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 The information on cannabidiol in the version of the resolution of 2 April 2020 (BAnz AT DD.MM.YYYY BX) is repealed.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

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 Dravet 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 Dravet 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	↔	No relevant difference for the benefit assessment
Side effects	↓	Disadvantages 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

GWEP1424 study: RCT 14 weeks. Relevant sub-populations: Cannabidiol 10 mg/kg/d and 20 mg/kg/d in combination with clobazam.

GWEP1332 Study - Part B: 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					
GWEP1424	44	0	41	0	-
Cannabidiol 20 mg/kg/d					
GWEP1424	41	0	41	0	-
GWEP1332 B	40	0	38	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	Baseline [95%-CI]	Treatment/Baseline Ratio [95%-CI]	N	Baseline [95%-CI]	Treatment/Baseline Ratio [95%-CI]	Treatment effect[b] [95%-CI] p value
Frequency of convulsive seizures[c]							
Cannabidiol 10 mg/kg/d							
GWEP1424	45	-	0.39 [0.31; 0.50]	41	-	0.62 [0.49; 0.80]	0.63 [0.44; 0.88] 0.0083
Cannabidiol 20 mg/kg/d							
GWEP1424	40	-	0.43 [0.33; 0.55]	41	-	0.50 [0.33; 0.55]	0.87 [0.64; 1.18] 0.3572
GWEP1332 B	40	-	0.19 [0.14; 0.26]	38	-	0.28 [0.21; 0.38]	0.67 [0.43; 1.03] 0.0655
Meta-analysis							0.79 [0.62; 1.02] 0.0706

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[c] (Sensitivity Analysis)							
Cannabidiol 10 mg/kg/d							
GWEP1424	45/45	13.1 [6.0; 31.2]	-58,1 (–81,8; –14,7)	41/41	17.7 [6.0; 45.2]	-33,3 (-64,7; -4,2)	-18,55 [-34.15; 0.72] 0.056
Cannabidiol 20 mg/kg/d							
GWEP1424	40/40	9.6 [7.0; 22.0]	-57,8 [-75.0; -42.1]	41/41	17.7 [6.0; 45.2]	-33,3 (-64,7; -4,2)	-22,82 [-38.43; -6.16] 0.0098
GWEP1332 B	40/40	10.8 [6.0; 26.0]	-45,0 [-73.0; -14.2]	38/38	15.9 [7.0; 35.7]	-9,9 (-49,6; 31,0)	-31,83 [-55.88; -10.21] 0.0064
Frequency of non-convulsive seizures[d]							
Cannabidiol 10 mg/kg/d							
GWEP1424	34/45	9.7 [6.0; 82.0]	-78,8 (-95,2; -34,1)	32/41	23.0 [1.9; 143.4]	-59,3 (-67,4; -11,3)	-21,72 [-37.42; 0.47] 0.0823
Cannabidiol 20 mg/kg/d							
GWEP1424	28/40	22.0 [5.4; 272.4]	-71,4 (-84,8; 37,6)	32/41	23.0 [1.9; 143.4]	-59,3 (-67,4; 11,3)	-10,53 [-32,65; 9,52] 0.3055

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
GWEP1332 B	22/ 40	12.1 [2.6; 126.0]	-37,1 [-95.6; -13.7]	25/ 38	67.6 [14.0; 439.5]	-34,7 (-97,5; -0,7)	0.00 [-38,03; 31,59] 0.8639
Total frequency of seizures							
Cannabidiol 10 mg/kg/d							
GWEP1424	45/ 45	23.0 (10,4; 100)	-60.0 (-88,1; -36,1)	41/ 41	46.0 (13,0; 193)	-41,2 (-62,3; -2,6)	-22,90 [-37.22; -6.31] 0.0057
Cannabidiol 20 mg/kg/d							
GWEP1424	40/ 40	26.6 [10.5; 215.5]	-55,3 [-73.2; -39.9]	41/ 41	46.0 [13.0; 192.7]	-41,2 (-62,3; -2,6)	-18,29 [-34,98; -3,83] 0.0184
GWEP1332 B	40/ 40	22.6 [10.0; 119.7]	-39,5 [-79.7; -7.9]	38/ 38	41.5 [14.0; 417.1]	-8,1 (-44,6; 21,1)	-24,52 [-55,34; -2,58] 0.0224

a) The two study arms placebo 10 mg / kg / d, and placebo 20 mg/kg/d of the GWEP1424 study were pooled.
b) negative-binomial model
c) include all tonic-clonic, tonic, clonic and atonic seizures
d) Include all myoclonic, countable partial and other partial seizures or absences. Only patients with reported non-convulsive seizures at baseline.

