Gemeinsamer Bundesausschuss

Justification

to the Resolution of the Federal Joint Committee (G-BA) 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

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company have conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application,
7. number of study participants who participated in the clinical studies at study sites within the scope of SGB V, and total number of study participants.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decide on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient concizumab on 1 May 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 28 April 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 August 2025 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of concizumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. In order to determine the

extent of the additional benefit, the G-BA have evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of concizumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of Concizumab (Alhemo) in accordance with the product information

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 16.10.2025):

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.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

<u>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</u>

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

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

On 1. In the therapeutic indication of haemophilia B, the following active ingredients are approved:

- Recombinant factor IX products: albutrepenonacog alfa, eftrenonacog alfa, nonacog alfa, nonacog beta pegol and nonacog gamma
- human plasma factor IX products;
- factor VIII inhibitor bypassing activity enriched human plasma fraction;
- recombinant blood coagulation factor VIIa product: eptacog alfa;
- gene therapy: etranacogene dezaparvovec,
- monoclonal antibody: marstacimab.

The recombinant and human plasma-derived factor IX products and factor VIII inhibitor bypassing activity enriched human plasma fraction are approved for long-term routine prophylaxis.

For patients with factor IX inhibitors, the factor VIII inhibitor bypassing activity enriched human plasma fraction is approved for treatment and prevention, and eptacog alfa is approved for treatment and prevention in connection with surgical or invasive procedures.

On 2. A non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication.

On 3. The following resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication "Haemophilia B" are available:
- albutrepenonacog alfa from 1 December 2016 (repealed) and from 7 April 2022,
- eftrenonacog alfa from 15 December 2016 (repealed) and from 1 February 2024,
- nonacog beta pegol from 19 April 2018 and from 15 February 2024,
- etranacogene dezaparvovec from 19 October 2023,
- marstacimab from 17 July 2025.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

It is assumed that the patient population in the present indication is haemophilia patients requiring replacement. Patients 12 years of age or more are included in the provisional therapeutic indication. The marketing authorisation of the respective medicinal product must be observed.

The aggregated evidence results in a body of evidence limited in the level of evidence overall for haemophilia B patients with factor IX inhibitors. In everyday care, patient-individual factors such as inhibitor titre, bleeding events, bleeding risk, tolerability or response to previous treatments including immunotolerance induction with factor IX products are decisive for the medical treatment decision. As a rule, patients with haemophilia B with factor IX inhibitors first undergo immunotolerance induction with factor IX preparations with the aim of eliminating inhibitors; this immunotolerance therapy is often only possible in conjunction with immunosuppression due to the anaphylaxis occurring during administration of factor IX.

The "WFH guidelines for the management of haemophilia" (Srivastava A et al., 2020) and the "International consensus recommendations on the management of people with haemophilia B" (Hart D.P. et al., 2011) recommend factor IX products for the treatment of acute bleeding in haemophilia B patients with low-responder factor IX inhibitors. Treatment with either recombinant, activated factor VII or activated prothrombin complex is recommended for patients with high-responder factor IX inhibitors. Recombinant, activated factor VII or, if no allergic reactions to factor IX products have occurred, activated prothrombin complex is recommended for prophylaxis.

The scientific-medical societies involved in accordance with Section 35a paragraph 7 SGB V recommend the administration of factor IX concentrate for haemophilia B patients with inhibitor activity below 5 Bethesda titres (B.E.). Either recombinant, activated factor VII or activated prothrombin complex can be used for patients with inhibitor activity above 5 B.U. or if factor IX preparations have failed.

The recombinant and human plasma-derived factor IX products as well as with factor VIII inhibitor bypassing activity enriched human plasma fraction (activated prothrombin complex), which also contains factor IX, are not suitable for patients with high factor IX inhibitor titres and a history of allergic reactions to factor IX products. For these patients, treatment on demand with eptacog alfa (activated factor VII) is an appropriate therapy option.

A treatment on demand with factor VIII inhibitor bypassing activity enriched human plasma fraction (activated prothrombin complex) can be used in patients with high factor IX inhibitor titres, provided no allergic reactions to factor IX products have occurred.

