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
Fenfluramine (new therapeutic indication: Lennox-Gastaut syndrome, add-on therapy, ≥ 2 years)

of 3 August 2023

At its session on 3 August 2023, 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 D 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 Fenfluramine in accordance with the resolution of 15 July 2021:

Fenfluramine

Resolution of: 3 August 2023
Entry into force on: 3 August 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 24 January 2023):

Fintepla is indicated for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut 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 3 August 2023):

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

1. Extent 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 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).

<u>Patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome</u>

Extent of the additional benefit and significance of the evidence of fenfluramine as an add-on therapy to other anti-epileptic medicines:

Hint for a considerable additional benefit.

Study results according to endpoints:[1]

Patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment
Morbidity	↑	Advantages in reducing seizures and improving clinical global impression
Health-related quality of life	↔	No relevant differences for the benefit assessment
Side effects	↔	No relevant differences for the benefit assessment, in detail disadvantages in the specific AEs infections and infestations as well as reduced appetite
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 ∅: No data available. n.a.: not assessable		

1601 study (part 1): RCT over 14 weeks; fenfluramine versus placebo (in each case as add-on therapy to other anti-epileptic medicines)

Mortality

Endpoint	Fenfluramine		Placebo		Fenfluramine vs placebo
	N[a]	*Patients with event n (%)*	N[a]	*Patients with event n (%)*	Effect estimator [95% CI] p value
Mortality					
	87	1.1	87	0	not calculable

1 Data from the dossier assessment of the G-BA (published on 15. Mai 2023), unless otherwise indicated.

Morbidity

Endpoint	Fenfluramine N = 87[b]		Placebo N = 87[b]		Fenfluramine vs placebo
	Median (min; max)	**% change from baseline Median** (min; max)	**Median** (min; max)	**% change from baseline** Median (min; max)	**Hodges-Lehmann estimator [95% CI]; p value[c]**
Epileptic seizures					
Change in frequency of epileptic seizures normalised to 28 days					
Motor seizures	Baseline 111.0 (10.0; 1897.0) T/M period 67.0 (1.6; 1562.0)	-26.3 (-91.9; 402.1)	Baseline 68.0 (14.0; 1761.0) T/M period 54.9 (6.8; 1683.8)	-8.4 (-80.8; 497.8)	-18.2 [-28.2; -8.2]; 0.0011
Non-motor seizures	Baseline 16.0 (0; 4891) T/M period 11.7 (0; 7843.7)	n.d.	Baseline 11.0 (0; 1269) T/M period 6.3 (0; 1310.3)	n.d.	5.2 [-16.5; 26.8]; 0.6371
Status epilepticus (supplementary)	Baseline 0 (0; 82.0) T/M period 0.3 (0; 78.8)	n.d.	Baseline 0 (0; 62.0) T/M period 0 (0; 82.6)	n.d.	-0.2 [-0.3; 0.0]; 0.3641

Endpoint; Evaluation	Fenfluramine N = 87		Placebo N = 87		Fenfluramine vs placebo
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	Relative risk [95% CI]; p value
Motor seizures - percentage of subjects with an improvement in frequency					
Reduction by > 0%	87	69 (79.3)	87	57 (65.5)	1.23 [1.02; 1.47]; 0.0262
Reduction by ≥ 25%	87	44 (50.6)	87	29 (33.3)	1.49 [1.04; 2.13]; 0.0317
Reduction by ≥ 50%	87	22 (25.3)	87	8 (9.2)	2.63 [1.23; 5.61]; 0.0123
Reduction by ≥ 75%	87	6 (6.9)	87	2 (2.3)	3.19 [0.66; 15.40]; 0.1479

Reduction by 100%	87	0	87	0	not calculable
Non-motor seizures - percentage of subjects with an improvement in frequency					
Reduction by > 0%	57[e]	36 (63.2)	63[e]	42 (66.7)	0.98 [0.76; 1.26]; 0.8639
Reduction by ≥ 25%	57[e]	25 (43.9)	63[e]	33 (52.4)	0.87 [0.60; 1.26]; 0.4649
Reduction by ≥ 50%	57[e]	20 (35.1)	63[e]	19 (30.2)	1.24 [0.75; 2.05]; 0.3954
Reduction by ≥ 75%	57[e]	7 (12.3)	63[e]	9 (14.3)	not available
Reduction by 100%	57[e]	2 (3.5)	63[e]	2 (3.2)	1.90 [0.36; 9.88]; 0.4476
Status epilepticus - incidence during the titration and maintenance period (supplementary)					
Percentage of subjects with event	87	45 (51.7)	87	41 (47.1)	1.00 [0.93; 1.09]; 0.9117
Clinical Global Impression - Change in Clinical Global Impression – Improvement (CGI-I)					
Any improvement	80	49 (61.3)	81	30 (37.0)	1.68 [1.20; 2.35]; 0.0027
Strong or very strong improvement	80	27 (33.8)	81	4 (4.9)	7.14 [2.62; 19.42]; 0.0001
Deterioration	80	9 (11.3)	81	8 (9.9)	1.21 [0.50; 2.97]; 0.6716

