Resolution

Gemeinsamer Bundesausschuss

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Cannabidiol - Reassessment after expiry of the deadline (Lennox-Gastaut-Syndrome, ≥ 2 years, combination with Clobazam)

of 15 April 2021

At its session on 15 April 2021, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on DD Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. The information on cannabidiol in the version of the resolution of 2 April 2020 (BAnz AT DD.MM.YYYY BX) is repealed.

2. Annex XII shall be amended in alphabetical order to include Cannabidiol as follows:

Cannabidiol

Resolution of: 15 April 2021
Entry into force on: 15 April 2021
BAnz AT TT MM JJJJ Bx

New therapeutic indication (according to the marketing authorisation of 19 September 2019):

Epidyolex is a medicine used in addition to clobazam, to treat patients from two years of age with Lennox-Gastaut-Syndrome (LGS) or Dravet Syndrome (DS).

Therapeutic indication of the resolution (resolution from the 15/04/2021):
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).

1. Extent of the additional benefit and the 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 Lennox-Gastaut-Syndrome

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

Hint of a considerable additional benefit

Study results according to endpoints:[1]

Patients 2 years and older with Lennox-Gastaut-Syndrome

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	There were no deaths.
Morbidity	↑	Benefits in reducing seizures and improving health status
Health-related quality of life	n.c.	There are no evaluable data.
Side effects	↓	Disadvantages in the SAE and in the therapy discontinuation due to AEs below 20 mg/kg per day

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

GWEP1414 study: RCT 14 weeks. Relevant sub-populations: Cannabidiol 10 mg/kg/d and 20 mg/kg/d in combination with clobazam.

GWEP1423 study: RCT 14 weeks. Relevant sub-population: Cannabidiol 20 mg/kg/d in combination with clobazam.

Mortality

Endpoint	Cannabidiol		Placebo		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator
Overall mortality					
Cannabidiol 10 mg/kg/d					
GWEP1414	35	0	37	0	–
Cannabidiol 20 mg/kg/d					
GWEP1414	38	0	37	0	–
GWEP1423	41	0	43	0	–

[1]Data from the dossier assessment of the G-BA (published on 15 January 2021), and from the amendment to the dossier assessment, unless otherwise indicated.

Morbidity

Endpoint; Study	Cannabidiol			Placebo[a]			Cannabidiol vs placebo
	n/ N	Baseline Median [Q1; Q3]	% Median Change [Q1; Q3]	n/ N	Baseline Median [Q1; Q3]	% Median Change [Q1; Q3]	Median difference [95%-CI] p value
Frequency of convulsive seizures[b]							
Cannabidiol 10 mg/kg/d							
GWEP1414	37/ 37	98.9 [54,0; 223,1]	-45,4 [-65,8; -23,8]	37/ 37	103.0 [54,3; 175,7]	-26,5 [-39,0; -13,2]	-19,6 [-33,5; -4,5] 0.0164
Cannabidiol 20 mg/kg/d							
GWEP1414	36/ 36	93.0 [49,2; 138,1]	-54,2 [-80,9; -27,1]	37/ 37	103.0 [54,3; 175,7]	-26,5 [-39,0; -13,2]	-27,5 [-42,6; -11,6] 0.0013
GWEP1423	42/ 42	75.7 [30.0; 117,8]	-60,2 [-88,3; -29,8]	42/ 42	129.9 [64,7; 230,8]	-29,7 [-50,2; 6,3]	-34,1 [-50,2; -16,1] 0.0004
Frequency of non-convulsive seizures[c]							
Cannabidiol 10 mg/kg/d							
GWEP1414	21/ 37	61.8 [12,6; 110,1]	-78,2 [-86,3; -42,9]	32/ 37	27.4 [8,9; 92,9]	-30,4 [–75,4; 1,4]	–32,6 [–59,9; –1,2] 0.039
Cannabidiol 20 mg/kg/d							
GWEP1414	26/ 36	52.0 [8,4; 134,1]	-88,2 [-97,2; -51,6]	32/ 37	27.4 [8,9; 92,9]	-30,4 [-75,4; 1,4]	-40,4 [-66,7; -8,7] 0.005
GWEP1423	35/ 42	62.0 [7,2; 165,0]	-63,3 [-94,1; -39,9]	32/ 42	58.5 [17,7; 156,1]	-20,6 [-70,1; 15,1]	-38,1 [-63,1; -10,6] 0.0035
Total frequency of seizures							
Cannabidiol 10 mg/kg/d							
GWEP1414	37/ 37	150.5 [81,3; 333,2]	-46,3 [-64,8; -24,3]	37/ 37	138.1 [86,0; 270.0]	-26,4 [-42,4; -2,9]	-22,2 [-37,3; -7,4] 0.0049
Cannabidiol 20 mg/kg/d							
GWEP1414	36/ 36	139.3 [77,2; 269,3]	-58,5 [-80,9; -34,3]	37/ 37	138.1 [86,0; 270.0]	-26,4 [-42,4; -2,9]	-33,2 [-47,0; -18,1] 0.0001
GWEP1423	42/ 42	126.2 [69,5; 337,6]	-57,1 [-83,5; -30,9]	42/ 42	187.1 [107.6; 446.2]	-19,2 [-47,3; 2,0]	-36,4 [-51,8; -20,2] <0.0001