Abbreviations: 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					
Reduction ≥ 25%					
Cannabidiol 10 mg/kg/d					
GWEP1424	45	31 (68.9)	41	24 (58.5)	1.09 [0.78; 1.51] 0.3325
Cannabidiol 20 mg/kg/d					
GWEP1424	40	34 (85.0)	41	24 (58.5)	1.39 [1.03; 1.87] 0.0098
GWEP1332 B	40	26 (65.0)	38	16 (42.1)	1.53 [0.99; 2.35] 0.0489
Meta-analysis					1.43 [1.12; 1.83] 0.0040

Reduction ≥ 50%

Endpoint; Study	Cannabidiol		Placebo[a]		Cannabidiol vs placebo
	N	Patients with event *n (%)*	N	Patients with event *n (%)*	RR [95%- CI] p value
Cannabidiol 10 mg/kg/d					
GWEP1424	45	25 (55.6)	41	15 (36.6)	1.51 [0.95; 2.42] 0.0599
Cannabidiol 20 mg/kg/d					
GWEP1424	40	25 (62.5)	41	15 (36.6)	1.70 [1.07; 2.71] 0.0145
GWEP1332 B	40	19 (47.5)	38	9 (23.7)	1.80 [0.93; 3.46] 0.0429
Meta-analysis					1.73 [1.18; 2.53] 0.0046
Reduction ≥ 75%					
Cannabidiol 10 mg/kg/d					
GWEP1424	45	16 (35.6)	41	4 (9.8)	3.78 [1.38; 10.4] 0.0042
Cannabidiol 20 mg/kg/d					
GWEP1424	40	10 (25.0)	41	4 (9.8)	2.64 [0.91; 7.65] 0.0652
GWEP1332 B	40	10 (25.0)	38	5 (13.2)	1.78 [0.68; 4.65] 0.2525
Meta-analysis					2.13 [1.04; 4.33] 0.0381
100 % reduction					
Cannabidiol 10 mg/kg/d					
GWEP1424	45	2 (4.4)	41	1 (2.4)	1.98 [0.18; 21.43] 0.5747
Cannabidiol 20 mg/kg/d					
GWEP1424	40	2 (5.0)	41	1 (2.4)	1.79 [0.17; 18.90] 0.6312
GWEP1332 B	40	3 (7.5)	38	0	6.66 [0.36; 124.77] 0.1255
Meta-analysis					3.00 [0.48; 18.82] 0.2412
Increase > 0%					
Cannabidiol 10 mg/kg/d					
GWEP1424	45	no data available	41	9 (22.0)	0.66 [0.27; 1.61] 0.3775
Cannabidiol 20 mg/kg/d					
GWEP1424	40	4 (10.0)	41	9 (22.0)	0.42 [0.14; 1.25] 0.1227
GWEP1332 B	40	7 (17.5)	38	16 (42.1)	0.40 [0.19; 0.85] 0.0145

Endpoint; Study	Cannabidiol		Placebo[a]		Cannabidiol vs placebo
	N	Patients with event *n (%)*	N	Patients with event *n (%)*	RR [95%- CI] p value
Meta-analysis					0.41 [0.22; 0.76] 0.0046
Convulsive status epilepticus[b]					
Cannabidiol 10 mg/kg/d					
GWEP1424	45	2 (4.4)	41	4 (9.8)	No data available p = 0,3102
Cannabidiol 20 mg/kg/d					
GWEP1424	40	5 (12.5)	41	4 (9.8)	No data available p = 0,7767
GWEP1332 B	40	1 (2.5)	38	0	No data available p = 0,3172
Meta-analysis					no data available
Non-convulsive status epilepticus[c]					
Cannabidiol 10 mg/kg/d					
GWEP1424	45	3 (6.7)	41	2 (4.9)	No data available p = 0,7811
Cannabidiol 20 mg/kg/d					
GWEP1424	40	2 (5.0)	41	2 (4.9)	0.65 [0.10; 4.30] 0.8593
GWEP1332 B	40	1 (2.5)	38	1 (2.6)	No data available p = 1,0000
Meta-analysis					no data available
Hospitalisations due to epilepsy					
Cannabidiol 10 mg/kg/d					
GWEP1424	45	6 (13.3)	41	2 (4.9)	2.94 [0.67; 12.85] 0.1591
Cannabidiol 20 mg/kg/d					
GWEP1424	40	5 (12.5)	41	2 (4.9)	3.00 [0.62; 14.62] 0.1694
GWEP1332 B	40	2 (5.0)	38	0 (0)	4.76 [0.24; 95.96] 0.1501
Meta-analysis					3.32 [0.82; 13.46] 0.0930
Caregiver Global Impression of Change (CGIC) - Improvement[d] to end of studies[e]					
Cannabidiol 10 mg/kg/d					
GWEP1424	45	33 (73.3)	41	17 (41.5)	1.74 [1.17; 2.61] 0.0020
Cannabidiol 20 mg/kg/d					
GWEP1424	39	30 (76.9)	41	17 (41.5)	1.79 [1.21; 2.67] 0.0010

