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 (paroxysmal nocturnal haemoglobinuria, pretreated patients)

of 15 September 2022

At its session on 15 September 2022, 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 Pegcetacoplan as follows:

Pegcetacoplan

Resolution of: 15 September 2022
Entry into force on: 15 September 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 13 December 2021):

Aspaveli is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months.

Therapeutic indication of the resolution (resolution of 15 September 2022):

See therapeutic indication according to marketing authorisation.

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 are anaemic after treatment with a C5 inhibitor for at least 3 months</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 are anaemic after treatment with a C5 inhibitor for at least 3 months

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 ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

PEGASUS study

Study design: - Run-in period (pegcetacoplan + eculizumab)
- Open-label, randomised, controlled period (pegcetacoplan **vs** eculizumab)
- Open-label treatment period (pegcetacoplan)

Comparison: - Pegcetacoplan **vs** eculizumab (16-week, randomised, controlled period)

Mortality

Endpoint	Pegcetacoplan		Eculizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	41	0 (0)	39	0 (0)	-

[1] Data from the dossier assessment of the G-BA (published on 1. July 2022), and from the amendment to the dossier assessment of the G-BA, unless otherwise indicated.

Morbidity

Endpoint	Pegcetacoplan		Eculizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value Absolute difference (AD)[a]
Thrombotic events					
	41	0 (0)	39	0 (0)	-
Cardiovascular events					
	41	0 (0)	39	0 (0)	-
Transfusion independence (presented additionally)					
Subjects without transfusion	41	35 (85.4)		6 (15.4)	5.55 [2.63; 11.71] < 0.0001 AD = 70.0 %
FACIT fatigue					
Improvement by ≥ 15% of the scale range					
	41	22 (53.7)	39	3 (7.7)	6.98 [2.27; 21.46] < 0.0001 AD = 46.0 %
Deterioration by 15% of the scale range					
	41	6 (14.6)	39	12 (30.8)	0.48 [0.20; 1.14] 0.1104

Health-related quality of life

Endpoint	Pegcetacoplan		Eculizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Linear Analogue Scale Assessment (LASA)					
Improvement by ≥ 15% of the scale range					
Activity level	41	21 (51.2)	39	6 (15.4)	3.33 [1.50; 7.37]

Endpoint	Pegcetacoplan		Eculizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
					0.0009 AD = 35.8 %
Ability to carry out daily activities	41	20 (48.8)	39	7 (17.9)	2.72 [1.30; 5.70] 0.0046 AD = 30.9 %
General quality of life	41	19 (46.3)	39	4 (10.3)	4.52 [1.69; 12.10] 0.0004 AD = 36.0 %
Deterioration by 15% of the scale range					
Activity level	41	7 (17.1)	39	8 (20.5)	0.83 [0.33; 2.08] 0.7785
Ability to carry out daily activities	41	8 (19.5)	39	12 (30.8)	0.63 [0.29; 1.38] 0.3055
General quality of life	41	10 (24.4)	39	8 (20.5)	1.19 [0.52; 2.70] 0.7910
EORTC QLQ-C30 Functional Scales/ General Health Status					
Improvement by ≥ 10 points					
General health status	41	23 (56.1)	39	5 (12.8)	4.38 [1.85; 10.36] < 0.0001 AD = 43.3 %
Role functioning	41	19 (46.3)	39	9 (23.1)	2.01 [1.04; 3.89] 0.0364 AD = 23.2 %
Emotional functioning	41	14 (34.1)	39	11 (28.2)	1.21 [0.63; 2.33] 0.6338
Physical functioning	41	24 (58.5)	39	7 (17.9)	3.26 [1.59; 6.69] 0.0002 AD = 40.6 %
Cognitive functioning	41	14 (34.1)	39	6 (15.4)	2.22 [0.95; 5.19]

Endpoint	Pegcetacoplan		Eculizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
					0.0715
Social functioning	41	18 (43.9)	39	13 (33.3)	1.32 [0.75; 2.31] 0.3663
Deterioration by ≥ 10 points					
General health status	41	9 (22.0)	39	16 (41.0)	0.54 [0.27; 1.07] 0.0915
Role functioning	41	10 (24.4)	39	16 (41.0)	0.59 [0.31; 1.15] 0.1527
Emotional functioning	41	11 (26.8)	39	13 (33.3)	0.80 [0.41; 1.58] 0.6276
Physical functioning	41	6 (14.6)	39	8 (20.5)	0.71 [0.27; 1.87] 0.5640
Cognitive functioning	41	10 (24.4)	39	15 (38.5)	0.63 [0.32; 1.24] 0.2292
Social functioning	41	7 (17.1)	39	11 (28.2)	0.61 [0.26; 1.40] 0.2890

Side effects

Endpoint	Pegcetacoplan		Eculizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	41	36 (87.8)	39	34 (84.6)	-
Serious adverse events (SAE)					
	41	7 (17.1)	39	6 (15.4)	1.11 [0.41; 3.01]

Endpoint	Pegcetacoplan		Eculizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value Absolute difference (AD)[a]
					1.0000
Severe adverse events [b]					
	41	8 (19.5)	39	5 (12.8)	1.52 [0.54; 4.25] 0.5478
Therapy discontinuation due to adverse events					
	41	3 (7.3)	39	0 (0)	6.67 [0.36; 125.02] 0.2410
SAE (incidence ≥ 5%) SOC					
Blood and lymphatic system disorders	41	2 (4.9)	39	4 (10.3)	0.48 [0.09; 2.45] 0.4261
General disorders and administration site conditions	41	1 (2.4)	39	2 (5.1)	0.48 [0.04; 5.04] 0.6108
Severe AEs[b] (incidence ≥ 5%) SOC					
Blood and lymphatic system disorders	41	3 (7.3)	39	4 (10.3)	0.71 [0.17; 2.99] 0.7087
AEs of special interest of any severity grade SOC					
Infections and infestations	41	12 (29.3)	39	10 (25.6)	1.14 [0.56; 2.33] 0.8045
Reactions at the injection site	41	15 (36.6)	39	1 (2.6)	14.27 [1.98; 102.95] 0.0001
Reaction in connection with an infusion	41	11 (26.8)	39	1 (2.6)	10.46 [1.42; 77.29] 0.0034

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation

Endpoint	Pegcetacoplan		Eculizumab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value Absolute difference (AD)[a]

[b] The classification of AEs according to severity grade was based on the following criteria:
- Mild: asymptomatic or only mild symptoms or only clinical/ diagnostic observations or intervention not indicated
- Moderate: minimal, local or non-invasive treatment required, or restriction of the age-appropriate activity of daily living (e.g. when preparing meals, shopping for food or clothes, using the telephone, handling money)
- Severe: medically significant but not life-threatening or hospitalisation or prolongation of hospitalisation required or disabling or limiting activities related to self-care in daily life (when bathing, dressing and undressing, feeding oneself, using the toilet, taking medication; be bedridden)

Abbreviations used:
AD = absolute difference; CI = confidence interval; LS = least square; MV = mean value; N = number of patients evaluated; n = number of patients with (at least one) event; RR = relative risk; SD = standard deviation; SE = standard error; SOC = system organ class; vs = versus

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

Adults with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months

approx. 190 – 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 Aspaveli (active ingredient: pegcetacoplan) at the following publicly accessible link (last access: 9 August 2022):

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 are anaemic after treatment with a C5 inhibitor for at least 3 months

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pegcetacoplan	€ 426,219.99

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2022)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 15 September 2022.

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

Berlin, 15 September 2022

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

Prof. Hecken