Routine prophylaxis with factor IX products is an appropriate therapy option for patients with low factor IX inhibitor titres and no history of allergic reactions.

In summary, given the therapy options available for the treatment of 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, an individualised therapy is recommended in the form of a treatment on demand with selection of a product with bypassing activity (with factor VIII inhibitor bypassing activity enriched human plasma fraction) or eptacog alfa or routine prophylaxis with recombinant or human plasma-derived factor IX products is considered appropriate.

Individualised therapy is based on the assumption that several treatment options, which allow an individualised medical treatment decision, are available. When making the treatment decision, in particular the inhibitor titre, the bleeding events, the bleeding risk and the tolerability must be considered, taking into account the available evidence.

Irrespective of a decision on the appropriate patient-individual therapy, a treatment on demand for bleeding events ("rescue therapy") should be possible for all patients as a rule.

The term "individualised therapy" is used instead of previously used terms such as "patient-individual therapy" or "therapy according to doctor's instructions". This harmonises the terms used in the European assessment procedures (EU-HTA).

Change in the appropriate comparator therapy

To date, a patient-individual therapy - taking into account factors such as the inhibitor titre, bleeding events, bleeding risk and tolerability using a treatment on demand or

routine prophylaxis with a product with bypassing activity (with factor VIII inhibitor bypassing activity enriched human plasma fraction), a treatment on demand or routine prophylaxis with eptacog alfa or a treatment on demand or routine prophylaxis with recombinant or human plasma-derived factor IX products - is considered the appropriate comparator therapy for 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.

In the opinion of the clinicians involved in the written statement procedure, this does not correspond to the current medical treatment situation. In particular, the anaphylactic reactions caused by factor IX products, the high inhibitor titres and the short half-lives of the available products make routine prophylaxis with bypassing agents impracticable for a large percentage of the patients covered by the therapeutic indication. Therefore, routine prophylaxis with bypassing agents (with factor VIII inhibitor bypassing activity enriched human plasma fraction or eptacog alfa) is not determined here as part of the appropriate comparator therapy.

Routine prophylaxis with factor IX products is an appropriate comparator therapy for patients with low inhibitor titres and no history of allergic reactions.

The G-BA therefore considers it appropriate to change the appropriate comparator therapy at this point in time and to adapt it to the current state of medical knowledge. Accordingly, an individualised therapy in the form of a treatment on demand with the selection of a product with bypassing activity (with factor VIII inhibitor bypassing activity enriched human plasma fraction) or eptacog alfa or routine prophylaxis with recombinant or human plasma-derived factor IX products is determined as the appropriate comparator therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of concizumab is assessed as follows:

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

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.

Justification:

The pharmaceutical company presented the Explorer7 study for the benefit assessment of concizumab.

The Explorer7 study is the label-enabling, open-label, multicentre, partially randomised phase III study consisting of a main phase and an extension phase with two randomised and two non-randomised arms. 52 adult males and adolescent males 12 years of age or more with congenital haemophilia A or B of any disease severity with factor VIII or factor IX inhibitors were enrolled, assigned in a 2:1 ratio to each arm and stratified by haemophilia type (A vs B) and bleeding frequency in the last 24 weeks (< 9 vs ≥ 9 bleeding episodes). A total of 25 patients with haemophilia B were enrolled, randomised and assigned to either routine prophylaxis with concizumab (n = 15) or continuation of their treatment on demand with recombinant factor VIIa (eptacog alfa) or activated aPCC (n = 10). The main phase of the study lasted 32 weeks for the concizumab arms and at least 24 weeks for the control arm with a subsequent extension phase of 128 and 136 weeks respectively. The primary endpoint of the study was the number of treated traumatic and spontaneous bleeding episodes. In addition, other endpoints in the categories of morbidity, health-related quality of life and side effects were assessed.

As the appropriate comparator therapy in the study has only been implemented for patients who are eligible for treatment on demand with bypassing agents, the results of the study are only used for this patient group.