Endpoint; Study	Cannabidiol		Placebo[a]		Cannabidiol vs placebo
	N	Patients with event *n (%)*	N	Patients with event *n (%)*	RR [95%- CI] p value
GWEP1332 B	39	24 (61.5)	37	11 (29.7)	1.85 [1.06; 3.22] 0.0096
Meta-analysis					1.81 [1.31; 2.50] 0.0003
Caregiver Global Impression of Change (CGIC) - deterioration[f] to end of studies					
Cannabidiol 10 mg/kg/d					
GWEP1424	45	1 (2.2)	41	3 (7.3)	0.38 [0.04; 3.31] 0.4105
Cannabidiol 20 mg/kg/d					
GWEP1424	39	4 (10.3)	41	3 (7.3)	1.53 [0.40; 5.82] 0.4687
GWEP1332 B	39	5 (12.8)	37	5 (13.5)	0.96 [0.30; 3.03] 0.9468
Meta-analysis					1.17 [0.49; 2.80] 0.7264

a) The two study arms placebo 10 mg / kg / d, and placebo 20 mg/kg/d of the GWEP1424 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) Assessment for the end of study time point was planned if there were deviations compared to the end of treatment.
f) 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: CI = confidence interval; RR = relative risk

Health-related quality of life

Endpoint; Study	Cannabidiol			Placebo			Cannabidiol vs placebo
	n/N (%)	Baseline MV (SD)	Delta[a] MV (SE)	n/N (%)	Baseline MV (SD)	Delta[a] MV (SE)	LS-MD [95%- CI] p value
QOLCE – Physical activity							
Physical limitations							
Cannabidiol 10 mg/kg/d							
GWEP1424	41/45 (91)	19.1 (12.6)	-0.66 (1.77)	38/41 (93)	21.3 (14.9)	-2.03 (1.77)	1.38 [-3.55; 6.30] 0.5791
Cannabidiol 20 mg/kg/d							
GWEP1424	29/40 (73)	20.0 (10.3)	3.71 (2.09)	38/41 (93)	21.3 (14.9)	-1.79 (1.81)	5.50 [0.01; 10.98] 0.0494 *Hedges' g:* 0.49 [0.00; 0.98]

Endpoint; Study	Cannabidiol			Placebo			Cannabidiol vs placebo
	n/N (%)	Baseline MV (SD)	Delta[a] MV (SE)	n/N (%)	Baseline MV (SD)	Delta[a] MV (SE)	LS-MD [95%- CI] p value
GWEP1332 B	34/40 (85)	24.7 (13.0)	4.01 (2.33)	32/38 (84)	19.3 (13.1)	–0,13 (2,41)	4.14 [–2,58; 10,87] 0.2226
Meta-analysis							0.39 [0.05; 0.74] no data available
Energy/Fatigue							
Cannabidiol 10 mg/kg/d							
GWEP1424	42/45 (93)	55.7 (18.6)	1.49 (3.46)	39/41 (95)	57.4 (18.1)	1.66 (3.47)	-0,17 [-9.74; 9.40] 0.9716
Cannabidiol 20 mg/kg/d							
GWEP1424	35/40 (93)	53.2 (16.7)	–2,91 (3,73)	39/41 (95)	57.4 (18.1)	2.44 (3.39)	–5,35 [–15,25; 4,54] 0.2844
GWEP1332 B	35/40 (88)	53.9 (21.4)	–4,80 (3,24)	34/38 (90)	50.4 (20.8)	3.88 (3.30)	–8,69 [–17,95; 0,58] 0.0656
Meta-analysis							0.34 [–0.67; –0.01] no data available
QOLCE – Cognition							
There are no suitable data.							
QOLCE – Well-being							
There are no suitable data.							
QOLCE – Social activity							
Social Interaction							
Cannabidiol 10 mg/kg/d							
GWEP1424	32/45 (71)	46.2 (29.3)	3.99 (6.15)	27/41 (66)	30.9 (27.5)	8.50 (6.59)	-4.52 [-22.43; 13.4] 0.6155
Cannabidiol 20 mg/kg/d							
GWEP1424	28/40 (70)	31.4 (29.4)	6.14 (5.15)	27/41 (66)	30.9 (27.5)	8.42 (4.77)	-2.28 [-16.05; 11.50] 0.7414
GWEP1332 B	27/40 (68)	36.9 (30.6)	7.20 (5.14)	27/38 (71)	36.4 (27.2)	5.52 (5.28)	1,68 [–13,13; 16,48] 0.8211
Meta-analysis							–0.01 [–0.39; 0.36]
Social activity							
Cannabidiol 10 mg/kg/d							
GWEP1424	36/45 (80)	19.1 (21.6)	15.45 (4.56)	36/41 (88)	16.1 (16.1)	8.22 (4.46)	7.23 [-5.37; 19.82] 0.2563
Cannabidiol 20 mg/kg/d							

