Gemeinsamer Bundesausschuss

# 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
BAnz 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).



<u>Patients 2 years and older with seizures associated with tuberous sclerosis, adjunctive therapy</u>

**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:<br>↑: statistically significant and relevant positive effect with low/unclear reliability of data<br>↓: statistically significant and relevant negative effect with low/unclear reliability of data<br>↑↑: statistically significant and relevant positive effect with high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data<br>↔: no statistically significant or relevant difference<br>∅: There are no usable data for the benefit assessment.<br>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:<br>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 |

A The two study arms placebo 25 mg/kg/d and placebo 50 mg/kg/d were pooled.
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.
c Absences, myoclonic seizures, partial sensory seizures, and infantile or epileptic spasms.

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



| 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 |

a The two study arms placebo 25 mg/kg/d and placebo 50 mg/kg/d were pooled.
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.
c Any type of seizure (convulsive and non-convulsive) lasting 30 minutes or longer.
d An improvement in the global impression of change is defined as (1) very much improved, (2) much improved, (3) slightly improved.
e ITT population; subjects with no response are counted as non-responders.

| Endpoint | Cannabidiol | | Placebo[a] | | Cannabidiol vs placebo |
|---|---|---|---|---|---|
| | N | Patients with event n (%) | N | Patients with event n (%) | RR [95% CI] p-value |
| f A deterioration in the global impression of change is defined as (4) slightly deteriorated, (5) strongly deteriorated, (6) very strongly deteriorated.<br><br>Abbreviations used:<br>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 | | | | | |

| 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 *Hedges' g:* 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 |

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:
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

**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 ≥ 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