Endpoint	**Fenfluramine**			**Placebo**			**Fenfluramine vs placebo**
	N[a]	**Baseline** Median (min; max)	**End of study** Median (min; max)	**N[a]**	**Baseline** Median (min; max)	**End of study** Median (min; max)	**Hodges-Lehmann estimator [95% CI]; p value**
Executive function - BRIEF-P / BRIEF[f]							
BRIEF for age group 6-18 years *(fenfluramine N = 57; placebo N = 55)*							
Behavioural regulation index	47	55.0 (28.0; 81.0)	51.0 (28.0; 81.0)	46	51.5 (28.0; 80.0)	53.0 (28.0; 78.0)	-3.5 [-9.0; 2.0]; 0.2506
Metacognition index	45	100.0 (44.0; 128.0)	98.0 (44.0; 130.0)	46	97.5 (44.0; 126.0)	93.5 (44.0; 131.0)	-3.5 [-9.0; 2.0]; 0.2506
Executive total value	45	157.0 (72.0; 205.0)	151.0 (72.0; 211.0)	46	145.0 (72.0; 200.0)	145.0 (72.0; 209.0)	-3.5 [-12.0; 5.0]; 0.5399
BRIEF-P; 2-5 years *(fenfluramine N = 11; placebo N = 9)*							
Inhibitory self-control index	10	45.0 (31.0; 69.0)	43.5 (26.0; 72.0)	8	51.0 (26.0; 73.0)	46.5 (29.0; 61.0)	-2.5 [-10.0; 5.0]; 0.6613
Flexibility index	10	31.5 (22.0; 53.0)	26.0 (20.0; 55.0)	8	32.5 (20.0; 52.0)	30.5 (20.0; 50.0)	-2.5 [-8.0; 3.0]; 0.6608

Endpoint	Fenfluramine			Placebo			Fenfluramine vs placebo
	N[a]	Baseline Median (min; max)	End of study Median (min; max)	N[a]	Baseline Median (min; max)	End of study Median (min; max)	Hodges-Lehmann estimator [95% CI]; p value
Metacognitive development index	10	57.0 (30.0; 78.0)	57.5 (27.0; 80.0)	7	59.0 (34.0; 72.0)	62.0 (29.0; 76.0)	1.0 [-11.0; 13.0]; 0.7729
Executive total value	10	117.5 (73.0; 175.0)	115.5 (63.0; 179.0)	7	121.0 (72.0; 162.0)	125.0 (70.0; 164.0)	5.5 [-21.0; 32.0]; 0.3671
BRIEF-A; 19 to 35 years *(fenfluramine N = 20; placebo N = 25)*							
Behavioural regulation index	16	59.0 (32.0; 82.0)	52.0 (30.0; 89.0)	23	55.0 (30.0; 86.0)	60.0 (30.0; 82.0)	-4.0 [-9.0; 1.0]; 0.1303
Metacognition index	16	94.5 (40.0; 118.0)	95.0 (40.0; 120.0)	23	78.0 (40.0; 119.0)	85.0 (40.0; 119.0)	-10.5 [-23.0; 2.0]; 0.1241
Executive total value	16	148.5 (75.0; 196.0)	147.5 (70.0; 209.0)	23	136.0 (70.0; 205.0)	147.0 (71.0; 201.0)	-15.0 [-31.0; 1.0]; 0.0711

Health-related quality of life

Endpoint Subscale	Fenfluramine N = 87		Placebo N = 87		Fenfluramine vs placebo
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p value
QOLCE - percentage of subjects with a 15% improvement in the					
overall quality of life (OQL)[g]					
Average of all subscales	79	16 (20.3)	80	10 (12.5)	not calculable
QOLCE subscales[h]					
Physical limitations	75	8 (10.7)	78	10 (12.8)	0.85 [0.36; 2.03]; 0.7178
Energy/ fatigue	71	13 (18.3)	77	9 (11.7)	not calculable
Depression	66	6 (9.1)	68	6 (8.8)	not calculable
Anxiety	65	15 (23.1)	66	12 (18.2)	not calculable
Attention	64	19 (29.7)	65	15 (23.1)	1.02 [0.59; 1.76]; 0.9431
Social activities	78	22 (28.2)	79	22 (27.8)	1.02 [0.62; 1.66]; 0.9512