Endpoint; Study	Cannabidiol			Placebo			Cannabidiol vs placebo
	n/N (%)	Baseline MV (SD)	Delta[a] MV (SE)	n/N (%)	Baseline MV (SD)	Delta[a] MV (SE)	LS-MD [95%- CI] p value
GWEP1424	33/40 (83)	22.9 (23.4)	6.62 (4.33)	36/41 (88)	16.1 (16.1)	6.60 (3.95)	0.02 [-11.61; 11.65] 0.9976
GWEP1332 B	33/40 (83)	21.2 (23.5)	12.11 (4.11)	33/38 (87)	19.7 (20.4)	–1,04 (4,13)	13.15 [1.56; 24.75] 0.0269 *Hedge's g:* 0.55 [0.06; 1.04]
Meta-analysis							0.27 [-0.08; 0.61]
Stigma							
Cannabidiol 10 mg/kg/d							
GWEP1424	30/45 (67)	48.3 (36.5)	14.91 (7.49)	30/41 (73)	42.5 (31.6)	4.91 (7.32)	10.00 [-10.78; 30.79] 0.3391
Cannabidiol 20 mg/kg/d							
GWEP1424	30/40 (75)	40.0 (27.5)	2.20 (6.05)	30/41 (73)	42.5 (31.6)	5.12 (5.70)	-2.92 [-19.34; 13.50] 0.7228
GWEP1332 B	27/40 (68)	51.9 (35.3)	–0.09 (7.20)	31/38 (82)	46.8 (31.5)	12.69 (6.81)	-12.78 [-32.75; 7.20] 0.2051
Meta-analysis							–0,21 [–0,57; 0,15]
QOLCE – Behaviour							
Cannabidiol 10 mg/kg/d							
GWEP1424	37/45 (82)	50.3 (11.2)	4.32 (1.86)	32/41 (78)	53.0 (15.7)	0.12 (1.95)	4.20 [-1.09; 9.48] 0.1174
Cannabidiol 20 mg/kg/d							
GWEP1424	34/40 (85)	49.0 (13.4)	1.14 (1.81)	32/41 (78)	53.0 (15.7)	1.22 (1.82)	-0.08 [-5.12; 4.95] 0,9738
GWEP1332 B	32/40 (80)	52.7 (12.7)	-0.30 (2.02)	30/38 (79)	53.5 (14.4)	1.33 (2.11)	-1.64 [-7.55; 4.28] 0.5821
Meta-analysis							-0.07 [–0.42; 0.28]
QOLCE – global health							
Cannabidiol 10 mg/kg/d							
GWEP1424	42/45 (93)	35.7 (28.2)	13.2 (4.75)	41/41 (100)	26.2 (24.3)	10.8 (4.62)	2.34 [-10.69; 15.37] 0.7216
Cannabidiol 20 mg/kg/d							
GWEP1424	36/40 (90)	22.9 (22.7)	14.73 (4.35)	41/41 (100)	26.2 (24.3)	12.14 (3.94)	2.60 [-8.96; 14.15] 0.6556
GWEP1332 B	36/40 (90)	22.2 (23.7)	9.98 (3.77)	35/38 (92)	31.4 (29.3)	3.06 (3.86)	6,93 [-3,83; 17,68] 0,2029
Meta-analysis							0,20 [–0,13; 0,52]
QOLCE – Quality of life							
Cannabidiol 10 mg/kg/d							
GWEP1424	42/45 (93)	53.0 (27.7)	6.81 (4.36)	41/41 (100)	42.1 (28.7)	3.74 (4.25)	3.06 [-8.90; 15.0] 0.6120

