Gemeinsamer Bundesausschuss

Resolution

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-L):

Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Fenfluramine (Dravet syndrome, ≥ 2 years)

of 15 July 2021

At its session on 15 July 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 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 fenfluramine as follows:

Fenfluramine

Resolution of: 15 July 2021
Entry into force on: 15 July 2021
BAnz AT TT. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 18 December 2020):

Fintepla is indicated for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.

Therapeutic indication of the resolution (resolution of 15 July 2021):

see therapeutic indication according to marketing authorisation.

1. Extend of the additional benefit and significance of the evidence

Fenfluramine 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 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 seizures associated with Dravet syndrome

Extend of the additional benefit and significance of the evidence of fenfluramine:

Hint of a considerable additional benefit

Study results according to endpoints:[1]

Patients 2 years of age and older with seizures associated with Dravet syndrome

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Benefits in reducing seizures and improving health status
Health-related quality of life	↔	No relevant difference for the benefit assessment
Side effects	↔	For Serious Adverse Events (SAE) and Adverse Events of Special Interest (AESI): No relevant difference for the benefit assessment; For severe adverse events (severe AEs) and adverse events that led to discontinuation of study medication: There are no assessable data.
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		

Study 1: RCT 14 weeks.

Study 1504: RCT 15 weeks.

Mortality

Endpoint;	Fenfluramine		Placebo		Fenfluramine vs placebo
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Effect estimator
Overall mortality					
Study 1	40	0	40	0	-
Study 1504	43	0	44	0	-

[1]Data from the dossier assessment of the G-BA (published on the 3 May 2021), unless otherwise indicated.

Morbidity

Endpoint; Study	Fenfluramine			Placebo			Fenfluramine vs placebo	
	N	MV (SD)	LS Mean Difference (SE)[a]	N	MV (SD)	LS Mean Difference (SE)[a]	LS Mean Difference[a] [95% CI] p value	Percentage difference[b] [95% CI] p value
Frequency of convulsive seizures (normalised to 28 days)								
Study 1	40	Baseline: 31.35 (30.56) EoT: 18.24 (31.92)	2.00 (0.12)	40	Baseline: 44.21 (40.18) EoT: 37.50 (37.97)	3.00 (0.12)	-0.98 [-1.30, -0.65] < 0.001	-62.29 [-72.80; -47.72] < 0.001
Study 1504	43	Baseline: 27.90 (36.94) EoT: 24.72 (72.05)	1.94 (0.13)	44	Baseline: 21.62 (27.65) EoT: 20.97 (27.70)	2.72 (0.13)	-0.78 [-1.12; -0.44] < 0.001	-54.04 [-67.23; -35.55] < 0.001

Endpoint; Study	Placebo		Fenfluramine		Placebo vs fenfluramine
	N	Patients with event *n (%)*	N	Patients with event *n (%)*	Relative Risk [95% CI]; p value
Reduction in the frequency of convulsive seizures ≥ 25%					
Study 1	40	14 (35.0)	40	36 (90.0)	0.39 [0.25; 0.60]; < 0.0001
Study 1504	44	12 (27.3)	43	30 (69.8)	0.39 [0.23; 0.66]; 0.0004
Meta-analysis					0.39 [0.28; 0.54]; < 0.0001
Reduction in the frequency of convulsive seizures ≥ 50%					
Study 1	40	5 (12.5)	40	27 (67.5)	0.19 [0.08; 0.44]; 0.0001
Study 1504	44	2 (4.5)	43	23 (53.5)	0.08 [0.02; 0.34]; 0.0004
Meta-analysis					0.15 [0.07; 0.31]; 0.0001
Reduction in the frequency of convulsive seizures ≥ 75%					
Study 1	40	1 (2.5)	40	20 (50.0)	0.05 [0.01; 0.36]; 0.0028
Study 1504	44	1 (2.3)	43	15 (34.9)	0.06 [0.01; 0.47]; 0.0067

Endpoint; Study	Placebo		Fenfluramine		Placebo vs fenfluramine
	N	Patients with event *n (%)*	N	Patients with event *n (%)*	Relative Risk [95% CI]; p value
Meta-analysis					0.06 [0.01; 0.23]; < 0.0001
Reduction in the frequency of convulsive seizures ≥ 100%					
Study 1	40	3 (7.5)	40	0	n.c
Study 1504	43	1 (2.3)	44	0	n.c
Meta-analysis					n.c