Behaviour	68	9 (13.2)	70	10 (14.3)	not calculable
General health (1 item)	78	25 (32.1)	80	25 (31.3)	0.94 [0.61; 1.46]; 0.7955
Quality of life (1 item)	77	33 (42.9)	80	23 (28.8)	1.40 [0.92; 2.12]; 0.1135
Total quality of life [g]	79	16 (20.3)	80	10 (12.5)	not calculable

Side effects

Endpoints *MedDRA system organ classes;* Preferred terms	**Fenfluramine N = 87** Patients with event n (%)	**Placebo N = 87** Patients with event n (%)	**Fenfluramine vs placebo** Relative risk [95% CI][a]; p value[b]
Summary of the AEs			
AE (presented additionally)	78 (89.7)	70 (80.5)	-
Severe AEs	3 (3.4)	1 (1.1)	3.15 [0.34; 29.04]; 0.3114
SAE	10 (11.5)	4 (4.6)	2.59 [0.86; 7.81]; 0.0911
AEs which led to the discontinuation of the study medication	6 (6.9)	0	not calculable
AEs with incidence ≥ 10% and statistically significant difference between treatment arms (according to *MedDRA system organ* class/ preferred term)			
Infections and infestations	36 (41.4)	22 (25.3)	1.63 [1.05; 2.53]; 0.0279
Reduced appetite	32 (36.8)	13 (14.9)	2.46 [1.40; 4.32]; 0.0017

a. Number of subjects in the evaluation
b. Number of randomised patients: corresponds in the present case to the mITT and safety population as well as to the number of subjects in the evaluation
c. p value for comparison of percentage change in frequency based on Wilcoxon rank sum test.
d. Primary endpoint of 1601 study part 1
e. Subjects in the mITT population with non-motor seizures at baseline
f. Higher values mean more impaired function.
g. There is no information available on how missing subscale values were dealt with in the formation of the overall quality of life value. A limited validity of the overall quality of life value can be assumed due to missing subscale values.
h. The subscales control/ helplessness, self-confidence, ability to recollect, language, other cognitive abilities, interaction and stigma are not shown in the evaluation due to the low percentage of randomised patients (< 70%).
i. Not calculable as the model does not converge.

Abbreviations used: BRIEF = Behaviour Rating Inventory of Executive Function; BRIEF-A = Behaviour Rating Inventory of Executive Function - Adult; BRIEF-P = Behaviour Rating Inventory of Executive Function -

Preschool; CGI-I = Clinical Global Impression - Improvement; ESC = Epilepsy Study Consortium; n.d. = no data available; CI = confidence interval; max = maximum; min = minimum; N = number of patients evaluated; n = number of patients with (at least one) event; QOLCE = Quality of Life in Childhood Epilepsy; RR = relative risk; (S)AE = (Serious) Adverse Event; T/M period = titration and maintenance period; vs = versus

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

Patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome

approx. 2,100 - 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 Fintepla (active ingredient: fenfluramine) at the following publicly accessible link (last access: 18 April 2023):

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

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

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients.

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 arterial hypertension. Among other things, this guideline should point out the importance of regular monitoring of heart function by means of echocardiography.

A controlled access programme (CAP) for fenfluramine has been set up, through which only registered doctors experienced in epilepsy therapy may prescribe the medicinal product.

4. Treatment costs

Annual treatment costs:

Patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Fenfluramine	€ 12,191.28 - € 33,248.95
Additionally required SHI services	€ 35.28

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 2023)

5. Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with fenfluramine

Medicinal products with the new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with fenfluramine for the treatment of seizures associated with Lennox-Gastaut syndrome as add-on therapy to other anti-epileptic medicines on the basis of the marketing authorisation granted under Medicinal Products Act:

Patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome

A designation of the concomitant active ingredients shall be made in a further resolution. The adoption of the resolution will be preceded by a written and oral written statement procedure pursuant to Chapter 5 Section 19 of the Regulation, in the course of which the pharmaceutical companies concerned will be given the opportunity to comment on the planned designation.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 3 August 2023.

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

Berlin, 3 August 2023

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

Prof. Hecken