Endpoint; Study	Cannabidiol			Placebo			Cannabidiol vs placebo
	n/N (%)	Baseline MV (SD)	Delta[a] MV (SE)	n/N (%)	Baseline MV (SD)	Delta[a] MV (SE)	LS-MD [95%- CI] p value
Cannabidiol 20 mg/kg/d							
GWEP1424	35/40 (88)	42.1 (25.6)	6.55 (4.39)	41/41 (100)	42.1 (28.7)	3.81 (3.90)	2.74 [-8.83; 14.30] 0.6384
GWEP1332 B	37/40 (93)	41.9 (24.3)	4.43 (4.25)	34/38 (89)	44.1 (23.1)	0.08 (4.46)	4.35 [-7.98; 16.68] 0.4837
Meta-analysis							0,14 [–0,19; 0,46]
QOLCE – Quality of life Total							
Cannabidiol 10 mg/kg/d							
GWEP1424	38/45 (84)	45.1 (13.6)	7.43 (1.94)	29/41 (71)	43.9 (11.2)	3.52 (2.14)	3.91 [-1.76; 9.58] 0.1731
Cannabidiol 20 mg/kg/d							
GWEP1424	32/40 (80)	42.6 (14.6)	2.36 (2.12)	29/41 (71)	43.9 (11.2)	3.72 (2.15)	-1.36 [-7.31; 4.59] 0.6488
GWEP1332 B	31/40 (76)	43.9 (13.2)	3.25 (2.18)	30/38 (79)	41.3 (13.5)	4.24 (2.27)	-0.99 [-7.29; 5.30] 0.7533
Meta-analysis							0.10 [-0.45; 0.26]

a) Evaluation period Study visit 8 (end of treatment).

Abbreviations: n / a: not specified; CI: Confidence interval; LS-MW: Least squares mean; LS-MD: Least square mean difference; MW: Mean; QOLCE: Quality of Life in Childhood Epilepsy; SD: Standard deviation; SE: Standard error.

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					
GWEP1424	44	40 (90.9)	41	40 (97.6)	-
Cannabidiol 20 mg/kg/d					
GWEP1424	41	38 (92.7)	41	40 (97.6)	-
GWEP1332 B	40	39 (97.5)	38	29 (76.3)	-
SAE					
Cannabidiol 10 mg/kg/d					
GWEP1424	44	10 (22.7)	41	7 (17.1)	1.21 [0.53; 2.76] 0.6574
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
GWEP1424	41	11 (26.8)	41	7 (17.1)	1.47 [0.64; 3.39] 0.3082
GWEP1332 B	40	8 (20.0)	38	1 (2.6)	7.48 [1.00; 56.04] 0.0158
Meta-analysis					1,87 [0,86; 4,03] 0,1125
Therapy discontinuation due to AE					
Cannabidiol 10 mg/kg/d					
GWEP1424	44	0	41	0	-
Cannabidiol 20 mg/kg/d					
GWEP1424	41	4 (9.8)	41	0 (0)	9.00 [0.50; 161.98] 0.0440
GWEP1332 B	40	6 (15.0)	38	1 (2.6)	5.02 [0.63; 39.79] 0.0768
Meta-analysis					6.12 [1.14; 32.93] 0.0349
AEs with an incidence of ≥ 10% and statistically significant differences between the treatment groups					
Cannabidiol 10 mg/kg/d					
Pneumonia					
GWEP1424	44	5 (11.4)	41	0 (0.0)	10.27 [0.59; 180.05] 0.04
Cannabidiol 20 mg/kg/d					
Gastrointestinal disorders					
GWEP1424	41	14 (34.2)	41	10 (24.4)	1.43 [0.71; 2.85] 0.3291
GWEP1332 B	40	20 (50.0)	38	8 (21.1)	2.77 [1.45; 5.31] 0.0028
Meta-analysis					2.01 [1.05; 3.85] no data available
Diarrhoea					
GWEP1424	41	9 (22.0)	41	4 (9.8)	2.40 [0.80; 7.19] 0.1110
GWEP1332 B	40	13 (32.5)	38	4 (10.5)	3.45 [1.25; 9.50] 0.0129
Meta-analysis					2.92 [1.39; 6.14] no data available
Vomiting					
GWEP1424	41	5 (12.2)	41	3 (7.3)	1.56 [0.40; 6.12] 0.5476