Endpoint; Study	Fenfluramine		Placebo		Fenfluramine vs placebo
	N	Patients with event *n (%)*	N	Patients with event *n (%)*	Relative Risk [95% CI]; p value
Reduction in the frequency of convulsive seizures> 0%					
Study 1	40	3 (7.5)	40	14 (35.0)	0.21 [0.07; 0.68]; 0.0088
Study 1504	43	10 (23.3)	44	21 (47.7)	0.49 [0.26; 0.91]; 0.0236
Meta-analysis					0.40 [0.23; 0.70]; 0.0012

Endpoint; Study	Fenfluramine				Placebo				Fenfluramine vs placebo
	N	Baseline MV (SD)	MV (SD)	LS Mean (SE)	N	Baseline MV (SD)	MV (SD)	LS Mean (SE) (SE)	LS Mean Difference [95% CI] p value
Frequency of non-convulsive seizures (normalised to 28 days)									
Study 1	24	330.73 (756.43)	-207.62 (499.90)	n. v.	21	67.41 (87.42)	66.20 (419.59)	n. v.	n. v. [n. v.]; 0.046

Study 1504	17	44.57 (74.80)	33.52 (90.97)	n. v.	22	132.46 (485.24)	-29.18 (113.94)	n. v.	n. v. [n. v.]; 0.182

Endpoint; Study	Fenfluramine				Placebo				Fenfluramine vs placebo
	N	Baseline MV (SD)	MV (SD)	LS Mean (SE)	N	Baseline MV (SD)	MV (SD)	LS Mean (SE) (SE)	LS Mean Difference [95% CI] p value
Frequency of convulsive and non-convulsive seizures (total) (normalised to 28 days)									
Study 1	40	229.79 (608.66)	-137.65 (401.12)	n. v.	40	79.60 (86.06)	30.38 (298.35)	n. v.	n. v. [n. v.]; < 0.001
Study 1504	43	45.52 (62.40)	10.39 (76.74)	n. v.	44	87.85 (344.77)	-14.88 (80.73)	n. v.	n. v. [n. v.]; 0.137

Endpoint; Study	Fenfluramine			Placebo			Fenfluramine vs placebo
	N	Distribution of seizures %		N	Distribution of seizures %		[Effect estimator 95% CI]; p Value
		Baseline	Treatment period[m]		Baseline	Treatment period[m]	
Duration of seizures							
Study 1 < 2 minutes 2– 10 minutes > 10 minutes	40	 71.6 24.2 4.2	N = 39 72.3 22.9 4.8	40	 69.3 26.9 3.9	 71.3 26.3 2.4	n. d.

Study 1504 < 2 minutes 2– 10 minutes > 10 minutes	43	 83.5 15.9 0.6	N = 42 81.2 17.1 1.8	44	 76.6 22.1 1.3	 78.1 20.6 1.3	n. d.
	N	**Patients with event** n (%)		**N**	**Patients with event** n (%)		**Effect estimator [95% CI]; p Value**
Status epilepticus (supplementary)							
Study 1	40	n. d.	14 (35.0)	40	n. d.	11 (27.5)	n. v. [n. v.]; 0.461
Study 1504	43	n. d.	14 (32.6)	44	n. d.	8 (18.2)	n. v. [n. v.]; 0.128
Epilepsy-related hospitalisations (supplementary)							
Study 1	40	n. d.	6 (15.0)	40	n. d.	9 (22.5)	n. v. [n. v.]; 0.568
Study 1504	43	n. d.	15 (34.9)	44	n. d.	8 (29.5)	n. v. [n. v.]; 0.651

Endpoint; Study	**Placebo**		**Fenfluramine**		**Placebo vs fenfluramine**
	N	**Patients with event** *n (%)*	**N**	**Patients with event** *n (%)*	**Relative Risk [95% CI]; p value**
CGI-I Improvement					
Study 1	40	12 (30.0)	40	26 (65.0)	0.47 [0.28; 0.80]; 0.0049
Study 1504	44	16 (36.4)	43	26 (60.5)	0.57 [0.36; 0.90]; 0.0156
Meta-analysis					0.53 [0.37; 0.74]; 0.0002

Endpoint; Study	**Fenfluramine**		**Placebo**		**Fenfluramine vs placebo**
	N	**Patients with event** *n (%)*	**N**	**Patients with event** *n (%)*	**Relative Risk [95% CI]; p value**
CGI-I deterioration					
Study 1	40	5 (12.5)	40	10 (25.0)	0.49 [0.18; 1.29]; 0.1478
Study 1504	43	5 (11.6)	44	3 (6.8)	1.80 [0.46; 7.09]; 0.3982
Meta-analysis[6)]					0.76 [0.34; 1.68]; 0.4931

