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
Crovalimab (paroxysmal nocturnal haemoglobinuria, ≥ 12 years, ≥ 40 kg)

of 6 March 2025

At its session on 6 March 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 Crovalimab as follows:

Crovalimab

Resolution of: 6 March 2025
Entry into force on: 6 March 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 24 August 2024):

Piasky as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH):

- In patients with haemolysis with clinical symptom(s) indicative of high disease activity.
- In patients who are clinically stable after having been treated with a complement component 5 (C5) inhibitor for at least the past 6 months.

Therapeutic indication of the resolution (resolution of 6 March 2025):

See therapeutic indication according to marketing authorisation.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

a) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) and haemolysis with clinical symptom(s) indicative of high disease activity

Appropriate comparator therapy:

Eculizumab or ravulizumab

Extent and probability of the additional benefit of crovalimab compared to eculizumab:

An additional benefit is not proven.

b) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) who have been receiving a C5 inhibitor for ≥ 6 months and are clinically stable

Appropriate comparator therapy:

Eculizumab or ravulizumab

Extent and probability of the additional benefit of crovalimab compared to eculizumab:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) and haemolysis with clinical symptom(s) indicative of high disease activity

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.
Health-related quality of life	n.a.	There are no assessable data.
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		

COMMODORE 2 study:

- Open-label, randomised controlled trial, crovalimab versus eculizumab
- Relevant sub-population: adult patients without pretreatment with a C5 complement inhibitor, with at least one PNH-associated symptom within the last 3 months prior to screening and an elevated lactate dehydrogenase level at screening
- Pre-specified primary data cut-off from 16.11.2022

[1] Data from the dossier assessment of the IQWiG (A24-94) and from the addendum (A25-12), unless otherwise indicated.

Mortality

Endpoint	Crovalimab		Eculizumab		Crovalimab vs Eculizumab
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value
Overall survival[a]					
	134	1 (0.7)	69	1 (1.4)	0.51 [0.03; 8.11]; 0.736[b]

Morbidity

Endpoint	Crovalimab		Eculizumab		Crovalimab vs Eculizumab
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value
Transfusion independence (from the start of the study until week 25)					
Subjects without transfusion[c]	134	88 (65.7)	69	47 (68.1)	0.96 [0.79; 1.18]; 0.790[d]
MAVE (Major Adverse Vascular Event)[e]					
	134	0 (0.0)	69	1 (1.4)	0.17 [0.01; 4.19]; 0.173[d]
Breakthrough haemolysis					
No suitable data					
Fatigue (FACIT-Fatigue) Improvement by ≥ 8 points at week 25 compared to the start of the study[f]					
	128	55 (43.0)	66	23 (34.8)	1.23 [0.84; 1.81]; 0.322[d]
Health status (EQ-5D VAS) Improvement by ≥ 15 points at week 25 compared to the start of the study[g]					
	127	31 (24.4)	68	17 (25.0)	0.98 [0.58; 1.63]; 0.964[d]
Symptomatology					
PGIS	No suitable data				

Health-related quality of life

Endpoint	Crovalimab		Eculizumab		Crovalimab vs Eculizumab
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value
EORTC QLQ-C30 functional scales	No suitable data				

Side effects

Endpoint	Crovalimab		Eculizumab		Crovalimab vs Eculizumab
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value
Total adverse events (presented additionally)					
	135	105 (77.8)	69	55 (79.7)	-
Serious adverse events (SAE)					
	135	14 (10.4)	69	9 (13.0)	0.80 [0.36; 1.74]; 0.615[h]
Severe adverse events (CTCAE grade 3 or 4)					
	135	24 (17.8)	69	17 (24.6)	0.72 [0.42; 1.25]; 0.309[h]
Therapy discontinuation due to adverse events					
	135	1 (0.7)	69	1 (1.4)	0.51 [0.03; 8.05]; 0.736[h]
Specific adverse events					
Type III hypersensitivity reaction[i] (type III allergy [PT, AEs])	135	0 (0.0)	69	0 (0.0)	-
Reactions at the injection site[j]	No suitable data				
Reactions in connection with an infusion[j]	No suitable data				
Infections[j,k] (infections and infestations [SOC, AEs])	135	32 (23.7)	69	25 (36.2)	0.65 [0.42; 1.01]; 0.061[h]

