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
Concizumab (haemophilia B, ≥ 12 years, with factor IX inhibitors)

of 16 October 2025

At their session on 16 October 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. In Annex XII, the following information shall be added after No. 6 to the information on the benefit assessment of Concizumab in the version of the resolution of 16 October 2025 on the therapeutic indication "Haemophilia A, ≥ 12 years, with factor VIII inhibitors":

Concizumab

Resolution of: 16 October 2025
Entry into force on: 16 October 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 13 December 2024):

Concizumab (Alhemo) is indicated for routine prophylaxis of bleeding in patients 12 years of age or more with:

- haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors.
- haemophilia B (congenital factor IX deficiency) with FIX inhibitors.

Therapeutic indication of the resolution (resolution of 16 October 2025):

Concizumab is indicated for routine prophylaxis of bleeding in patients 12 years of age or more with haemophilia B (congenital factor IX deficiency) with FIX inhibitors.

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

Adults and adolescents 12 years of age or more with haemophilia B (congenital factor IX deficiency) with factor IX inhibitors with an indication for routine prophylaxis

Appropriate comparator therapy:

- Individualised therapy with selection of
  - a treatment on demand with a product with bypassing activity (with factor VIII inhibitor bypassing activity enriched human plasma fraction),
  - a treatment on demand with eptacog alfa and
  - routine prophylaxis with recombinant or human plasma-derived factor IX products

Extent and probability of the additional benefit of concizumab compared to the bypassing agents:

a) Adults and adolescents 12 years of age or more with haemophilia B (congenital factor IX deficiency) with factor IX inhibitors with an indication for routine prophylaxis, for whom treatment on demand with bypassing agents alone (with factor VIII inhibitor bypassing activity enriched human plasma fraction or eptacog alfa) is the appropriate patient-individual therapy

Hint for a considerable additional benefit

b) Adults and adolescents 12 years of age or more with haemophilia B (congenital factor IX deficiency) with factor IX inhibitors with an indication for routine prophylaxis, for whom treatment on demand with bypassing agents alone (with factor VIII inhibitor bypassing activity enriched human plasma fraction or eptacog alfa) is not the appropriate patient-individual therapy

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adults and adolescents 12 years of age or more with haemophilia B (congenital factor IX deficiency) with factor IX inhibitors with an indication for routine prophylaxis, for whom treatment on demand with bypassing agents alone (with factor VIII inhibitor bypassing activity enriched human plasma fraction or eptacog alfa) is the appropriate patient-individual therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↑	Advantages in the absence of bleeding and treated bleeding.
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		

Explorer7 study: open-label, multicentre, partially randomised, controlled study; routine prophylaxis with concizumab **vs** treatment on demand with bypassing agents; relevant sub-population: patients with haemophilia B with factor IX inhibitors

[1] Data from the dossier assessment of the IQWiG (A25-56) and from the addenda (A25-115 and G25-27), unless otherwise indicated.

Mortality

Endpoint	Routine prophylaxis with concizumab		Treatment on demand with bypassing agents		Concizumab vs bypassing agents
	N	*Patients with event n (%)*	*N*	*Patients with event n (%)*	*RR [95% CI] p value*
Mortality					
Overall mortality[a)]	12	2 (16.7)	10	0 (0)	4.23[b)] [0.23; 79.10]; 0.207[c)]

Morbidity

Endpoint	Routine prophylaxis with concizumab		Treatment on demand with bypassing agents		Concizumab vs bypassing agents
	N	*Patients with event n (%)*	*N*	*Patients with event n (%)*	*RR [95% CI] p value*
Complete absence of bleeding	12	9 (75.0)	10	1 (10.0)	7.50 [1.14; 49.54]; 0.002[d)]

Endpoint	Routine prophylaxis with concizumab		Treatment on demand with bypassing agents		Concizumab vs bypassing agents
	N	*ABR [95% CI]*	*N*	*ABR [95% CI]*	*ABR ratio[e)] [95% CI] p value*
Treated bleeding (annualised bleeding rate)					
- Treated bleeding[f)]	12	1.37 [0.54; 3.46]	10	7.04 [3.08; 16.08]	0.19 [0.06; 0.65]; 0.008
- Treated joint bleeding[f)]	12	0.91 [0.37; 2.24]	10	5.25 [2.61; 10.58]	0.17 [0.06; 0.52]; 0.002
- Treated target joint bleeding[f)]	12	0.21 [0.04; 1.01]	10	0.92 [0.26; 3.20]	0.23 [0.05; 1.13]; 0.070
- All treated and untreated bleeding[f)] (presented additionally)	12	3.15 [1.60; 6.19]	10	9.06 [4.56; 18.00]	0.35 [0.13; 0.90]; 0.029
- Major bleeding	No suitable data				

Endpoint	Routine prophylaxis with concizumab		Treatment on demand with bypassing agents		Concizumab vs bypassing agents
	Values at the start of study MV (SD)	*Change at week 24 MV (SE)*	*Values at the start of study MV (SD)*	*Change at week 24 MV (SE)*	*Effect [95% CI] p value*
Symptomatology					
Symptomatology	No suitable data				

Health-related quality of life

Endpoint	Routine prophylaxis with concizumab		Treatment on demand with bypassing agents		Concizumab vs bypassing agents
	Values at the start of study MV (SD)	*Change at week 24 MV (SE)*	*Values at the start of study MV (SD)*	*Change at week 24 MV (SE)*	*Effect [95% CI] p value*
Short Form-36 Health Survey Version 2 (SF-36v2)					
SF-36v2	No suitable data				

