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
Elafibranor (primary biliary cholangitis)

of 3 April 2025

At their session on 3 April 2025, 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. Annex XII shall be amended in alphabetical order to include the active ingredient Elafibranor as follows:

Elafibranor

Resolution of: 3 April 2025
Entry into force on: 3 April 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 19 September 2024):

Iqirvo is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA.

Therapeutic indication of the resolution (resolution of 3 April 2025):

See therapeutic indication according to marketing authorisation.

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

Elafibranor 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 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>Adults with primary biliary cholangitis (PBC) and inadequate response or intolerance to ursodeoxycholic acid (UDCA)</u>

Extent of the additional benefit and significance of the evidence of elafibranor:

Hint for a minor additional benefit

Study results according to endpoints:[1]

Adults with primary biliary cholangitis (PBC) and inadequate response or intolerance to ursodeoxycholic acid (UDCA)

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment.
Morbidity	↔	No relevant differences for the benefit assessment. In detail advantages in the endpoint of 5-D itch (domain "severity" and "direction").
Health-related quality of life	↑	Advantage in the endpoint of PBC-40 domain "Itching".
Side effects	↔	No relevant differences for the benefit assessment.
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		

ELATIVE study: Phase III RCT, elafibranor versus placebo, 52 to 104-week double-blind treatment phase

Mortality

Endpoint	Elafibranor N = 108	Placebo N = 53	Elafibranor vs placebo
	Patients with event n (%)	*Patients with event n (%)*	*RR [95% CI] p value*
Overall mortality[a)]			
Deaths	2 (1.9)	0 (0)	2.48 [0.12; 50.7] 0.32

[1] Data from the dossier assessment of the G-BA (published on 15. January 2025), and from the amendment to the dossier assessment from 14 March 2025, unless otherwise indicated.

Morbidity

Endpoint	Elafibranor N = 108	Placebo N = 53	Elafibranor vs placebo
	Patients with event n (%)	*Patients with event n (%)*	*RR [95% CI] p value*
Biochemical response[b] *(presented additionally)*			
ALP < 1.67 × ULN and TB ≤ ULN and ALP reduction ≥ 15%	55 (50.9)	2 (3.8)	13.5 [3.4; 53.2] < 0.0001
Clinical events[c]			
Uncontrolled ascites requiring treatment	1 (1.6)	0 (0)	-
Itching			
PBC worst itch NRS (Improvement by ≥ 15%)	23 (21.3)	8 (15.1)	1.43 [0.74; 2.78] 0.28
5-D itch total score (Improvement by ≥ 15%)	37 (34.3)	12 (22.6)	1.53 [0.88; 2.64] 0.10
- *5-D itch duration (Improvement by ≥ 15%)*	21 (19.4)	5 (9.43)	2.09 [0.87; 5.02] 0.08
- *5-D itch severity (improvement by ≥ 15%)*	38 (35.2)	8 (15.1)	2.36 [1.23; 4.52] 0.003
- *5-D itch direction (Improvement by ≥ 15%)*	41 (38.0)	11 (20.8)	1.84 [1.04; 3.25] 0.02
- *5-D itch distribution (Improvement by ≥ 15%)*	32 (29.6)	14 (26.4)	1.13 [0.68; 1.89] 0.64
- *5-D itch disability (improvement by ≥ 15%)*	37 (34.3)	16 (30.2)	1.14 [0.70; 1.87] 0.57
Health status			
EQ-5D-5L VAS[f] (Improvement by ≥ 15%)	18 (16.7)	7 (13.2)	1.28 [0.59; 2.76] 0.53
Daytime sleepiness			
Epworth Sleepiness Scale (ESS)[g] (Improvement by ≥ 15%)	14 (13.0)	7 (13.2)	0.99 [0.43; 2.28] 0.97
Fatigue			
PROMIS Fatigue Short Form 7a[h] (Improvement by ≥ 15%)	21 (19.4)	7 (13.2)	1.47 [0.67; 3.25] 0.33