Against this background, a separate assessment of the additional benefit was made for patients with haemophilia B and factor IX inhibitors who were eligible or ineligible for treatment on demand with 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

Extent and probability of the additional benefit

Mortality

In the Explorer7 study, two patients in the concizumab arm died, while none in the control arm died. There was no statistically significant difference between the treatment arms.

Morbidity

Annualised bleeding rates (ABR) and complete absence of bleeding

The number of treated traumatic and spontaneous bleeding episodes is the primary endpoint of the Explorer7 study. Bleeding events that occurred at the same anatomical site within 72 hours of the end of treatment with a factor product were summarised in one bleeding episode. The bleeding episodes, including the treatments carried out, were documented by the patients in an electronic diary.

The annualised bleeding rates are presented for all treated and untreated bleeding episodes and differentiated according to treated joint and target joint bleeding episodes. In addition, results on complete absence of bleeding and major bleeding are presented. In particular, bleeding that requires treatment is considered patient-relevant. The endpoint "all treated and untreated bleeding episodes" is presented additionally.

In the endpoints of complete absence of bleeding, treated bleeding and treated joint bleeding episodes, there was a statistically significant advantage of concizumab over treatment on demand with bypassing agents.

Symptomatology/ health status

The following patient-reported outcomes (PROs) were collected for the endpoints for assessment of symptomatology and health status: Patient Global Impression of Change (PGI-C), Patient Global Impression of Severity (PGI-S) and Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form v2.0.

The results cannot be used for the present assessment due to the low return rates of the PGI-S and PROMIS even at baseline and the inappropriate non-responder imputations made in the PGI-C.

Quality of life

The following patient-reported outcomes (PROs) were collected for the endpoints for assessment of the health-related quality of life: Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL), Haemophilia Treatment Experience Measure (Hemo-TEM) and Short Form-36 Health Survey Version 2 (SF-36v2).

The results cannot be used for the present assessment due to low return rates of all PROs even at baseline.

Side effects

For the patient-relevant endpoints of serious adverse events (SAEs) and discontinuation due to AEs, there were no statistically significant differences between the treatment arms in each case. Furthermore, no thromboembolic events occurred in the study.

Overall assessment

The results of the Explorer7 study for the endpoint categories of mortality, morbidity, quality of life and side effects are available for the benefit assessment of concizumab compared to treatment on demand with bypassing agents for the treatment of 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, who are eligible for treatment on demand with bypassing agents (with factor VIII inhibitor bypassing activity enriched human plasma fraction or eptacog alfa).

For the endpoint of overall survival, there was no statistically significant difference between the treatment groups.

In the endpoints of complete absence of bleeding, treated bleeding and treated joint bleeding episodes of the morbidity endpoint category, there was a statistically significant advantage of concizumab over treatment on demand with bypassing agents. No suitable data are available for the endpoint of symptomatology.

In the endpoint category of health-related quality of life, no suitable data were presented.

In the endpoints of SAEs and discontinuation due to AEs of the category of side effects, there were no statistically significant differences between the treatment arms in each case.

In the overall assessment, an additional benefit of concizumab - classified as considerable in its extent - in adults and adolescents 12 years of age or more with haemophilia B with factor IX inhibitors, who are eligible for treatment on demand with bypassing agents, can be derived on the basis of the positive effects in the morbidity endpoints.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the open-label, multicentre, partially randomised phase III Explorer7 study.

Due to the lack of concurrence between the two study arms, the risk of bias at study level and for the results of all endpoints is classified as high.

In addition, the results on mortality, treated bleeding episodes, treated joint bleeding episodes and complete absence of bleeding show high percentages of patients not included in the evaluation in the intervention arm, and large differences between the treatment groups.

Due to the lack of blinding in the subjective decision on the treatment on demand of breakthrough bleeding in the intervention arm and bleeding in the control arm, the risk of bias for the endpoints of treated bleeding episodes, treated joint bleeding episodes and complete absence of bleeding is also estimated to be high.