Side effects

Endpoint	Routine prophylaxis with concizumab		Treatment on demand with bypassing agents		Concizumab vs bypassing agents
	N	*Patients with event n (%)*	*N*	*Patients with event n (%)*	*RR [95% CI] p value*
Adverse events in total					
AEs (presented additionally)	12	6 (50.0)	10	3 (30.0)	-
Serious adverse events (SAE)					
SAEs	12	2 (16.7)	10	2 (20.0)	0.83[b] [0.14; 4.90]; 0.911[c]
Therapy discontinuation due to adverse events					
Therapy discontinuation due to AEs	12	1 (8.3)	10	0 (0)	2.54[b] [0.11; 56.25]; 0.512[c]

a) The results on overall mortality are based on the data on fatal AEs.
b) Calculation based on the fourfold table with zero cell correction (addition of 0.5 in all cells)
c) Calculated using Barnard's test (unconditional exact test).
d) IQWiG calculation: Effect and CI: asymptotic, p value: unconditional exact test
e) Calculated using negative-binomial regression adjusted for treatment, bleeding frequency before screening and the logarithm of the duration of observation as an offset variable.
f) Operationalised as spontaneous and traumatic bleeding episodes or joint bleeding episodes; bleeding events that occurred at the same anatomical site (including deterioration due to swelling or pain) within 72 h after the end of treatment with a factor product were combined into 1 bleeding episode.

Abbreviations used: ABR = annualised bleeding rate; CTCAE = Common Terminology Criteria for Adverse Events; CI = confidence interval; 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; SAE = serious adverse event; AE = adverse event; vs = versus

b) Adults and adolescents 12 years of age or more with haemophilia B (congenital factor IX deficiency) with factor IX inhibitors with an indication for routine prophylaxis, for whom treatment on demand with bypassing agents alone (with factor VIII inhibitor bypassing activity enriched human plasma fraction or eptacog alfa) is not the appropriate patient-individual therapy

No data available.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

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

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

Adults and adolescents 12 years of age or more with haemophilia B (congenital factor IX deficiency) with factor IX inhibitors with an indication for routine prophylaxis

Approx. 1 to 12 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 Alhemo (active ingredient: concizumab) at the following publicly accessible link (last access: 7 October 2025):

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

Treatment with concizumab should only be initiated and monitored by specialists who are experienced in the treatment of patients with haemophilia and/or other blood coagulation disorders.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients and caregivers (including patient identification card). In particular, the training material contains information and warnings on dealing with thromboembolic events and the use of bypassing agents.

4. Treatment costs

Annual treatment costs:

Adults and adolescents 12 years of age or more with haemophilia B (congenital factor IX deficiency) with factor IX inhibitors with an indication for routine prophylaxis

Designation of the therapy	Annual treatment costs/ patient	
Medicinal product to be assessed:		
Concizumab	Adults	€ 532,150.33 - € 859,627.45
	12 to < 18 years	€ 287,018.48 - € 777,758.17
Appropriate comparator therapy:		
Human plasma protein with factor VIII inhibitor bypassing activity		
Human plasma protein with factor VIII inhibitor bypassing activity[2]		
Treatment on demand:	Different from patient to patient	
Recombinant blood coagulation factor VIIa product		
Eptacog alfa		
Treatment on demand:	Different from patient to patient	
Recombinant blood coagulation factor IX products		
Albutrepenonacog alfa		
Routine prophylaxis:	Adults	€ 283,563.11 - € 393,582.80
	12 to < 18 years	€ 154,940.71 - € 347,681.86
Eftrenonacog alfa		
Routine prophylaxis:	Adults	€ 254,823.18 - € 345,048.37
	12 to < 18 years	€ 141,874.55 - € 295,793.45
Nonacog alfa		
Routine prophylaxis:	Adults	€ 329,950.90 - € 439,814.06

[2] Cost representation based on the requirements in the product information for FEIBA. Other proprietary medicinal products are available.

Designation of the therapy	Annual treatment costs/ patient	
	12 to < 18 years	€ 189,353.46 - € 375,201.10
Nonacog beta pegol		
Routine prophylaxis:	Adults	€ 317,484.38
	12 to < 18 years	€ 181,529.95 - € 270,839.77
Nonacog gamma		
Routine prophylaxis:	Adults	€ 347,735.22 - € 695,939.02
	12 to < 18 years	€ 199,468.59 - € 598,552.25
Human plasma-derived coagulation factor IX products		
Human plasma-derived products[3]		
Routine prophylaxis:	Adults	€ 157,671.45 - € 368,378.60
	12 to < 18 years	€ 78,835.72 - € 315,256.55

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 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 and adolescents 12 years of age or more with haemophilia B (congenital factor IX deficiency) with factor IX inhibitors with an indication for routine prophylaxis

- No medicinal product with new active ingredients that can be used in a combination therapy that 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.

6. Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product Alhemo is a medicinal product placed on the market from 1 January 2025.

[3] Cost representation based on the requirements in the product information for AlphaNine. Other proprietary medicinal products are available.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is < 5% of the total number of study participants.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant extent within the scope of SGB V.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 October 2025.

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

Berlin, 16 October 2025

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

Prof. Hecken