:

Patients 2 years and older with seizures associated with tuberous sclerosis, adjunctive therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Cannabidiol	€ 6,411.11 – € 87,923.77

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 October 2021)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 4 November 2021.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 4 November 2021

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

Prof. Hecken