The high cross-study risk of bias and the incomplete observation result in a high risk of bias of the results on the endpoint "SAEs", while the lack of blinding in the subjective endpoint assessment also resulted in a high risk of bias of the results on the endpoint "discontinuation due to AEs".

Furthermore, there is inadequate information on whether routine prophylaxis with factor IX products would have been suitable for the study participants. However, the percentage of patients with haemophilia B with factor IX inhibitors, who are eligible for routine prophylaxis

with factor IX preparations, is estimated to be low. Routine prophylaxis with factor IX products can only be considered for patients with haemophilia B with factor IX inhibitors who have low factor IX inhibitor titres and no history of allergic reactions. Due to the lack of information on this in the patient characteristics at the start of the study, uncertainties remain as to whether the continuation of this treatment on demand is an adequate patient-individual therapy option for all patients.

These uncertainties lead to a limitation of the reliability of data of the study results. Therefore, a hint is derived for the reliability of data of the additional benefit identified.

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

In the present benefit assessment, statements can only be made - based on the data presented - on those patients who are eligible for treatment on demand with bypassing agents. No data are available for adults and adolescents 12 years of age or more with haemophilia B with factor IX inhibitors with an indication for routine prophylaxis, who are ineligible for treatment on demand with bypassing agents.

Overall, it is therefore concluded that an additional benefit of concizumab is not proven for adults and adolescents 12 years of age or more with haemophilia B with factor IX inhibitors with an indication for routine prophylaxis, who are ineligible for treatment on demand with bypassing agents.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Alhemo with the active ingredient concizumab.

The therapeutic indication assessed here is as follows: "Routine prophylaxis of bleeding in patients 12 years of age or more with haemophilia B (congenital factor IX deficiency) with FIX inhibitors."

The G-BA determined the appropriate comparator therapy to be an individualised therapy with selection of treatment on demand with a product with bypassing activity (with factor VIII inhibitor bypassing activity enriched human plasma fraction), treatment on demand with eptacog alfa and routine prophylaxis with recombinant or human plasma-derived factor IX products.

The pharmaceutical company presented the label-enabling, multi-centre, partially randomised, open-label Explorer7 study with a comparison between routine prophylaxis with concizumab and treatment on demand with bypassing agents; male patients 12 years of age or more with congenital haemophilia A or B of any disease severity with factor VIII or factor IX inhibitors were enrolled in the study.

As the appropriate comparator therapy in the study has only been implemented for patients who are eligible for treatment on demand with bypassing agents, the results of the study are only used for this patient group.

Against this background, the G-BA made a separate assessment of the additional benefit for patients with haemophilia B and factor IX inhibitors who were eligible or ineligible for treatment on demand with 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, who are eligible for treatment on demand with bypassing agents (with factor VIII inhibitor bypassing activity enriched human plasma fraction or eptacog alfa)

For the endpoint of overall survival, there was no statistically significant difference between the treatment groups.

In the endpoints of complete absence of bleeding, treated bleeding and treated joint bleeding episodes of the morbidity endpoint category, there was a statistically significant advantage of concizumab over treatment on demand with bypassing agents. No suitable data are available for the endpoint of symptomatology.

In the endpoint category of health-related quality of life, no suitable data were presented.

In the endpoints of SAEs and discontinuation due to AEs of the category of side effects, there were no statistically significant differences between the treatment arms.

In the overall assessment, an additional benefit of concizumab - classified as considerable in its extent - in adults and adolescents 12 years of age or more with haemophilia B with factor IX inhibitors, who are eligible for treatment on demand with bypassing agents, can be derived on the basis of the positive effects in the morbidity endpoints.

Uncertainties in the results on mortality, treated bleeding episodes, treated joint bleeding episodes and complete absence of bleeding in the intervention arm arise due to the lack of concurrence between the two study arms and the high percentage of patients not included in the evaluation. In addition, there was a lack of blinding in the subjective decision on the treatment on demand of breakthrough bleeding in the intervention arm and bleeding in the control arm.