[a] The results on overall mortality are based on the data on fatal AEs. In the crovalimab arm, another female patient died on study day 2. According to the information provided by the pharmaceutical company, the reason was a myocardial infarction that had already occurred prior to the administration of crovalimab. As no data on the LDH value was collected for the patient after the start of the study, she is not included in the primary analysis population.
[b] IQWiG calculation of RR, CI (asymptotic) and p value (unconditional exact test, CSZ method)
[c] Defined as the percentage of patients who did not receive a transfusion with red blood cell concentrate from the start of the study until week 25 and who did not require a transfusion according to the guidelines specified in the protocol.
[d] IQWiG calculation of RR, CI (asymptotic) and p value (unconditional exact test CSZ method); the pharmaceutical company presented p values for the effect-size-weighted risk reduction, these are not relevant for the benefit assessment
[e] Defined as the occurrence of one of the following events: Thrombophlebitis/ deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack (TIA), unstable angina pectoris, renal vein thrombosis, acute peripheral vascular occlusion, mesenteric/ visceral venous thrombosis or infarction, mesenteric/ visceral arterial thrombosis or infarction, hepatic vein/ portal vein thrombosis (Budd-Chiari syndrome), cerebral arterial occlusion/ stroke, cerebral venous occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other
[f] An increase in score by ≥ 8 points at week 25 compared to the start of the study is considered a clinically relevant improvement (scale range: 0 to 52).
[g] An increase in score by ≥ 15 points at week 25 compared to the start of the study is considered a clinically relevant improvement (scal e range: 0 to 100).
[h] IQWiG calculations, p value unconditional exact test (CSZ method).
[i] Predefined as AE of special interest (AESI) according to the study protocol.
[j] Presented in the study as "selected AE".
[k] Including no cases of meningococcal meningitis.

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; CI = confidence interval; LDH: lactate dehydrogenase; MAVE = Major Adverse Vascular Event; N = number of patients evaluated; n = number of patients with (at least one) event; PGIS: Patient Global Impression of Severity Survey; PT: preferred term; SOC: system organ class; SAE: serious adverse event; AE: adverse event; vs = versus; VAS: visual analogue scale.

b. Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) who have been receiving a C5 inhibitor for ≥ 6 months and are clinically stable

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantage in the endpoint of fatigue
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↓↓	Disadvantages in the endpoint of severe AEs [CTCAE grade ≥ 3)
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		

COMMODORE 1 study:

- Open-label, randomised controlled trial, crovalimab versus eculizumab
- Relevant sub-population: adult patients who have been treated with eculizumab for ≥ 6 months according to the marketing authorisation and are clinically stable
- Evaluations with data as of 31.05.2023 (required by the Food and Drug Administration)

Mortality

Endpoint	Crovalimab		Eculizumab		Crovalimab vs Eculizumab
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value
Overall survival[a]					
	44	0 (0)	42	0 (0)	-

Morbidity

Endpoint	Crovalimab		Eculizumab		Crovalimab vs Eculizumab
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value Absolute difference (AD)[b]
Transfusion independence (from the start of the study until week 25)					
Subjects without transfusion[c]	44	35 (79.5)	42	34 (81.0)	0.98 [0.80; 1.21]; 0.913[d]
MAVE (Major Adverse Vascular Event)[e]					
	44	0 (0)	42	1 (2.4)	0.32 [0.01; 7.61]; 0.363[d]
Breakthrough haemolysis					
No suitable data					
Fatigue (FACIT-Fatigue)[f] Improvement by ≥ 8 points at week 25 compared to the start of the study					
	43	10 (23.3)	37	1 (2.7)	8.60 [1.16; 64.10]; 0.008[d] AD = 20.6%
Health status (EQ-5D VAS) Improvement by ≥ 15 points at week 25 compared to the start of the study[g]					
	43	11 (25.6)	37	7 (18.9)	1.35 [0.58; 3.13]; 0.591[d]

Health-related quality of life

Endpoint	Crovalimab		Eculizumab		Crovalimab vs Eculizumab
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value
EORTC QLQ-C30 functional scales	No suitable data				

Side effects

Endpoint	Crovalimab		Eculizumab		Crovalimab vs Eculizumab
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value Absolute difference (AD)[b]
Total adverse events (presented additionally)					
	44	35 (79.5)	42	28 (66.7)	-
Serious adverse events (SAE)					
	44	6 (13.6)	42	1 (2.4)	5.73 [0.72; 45.59]; 0.066[h]
Severe adverse events (CTCAE grade 3 or 4)					
	44	8 (18.2)	42	1 (2.4)	7.64 [0.998; 58.46]; 0.018[h,i] AD = 15.8%
Therapy discontinuation due to adverse events					
	44	0 (0)	42	0 (0)	-
Specific adverse events					
Type III hypersensitivity reaction[j] (type III allergy [PT, AEs])	44	7 (15.9)	42	0 (0)	-[k]; 0.007[h]
Reactions at the injection site[l]	No suitable data				
Reactions in connection with an infusion[l]	No suitable data				
Infections[l,m] (infections and infestations [SOC, AEs])	44	19 (43.2)	42	17 (40.5)	1.07 [0.65; 1.76]; 0.827[h]