Health-related quality of life

Endpoint	Elafibranor N = 108	Placebo N = 53	Elafibranor vs placebo
	Patients with event n (%)	*Patients with event n (%)*	*RR [95% CI] p value*
Domains Questionnaire PBC-40[i)]			
- *Itching (Improvement by ≥ 15%)*	40 (37.0)	9 (17.0)	2.19 [1.16; 4.15] 0.008
- *General symptoms (Improvement by ≥ 15%)*	8 (7.40)	7 (13.2)	0.56 [0.21; 1.49] 0.24
- *Fatigue (Improvement by ≥ 15%)*	23 (21.3)	5 (9.43)	2.27 [0.92; 5.61] 0.06
- *Cognitive functioning (Improvement by ≥ 15%)*	22 (20.4)	11 (20.8)	0.98 [0.51; 1.88] 0.96
- *Emotional functioning (Improvement by ≥ 15%)*	27 (25.0)	14 (26.4)	0.95 [0.55; 1.66] 0.86
- *Social functioning (Improvement by ≥ 15%)*	21 (19.4)	8 (15.1)	1.29 [0.61; 2.72] 0.50

Side effects

Endpoint MedDRA system organ classes/ preferred terms/ AEs of special interest	Elafibranor N = 108	Placebo N = 53	Elafibranor vs placebo
	Patients with event n (%)	*Patients with event n (%)*	*RR [95% CI] p value*
Total adverse events (presented additionally)	104 (96.3)	48 (90.6)	-
Serious adverse events (SAE)	11 (10.2)	7 (13.2)	0.77 [0.32; 1.88] 0.57
Severe adverse events (CTCAE grade 3 or 4)	11 (10.2)	6 (11.3)	0.90 [0.35; 2.30] 0.83
Therapy discontinuation due to adverse events	11 (10.2)	5 (9.4)	1.08 [0.40; 2.95] 0.88
Severe adverse events according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)			
- No significant differences			
SAEs according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)			
- No significant differences			

Adverse events of special interest (with statistically significant difference between the treatment arms)
- No significant differences

a. Collected until the end of the entire DB phase (up to week 104).
b. Primary endpoint. Composite endpoint defined as ALP < 1.67 × ULN and TB ≤ ULN and ALP reduction ≥ 15%.
c. Only the individual components considered patient-relevant are taken into account: "Liver transplantation", "Uncontrolled ascites", "Hospitalisation (due to new or recurrent variceal haemorrhage, hepatic encephalopathy or spontaneous bacterial peritonitis) and "Deaths", where "Deaths" are presented via mortality. Results are only shown if an event has occurred in a treatment arm.
d. Participants rate the intensity of the worst itching on an 11-point scale ("0: no itching" to "10: worst perceivable itching") on a daily basis.
e. The total score to be achieved is between 5 and 25 points. Each domain can achieve a value of 1 to 5 points. Higher points indicate more severe pruritus.
f. Total score: "0" (= worst perceivable health status) to "100" (= best perceivable health status).
g. Total score: 0-24 points. Lower values represent a low burden, higher values a higher burden.
h. Total score as a raw value: 7-35 points. Lower values represent a low burden, higher values a higher burden. The raw value is converted into a T-score. The T-score scales the raw score to a standardised value with an MV of 50 and an SD of 10.
i. Depending on the number of items in the individual domains, there are different ranges of values for the scores of the domains, which range from 3 to 55 points. Higher scores reflect a deterioration, while lower scores indicate an improvement.

Abbreviations used: CTCAE = Common Terminology Criteria for Adverse Events; n.d.: no data available; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; PT = preferred term; RR = relative risk; SOC = system organ class; vs = versus

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

Adults with primary biliary cholangitis (PBC) and inadequate response or intolerance to ursodeoxycholic acid (UDCA)

Approx. 6,000 – 13,000 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 Iqirvo (active ingredient: elafibranor) at the following publicly accessible link (last access: 25 March 2025):

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

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

Adults with primary biliary cholangitis (PBC) and inadequate response or intolerance to ursodeoxycholic acid (UDCA)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Elafibranor	€ 67,710.42

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2025)

Costs for additionally required SHI services: not applicable

5. Designation of 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 the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults with primary biliary cholangitis (PBC) and inadequate response or intolerance to ursodeoxycholic acid (UDCA)

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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. Entry into force

1. The resolution will enter into force on the day of its publication on the internet on the website of the Federal Joint Committee on 3 April 2025.

2. The period of validity of the resolution is limited to 1 December 2030.

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

Berlin, 3 April 2025

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

Prof. Hecken