There is inadequate information on whether routine prophylaxis with factor IX products would have been suitable for the study participants. However, the percentage of patients with haemophilia B with factor IX inhibitors, who are eligible for routine prophylaxis with factor IX preparations, is estimated to be low. Due to the lack of information on the presence of allergic reactions and the number of inhibitor titres in the patient characteristics at the start of the study, uncertainties remain as to whether the continuation of this treatment on demand is an adequate patient-individual therapy option for all patients.

In the overall assessment, a hint for a considerable additional benefit of concizumab compared to the treatment on demand with bypassing agents is identified.

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, who are ineligible for treatment on demand with bypassing agents (with factor VIII inhibitor bypassing activity enriched human plasma fraction or eptacog alfa)

No data are available to demonstrate the additional benefit for 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, who are ineligible for treatment on demand with bypassing agents (with factor VIII inhibitor bypassing activity enriched human plasma fraction or eptacog alfa).

An additional benefit of concizumab is therefore not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA based the present resolution on the patient numbers derived by the pharmaceutical company, which are generally considered plausible. There are uncertainties regarding the transfer of the prevalence rate of male children and adolescents with haemophilia B with factor IX inhibitors to the number of adolescents.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

According to the available product information, both the dosage and the duration of the treatment on demand vary depending on the severity, localisation and extent of the bleeding. The costs of the treatment on demand for haemophilia B patients are therefore represented as "different from patient to patient".

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Concizumab	Continuously, 1 x daily	365.0	1	365.0
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*			
	Continuously, 1 x every 7 or 1 x every 10 to 14 days	52.1 or 26.1 – 36.5	1	52.1 or 26.1 – 36.5
Eftrenonacog alfa	*Routine prophylaxis*			
	Continuously, 1 x every 7 or 1 x every 10 days	52.1 - 36.5	1	52.1 - 36.5
Nonacog alfa	*Routine prophylaxis*			
	Continuously, 1 x every 3 to 4 days	91.3 - 121.7	1	91.3 - 121.7
Nonacog beta pegol	*Routine prophylaxis*			
	Continuously, 1 x every 7 days	52.1	1	52.1
Nonacog gamma	*Routine prophylaxis*			
	Continuously, 1 x every 3 to 4 days	91.3 - 121.7	1	91.3 - 121.7
Human plasma-derived coagulation factor IX products				

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Human plasma-derived products[3]	*Routine prophylaxis*			
	Continuously, every 3 to 4 days	91.3 – 121.7	1	91.3 – 121.7

Consumption:

The theoretical annual consumption of concizumab and the factor IX products of the appropriate comparator therapy required for the prevention of bleeding in patients 12 years of age and older with haemophilia B is presented.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Consumption is calculated per injection for the relevant age groups (adolescents aged 12 to below 18 years and adults) according to the respective product information.

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population"[4] as well as "Microcensus 2021 – body measurements of the population"[5] were applied. For body weight, the average weight of an adult male aged 18 years and over is therefore assumed to be 85.8 kg. For the underlying weight in the respective male age groups, the ranges were determined from 12 to below 18 years (47.6 kg – 74.6 kg).

The following dosage ranges are used for the cost calculation:

The cost representation is by indicating the cheapest and most expensive dosage possible. The dosage range can depend on both the frequency of application and the body weight.

Shorter dosing intervals or higher doses may be generally required in some cases, especially in younger patients.

Since factor IX products can be stored only for a maximum of 8 hours after reconstitution, discarding must be taken into account, consequently the consumption per injection is presented.

The consumption of vials and pre-filled syringes was optimised according to the packaging size on the basis of the weight-adjusted demand for factor IX I.U./ injection. For example, for a 12-year-old child requiring 1,666 I.U./ injection, this was composed of three vials each of 1,000 I.U., 500 I.U. and 250 I.U. of factor IX.