Endpoint; Study	Cannabidiol			Placebo[a]			Cannabidiol vs placebo
	n/ N	Baseline Median [Q1; Q3]	% Median Change [Q1; Q3]	n/ N	Baseline Median [Q1; Q3]	% Median Change [Q1; Q3]	Median difference [95%-CI] p value

a) The two study arms placebo 10 mg / kg / d, and placebo 20 mg/kg/d of the GWEP1414 study were pooled.
b) include all tonic-clonic, tonic, clonic and atonic seizures
c) Include all myoclonic, countable partial and other partial seizures or absences. Only patients with reported non-convulsive seizures at baseline.

Abbreviations used:
KI = confidence interval; Q = quartile

Endpoint; Study	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 convulsive seizures[b]					
Reduction ≥ 25%					
Cannabidiol 10 mg/kg/d					
GWEP1414	37	27 (73.0)	37	20 (54.1)	1.35 [0.95; 1.93] 0.0529
Cannabidiol 20 mg/kg/d					
GWEP1414	36	28 (77.8)	37	20 (54.1)	1.44 [1.02; 2.03] 0.0319
GWEP1423	42	32 (76.2)	42	22 (52.4)	1.45 [1.04; 2.02] 0.0171
Meta-analysis					1.44 [1.14; 1.83] 0.0027
Reduction ≥ 50%					
Cannabidiol 10 mg/kg/d					
GWEP1414	37	18 (48.7)	37	7 (18.9)	2.62 [1.23; 5.56] 0.0065
Cannabidiol 20 mg/kg/d					
GWEP1414	36	20 (55.6)	37	7 (18.9)	2.99 [1.42; 6.29] 0.0023
GWEP1423	42	23 (54.8)	42	11 (26.2)	2.10 [1.20; 3.68] 0.0026
Meta-analysis					2.39 [1.53; 3.73] 0.0001
Reduction ≥ 75%					
Cannabidiol 10 mg/kg/d					
GWEP1414	37	5 (13.5)	37	1 (2.7)	5.00 [0.61; 40.75] 0.1268
Cannabidiol 20 mg/kg/d					

