Resolution

Gemeinsamer Bundesausschuss

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 (Dravet Syndrome, ≥ 2 years)

of 2 April 2020

On 2 April 2020, the Federal Joint Committee (G-BA) resolved by written statement 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 dated 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient cannabidiol as follows:

Cannabidiol

Resolution of: 2 April 2020
Entry into force on: 2 April 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

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

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.

The present resolution relates exclusively to the indication Dravet syndrome.

1. Extent and probability of the additional benefit of the medicinal product

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. According to 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 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 of age and older with Dravet syndrome

Extent of the additional benefit of cannabidiol in combination with clobazam indicating the significance of the evidence:

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

Study results according to endpoints:[1]

Patients 2 years of age and older with Dravet syndrome

Study GWEP1424: RCT; 14 weeks. Relevant sub-population: Cannabidiol 10mg/kg/d in combination with clobazam.

No data was presented for dosing steps above 10mg/kg/d.

[1] Data from the dossier evaluation by the G-BA (published on 15 January 2020) unless otherwise indicated.

Mortality

Endpoint	Cannabidiol		Placebo		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator
Overall mortality	44	0	41	0	–

Morbidity

Endpoint	Cannabidiol			Placebo			Cannabidiol vs placebo
	N	Baseline [95% CI]	Treatment/baseline ratio [95% CI]	N	Baseline [95% CI]	Treatment/baseline ratio [95% CI]	Treatment effect[a] [95%-CI] p value
Frequency of convulsive seizures[b]	45	no data available	0.39 [0.31; 0.50]	41	no data available	0.62 [0.49; 0.80]	0.63 [0.44; 0.88] 0.0083
	n/ N	Median baseline [Q1; Q3]	Median Change from baseline [Q1; Q3]	n/ N	Median baseline [Q1; Q3]	Median Change from baseline [Q1; Q3]	Treatment effect[c] [95% CI] p value
Frequency of convulsive seizures[b] (sensitivity analysis)	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] 0.0596
Frequency of non-convulsive seizures	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
Frequency of all seizures	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

a) Negative binomial model
b) Includes all tonic-clonic, tonic, clonic and atonic seizures
c) Median difference
d) Includes all myoclonic, countable partial and other partial seizures or absences. Only patients with reported non-convulsive seizures at baseline.

Abbreviations used:
CI = confidence interval; Q = quartile

Endpoint	Cannabidiol		Placebo		Cannabidiol vs placebo
	N	Patients with event *n (%)*	N	Patients with event *n (%)*	RR [95% CI] p value
Frequency of convulsive seizures					
Reduction of ≥ 25%	45	31 (68.9)	41	24 (58.5)	1.09 [0.78; 1.51] 0.33
Reduction of ≥ 50%	45	25 (55.6)	41	15 (36.6)	1.51 [0.95; 2.42] 0.06

Endpoint	Cannabidiol		Placebo		Cannabidiol vs placebo
	N	**Patients with event** *n (%)*	**N**	**Patients with event** *n (%)*	**RR [95% CI] p value**
Reduction of ≥ 75%	45	16 (35.6)	41	4 (9.8)	3.78 [1.38; 10.4] 0.004
Reduction of 100%	45	2 (4.44)	41	1 (2.44)	1.98 [0.18; 21.4] 0.57
Increase of > 0%	no data available	no data available	no data available	no data available	no data available
Status epilepticus					
Convulsive status epilepticus[a]	45	2 (4.44)	41	4 (9.76)	p = 0.09
Non-convulsive status epilepticus[b]	45	3 (6.67)	41	2 (4.88)	p = 0.68
Hospitalisations					
Epilepsy-related hospitalisations[c]	45	6 (13.3)	41	2 (4.9)	2.94 [0.67; 12.85] 0.16
Caregiver Global Impression of Change (CaGIC)					
Improvement[d] in CaGIC at end of treatment	42	31 (73.8)	41	17 (41.5)	1.74 [1.16; 2.62] 0.002
Improvement[d] in CaGIC at end of treatment[e]	45	33 (73.3)	41	17 (41.5)	1.74 [1.17; 2.61] 0.002

a) Includes all types of convulsive seizures (all tonic-clonic, tonic, clonic and atonic seizures) lasting 30 minutes or longer.
b) Includes all types of non-convulsive seizures (myoclonic, countable partial and other partial seizures or absences) lasting 30 minutes or longer.
c) Assessment by the caregiver.
d) The Caregiver Global Impression of Change (CaGIC) is a rated scale defining improvement as 1 (very much improved), 2 (much improved) and 3 (a little improved).
e) The study protocol foresaw an evaluation at the end of the study if changes were experienced compared to the end of treatment.