[3] Cost representation based on the requirements in the product information for AlphaNine. Other proprietary medicinal products are available.
[4] Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de
[5] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Concizumab	0.15 mg/ kg – 0.25 mg/ kg	**Adults**			
		12.9 mg – 21.4 mg	13 mg – 21 mg	365.0	15.8 x 300 mg – 25.6 x 300 mg
		12 to < 18 years			
		7 mg – 18.7 mg	1/21 x 150 mg – 1/15 x 300 mg	365.0	17.4 x 150 mg – 24.3 x 300 mg
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*				
	35 – 50 I.U./kg	**Adults**			
		3,003 I.U. - 4,290 I.U.	1 x 2,000 I.U. + 1 x 1,000 I.U. + 1 x 250 I.U. – 2 x 2,000 I.U. + 1 x 500 I.U.	52.1	52.1 x 2,000 I.U. + 52.1 x 1,000 I.U. + 52.1 x 250 I.U. – 104.2 x 2,000 I.U. + 52.1 x 500 I.U.
		12 to < 18 years			
		1,666 I.U. – 3,730 I.U.	1 x 1,000 I.U. + 1 x 500 I.U. + 1 x 250 I.U. - 1 x 3,500 I.U. + 1 x 250 I.U.	52.1	52.1 x 1,000 I.U. + 52.1 x 500 I.U. + 52.1 x 250 I.U. - 52.1 x 3,500 I.U. + 52.1 x 250 I.U.
	75 I.U./kg	**Adults**			

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
		6,435 I.U.	1 x 3,500 I.U. + 1 x 2,000 I.U. + 1 x 1,000 I.U.	26.1 – 36.5	26.1 x 3,500 I.U. + 26.1 x 2,000 I.U. + 26.1 x 1,000 I.U. - 36.5 x 3,500 I.U. + 36.5 x 2,000 I.U. + 36.5 x 1,000 I.U.
		12 to < 18 years			
		3,570 I.U. - 5,595 I.U.	1 x 3,500 I.U. + 1 x 2,000 I.U. + 1 x 250 I.U.	26.1 - 36.5	26.1 x 3,500 I.U. + 26.1 x 250 I.U. - 36.5 x 3,500 I.U. + 36.5 x 2,000 I.U. + 36.5 x 250 I.U.
Eftrenonacog alfa	*Routine prophylaxis*				
	50 – 100 I.U./kg	**Adults**			
		4,290 – 8,580 I.U.	2 x 2,000 I.U. + 1 x 500 I.U. - 2 x 3,000 I.U. + 1 x 2,000 I.U. + 1 x 500 I.U. + 1 x 250 I.U.	52.1 – 36.5	104.2 x 2,000 I.U. + 52.1 x 500 I.U. - 73 x 3,000 I.U. + 36.5 x 2,000 I.U. + 36.5 x 500 I.U. + 36.5 x 250 I.U.
		12 to < 18 years			
		2,380 – 7,460 I.U.	1 x 2,000 I.U. + 1 x 500 I.U. - 2 x 3,000 I.U. + 1 x 1,000 I.U. + 1 x 500 I.U.	52.1 - 36.5	52.1 x 2,000 I.U. + 52.1 x 500 I.U. - 73 x 3,000 I.U. + 36.5 x 1,000 I.U. + 36.5 x 500 I.U.
Nonacog alfa	*Routine prophylaxis*				

