Gemeinsamer Bundesausschuss

Cannabidiol

Resolution of: 2 April 2020 Valid: 15 October 2020
Entry into force on: 2 April 2020
Federal Gazette, BAnz AT 14 05 2020 B4

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 Lennox-Gastaut 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 Lennox-Gastaut syndrome

Extent and probability of the additional benefit of cannabidiol (in conjunction with clobazam):

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 Lennox-Gastaut syndrome

Study GWEP1414: RCT; 14 weeks. Relevant sub-population: Cannabidiol 10mg/kg/d in combination with clobazam.

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

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

Mortality

Endpoint	Cannabidiol		Placebo		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator
Overall mortality	35	0	37	0	–

Morbidity

Endpoint	Cannabidiol			Placebo			Cannabidiol vs placebo
	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 [a] [95% CI] p value
Frequency of convulsive seizures[b]	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
Frequency of non-convulsive seizures[c]	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]	-32.57 [-59.90; -1.24] 0.0390
Frequency of all seizures	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

a) Median difference
b) Includes all tonic-clonic, tonic, clonic and atonic seizures
c) 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; n/N = number; Q = quartile; vs = versus

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 %	37	27 (73.0)	37	20 (54.0)	1.35 [0.95; 1.93] 0.0529
Reduction of ≥ 50 %	37	18 (48.6)	37	7 (18.9)	2.62 [1.23; 5.56] 0.0065
Reduction of ≥ 75%	37	5 (13.5)	37	1 (2.7)	5.00 [0.61; 40.75]4) 0.1268
Reduction of 100%	37	0	37	0	n.a.

Endpoint	Cannabidiol		Placebo		Cannabidiol vs placebo
	N	Patients with event *n (%)*	N	Patients with event *n (%)*	RR [95% CI] p value
Increase of > 0%	no data available	no data available	no data available	no data available	no data available
Status epilepticus					
Convulsive status epilepticus[a]	37	1 (2.7)	37	0	p = 0.4450
Non-convulsive status epilepticus[b]	37	1 (2.7)	37	0	p = 0.1904

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.

Abbreviations used:
no data available = not specified; CI = confidence interval; n.a.: not assessable; n/N = number; RR = relative risk; vs = versus

Endpoint	Cannabidiol		Placebo		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	LS MD [95% CI] p value
Caregiver Global Impression of Change (CaGIC)					
Improvement[b] in CaGIC at end of treatment	37	28 (75.7)	37	17 (46.0)	1.72 [1.18; 2.50] 0.0057

a) Evaluation not planned *a priori* for the end of the study; evaluation by means of LOCF; no information on the number of imputations.
b) 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).

Abbreviations used:
CI: confidence interval; LOCF: Last Observation Carried Forward; LS MV: least squares mean value; LS MD: least squares mean difference; n/N: number of patients in the assessment; SE: standard error

Health-related quality of life

No relevant data are available.

Side effects

	Cannabidiol		Placebo		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
AEs	35	31 (88.6)	37	28 (75.7)	-
SAEs	35	8 (22.9)	37	4 (10.8)	1.76 [0.58; 5.27] 0.2661
Therapy discontinuation due to AE	35	1 (2.9)	37	0	3.17 [0.13; 75.24] 0.3173
AEs with incidence ≥ 10% (SOC / PT as per MedDRA)					
Gastrointestinal disorders	35	7 (20.0)	37	13 (35.1)	0.57 [0.26; 1.26] 0.1176
Vomiting	35	2 (5.7)	37	6 (16.2)	0.35 [0.08; 1.63] 0.2276
General disorders and administration site conditions	35	9 (25.7)	37	9 (24.3)	1.15 [0.53; 2.50] 0.7544
Fatigue	35	5 (14.3)	37	0 (0.0)	11.61 [0.67; 202.53] 0.0293
Fever	35	3 (8.6)	37	7 (18.9)	0.63 [0.19; 2.11] 0.3192
Infections and infestations	35	16 (45.7)	37	17 (46.0)	1.10 [0.69; 1.76] 0.9851
Upper respiratory tract infections	35	5 (14.3)	37	7 (18.9)	0.76 [0.26; 2.16] 0.8773
Nasopharyngitis	35	0 (0.0)	37	5 (13.5)	0.10 [0.01; 1.67] 0.0344
Pneumonia	35	4 (11.4)	37	0 (0.0)	9.50 [0.53; 170.25] 0.0477
Injury, poisoning and procedural complications	35	5 (14.3)	37	4 (10.8)	1.42 [0.42; 4.78] 0.5884
Investigations	35	11 (31.4)	37	6 (16.2)	1.98 [0.82; 4.79] 0.1551
Metabolism and nutrition disorders	35	7 (20.0)	37	3 (8.1)	2.47 [0.68; 8.93] 0.1467
Reduced appetite	35	4 (11.4)	37	3 (8.1)	1.49 [0.37; 5.93] 0.5501
Nervous system disorders	35	19 (54.3)	37	9 (24.3)	2.23 [1.17; 4.23] 0.0095
Somnolence	35	11 (31.4)	37	1 (2.7)	11.63 [1.58; 85.43] 0.0008

	Cannabidiol		Placebo		Cannabidiol vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Psychiatric disorders	35	7 (20.0)	37	2 (5.4)	3.34 [0.73; 15.21] 0.0951
Respiratory, thoracic, and mediastinal disorders	35	5 (14.3)	37	5 (13.5)	1.21 [0.40; 3.63] 0.7973
Skin and subcutaneous tissue disorders	35	5 (14.3)	37	1 (2.7)	5.15 [0.62; 42.61] 0.0976
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 and non-convulsive seizures.
Health-related quality of life	n.a.	The presented data cannot be used 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 Lennox-Gastaut syndrome

approx. 2,600–22,700 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) 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 Lennox-Gastaut 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