Endpoint; Study	Cannabidiol		Placebo[a]		Cannabidiol vs placebo
	N	Patients with event *n (%)*	N	Patients with event *n (%)*	RR [95%- CI] p value
GWEP1414	36	10 (27.8)	37	1 (2.7)	10.28 [1.39; 76.23] 0.0064
GWEP1423	42	12 (28.6)	42	2 (4.8)	6.00 [1.43; 25.19] 0.0005
Meta-analysis					7.20 [2.24; 23.12] 0.0009
100 % reduction					
Cannabidiol 10 mg/kg/d					
GWEP1414	37	0	37	0	n.c.
Cannabidiol 20 mg/kg/d					
GWEP1414	36	0	37	0	n.c.
GWEP1423	42	0	42	0	n.c.
Meta-analysis					-
Increase (> 0%) in the frequency of convulsive seizures[b]					
Cannabidiol 10 mg/kg/d					
GWEP1414	37	6 (16.2)	37	6 (16.2)	0.84 [0.32; 2.18] 0.5606
Cannabidiol 20 mg/kg/d					
GWEP1414	36	4 (11.1)	37	6 (16.2)	0.60 [0.19; 1.91] 0.3758
GWEP1423	42	6 (14.3)	42	14 (33.3)	0.39 [0.17; 0.91] 0.0244
Meta-analysis					0.45 [0.23; 0.89] 0.0224
Convulsive status epilepticus[b]					
Cannabidiol 10 mg/kg/d					
GWEP1414	37	1 (2.7)	37	0	n.c. p = 0.4450
Cannabidiol 20 mg/kg/d					
GWEP1414	36	1 (2.8)	37	0	n.c. p = 0.2770
GWEP1423	42	1 (2.4)	42	0	n.c. p = 0.2689
Meta-analysis					no data available
Non-convulsive status epilepticus[c]					
Cannabidiol 10 mg/kg/d					
GWEP1414	37	1 (2.7)	37	0	no data available p = 0.1904
Cannabidiol 20 mg/kg/d					
GWEP1414	36	0	37	0	n.c.

Endpoint; Study	Cannabidiol		Placebo[a]		Cannabidiol vs placebo
	N	Patients with event *n (%)*	N	Patients with event *n (%)*	RR [95%- CI] p value
GWEP1423	42	1 (2.4)	42	0	n.c. p = 0.3026
Meta-analysis					no data available
Hospitalisations due to epilepsy					
Cannabidiol 10 mg/kg/d					
GWEP1414	37	5 (13.5)	37	4 (10.8)	1.01 [0.31; 3.35] 0.9608
Cannabidiol 20 mg/kg/d					
GWEP1414	36	3 (8.3)	37	4 (10.8)	0.62 [0.14; 2.65] 0.5572
GWEP1423	41	4 (9.8)	42	2 (4.8)	2.05 [0.40; 10.58] 0.2472
Meta-analysis					1.05 [0.35; 3.11] 0.9355
Caregiver Global Impression of Change (CGIC) - Improvement[d] to end of studies					
Cannabidiol 10 mg/kg/d					
GWEP1414	37	28 (75.7)	37	17 (46.0)	1.72 [1.18; 2.50] 0.0057
Cannabidiol 20 mg/kg/d					
GWEP1414	36	28 (77.8)	37	17 (46.0)	1.69 [1.15; 2.50] 0.0040
GWEP1423	42	32 (78.1)	42	13 (31.0)	2.52 [1.56; 4.07] <0.0001
Meta-analysis					1.98 [1.47; 2.69] <0.0001
Caregiver Global Impression of Change (CGIC) - deterioration[e] to end of studies					
Cannabidiol 10 mg/kg/d					
GWEP1414	37	3 (8.1)	37	3 (8.1)	0.78 [0.17; 3.52] 0.7459
Cannabidiol 20 mg/kg/d					
GWEP1414	36	3 (8.3)	37	3 (8.1)	0.86 [0.19; 3.94] 0.8521
GWEP1423	41	4 (9.8)	42	8 (19.1)	0.46 [0.15; 1.41] 0.1727
Meta-analysis					0.58 [0.23; 1.42] 0.2294

Endpoint; Study	Cannabidiol		Placebo[a]		Cannabidiol vs placebo
	N	Patients with event *n (%)*	N	Patients with event *n (%)*	RR [95%- CI] p value

a) The two study arms placebo 10 mg / kg / d, and placebo 20 mg/kg/d of the GWEP1414 study were pooled.
b) includes any type of convulsive seizure (all tonic-clonic, tonic, clonic and atonic seizures) lasting 30 minutes or more.
c) includes any type of non-convulsive seizure (myoclonic, countable partial and other partial seizures or absences) lasting 30 minutes or more.
d) Improvement is defined as the point values 1 (very much improved), 2 (much improved) and 3 (slightly improved) on the change in global caregiver impression (CGIC) scale.
e) Deterioration is defined as the point values 7 (very badly deteriorated), 6 (very badly deteriorated) and 5 (slightly deteriorated) on the scale change in global caregiver impression (CGIC).