Endpoint; Study	**Fenfluramine**			**Placebo**			**Fenfluramine vs placebo**
	N	**Baseline** *MV (SD)*	**Change from baseline** *MV (SD)*	**N**	**Baseline** *MV (SD)*	**Change from baseline** *MV (SD)*	**LS Mean Difference [95% CI]; p-value**
BRIEF-P / BRIEF							
BRIEF-P - Global Executive Total Score (GEC)							

Endpoint; Study	Fenfluramine			Placebo			Fenfluramine vs placebo
	N	Baseline *MV (SD)*	Change from baseline *MV (SD)*	N	Baseline *MV (SD)*	Change from baseline *MV (SD)*	LS Mean Difference [95% CI]; p-value
Study 1	6	127.14 (13.87)	0.17 (22.13)	8	138.33 (22.57)	4.13 (7.72)	6.25 [-8.67; 21.17] 0.3876
Study 1504	10	129.10 (20.98)	-1.10 (14.75)	9	130.80 (18.68)	-0.56 (9.07)	0.10 [-13.15; 13.36] 0.9868
BRIEF-P -Inhibitory Self-Control Index (ISCI)							
Study 1	6	55.43 (6.35)	-3.00 (8.69)	8	57.89 (8.01)	1.13 (4.49)	4.79 [-1.93 11.52]; 0.1500
Study 1504	10	55.10 (11.23)	-2.50 (7.82)	9	54.40 (9.52)	0.33 (6.52)	2.02 [-4.69; 8.72] 0.5297
BRIEF-P - Flexibility Index (FI)							
Study 1	6	35.71 (7.78)	0.00 (9.70)	8	40.00 (8.62)	0.00 (3.63)	2.35 [-3.83; 8.53] 0.4322
Study 1504	10	35.80 (9.58)	-0.40 (4.22)	9	34.30 (8.12)	0.11 (2.98)	-0.30 [-4.31; 3.71] 0.8756
BRIEF-P - Metacognitive Development Index (EMI)							
Study 1	6	54.57 (10.97)	2.00 (9.34)	8	61.22 (13.01)	2.50 (2.93)	1.28 [-4.98; 7.53] 0.6706
Study 1504	10	57.40 (10.61)	0.30 (9.51)	9	59.70 (8.12)	0.11 (6.13)	0.11 [-7.70; 7.92] 0.9762
BRIEF - Global Executive Total Score (GEC)							
Study 1	30	181.39 (40.87)	-11.03 (29.13)	25	177.38 (40.19)	8.92 24.87	18.48 [5.85; 31.11] 0.0047 Hedges' g [95%-CI]: 0.72 [0.17; 1.27]
Study 1504	23	183.33 (27.92)	5.17 (28.86)	26	189.42 (29.39)	-2.69 (30.72)	-6.30 [-21.61; 9.00] 0.4101
BRIEF - Behaviour Regulation Index (BRI)							
Study 1	30	75.13 (18.27)	-4.43 (10.47)	25	73.66 (18.13)	3.04 (8.66)	6.99 [2.48; 11.51] 0.0029 Hedges' g [95%-CI]: 0.76 [0.21; 1.31]
Study 1504	23	74.75 (11.19)	0.43 (9.64)	26	76.50 (13.62)	-1.19 (9.64)	-1.29 [-6.87; 4.29] 0.6420
BRIEF - Metacognition Index (MI)							

Endpoint; Study	Fenfluramine			Placebo			Fenfluramine vs placebo
	N	Baseline *MV (SD)*	Change from baseline *MV (SD)*	N	Baseline *MV (SD)*	Change from baseline *MV (SD)*	LS Mean Difference [95% CI]; p-value
Study 1	30	106.26 (25.00)	-6.60 (20.68)	25	103.72 (25.12)	5.88 (19.14)	11.32 [2.13; 20.51] 0.0165 Hedges' g [95%-CI]: 0.62 [0.07; 1.16]
Study 1504	23	108.58 (20.96)	4.74 (22.06)	26	112.92 (18.46)	-1.50 (22.42)	-4.88 [-15.73; 5.97] 0.3687

a) ANCOVA with stratification factor age and treatment group as independent variables, log seizure frequency at baseline as the covariate, and log-transformed seizure frequency during titration and maintenance phases (with addition +1 to avoid logarithm of zero) as a dependent variable.

b) Calculated from LS Mean on the logarithmic scale as follows: 100 x [1 - exp(LS Mean$_{Fenfluramine}$ - LS Mean$_{Placebo}$)].