[a] The results on overall mortality are based on the data on fatal AEs.
[b] Data on absolute difference (AD) only in the case of statistically significant difference; own calculation.
[c] Defined as the percentage of patients who did not receive a transfusion with red blood cell concentrate from the start of the study until week 25 and who did not require a transfusion according to the guidelines specified in the protocol.
[d] IQWiG calculation of RR, CI (asymptotic) and p value (unconditional exact test CSZ method); the pharmaceutical company presented p values for the effect-size-weighted risk reduction, these are not relevant for the benefit assessment
[e] Defined as the occurrence of one of the following events: Thrombophlebitis/ deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack (TIA), unstable angina pectoris, renal vein thrombosis, acute peripheral vascular occlusion, mesenteric/ visceral venous thrombosis or infarction, mesenteric/ visceral arterial thrombosis or infarction, hepatic vein/ portal vein thrombosis (Budd-Chiari

syndrome), cerebral arterial occlusion/ stroke, cerebral venous occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other

[f] An increase in score by ≥ 8 points at week 25 compared to the start of the study is considered a clinically relevant improvement (scale range: 0 to 52).

[g] An increase in score by ≥ 15 points at week 25 compared to the start of the study is considered a clinically relevant improvement (scale range: 0 to 100).

[h] IQWiG calculations, p value unconditional exact test (CSZ method)

[i] Discrepancy between p value (exact) and CI (asymptotic) due to different calculation methods.

[j] Predefined as AE of special interest (AESI) according to the study protocol

[k] No presentation of effect estimate and CI, as not informative

[l] Presented in the study as "selected AE"

[m] Including no cases of meningococcal meningitis

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; CI = confidence interval; LDH: lactate dehydrogenase; MAVE = Major Adverse Vascular Event; N = number of patients evaluated; n = number of patients with (at least one) event; PGIS: Patient Global Impression of Severity Survey; PT: preferred term; SOC: system organ class; SAE: serious adverse event; AE: adverse event; vs = versus; VAS: visual analogue scale.

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

a) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) and haemolysis with clinical symptom(s) indicative of high disease activity

Approx. 210 – 595 patients

b) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) who have been receiving a C5 inhibitor for ≥ 6 months and are clinically stable

Approx. 50 – 154 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 Piasky (active ingredient: crovalimab) at the following publicly accessible link (last access: 10 December 2024):

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

Treatment with crovalimab 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 pass. The training material and the patient pass contain in particular information on serious infections, meningococcal infections and serious haemolysis post discontinuation of crovalimab. The

patient pass also contains information about reactions in connection with an infusion and injection-related reactions.

There are no data on the switch-over to crovalimab in clinically unstable patients who continue to show high disease activity post treatment with a C5 inhibitor.

4. Treatment costs

Annual treatment costs:

a) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) and haemolysis with clinical symptom(s) indicative of high disease activity

and

b) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) who have been receiving a C5 inhibitor for ≥ 6 months and are clinically stable

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Crovalimab Initial dose Maintenance dose **Total:**	 € 99,161.86 - € 127,493.82 € 339,983.52 - € 509,975.28 **€ 439,145.38 - € 637,469.10**
Appropriate comparator therapy:	
Eculizumab Initial dose Maintenance dose **Total:**	 € 42,132.08 € 341,269.85 - € 450,286.61 **€ 383,401.93 - € 492,418.69**
Ravulizumab Initial dose Maintenance dose **Total:**	 € 35,109.36 - € 43,886.70 € 276,486.21 - € 331,346.48 **€ 311,595.57 - € 375,233.18**

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

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Crovalimab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	1.0	€ 100
Appropriate comparator therapy:					
Eculizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	25.6 – 32.5	€ 2,560 - € 3,250
Ravulizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	7.3	€ 730

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) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) and haemolysis with clinical symptom(s) indicative of high disease activity

– 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) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) who have been receiving a C5 inhibitor for ≥ 6 months and are clinically stable

- 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 6 March 2025.

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

Berlin, 6 March 2025

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

Prof. Hecken