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	40 I.U./kg	**Adults**			
		3,432 I.U.	1 x 3,000 I.U. + 1 x 500 I.U.	91.3 – 121.7	91.3 x 3,000 I.U. + 91.3 x 500 I.U. - 121.7 x 3,000 I.U. + 121.7 x 500 I.U.
		12 to < 18 years			
		1,904 I.U. - 2,984 I.U.	1 x 2,000 I.U. - 1 x 3,000 I.U.	91.3 – 121.7	91.3 x 2,000 I.U. - 121.7 x 3,000 I.U.
Nonacog beta pegol	*Routine prophylaxis*				
	40 I.U./kg	**Adults**			
		3,432 I.U.	1 x 3,000 I.U. + 1 x 500 I.U.	52.1	52.1 x 3,000 I.U. + 52.1 x 500 I.U.
		12 to < 18 years			
		1,904 I.U. - 2,984 I.U.	1 x 2,000 I.U. - 1 x 3,000 I.U.	52.1	52.1 x 2,000 I.U. - 52.1 x 3,000 I.U.
Nonacog gamma	*Routine prophylaxis*				
	40 – 60 I.U./kg	**Adults**			
		3,432 I.U. - 5,136 I.U.	1 x 3,000 I.U. + 1 x 500 I.U. - 1 x 3,000 I.U. + 1 x 2,000 I.U. + 1 x 250 I.U.	91.3 – 121.7	91.3 x 3,000 I.U. + 91.3 x 500 I.U. - 121.7 x 3,000 I.U. + 121.7 x 2,000 I.U. + 121.7 x 250 I.U.
		12 to < 18 years			
		1,904 I.U. – 4,476 I.U.	1 x 2,000 I.U. - 1 x 3,000 I.U. + 1 x 1,000 I.U. + 1 x 500 I.U.	91.3 – 121.7	91.3 x 2,000 I.U. - 121.7 x 3,000 I.U. + 121.7 + 1,000 I.U. +

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					121.7 x 500 I.U.
Human plasma-derived coagulation factor IX products					
Human plasma-derived products[3]	*Routine prophylaxis*				
	20 - 40 I.U./kg	**Adults**			
		1,716 – 3,432 I.U.	2 x 1,000 I.U. - 3 x 1,000 I.U. + 1 x 500 I.U.	91.3 – 121.7	182.6 x 1,000 I.U. - 365.1 x 1,000 I.U. + 121.7 x 500 I.U.
		12 to < 18 years			
		952 I.U. – 2,984 I.U.	1 x 1,000 I.U. - 3 x 1,000 I.U.	91.3 – 121.7	91.3 x 1,000 I.U. - 365.1 x 1,000 I.U.

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Concizumab 150 mg	1 SFI	€ 17,869.40	€ 1.77	€ 1,017.23	€ 16,850.40
Concizumab 300 mg	1 SFI	€ 35,681.15	€ 1.77	€ 2,034.47	€ 33,644.91
Appropriate comparator therapy					
Human plasma protein with factor VIII inhibitor bypassing activity					
FEIBA 500 U.	1 PSS	€ 968.41	€ 1.77	€ 52.99	€ 913.65
FEIBA 1,000 U.	1 PSS	€ 1,913.31	€ 1.77	€ 105.98	€ 1,805.56
Recombinant blood coagulation factor VIIa product					