Abbreviations used:
CI = confidence interval; RR = relative risk

Health-related quality of life

There are no suitable data.

Side effects

Endpoint; Study	Cannabidiol		Placebo[a]		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%- CI] p value
Total rates					
EU					
Cannabidiol 10 mg/kg/d					
GWEP1414	35	31 (88.6)	37	28 (75.7)	-
Cannabidiol 20 mg/kg/d					
GWEP1414	38	35 (92.1)	37	28 (75.7)	-
GWEP1423	41	39 (95.1)	43	30 (69.8)	-
SAE					
Cannabidiol 10 mg/kg/d					
GWEP1414	35	8 (22.9)	37	4 (10.8)	1.76 [0.58; 5.27] 0.2661
Cannabidiol 20 mg/kg/d					
GWEP1414	38	6 (15.8)	37	4 (10.8)	1.41 [0.41; 4.80] 0.5763
GWEP 1423	41	12 (29.3)	43	2 (4.7)	6.73 [1.61; 28.11] 0.0016
Meta-analysis					2.73 [1.08; 6.93] 0.0341

Endpoint; Study	Cannabidiol		Placebo[a]		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%- CI] p value
Therapy discontinuation due to AE					
Cannabidiol 10 mg/kg/d					
GWEP1414	35	1 (2.9)	37	0	3.17 [0.13; 75.24] 0.3173
Cannabidiol 20 mg/kg/d					
GWEP1414	38	3 (7.9)	37	0	6.82 [0.36; 127.64] 0.0536
GWEP1423	41	8 (19.5)	43	0	17.81 [1.06; 298.98] 0.0040
Meta-analysis					11.22 [1.47; 85.61] 0.0197
AEs with an incidence of ≥ 10% and statistically significant differences between the treatment groups in at least one study					
Cannabidiol 10 mg/kg/d					
Fatigue					
GWEP1414	35	5 (14.3)	37	0	11.61 [0.67; 202.53] 0.0293
Nasopharyngitis					
GWEP1414	35	0	37	5 (13.5)	0.10 [0.01; 1.67] 0.0344
Pneumonia					
GWEP1414	35	4 (11.4)	37	0	9.50 [0.53; 170.25] 0.0477
Nervous system disorders					
GWEP1414	35	19 (54.3)	37	9 (24.3)	2.23 [1.17; 4.23] 0.0095
Somnolence					
GWEP1414	35	11 (31.4)	37	1 (2.7)	11.63 [1.58; 85.43] 0.0008
Cannabidiol 20 mg/kg/d					
General disorders and administration site conditions					
GWEP1414	38	11 (29.0)	37	9 (24.3)	1.18 [0.55; 2.51] 0.6849
GWEP1423	41	12 (29.3)	43	5 (11.6)	2.52 [0.97; 6.52] 0.0448
Meta-analysis					1.63 [0.78; 3.40] no data available
Fatigue					
GWEP1414[b]	38	6 (15.8)	37	0	12.67 [0.74; 217.13] 0.0240
Investigations, examinations					