Endpoint; Study	Cannabidiol		Placebo[a]		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%- CI] p value
GWEP1332 B	40	8 (20.0)	38	2 (5.3)	4.06 [0.92; 17.88] 0.0472
Meta-analysis					2.42 [0.89; 6.61] no data available
General disorders and administration site conditions					
GWEP1424	41	17 (41.5)	41	14 (34.2)	1.23 [0.70; 2.15] 0.4827
GWEP1332 B	40	17 (42.5)	38	5 (13.2)	3.09 [1.28; 7.47] 0.0060
Meta-analysis					1.82 [0.74; 4.48] no data available
Fatigue					
GWEP1424	41	12 (29.3)	41	5 (12.2)	2.43 [0.93; 6.31] 0.0590
GWEP1332 B	40	10 (25.0)	38	1 (2.6)	8.80 [1.19; 64.98] 0.0069
Meta-analysis					3.38 [1.12; 10.20] no data available
Investigations, examinations					
GWEP1424	41	16 (39.0)	41	5 (12.2)	3.30 [1.34; 8.13] 0.0037
GWEP1332 B	40	14 (35.0)	38	5 (13.2)	2.77 [1.12; 6.86] 0.0249
Meta-analysis					3.03 [1.60; 5.73] no data available
Alanine aminotransferase increased					
GWEP1424[b]	41	6 (14.6)	41	0 (0)	13.0 [0.76; 223.50] 0.0083
Aspartate aminotransferase increased					
GWEP1424[b]	41	7 (17.1)	41	0 (0)	15.0 [0.88; 254.33] 0.0033
Weight decrease					
GWEP1332 B[c]	41	5 (12.5)	41	0 (0)	10.46 [0.60; 183.01] 0.0175
Metabolism and nutrition disorders					
GWEP1424	41	13 (31.7)	41	7 (17.1)	2.11 [0.94; 4.75] 0.0866
GWEP1332 B	40	17 (42.5)	38	2 (5.3)	7.87 [1.95; 31.81] 0.0002
Meta-analysis					3.59 [1.01; 12.67] no data available
Decreased appetite					

Endpoint; Study	Cannabidiol		Placebo[a]		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%- CI] p value
GWEP1424	41	12 (29.3)	41	6 (14.6)	2.27 [0.94; 5.47] 0.0886
GWEP1332 B	40	14 (35.0)	38	2 (5.3)	6.64 [1.62; 27.30] 0.0012
Meta-analysis					3.35 [1.22; 9.22] no data available
Nervous system disorders					
GWEP1424	41	22 (53.7)	41	23 (56.1)	0.98 [0.66; 1.46] 0.8709
GWEP1332 B	40	26 (65.0)	38	13 (34.2)	1.82 [1.11; 2.99] 0.0037
Meta-analysis					1.31 [0.71; 2.40] no data available
Somnolence					
GWEP1424	41	13 (31.7)	41	8 (19.5)	1.63 [0.77; 3.48] 0.1810
GWEP1332 B	40	18 (45.0)	38	5 (13.2)	3.39 [1.42; 8.08] 0.0010
Meta-analysis					2.28 [1.12; 4.64] no data available
Psychiatric disorders					
GWEP1424	41	8 (19.5)	41	5 (12.2)	1.44 [0.51; 4.01] 0.4629
GWEP1332 B	40	9 (22.5)	38	2 (5.3)	4.05 [0.93; 17.62] 0.0376
Meta-analysis					2.10 [0.79; 5.60] no data available
SAEs with an incidence of ≥ 5 % and statistically significant differences between the treatment groups					
Cannabidiol 20 mg/kg/d					
Infections and infestations					
GWEP1424	41	6 (14.6)	41	0 (0)	13.00 [0.76; 223.50] 0.0166
GWEP1332 B	40	3 (7.5)	38	0 (0)	6.66 [0.36; 124.77] 0.0726
Meta-analysis					9.40 [1.22; 72.35] no data available

a) The two study arms placebo 10 mg / kg / d, and placebo 20 mg/kg/d of the GWEP1424 study were pooled.
b) No information for GWEP1332 study Part B.
c) No information for the GWEP1424 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 Dravet syndrome

approx. 1.100 to 3.100 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 Dravet 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