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Eptacog alfa 1 mg	1 PSI	€ 1,036.68	€ 1.77	€ 56.77	€ 978.14
Eptacog alfa 2 mg	1 PSI	€ 2,045.74	€ 1.77	€ 113.54	€ 1,930.43
Eptacog alfa 5 mg	1 PSI	€ 5,027.87	€ 1.77	€ 283.85	€ 4,742.25
Eptacog alfa 8 mg	1 PSI	€ 8,010.00	€ 1.77	€ 454.16	€ 7,554.07
Recombinant blood coagulation factor IX products					
Albutrepenonacog alfa 250 I.U.	1 PSI	€ 457.97	€ 1.77	€ 24.73	€ 431.47
Albutrepenonacog alfa 500 I.U.	1 PSI	€ 904.64	€ 1.77	€ 49.46	€ 853.41
Albutrepenonacog alfa 1,000 I.U.	1 PSI	€ 1,789.72	€ 1.77	€ 98.92	€ 1,689.03
Albutrepenonacog alfa 2,000 I.U.	1 PSI	€ 3,521.78	€ 1.77	€ 197.84	€ 3,322.17
Albutrepenonacog alfa 3,500 I.U.	1 PSI	€ 6,119.88	€ 1.77	€ 346.22	€ 5,771.89
Eftrenonacog alfa 250 I.U.	1 PSI	€ 300.14	€ 1.77	€ 15.99	€ 282.38
Eftrenonacog alfa 500 I.U.	1 PSI	€ 588.95	€ 1.77	€ 31.98	€ 555.20
Eftrenonacog alfa 1,000 I.U.	1 PSI	€ 1,166.58	€ 1.77	€ 63.96	€ 1,100.85
Eftrenonacog alfa 2,000 I.U.	1 PSI	€ 2,297.62	€ 1.77	€ 127.93	€ 2,167.92
Eftrenonacog alfa 3,000 I.U.	1 PSI	€ 3,417.60	€ 1.77	€ 191.89	€ 3,223.94
Nonacog alfa 500 I.U.	1 DSS	€ 563.25	€ 1.77	€ 30.56	€ 530.92
Nonacog alfa 2,000 I.U.	1 DSS	€ 2,197.97	€ 1.77	€ 122.23	€ 2,073.97
Nonacog alfa 3,000 I.U.	1 DSS	€ 3,268.12	€ 1.77	€ 183.35	€ 3,083.00
Nonacog beta pegol 500 I.U.	1 PSI	€ 948.97	€ 1.77	€ 51.91	€ 895.29
Nonacog beta pegol 3,000 I.U.	1 PSI	€ 5,511.71	€ 1.77	€ 311.48	€ 5,198.46
Nonacog gamma 250 I.U.	1 PSI	€ 302.43	€ 1.77	€ 16.12	€ 284.54
Nonacog gamma 500 I.U.	1 PSI	€ 593.54	€ 1.77	€ 32.24	€ 559.53
Nonacog gamma 1,000 I.U.	1 PSI	€ 1,175.79	€ 1.77	€ 64.47	€ 1,109.55
Nonacog gamma 2,000 I.U.	1 PSI	€ 2,315.47	€ 1.77	€ 128.94	€ 2,184.76
Nonacog gamma 3000 I.U.	1 PSI	€ 3,444.37	€ 1.77	€ 193.42	€ 3,249.18
Human plasma-derived coagulation factor IX products					
ALPHANINE 500 I.U.	1 DSS	€ 463.30	€ 1.77	€ 25.03	€ 436.50
ALPHANINE 1000 I.U.	1 DSS	€ 915.30	€ 1.77	€ 50.05	€ 863.48
Abbreviations: PSS = powder and solvent for the preparation of an infusion solution; PSI = powder and solvent for solution for injection; DSS = dry substance with solvent					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the

information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active

ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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.

Justification for the findings on designation in the present resolution:

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.

References:
Product information for concizumab (Alhemo); Alhemo; last revised: August 2025

2.6 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. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV. Approval studies include all studies submitted to the regulatory authority in the authorisation dossier for the assessment of the clinical efficacy and safety of the medicinal product in the therapeutic indication to be assessed.

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% (4.5%) of the total number of study participants.

In the dossier, the pharmaceutical company took the data from the NN7415-3813 (explorer1), NN7415-3981, NN7415-3986 (explorer2), NN7415-4159 (explorer3), NN7415-4255 (explorer5), NN7415-4310 (explorer4), NN7415-4311 (explorer7) and NN7415-4307 (explorer8) studies as the basis. In addition, the pharmaceutical company subsequently submitted information on the calculation of study participants in the written statement procedure. However, this information does not clearly point out the number of participants at German study sites who have already taken part in a previous study.

Taking into account the information in the statement including the subsequently submitted information, a recalculation by IQWiG (G25-27) results in a number of 18 out of 403 study participants at German study sites for each therapeutic indication, and thus a percentage of study participants at German study sites of 4.47% in each case.

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.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At their session on 26 March 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 April 2025, the pharmaceutical company submitted a dossier for the benefit assessment of concizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 April 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient concizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 July 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 August 2025. The deadline for submitting statements was 22 August 2025.

The oral hearing was held on 9 September 2025.

By letter dated 9 September 2025, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 26 September 2025.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the Subcommittee on 7 October 2025, and the proposed draft resolution was approved.

At their session on 16 October 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	26 March 2024	Determination of the appropriate comparator therapy
Working group Section 35a	2 September 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	9 September 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	16 September 2025 30 September 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	7 October 2025	Concluding discussion of the draft resolution
Plenum	16 October 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 October 2025

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

Prof. Hecken