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

Health-related quality of life

Endpoint	Cannabidiol N = 45			Placebo N = 41			Cannabidiol vs placebo
	n (%)	Baseline MV (SD)	Delta[a] LS MV (SE)	n (%)	Baseline MV (SD)	Delta[a] LS MV (SE)	LS MD [95% CI] p value
QOLCE – physical activity							
Physical restrictions	41 (91)	19.1 (12.6)	-0.66 (1.77)	38 (93)	21.3 (14.9)	-2.03 (1.77)	1.38 [-3.55; 6.30] 0.58
Energy/fatigue	42 (93)	55.7 (18.6)	1.49 (3.46)	39 (95)	57.4 (18.1)	1.66 (3.47)	-0.17 [-9.74; 9.40] 0.97
QOLCE – cognition							
No relevant data are available.							
QOLCE – well-being							
No relevant data are available.							
QOLCE – social activity							
Social interaction	32 (71)	46.2 (29.3)	3.99 (6.15)	27 (66)	30.9 (27.5)	8.50 (6.59)	-4.52 [-22.43; 13.4] 0.62
Social activity	36 (80)	19.1 (21.6)	15.45 (4.56)	36 (88)	16.1 (16.1)	8.22 (4.46)	7.23 [-5.37; 19.82] 0.26
Stigma	30 (67)	48.3 (36.5)	14.91 (7.49)	30 (73)	42.5 (31.6)	4.91 (7.32)	10.00 [-10.78; 30.8] 0.34
QOLCE – behaviour							
Behaviour	37 (82)	50.3 (11.2)	4.32 (1.86)	32 (78)	53.0 (15.7)	0.12 (1.95)	4.20 [-1.09; 9.48] 0.12
QOLCE – general health							
General health	42 (93)	35.7 (28.2)	13.2 (4.75)	41 (100)	26.2 (24.3)	10.8 (4.62)	2.34 [-10.69; 15.4] 0.72
QOLCE – quality of life							
Quality of life	42 (93)	53.0 (27.7)	6.81 (4.36)	41 (100)	42.1 (28.7)	3.74 (4.25)	3.06 [-8.90; 15.0] 0.61
QOLCE – overall quality of life							
Overall quality of life	38 (84)	45.1 (13.6)	7.43 (1.94)	29 (71)	43.9 (11.2)	3.52 (2.14)	3.91 [-1.76; 9.58] 0.17

a) Evaluation time study visit 8 (end of treatment).

Abbreviations used:
CI: confidence interval; LS MV: least squares mean value; LS MD: least squares mean difference; MV: mean value; QOLCE: Quality of Life in Childhood Epilepsy; SD: standard deviation; SE: standard error

Side effects

Endpoint	Cannabidiol		Placebo		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Total rates					
AEs	44	40 (90.9)	41	40 (97.6)	-
SAEs	44	10 (22.7)	41	7 (17.1)	1.21 [0.53; 2.76] 0.66
Therapy discontinuation due to AE	44	0	41	0	-
AEs with incidence ≥ 10% (SOC / PT as per MedDRA)					
Gastrointestinal disorders	44	8 (18.2)	41	10 (24.4)	0.76 [0.33; 1.76] 0.52
Diarrhoea	44	7 (15.9)	41	4 (9.8)	1.70 [0.53; 5.45] 0.38
General disorders and administration site conditions	44	13 (29.6)	41	14 (34.1)	0.86 [0.46; 1.58] 0.50
Fever	44	9 (20.4)	41	9 (21.9)	0.85 [0.38; 1.89] 0.66
Infections and infestations	44	21 (47.7)	41	14 (34.1)	1.39 [0.83; 2.32] 0.22
Pneumonia	44	5 (11.4)	41	0 (0.0)	10.27 [0.59; 180.05] 0.04
Injury, poisoning and procedural complications	44	7 (15.9)	41	4 (9.8)	1.68 [0.53; 5.33] 0.35
Investigations	44	7 (15.9)	41	5 (12.2)	1.31 [0.45; 3.80] 0.64
Metabolism and nutrition disorders	44	8 (18.2)	41	7 (17.1)	0.98 [0.40; 2.39] 0.86
Reduced appetite	44	8 (18.2)	41	6 (14.6)	1.12 [0.44; 2.87] 0.90
Nervous system disorders	44	24 (54.5)	41	23 (56.1)	0.97 [0.66; 1.43] 0.84
Psychiatric disorders	44	7 (15.9)	41	5 (12.2)	1.20 [0.41; 3.47] 0.73
Respiratory, thoracic and mediastinal disorders	44	4 (9.1)	41	8 (19.5)	0.46 [0.15; 1.45] 0.18
Skin and subcutaneous tissue disorders	44	8 (18.2)	41	2 (4.9)	3.74 [0.83; 16.85] 0.07
Fatigue	44	4 (9.1)	41	5 (12.2)	0.72 [0.21; 2.50] 0.60

Endpoint	Cannabidiol		Placebo		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Somnolence	44	15 (34.1)	41	8 (19.5)	1.75 [0.83; 3.66] 0.12
Status epilepticus	44	5 (11.4)	41	5 (12.2)	0.93 [0.30; 2.90] 0.80
Abbreviations used: CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RR: relative risk; SOC: System organ class; (S)AEs: (serious) adverse event(s)					

Summary of results for relevant clinical endpoints

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

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

Patients 2 years of age and older with Dravet syndrome

approx. 1,100–3,100 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) at the following publicly accessible link (last access: 10 December 2019):

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

Treatment with cannabidiol should only be initiated and monitored by specialists who are experienced in the treatment of patients with epilepsy.

4. Treatment costs

Annual treatment costs:

Patients 2 years of age and older with Dravet syndrome

Designation of the therapy	Annual treatment costs/patient
Minimal dosage (2-year-old child)	
Cannabidiol	€ 8,807.38
Clobazam	€ 1,212.71
Total	€ 10,020.09
Maximal dosage (adult)	
Cannabidiol	€ 75,954.89
Clobazam	€ 638.90
Total	€ 76,593.79

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2020

Costs for additionally required SHI services: not applicable

II. Entry into force

1. **The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 2 April 2020.**

2. **The period of validity of the resolution is limited to 15 October 2020.**

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

Berlin, 2 April 2020

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

Prof. Hecken