Endpoint; Study	Cannabidiol		Placebo[a]		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%- CI] p value
GWEP1414	38	9 (23.7)	37	6 (16.2)	1.61 [0.63; 4.12] 0.3423
GWEP1423	41	14 (34.2)	43	4 (9.3)	3.29 [1.18; 9.21] 0.0109
Meta-analysis					2.23 [1.11; 4.48] no data available
Nervous system disorders					
GWEP1414	38	26 (68.4)	37	9 (24.3)	2.84 [1.57; 5.13] 0.0002
GWEP1423	41	24 (58.5)	43	13 (30.2)	1.99 [1.18; 3.36] 0.0156
Meta-analysis					2.33 [1.57; 3.45] no data available
Somnolence					
GWEP1414	38	15 (39.5)	37	1 (2.7)	14.61 [2.03; 105.04] 0.0001
GWEP1423	41	9 (22.0)	43	7 (16.3)	1.29 [0.52; 3.23] 0.6382
Meta-analysis					3.69 [0.35; 38.82] no data available
Sedation					
GWEP1423[c]	41	7 (17.1)	43	1 (2.3)	7.34 [0.94; 57.09] 0.0247
Psychiatric disorders					
GWEP1414	38	10 (26.3)	37	2 (5.4)	3.73 [0.087; 16.03] 0.0441
GWEP1423	41	12 (29.3)	43	5 (11.6)	2.54 [0.98; 6.58] 0.0442
Meta-analysis					2.85 [1.28; 6.32] no data available
Renal and urinary disorders					
GWEP1423[c]	41	5 (12.2)	43	0	11.52 [0.66; 202.03] 0.0278
Respiratory, thoracic and mediastinal disorders					
GWEP1414	38	7 (18.4)	37	5 (13.5)	1.42 [0.50; 4.03] 0.4946
GWEP1423	41	13 (31.7)	43	6 (14.0)	2.30 [0.97; 5.45] 0.0336
Meta-analysis					1.89 [0.97; 3.68] no data available
Skin and subcutaneous tissue disorders					

Endpoint; Study	Cannabidiol		Placebo[a]		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%- CI] p value
GWEP1414	38	7 (18.4)	37	1 (2.7)	7.36 [0.96; 56.38] 0.0222
GWEP1423	41	8 (19.5)	43	2 (4.7)	4.07 [0.92; 18.00] 0.0469
Meta-analysis					5.00 [1.51; 16.62] no data available
Rash					
GWEP1414	38	4 (10.5)	37	1 (2.7)	4.67 [0.55; 39.42] 0.1177
GWEP1423	41	5 (12.2)	43	0	11.52 [0.66; 202.03] 0.0278
Meta-analysis					6.45 [1.17; 35.67] no data available
SAEs with an incidence of ≥ 5% and statistically significant differences between the treatment groups in at least one study					
Cannabidiol 20 mg/kg/d					
Respiratory, thoracic and mediastinal disorders					
GWEP1423[c]	41	5 (12.2)	43	1 (2.3)	5.24 [0.64; 42.99] 0.0456
Acute respiratory insufficiencyz					
GWEP1423[c]	41	3 (7.3)	43	0	7.33 [0.39; 137.73] 0.0460

a) The two study arms placebo 10 mg / kg / d, and placebo 20 mg/kg/d of the GWEP1414 study were pooled.
b) No information for the GWEP1423 study
c) No information for the GWEP1414 study

Abbreviations: n / d: not specified; RR: Relative Risk; (S) AE: (Serious) adverse events

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

Patients 2 years and older with Lennox-Gastaut-Syndrome

approx. 2,600 to 22,700 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: 11 December 2020):

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

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

The combination of cannabidiol with clobazam causes pharmacokinetic interactions that can lead to an increase in adverse drug reactions. If somnolence or sedation occurs, a reduction in the dose of clobazam should be considered.

4. Treatment costs

Annual treatment costs:

Patients 2 years and older with Lennox-Gastaut-Syndrome

Designation of the therapy	Annual treatment costs/patient
Minimum dosage (2-year-old child)	
Cannabidiol	€ 8,177.43
Clobazam	€ 1,060.19
Total	€ 9,237.62
Maximum dosage (adult)	
Cannabidiol	€ 70,522.19
Clobazam	€ 638.90
Total	€ 71,161.09

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 March 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 15 April 2021.

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

Berlin, 15 April 2021

Federal Joint Committee in accordance with Section 91 SGB V The chairman

Prof. Hecken