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)
Iptacopan (paroxysmal nocturnal haemoglobinuria)

of 19 December 2024

At its session on 19 December 2024, 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 Iptacopan as follows:

Iptacopan

Resolution of: 19 December 2024
Entry into force on: 19 December 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 17 May 2024):

Fabhalta is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.

Therapeutic indication of the resolution (resolution of 19 December 2024):

See therapeutic indication according to marketing authorisation.

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

Iptacopan 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 patient numbers 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).

a) Therapy-naive adults with PNH who have haemolytic anaemia

Extent of the additional benefit and significance of the evidence of iptacopan as monotherapy:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

b) Pretreated adults with PNH who have haemolytic anaemia

Extent of the additional benefit and significance of the evidence of iptacopan as monotherapy:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

a) Therapy-naive adults with PNH who have haemolytic anaemia

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: ↑: 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		

APPOINT-PNH:

- single-arm phase III study
- 24-week main treatment phase and 24-week extension phase

Mortality

Endpoint	Iptacopan	
	N	Patients with event n (%)
Overall survival		
No deaths occurred.		

Morbidity

Endpoint	Iptacopan	
	N	Patients with event n (%)
Haemoglobin level-associated endpoint up to week 24 (primary endpoint; presented additionally)		
Hb increase by ≥ 2 g/dl with simultaneous transfusion independence	40	31 (77.5)

[1] Data from the dossier assessments of the G-BA (published on 1. Oktober 2024), and from the amendment to the dossier assessment from 28 November 2024, unless otherwise indicated.

Endpoint	Iptacopan	
	N	Patients with event n (%)
Transfusion independence for 48 weeks		
Subjects with transfusion independence for the entire study duration (day 1 to week 48)	40	34 (85)
Breakthrough haemolysis with the presence of symptoms (presented additionally)		
	40	2 (5.0%)
Fatigue (FACIT-Fatigue)[a]		
	40	22 (55)
Fatigue (PGIS)[b]		
	40	24 (60)
Health status (EQ-5D VAS)[c]		
	40	20 (50)
Major adverse vascular events (MAVE)		
No events occurred.		

Quality of life

Endpoint	Iptacopan	
	N	Patients with event n (%)
EORTC QLQ-C30 functional scales[d]		
General health status	40	30 (75)
Physical functioning	40	24 (60)
Role functioning	40	27 (67.5)
Emotional functioning	40	22 (55)
Cognitive functioning	40	13 (32.5)
Social functioning	40	20 (50)

Side effects

Endpoint MedDRA system organ classes/ AEs of special interest	**Iptacopan**	
	N	**Patients with event n (%)**
Total adverse events (presented additionally)	40	37 (92.5)
Serious adverse events (SAE)	40	8 (20)
Severe adverse events (CTCAE grade ≥ 3)	40	4 (10)
Therapy discontinuation due to adverse events	40	0 (0)
Severe adverse events according to MedDRA system organ class (with an incidence ≥ 10%)		
Infections	40	5 (12.5)
SAEs according to MedDRA system organ class (with an incidence ≥ 10%)		
Infections	40	5 (12.5)
AEs of special interest (with an incidence ≥ 10%)		
Hypersensitivity	40	4 (10)
Severe or serious infections	40	5 (12.5)

[a] Improvement by ≥ 8 points. Scale from 0 to 52. Higher values indicate fewer conditions.
[b] Improvement by ≥ 1 category. A change to ≥ 1 lower category is defined as an improvement.
[c] Improvement by ≥ 15 points. Values from 0 to 100; higher values correspond to better health status.
[d] Improvement by ≥ 10 points. Values from 0 to 100; higher values correspond to better functioning or health/ quality of life.

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire Core 30; EQ-5D VAS = visual analogue scale of the European Quality of Life - 5 Dimensions; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; N = number of patients evaluated; n = number of patients with (at least one) event; PGIS = Patient Global Impression of Severity

b) Pretreated adults with PNH who have haemolytic anaemia

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantages in the transfusion independence endpoint as well as in the symptom scales for fatigue and in the health status scale.
Health-related quality of life	↑	Advantages in the scales for physical, emotional and role functioning as well as in the general health scale.
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		

APPLY-PNH study:

- open-label, randomised controlled phase III study
- Iptacopan **vs** eculizumab or ravulizumab
- 24-week randomised controlled phase and 24-week extension phase

Mortality

Endpoint	Iptacopan		Eculizumab or ravulizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value Absolute difference (AD)[a]
Overall survival					
No deaths occurred.					

Morbidity

Endpoint	Iptacopan		Eculizumab or ravulizumab		Intervention vs control
	N	*Patients with event n (%)* *Model-estimated response rate (%) [95% CI]*	N	*Patients with event n (%)* *Model-estimated response rate (%) [95% CI]*	RR [95% CI] p value Absolute difference (AD)[a]
Haemoglobin level-associated endpoints up to week 24 (co-primary endpoints; presented additionally)					
Hb increase by ≥ 2 g/dl with simultaneous transfusion avoidance	60	51 (85.0) 82.3 [73.4; 90.2]	35	0 (0) 2.0 [1.1; 4.1]	40.20 [20.73; 74.82] < 0.0001 AD = 80.3%
Hb increase to ≥ 12 g/dl with simultaneous transfusion avoidance	60	42 (70.0) 68.8 [58.4; 78.9]	35	0 (0) 1.8 [0.9; 4.0]	38.22 [16.87; 78.63] < 0.0001 AD = 67.0%

Endpoint	Iptacopan		Eculizumab or ravulizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value Absolute difference (AD)[a]
Transfusion independence for 24 weeks[b]					
Day 1 to week 24	62	57 (91.9)	35	17 (48.6)	1.89 [1.34; 2.68] < 0.001 AD = 43.3%
Breakthrough haemolysis with the presence of symptoms (presented additionally)					
	62	1 (1.6)	35	6 (17.1)	0.09 [0.01; 0.75] 0.004 AD = 15.5%
Fatigue (FACIT-Fatigue)[c]					
	62	32 (51.6)	31	3 (9.7)	5.33 [1.77; 16.06]

Endpoint	Iptacopan		Eculizumab or ravulizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value Absolute difference (AD)[a]
					0.003 AD = 41.9%
Fatigue (PGIS)[d]					
	62	27 (43.6)	31	5 (16.1)	2.70 [1.15; 6.33] 0.02 AD = 27.5%
Health status (EQ-5D VAS)[e]					
	62	26 (41.9)	31	3 (9.7)	4.33 [1.42; 13.21] 0.01 AD = 32.2%
Major adverse vascular events (MAVE)					
	62	1 (1.6)	35	0 (0)	n. d. 0.32

Health-related quality of life

Endpoint	Iptacopan		Eculizumab or ravulizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value Absolute difference (AD)[a]
EORTC QLQ-C30 functional scales[f]					
General health status	62	37 (59.7)	31	7 (22.6)	2.64 [1.33; 5.23] 0.01 AD = 37.1%
Physical functioning	62	38 (61.3)	31	7 (22.6)	2.71 [1.37; 5.36] 0.004 AD = 38.7%

Endpoint	Iptacopan		Eculizumab or ravulizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value Absolute difference (AD)[a]
Role functioning	62	31 (50.0)	31	8 (25.8)	1.94 [1.01; 3.70] 0.045 AD = 24.2%
Emotional functioning	62	25 (40.3)	31	4 (12.9)	3.13 [1.19; 8.19] 0.02 AD = 27.4%
Cognitive functioning	62	22 (35.5)	31	9 (29.0)	1.22 [0.64; 2.33] 0.54
Social functioning	62	27 (43.5)	31	8 (25.8)	1.69 [0.87; 3.27] 0.12

Side effects

Endpoint MedDRA system organ classes/ preferred terms/ AEs of special interest	Iptacopan		Eculizumab or ravulizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Effect estimator [95% CI] p value
Total adverse events (presented additionally)	62	52 (83.9)	35	28 (80.0)	-
Serious adverse events (SAE)	62	6 (9.7)	35	5 (14.3)	0.68 [0.22; 2.06] 0.49
Severe adverse events (CTCAE grade 3 or 4)	62	3 (4.8)	35	3 (8.6)	0.56 [0.12; 2.65] 0.47
Therapy discontinuation due to adverse events	62	0 (0)	35	0 (0)	-
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)					

Endpoint MedDRA system organ classes/ preferred terms/ AEs of special interest	Iptacopan		Eculizumab or ravulizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Effect estimator [95% CI] p value
No significant differences.					
Adverse events of special interest (with statistically significant difference between the treatment arms)					
No significant differences.					

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] Includes the transfusions actually received with concurrent symptomatology.
[c] Improvement by ≥ 8 points from week 18 to week 24 compared to baseline. The mean values of the observed values of the 4 visits between week 18 and week 24 were shown. A value had to be available for at least one of the 4 visits. Scale from 0 to 52. Higher values indicate fewer conditions.
[d] Improvement by ≥ 1 category from week 18 to week 24 compared to baseline. The mean values of the observed values of the 4 visits between week 18 and week 24 were shown. A value had to be available for at least one of the 4 visits. 5-point Likert scale from 0 ("no symptoms") to 4 ("very severe symptoms").
[e] Improvement by ≥ 15 points. Values from 0 to 100; higher values correspond to better health status.
[f] Improvement by ≥ 10 points. Values from 0 to 100; higher values correspond to better functioning or health/ quality of life.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire Core 30; EQ-5D VAS = visual analogue scale of the European Quality of Life - 5 Dimensions; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; 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; n.r. = not reached; PGIS = Patient Global Impression of Severity; RR = relative risk; vs = versus

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

a) Therapy-naive adults with PNH who have haemolytic anaemia

Approx. 100 to 425 patients

b) Pretreated adults with PNH who have haemolytic anaemia

Approx. 190 to 520 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 Fabhalta (active ingredient: iptacopan) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 20 November 2024):

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

Treatment with iptacopan should only be initiated and monitored by specialists who are experienced in the treatment of patients with haematological diseases.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients as well as a patient card. The training material as well as the patient card contain instructions in particular regarding the increased risk of infection with encapsulated bacteria under iptacopan. The training material also contains instructions regarding the risk of severe haemolysis after discontinuation of iptacopan. The patient card should be made available to the patients.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Iptacopan	€ 460,509.81

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 December 2024)

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:

a) Therapy-naive adults with PNH who have haemolytic anaemia

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

b) Pretreated adults with PNH who have haemolytic anaemia

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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 19 December 2024.

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

Berlin, 19 December 2024

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

Prof. Hecken