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)
Pegcetacoplan (new therapeutic indication: paroxysmal nocturnal haemoglobinuria, non-pretreated patients)

of 22 November 2024

At its session on 22 November 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. **In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Pegcetacoplan in accordance with the resolution of 15 September 2022:**

Pegcetacoplan

Resolution of: 22 November 2024
Entry into force on: 22 November 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 6 May 2024):

Aspaveli 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 22 November 2024):

Aspaveli is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia and have not received prior therapy with a complement inhibitor.

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

Pegcetacoplan is approved as a medicinal product for the treatment of rare diseases under 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>Adults with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia and have not received prior therapy with a complement inhibitor</u>

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

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

Study results according to endpoints:[1]

Adults with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia and have not received prior therapy with a complement inhibitor

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		

PRINCE study:

Study design - open-label RCT of phase III [crossover study]
- Screening period (up to 4 weeks)
- Randomised controlled period (RCP, 26 weeks)
- Safety follow-up (8 weeks) or open-label extension phase

Comparison - pegcetacoplan vs standard of care (26-week RCP)

[1] Data from the dossier assessment of the G-BA (published on 2. September 2024), and from the amendment to the dossier assessment from 29 October 2024, unless otherwise indicated.

Mortality

Endpoint	Pegcetacoplan		Standard of care		Intervention vs control
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	Hazard ratio [95% CI] p value
Mortality					
	35	1 (2.9)	18	1 (5.6)	n.d.

Morbidity

Endpoint	Pegcetacoplan		Standard of care		Intervention vs control
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	Relative risk [95% CI] p value
Stabilisation of the Hb value up to week 26 (co-primary study endpoint, presented additionally)					
Non-responder	35	5 (14.3)	18	18 (100)	n.d. 0.0001

Endpoint	Pegcetacoplan			Standard of care			Intervention vs control
			Change at week x			Change at week x	LS mean difference [95% CI] p value
	N[a]	MV (SD)	LS mean (SE)	N[a]	MV (SD)	LS mean (SE)	
Change in LDH level at week 26 (co-primary study endpoint, presented additionally) *Baseline*							
	35	2,151 (909)	-	18	1,946 (1004)	-	-
Week 26							
	35	205 (90)	-1,871 (101)	18	1,535 (752)	-400 (313)	-1,470 [-2,113; -827] < 0.0001

Endpoint	Pegcetacoplan		Standard of care		Intervention vs control
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI] p value
Transfusion independence (presented additionally) [d]					
Subjects without transfusion	35	32 (91.4)	18	4 (22.2)	4.11 [1.98; 17.35] < 0.0001

Endpoint	Pegcetacoplan		Standard of care		Intervention vs control
	N[a]	Median time to event in months [95% CI][b] *Patients with event n (%)*	N[a]	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard ratio [95% CI] p value [c]
FACIT fatigue (time to first deterioration, change by 15% of the scale range) [e]					
	35	n.a. *6 (17.1)*	18	14.36 [n.a.; n.a.] *9 (50.0)*	0.19 [0.07; 0.56]; 0.003

Health-related quality of life

Endpoint	Pegcetacoplan		Standard of care		Intervention vs control
	N[a]	Median time to event in months [95% CI][b] *Patients with event n (%)*	N[a]	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard ratio [95% CI] p value [c]
EORTC QLQ-C30 (time to first deterioration, change by ≥ 10 points) [g]					
Role functioning	35	n.a. *7 (20.0)*	18	4.14 [4.14; 4.29] *11 (61.1)*	0.18 [0.07; 0.49]; < 0.001
Emotional functioning	35	n.a. *6 (17.1)*	18	n.a. *3 (16.7)*	0.91 [0.22; 3.81]; 0.90
Physical functioning	35	n.a. *6 (17.1)*	18	n.a. *6 (33.3)*	0.39 [0.12; 1.24]; 0.11
Cognitive functioning	35	n.a. *11 (31.4)*	18	8.14 [4.14; 16.43] *12 (66.7)*	0.26 [0.11; 0.60]; 0.002
Social functioning	35	n.a. *8 (22.9)*	18	n.a. *7 (38.9)*	0.46 [0.17; 1.28]; 0.14
General health status / quality of life	35	n.a. *7 (20.0)*	18	n.a. *7 (38.9)*	0.35 [0.12; 1.03]; 0.06

Linear Analogue Scale Assessment (LASA) (time to first deterioration, change by ≥ 15% of the scale range)[h]					
Activity level	35	n.a. *6 (17.1)*	18	n.a. *6 (33.3)*	0.33 [0.11; 1.05]; 0.06
Ability to carry out daily activities	35	n.a. *7 (20.0)*	18	n.a. *6 (33.3)*	0.32 [0.11; 0.98]; 0.046
General quality of life	35	n.a. *5 (14.3)*	18	n.a. *7 (38.9)*	0.19 [0.06; 0.62]; 0.006

Side effects (safety population)

Endpoint	**Pegcetacoplan**		**Standard of care**		Intervention vs control
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	Hazard ratio [95% CI] p value
Total adverse events (presented additionally)					
	35	28 (80.0)	18	12 (66.7)	-
Serious adverse events (SAE)					
	35	3 (8.6)	18	3 (16.7)	0.46 [0.09; 2.34] 0.35
Severe adverse events (CTCAE grade 3 or 4)					
	35	3 (8.6)	18	2 (11.1)	0.68 [0.11; 4.15] 0.67
Therapy discontinuation due to adverse events					
	35	0	18	n.a.	n.d.
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 suitable data available.					
SAEs according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No suitable data available.					
Adverse events of special interest (with statistically significant difference between the treatment arms)					
No suitable data available.					

a) ITT population of the PRINCE study. The ITT population simultaneously corresponds to the safety population.
b) Kaplan-Meier estimator with 95% CI according to Brookmeyer-Crowley.
c) HR with p value calculated using a Cox regression model with "treatment" and "number of RBC transfusions" (< 4; ≥ 4) as stratification factors.
d) Calculation including the escape patients, in which only the receipt of a transfusion was categorised as a non-response. In addition, subjects who discontinued the study on day 1 were categorised as non-responders. Unstratified analysis with RR 95% CI (incl. p value) calculated using Fisher's exact test.

e) Scale from 0 to 52. Higher values indicate fewer conditions.
f) Scale from 0 to 100. Higher values indicate stronger symptomatology.
g) Scale from 0 to 100. Higher values indicate a better health status or better functionality.
h) Scale from 0 to 100. Higher values indicate better functionality/ 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; FACIT fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue Scale; HR = hazard ratio; ITT: Intention to Treat; n.d.: no data available; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.a. = not applicable; vs = versus

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

Adults with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia and have not received prior therapy with a complement inhibitor

Approx. 100 - 425 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 Aspaveli (active ingredient: pegcetacoplan) at the following publicly accessible link (last access: 23 July 2024):

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

Treatment with pegcetacoplan 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 pegcetacoplan. The patient card should be made available to the patients.

4. Treatment costs

Annual treatment costs:

Adults with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia and have not received prior therapy with a complement inhibitor

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pegcetacoplan	€ 376,581.28

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

Adults with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia and have not received prior therapy with a complement inhibitor

- 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 22 November 2024.

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

Berlin, 22 November 2024

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

Prof. Hecken