For further statistical evaluation methodology and endpoint operationalisation, see Benefit Assessment

Abbreviations used: ANCOVA: Analysis of Covariance; BRIEF(-P): Behaviour Rating Inventory of Executive Function (- Preschool Version; CGI-I: Clinical Global Impression scale - Improvement; CMH: Cochran-Mantel-Haenszel; n.d.: no data; CI: Confidence interval; LS: Least Squares; MV: Mean value; n. c.: not calculable; n. a.: not available; OR: Odds Ratio; RR: Relative Risk; SD: Standard deviation; SE: standard error; SMD: Adverse Event

Health-related quality of life

Endpoint; Study	Placebo			Fenfluramine			Placebo vs fenfluramine
	n/N (%)	Baseline *MV (SD)*	Difference Week 12 *MV (SD)*	n/N (%)	Baseline *MV (SD)*	Difference Week 12 *MV (SD)*	LS-MD [95% CI]; p Value Hedges'g [95% CI]
Change of the PedsQL							
QOLCE – Quality of life Total							
Study 1	32/40 (80.0)	48.7 (18.1)	5.9 (15.1)	32/40 (80.0)	45.6 (17.1)	-1.6 (10.4)	-7.58 [-13.44; -1.72] 0.012 -0.53 [-1.01; -0.04]

Endpoint; Study	Placebo			Fenfluramine			Placebo vs fenfluramine
	n/N (%)	**Baseline** *MV (SD)*	**Difference Week 12** *MV (SD)*	**n/N (%)**	**Baseline** *MV (SD)*	**Difference Week 12** *MV (SD)*	**LS-MD [95% CI]; p Value Hedges'g [95% CI]**
Study 1504	30/43 (69.8)	52.5 (12.1)	-0.9 (11.8)	36/44 (81.8)	50.2 (16.6)	-0.3 (12.4)	-1.17 [-7.05; 4.70] 0.691 -0.03 [-0.51; 0.46]
Pooled Hedges' g	-0.27 [-0.62; 0.07]; p = 0.12						
Abbreviations used: n.d: no data; CI: Confidence interval; MV: Mean value; n. a.: not available; PedsQL: Pediatric Quality of Life Inventory; SD: Standard deviation.							

Side effects

Endpoint; Study	Fenfluramine		Placebo		Fenfluramine vs placebo
	N	**Patients with event** *n (%)*	**N**	**Patients with event** *n (%)*	**RR [95% CI] p value**
Total rates					
AE					
Study 1	40	38 (95.0)	40	26 (65.0)	-
Study 1504	43	42 (97.7)	44	42 (95.5)	-
Meta-analysis					-
severe AE					
Study 1	40	3 (7.5)	40	2 (5.0)	n. d
Study 1504	43	2 (4.7)	44	0 (0)	n.c
Meta-analysis					n.c
SAE					
Study 1	40	5 (12.5)	40	4 (10.0)	1.17 [0.35; 3.92]; 0.7948

Study 1504	43	6 (14.0)	44	7 (15.9)	0.87 [0.32; 2.38]; 0.7849
Meta-analysis					0.98 [0.45; 2.13]; 0.9659
AE, which led to the discontinuation of the study medication					
Study 1	40	5 (12.5)	40	0 (0)	n.c
Study 1504	43	2 (4.7)	44	1 (2.3)	n. d
Meta-analysis					n.c
AESI					
Study 1	40	18 (45.0)	40	10 (25.0)	1.84 [0.99; 3.42]; 0.0526
Study 1504	43	10 (23.3)	44	10 (22.7)	1.03 [0.48; 2.22]; 0.9434
Meta-analysis					1.47 [0.91; 2.37]; 0.1201
Abbreviations used: AESI: AE of special interest End of Treatment; n. d.: no data; CI: Confidence interval; n: Number; n.c.: not calculable; RR: Relative Risk; (S) AE: (Serious) adverse events					

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

Patients 2 years of age and older with seizures associated with Dravet syndrome

approx. 450 to 2450 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 Fintepla (active ingredient: fenfluramine) at the following publicly accessible link (last access: 10 March 2021):

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

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

The European Public Assessment Report (EPAR) states that fenfluramine has not been studied in adults.

In accordance with the European Medicines Agency (EMA) requirements regarding additional measures to risk minimisation, the pharmaceutical company should provide training materials

for all healthcare professionals prescribing, dispensing and administering fenfluramine and to patients receiving fenfluramine.

Educational material for healthcare professionals includes guidance on the risk of valvular heart disease, pulmonary arterial hypertension and non-intended use for weight control.

Patient education materials include a guide regarding the risk of valvular heart disease and pulmonary hypertension.

4. Treatment costs

Annual treatment costs:

Patients 2 years of age and older with seizures associated with Dravet syndrome

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Fenfluramine	€ 19,066.83 - € 86,647.23
additionally required SHI services	€ 34.15

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 June 2021)

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 July 2021.

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

Berlin, 15 July 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken