Gemeinsamer Bundesausschuss

Justification

of 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 and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Emicizumab (new therapeutic indication:
moderate haemophilia A, without factor VIII inhibitor, with severe bleeding phenotype)

of 17 August 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of 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 trials the pharmaceutical company has 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.

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 decides 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 active ingredient emicizumab (Hemlibra) was listed for the first time on 1 April 2018 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 23 January 2023, emicizumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 17 February 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient emicizumab with the new therapeutic indication of moderate haemophilia A, without factor VIII inhibitors and with severe bleeding phenotype in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA came to a resolution on whether an additional benefit of emicizumab compared to 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. In order to determine the extent of the additional benefit, the G-BA has 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 emicizumab.

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 Emicizumab (invented name) in accordance with the product information

Hemlibra is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency):

- with factor VIII inhibitors
- without factor VIII inhibitors who have
  - severe disease (FVIII < 1%)
  - moderate disease (FVIII ≥ 1% and ≤ 5%) with severe bleeding phenotype.

Hemlibra can be used with all age groups.

Therapeutic indication of the resolution (resolution of 17 August 2023):

Emicizumab (Hemlibra) is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (FVIII ≥ 1% and ≤ 5%) with severe bleeding phenotype in all age groups.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients with moderate haemophilia A (congenital factor VIII deficiency, FVIII ≥ 1% and ≤ 5%) and a severe bleeding phenotype without factor VIII inhibitors who are eligible for routine prophylaxis

Appropriate comparator therapy:

- plasma-derived or recombinant blood coagulation factor VIII preparations used as routine prophylaxis

[1] General Methods, version 6.1 from 24.01.2022. 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:

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.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO:

on 1. Medicinal products with the following active ingredients are currently approved for the treatment of haemophilia A:

- Recombinant factor VIII products contain the genetically engineered human factor VIII glycoprotein. The factor VIII glycoproteins differ, among other things, in the length of their side chains. All preparations are approved for the treatment and prophylaxis of haemophilia A. The pegylated factor VIII preparations rurioctocog alfa pegol and damoctocog alfa pegol are only approved for patients with haemophilia A aged 12 years or older.

  - Octocog alfa contains the natural human factor VIII glycoprotein with the complete amino acid sequence2. Rurioctocog alfa pegol and damoctocog alfa pegol are both pegylated, recombinant blood coagulation factor-VIII octocog alfa.
  - Moroctocog alfa has a truncated side chain compared to the natural factor VIII glycoprotein.
  - Turoctocog alfa has a truncated side chain compared to the natural factor VIII glycoprotein.
  - Simoctocog alfa is composed of the active domains (domains A and C) of human factor VIII, domains A2 and A3 are linked by a linker sequence2.
  - Efmoroctocog alfa has a truncated side chain compared to the natural factor VIII glycoprotein, covalently bound to the Fc domain of human immunoglobulin G1.
  - Lonoctocog alfa is a single-chain polypeptide with a truncated B-domain that allows for a covalent bridge to link the factor VIII heavy and light chains.

[2] Various proprietary medicinal products are available.

- Human plasma factor VIII preparations[3] contain the human-identical factor VIII glycoprotein obtained from cryoprecipitates: They are obtained from large human plasma pools and are approved for the treatment and prevention of haemophilia A.
- A human plasma fraction enriched with factor VIII inhibitor bypassing activity is approved for the treatment and prevention of bleeding in haemophilia A patients with factor VIII inhibitors.
- A recombinant blood coagulation factor VIIa preparation (active ingredient: eptacog alfa) is approved for the treatment of bleeding and prevention of bleeding associated with surgical or invasive procedures in, among others, patients with congenital haemophilia with coagulation factor VIII inhibitors. It is not approved for the permanent treatment of moderate to severe haemophilia A requiring replacement.
- Emicizumab is a bispecific antibody that combines activated factors IX and factor X to replace the function of the missing activated factor VIII. Emicizumab is approved for the routine prophylaxis of patients with haemophilia A and existing factor VIII inhibitors on the one hand and for the routine prophylaxis of bleeding in severe haemophilia A without existing factor VIII inhibitors on the other.
- Valoctocogen roxaparvovec is a gene therapy medicinal product that expresses human coagulation factor VIII. It is a non-replicating, recombinant vector based on the adeno-associated virus serotype AAV5 and contains the cDNA of the gene for human coagulation factor VIII under the control of a liver-specific promoter.

Various approved plasma-derived or recombinant factor VIII preparations are available for the prophylaxis of haemophilia A bleeding with inhibitors, a human plasma fraction enriched with factor VIII inhibitor bypassing activity (FEIBA) - both for routine prophylaxis and treatment on demand, as well as emicizumab. In contrast, NovoSeven is not approved for routine prophylaxis, but only for the "prophylaxis of bleeding associated with surgical or invasive procedures".

on 2. Non-medicinal treatments are not considered for the therapeutic indication.

on 3. For the treatment of haemophilia patients, the guideline Speciality Outpatient Treatment in Hospitals according to Section 116b SGB V (Annex 2: Rare diseases and conditions with correspondingly low case numbers; letter c) haemophilia) must be considered.

In the therapeutic indication of haemophilia A, the following resolutions of the G-BA on the benefit assessment of medicinal products according to Section 35a SGB V are available:

- Turoctocog alfa (resolution of 3 July 2014)
- Simoctocog alfa (resolution of 7 May 2015)
- Efmoroctocog alfa (resolution of 16 June 2016)
- Lonoctocog alfa (resolution of 20 July 2017)
- Emicizumab (resolutions of 20 September 2018 and 5 September 2019)
- Rurioctocog alfa pegol (resolution of 1 November 2018)
- Damoctocog alfa pegol (resolution of 20 June 2019)
- Turoctocog alfa pegol (resolution of 6 February 2020)
- Valoctocogen roxaparvovec (resolution of 16 March 2023)

[3] Various proprietary medicinal products are available.

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 factor VIII replacement.

In the overall assessment of the aggregated evidence, the recombinant and human plasma-derived factor VIII preparations are to be regarded as equivalent and are therefore equally eligible as the appropriate comparator therapy. No evidence-based data have been found on therapeutic efficacy, side-effect profile (e.g. development of inhibitory haemophilia) or safety risk (e.g. risk of infection) that would lead to recombinant or human plasma-derived factor VIII preparations being regularly preferred in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). This also applies to recombinant factor VIII preparations with prolonged half-life, which are equally covered by the appropriate comparator therapy.

A human plasma fraction enriched with factor VIII inhibitor bypassing activity is only approved for patients with existing factor VIII inhibitors and is therefore not considered as an appropriate comparator therapy for the present therapeutic indication.

Against this background, plasma-derived or recombinant blood coagulation factor VIII preparations used as routine prophylaxis are identified as the appropriate comparator therapy. Adults, adolescents and children are included in the therapeutic indication. The marketing authorisation of the coagulation factor VIII preparations must be taken into consideration.

Treatment on demand alone is not an adequate appropriate comparator therapy in the present indication. An additional treatment on demand must be possible in all study arms, in general.

The active ingredient valoctocogen roxaparvovec is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 24 August 2022). Based on the generally accepted state of medical knowledge, valoctocogen roxaparvovec is not determined to be an appropriate comparator therapy for the present resolution.

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 emicizumab is assessed as follows:

For patients with moderate haemophilia A (congenital factor VIII deficiency, FVIII ≥ 1% and ≤ 5%) and a severe bleeding phenotype without factor VIII inhibitors who are eligible for routine

prophylaxis, the additional benefit of emicizumab as routine prophylaxis compared with the appropriate comparator therapy is not proven.

Justification:

In its dossier for the assessment of the additional benefit of emicizumab, the pharmaceutical company does not present any direct comparator studies versus the appropriate comparator therapy.

As a further investigation, the pharmaceutical company presents evaluations for the moderate haemophilia A sub-population of the single-arm HAVEN 6 study (BO41423).

The HAVEN 6 study is a 1-arm study in which patients of all age groups with mild (residual factor VIII activity > 5% and < 40%) or moderate (residual factor VIII activity ≥ 1% and ≤ 5%) congenital haemophilia A without factor VIII inhibitors were enrolled, for whom prophylaxis is indicated in the opinion of the principal investigator. More than half of the patients were already receiving routine prophylaxis with factor VIII preparations prior to enrolment in the study. The planned treatment duration was at least 52 weeks. The primary endpoint of the study was treated bleeding, operationalised as annualised bleeding rate.

The single-arm study is unsuitable for the assessment of an additional benefit due to the lack of comparison with the appropriate comparator therapy.

In addition, the pharmaceutical company states that no data on routine prophylaxis with coagulation factor VIII preparations are available in the therapeutic indication to be assessed and thus, no direct or indirect comparison is possible, whereby information on the appropriate comparator therapy was not procured.

Overall, based on the HAVEN 6 study, no additional benefit over the appropriate comparator therapy can be derived for patients with moderate haemophilia A and a severe bleeding phenotype without factor VIII inhibitors who are eligible for routine prophylaxis.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the medicinal product Hemlibra with the active ingredient emicizumab in a new therapeutic indication: "Routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (FVIII ≥ 1% and ≤ 5%) with severe bleeding phenotype in all age groups".

The G-BA determined recombinant or human plasma-derived blood coagulation factor VIII preparations in the prophylaxis regimen to be the appropriate comparator therapy.

The pharmaceutical company does not submit a direct comparator study for emicizumab versus the appropriate comparator therapy.

As a further investigation, the pharmaceutical company presents evaluations for the moderate haemophilia A sub-population of the single-arm HAVEN 6 study (BO41423). The single-arm study is unsuitable for the assessment of an additional benefit due to the lack of comparison with the appropriate comparator therapy.

In the overall assessment, an additional benefit of emicizumab over the appropriate comparator therapy in the routine prophylaxis of bleeding episodes in patients with moderate haemophilia A without factor VIII inhibitors with a severe bleeding phenotype 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 resolution is based on the information and the basic approach from the dossier of the pharmaceutical company. This information is based on figures from the German Haemophilia Registry (DHR) and is subject to uncertainties.

These uncertainties arise from the possible enrolment of patients with moderate haemophilia A without a severe bleeding phenotype who have received routine prophylaxis but are not included in the present therapeutic indication. Furthermore, it is unclear to what extent patients were counted as patients without prophylaxis treatment, either because of an incomplete data set or because of the pharmaceutical company's unjustified assumption that no patient had received prophylaxis among the collected reports. Overall, the range reported by the pharmaceutical company is underestimated.

In deviation from the pharmaceutical company's procedure, both the lower limit of the percentage value (14.2%) and the upper limit (43.3%) are to be taken into account mathematically for patients in the age group ≥ 18 years. IQWiG's own calculation, adjusted accordingly, results in a number of approximately 220 to 240 patients for the SHI target population, which is, however, still subject to the uncertainties already described.

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 Hemlibra (active ingredient: emicizumab) at the following publicly accessible link (last access: 10 July 2023):

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

Treatment with emicizumab should only be initiated and monitored by specialist doctors experienced in haemophilia treatment.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material for medical professionals, patients/ carers (patient pass and training material) as well as laboratory personnel. The training material contains specific information on the management of thrombotic microangiopathy and thromboembolism, the use of bypassing preparations and the influence of emicizumab on coagulation tests (risk of misinterpretation).

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: 1 August 2023).

The costs of treatment on demand for haemophilia A patients vary from person to person and are not shown. Only the costs of prevention therapy are presented. For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs. 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				
Emicizumab	Continuously, 1 x every 7 days, every 14 days or every 28 days	52.1; 26.1 or 13.0	1	52.1; 26.1 or 13.0
Appropriate comparator therapy				
plasma-derived or recombinant blood coagulation factor VIII preparations used as routine prophylaxis				
recombinant blood coagulation factor VIII preparations				
Damoctocog alfa pegol	Continuously, 1 x every 5 or 7 days or 2 x weekly	73.0; 52.1 or 104.3	1	73.0; 52.1 or 104.3
Efmoroctocog alfa	Continuously, 1 x every 3 to 5 days	73.0 - 121.7	1	73.0 - 121.7
Lonoctocog alfa	Continuously, 2 to 3 x weekly	104.3 - 156.4	1	104.3 - 156.4
Moroctocog alfa	Continuously, every 2 to 3 days	121.7 - 182.5	1	121.7 - 182.5
Octocog alfa[4]	Continuously, 2 to 3 x weekly or every 2 days	104.3 - 182.5	1	104.3 - 156.4
Rurioctocog alfa pegol	Continuously, 2 x weekly	104.3	1	104.3
Simoctocog alfa[5]	Continuously, every 2 to 3 days	121.7 - 182.5	1	121.7 - 182.5
Turoctocog alfa	Continuously, every 2 to 3 days or 2 to 3 x weekly	104.3 - 156.4	1	104.3 - 156.4
Turoctocog alfa pegol	Continuously, every 4 days	91.3	1	91.3

[4] Cost representation based on the information in the Kovaltry product information. Other proprietary medicinal products are available.
[5] Cost representation based on the information in the Nuwiq product information. 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
Plasma-derived blood coagulation factor VIII preparations				
Human plasma-derived preparations[6]	Continuously, every 2 - 3 days	121.7 - 182.5	1	121.7 - 182.5

Consumption:

The theoretical annual consumption of emicizumab and the active ingredients (factor VIII preparations) of the appropriate comparator therapy required for the prevention of bleeding in patients with severe haemophilia A is presented. Turoctocog alfa pegol, damoctocog alfa pegol and rurioctocog alfa pegol are only approved for use in patients aged 12 years and above.

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 (children aged below 6 years, children aged 6 to below 12 years, 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"[7] were applied. For body weight, the average weight of an adult male aged 18 years and over is therefore assumed to be 85.0 kg. For the underlying weight in the respective male age groups, the ranges were determined from 12 to under 18 years (47.6 kg - 73.2 kg), from 6 to under 12 years (24.0 kg - 42.7 kg) and from 1 to under 6 years (12.0 kg - 21.0 kg).

The following dosage ranges are used for the cost calculation:

For the calculation of the upper cost range, the dosage with the most frequent application and the highest body weight of the respective age group is used. For the calculation of the lower cost limit, the dosage with the largest interval and the lowest body weight of the respective age range is used.

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

Since factor VIII preparations can be stored only for a maximum of 24 hours after reconstitution, discarding must be taken into account, consequently the consumption per injection is presented.

[6] Cost representation based on the information in the Fanhdi product information. Other proprietary medicinal products are available.

[7] Federal Statistical Office. Microcensus 2017: questions on health - body measurements of the population 2017 [online]. 02.08.2018 [accessed on: 09.12.2019]. URL: www.gbe-bund.de

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 VIII I.U./ injection. For example, for an adult requiring 1,686 I.U./ injection, this was composed of three vials each of 1,000 I.U., 500 I.U. and 250 I.U. of factor VIII.

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					
Emicizumab	1.5 – 6 mg/kg	**Adults**			
		127.5 mg - 510 mg	1 x 105 mg + 1 x 30 mg - 3 x 150 mg + 1 x 60 mg	52.1 - 13.0	52.1 x 105 mg + 52.1 x 30 mg - 39 x 150 mg + 13 x 60 mg
		12 to < 18 years			
		439.2 mg	3 x 150 mg	13.0	39 x 150 mg
		71.4 mg	1 x 60 mg + 1 x 30 mg	52.1	52.1 x 60 mg + 52.1 x 30 mg
		6 to < 12 years			
		256.2 mg	1 x 150 mg + 2 x 60 mg	13.0	13.0 x 150 mg + 26.0 x 60 mg
		36 mg	1 x 60 mg	52.1	52.1 x 60 mg
		< 6 years			
		126 mg	1 x 150 mg	13.0	13.0 x 150 mg
		18 mg	1 x 30 mg	52.1	52.1 x 30 mg
Appropriate comparator therapy					
recombinant blood coagulation factor VIII preparations					
Damoctocog alfa pegol	60 I.U./kg	**Adults**			
		5,100 I.U.	1 x 3000 I.U. + 1 x 2000 I.U. + 1 x 250 I.U.	52.1 - 73.0	52.1 x 3000 I.U. + 52.1 x 2000 I.U. + 52.1 x 250 I.U. - 73 x 3000 I.U. + 73 x 2000 I.U. + 73 x 250 I.U.
		12 to < 18 years			
		4392 I.U.	1 x 3000 I.U. + 1 x 1000 I.U. + 1 x 500 I.U.	73.0	73 x 3000 I.U. + 73 x 1000 I.U. + 73 x 500 I.U.
		2856 I.U.	1 x 3000 I.U.	52.1	52.1 x 3000 I.U.
	50 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
Efmoroctocog alfa		4250 I.U.	1 x 4000 I.U. + 1 x 250 I.U.	73.0 - 121.7	73 x 4000 I.U. + 73 x 250 I.U. - 121.7 x 4000 I.U. + 121.7 x 250 I.U.
		12 to < 18 years			
		3660 I.U.	1 x 3000 I.U. + 1 x 750 I.U.	121.7	121.7 x 3000 I.U. + 121.7 x 750 I.U.
		2380 I.U.	1 x 2000 I.U. + 1 x 500 I.U.	73.0	73 x 2000 I.U. 73 x 500 I.U.
		6 to < 12 years			
		2135 I.U.	1 x 2000 I.U. + 1 x 250 I.U.	121.7	121.7 x 2000 I.U. + 121.7 x 250 I.U.
		1200 I.U.	1 x 1000 I.U. + 1 x 250 I.U.	73.0	73 x 1000 I.U. + 73 x 250 I.U.
		< 6 years			
		1050 I.U.	1 x 1000 I.U. + 1 x 250 I.U.	121.7	121.7 x 1000 I.U. + 121.7 x 250 I.U.
		600 I.U.	1 x 750 I.U.	73.0	73 x 750 I.U.
Lonoctocog alfa	20 - 50 I.U. /kg	**Adults**			
		4250 I.U.	2 x 2000 I.U. + 1 x 250 I.U.	156.4	312.8 x 2000 I.U. + 156.4 x 250 I.U.
		1700 I.U.	1 x 1500 I.U. + 1 x 250 I.U.	104.3	104.3 x 1500 I.U. + 104.3 x 250 I.U.
		12 to < 18 years			
		3660 I.U.	1 x 3000 I.U. + 1 x 500 I.U. + 1 x 250 I.U.	156.4	156.4 x 3000 I.U. + 156.4 x 500 I.U. + 156.4 x 250 I.U.
		952 I.U.	1 x 1000 I.U.	104.3	104.3 x 1000 I.U.
	30 - 50 I.U. /kg	**6 to < 12 years**			
		2135 I.U.	1 x 2000 I.U. + 1 x 250 I.U.	156.4	156.4 x 2000 I.U. + 156.4 x 250 I.U.
		720 I.U.	1 x 500 I.U. + 1 x 250 I.U.	104.3	104.3 x 500 I.U. + 104.3 x 250
		< 6 years			
		1050 I.U.	1 x 1000 I.U. + 1 x 250 I.U.	156.4	156.4 x 1000 I.U. + 156.4 x 250 I.U.
		360 I.U.	1 x 500 I.U.	104.3	104.3 x 500 I.U.
	20 - 40	**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
Moroctocog alfa	I.U. /kg	3400 I.U.	1 x 3000 I.U. + 1 x 500 I.U.	182.5	182.5 x 3000 I.U. + 182.5 x 500 I.U.
		1700 I.U.	1 x 1000 I.U. + 1 x 500 I.U. + 1 x 250 I.U.	121.7	121.7 x 1000 I.U. + 121.7 x 500 I.U. + 121.7 x 250 I.U.
		12 to < 18 years			
		2928 I.U.	1 x 3000 I.U.	182.5	182.5 x 3000 I.U.
		952 I.U.	1 x 1000 I.U.	121.7	121.7 x 1000 I.U.
		6 to < 12 years			
		1708 I.U.	1 x 1000 I.U. + 1 x 500 I.U. + 1 x 250 I.U.	182.5	182.5 x 1000 I.U. + 182.5 x 500 I.U. + 182.5 x 250 I.U.
		480	1 x 500 I.U.	121.7	121.7 x 500 I.U.
		< 6 years			
		840 I.U.	1 x 1000 I.U.	182.5	182.5 x 1000 I.U.
		240 I.U.	1 x 250 I.U.	121.7	121.7 x 250 I.U.
Octocog alfa	20 - 40 I.U. /kg	**Adults**			
		3400 I.U.	1 x 3000 I.U. + 1 x 500 I.U.	156.4	156.4 x 3000 I.U. + 156.4 x 500 I.U.
		1700 I.U.	1 x 1000 I.U. + 1 x 500 I.U. + 1 x 250 I.U.	104.3	104.3 x 1,000 I.U.+ 104.3 x 500 I.U.+ 104.3 x 250 I.U.
		12 to < 18 years			
		2928 I.U.	1 x 3000 I.U.	156.4	156.4 x 3000 I.U.
		952 I.U.	1 x 1000 I.U.	104.3	104.3 x 1000 I.U.
	0 - 50 I.U. /kg	**6 to < 12 years**			
		2135 I.U.	1 x 2000 I.U. + 1 x 250 I.U.	182.5	182.5 x 2000 I.U. + 182.5 x 250 I.U.
		480	1 x 500 I.U.	104.3	104.3 x 500 I.U.
		< 6 years			
		1050 I.U.	1 x 1000 I.U. + 1 x 250 I.U.	182.5	182.5 x 1000 I.U. + 182.5 x 250 I.U.
		240 I.U.	1 x 250 I.U.	104.3	104.3 x 250 I.U.
Rurioctocog alfa pegol	40 – 50 I.U./kg	**Adults**			
		3400 I.U.	1 x 3000 I.U. + 1 x 500 I.U.	104.3	104.3 x 3000 I.U. + 104.3 x 500 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
		4250 I.U.	1 x 3000 I.U. + 1 x 1000 I.U. + 1 x 250 I.U.	104.3	104.3 x 3000 I.U.+ 104.3 x 1000 I.U.+ 104.3 x 250 I.U.
		12 to < 18 years			
		3660 I.U.	1 x 3000 I.U. + 1 x 500 I.U. + 1 x 250 I.U.	104.3	104.3 x 3000 I.U. + 104.3 x 500 I.U. + 104.3 x 250 I.U.
		1904 I.U.	1 x 2000 I.U.	104.3	104.3 x 2000 I.U.
Simoctocog alfa	20 - 40 I.U. /kg	**Adults**			
		3400 I.U.	1 x 3000 I.U. + 1 x 500 I.U.	182.5	182.5 x 3000 I.U. + 182.5 x 500 I.U.
		1700 I.U.	1 x 1000 I.U. + 1 x 500 I.U. + 1 x 250 I.U.	121.7	121.7 x 1000 I.U. + 121.7 x 500 I.U. + 121.7 x 250 I.U.
		12 to < 18 years			
		2928 I.U.	1 x 3000 I.U.	182.5	182.5 x 3000 I.U.
		952 I.U.	1 x 1000 I.U.	121.7	121.7 x 1000 I.U.
		6 to < 12 years			
		1708 I.U.	1 x 1000 I.U. + 1 x 500 I.U. + 1 x 250 I.U.	182.5	182.5 x 1000 I.U. + 182.5 x 500 I.U. + 182.5 x 250 I.U.
		480 I.U.	1 x 500 I.U.	121.7	121.7 x 500 I.U.
		< 6 years			
		840 I.U.	1 x 1000 I.U.	182.5	182.5 x 1000 I.U.
		240 I.U.	1 x 250 I.U.	121.7	121.7 x 250 I.U.
Turoctocog alfa[8]	20 I.U. /kg – 50 I.U. /kg	**Adults**			
		4250 I.U.	1 x 3000 I.U. + 1 x 1000 I.U. + 1 x 250 I.U.	156.4	156.4 x 3000 I.U. + 157 x 1000 I.U. + 156.4 x 250 I.U.
		1700 I.U.	1 x 1500 I.U. + 1 x 250 I.U.	156.4	156.4 x 1500 I.U. + 156.4 x 250 I.U.
		12 to < 18 years			
		3660 I.U.	1 x 3000 I.U. + 1 x 500 I.U. + 1 x 250 I.U.	156.4	156.4 x 3000 I.U. + 156.4 x 500 I.U. + 156.4 x 250 I.U.

[8] The product information for turoctocog alfa provides for different therapy regimens. In determining consumption, the dosing schemes with the widest range of consumption (from 12 years: 20 - 50 I.U. per kg body weight three times a week; under 12 years 25 - 60 I.U. per kg body weight three times a week) were used. Consumption using the other dosing schemes is within the calculated consumption range.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
		952 I.U.	1 x 1000 I.U.	156.4	156.4 x 1000 I.U.
	25 I.U. /kg – 60 I.U. /kg	**6 to < 12 years**			
		2562 I.U.	1 x 2000 I.U. + 1 x 500 I.U. + 1 x 250 I.U.	156.4	156.4 x 2000 I.U. + 156.4 x 500 I.U. + 156.4 x 250 I.U.
		600 I.U.	1 x 500 I.U. + 1 x 250 I.U.	156.4	156.4 x 500 I.U. + 156.4 x 250 I.U.
		< 6 years			
		1260 I.U.	1 x 1500 I.U.	156.4	156.4 x 1500 I.U.
		300 I.U.	1 x 500 I.U.	156.4	156.4 x 500 I.U.
Turoctocog alfa pegol	50 I.U. /kg	**Adults**			
		4250 I.U.	1 x 3000 I.U. + 1 x 1500 I.U.	91.3	91.3 x 3000 I.U. + 91.3 x 1500 I.U.
		12 to < 18 years			
		3660 I.U.	1 x 3000 I.U. + 1 x 1000 I.U.	91.3	91.3 x 3000 I.U. + 91.3 x 1000 I.U.
		2380 I.U.	1 x 2000 I.U. + 1 x 500 I.U.	91.3	91.3 x 2000 I.U. + 91.3 x 500 I.U.
Plasma-derived blood coagulation factor VIII preparations					
Human plasma-derived preparations	20 I.U. /kg – 40 I.U. /kg	**Adults**			
		3400 I.U.	2 x 1500 I.U. + 1 x 500 I.U.	182.5	365 x 1500 I.U. + 182.5 x 500 I.U.
		1700 I.U.	1 x 1500 I.U. + 1 x 250 I.U.	121.7	121.7 x 1500 I.U. + 121.7 x 250 I.U.
		12 to < 18 years			
		2928 I.U.	2 x 1500 I.U.	182.5	365 x 1500 I.U.
		952 I.U.	1 x 1000 I.U.	121.7	121.7 x 1000 I.U.
		6 to < 12 years			
		1708 I.U.	1 x 1500 I.U. + 1 x 250 I.U.	182.5	182.5 x 1500 I.U. + 182.5 x 250 I.U.
		480 I.U.	1 x 500 I.U.	121.7	121.7 x 500 I.U.
		< 6 years			
		840 I.U.	1 x 1000 I.U.	182.5	182.5 x 1000 I.U.
		240 I.U.	1 x 250 I.U.	121.7	121.7 x 250 I.U.

Costs:

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					
Emicizumab 30 mg/ml	1 SFI	€ 1,972.01	€ 2.00	€ 187.43	€ 1,782.58
Emicizumab 150 mg/ml 60 mg/ 0.4 ml	1 SFI	€ 3,886.40	€ 2.00	€ 374.85	€ 3,509.55
Emicizumab 150 mg/ml 105 mg/ 0.7 ml	1 SFI	€ 6,757.97	€ 2.00	€ 655.99	€ 6,099.98
Emicizumab 150 mg/ml 150 mg/ 1 ml	1 SFI	€ 9,629.58	€ 2.00	€ 937.13	€ 8,690.45
Appropriate comparator therapy					
recombinant blood coagulation factor VIII preparations					
Damoctocog alfa pegol 3000 I.U.	1 PSI	€ 2,304.09	€ 2.00	€ 219.94	€ 2,082.15
Damoctocog alfa pegol 1000 I.U.	1 PSI	€ 1,555.27	€ 2.00	€ 146.63	€ 1,406.64
Damoctocog alfa pegol 500 I.U.	1 PSI	€ 397.48	€ 2.00	€ 36.66	€ 358.82
Damoctocog alfa pegol 250 I.U.	1 PSI	€ 204.38	€ 2.00	€ 18.33	€ 184.05
Efmoroctocog alfa 4000 I.U.	1 PSI	€ 2,509.02	€ 2.00	€ 100.00	€ 2,407.02
Efmoroctocog alfa 3000 I.U.	1 PSI	€ 1,896.17	€ 2.00	€ 75.00	€ 1,819.17
Efmoroctocog alfa 2000 I.U.	1 PSI	€ 1,275.60	€ 2.00	€ 50.00	€ 1,223.60
Efmoroctocog alfa 1000 I.U.	1 PSI	€ 643.43	€ 2.00	€ 25.00	€ 616.43
Efmoroctocog alfa 750 I.U.	1 PSI	€ 485.40	€ 2.00	€ 18.75	€ 464.65
Efmoroctocog alfa 500 I.U.	1 PSI	€ 327.37	€ 2.00	€ 12.50	€ 312.87
Efmoroctocog alfa 250 I.U.	1 PSI	€ 169.33	€ 2.00	€ 6.25	€ 161.08
Lonoctocog alfa 1500 I.U.	1 PSI	€ 1,179.99	€ 2.00	€ 110.93	€ 1,067.06
Lonoctocog alfa 500 I.U.	1 PSI	€ 400.86	€ 2.00	€ 36.98	€ 361.88
Lonoctocog alfa 250 I.U.	1 PSI	€ 206.06	€ 2.00	€ 18.49	€ 185.57
Moroctocog alfa 1000 I.U.	1 PSI	€ 1,013.19	€ 2.00	€ 95.10	€ 916.09
Moroctocog alfa 500 I.U.	1 PSI	€ 512.24	€ 2.00	€ 47.55	€ 462.69
Moroctocog alfa 250 I.U.	1 PSI	€ 261.75	€ 2.00	€ 23.77	€ 235.98
Octocog alfa 3000 I.U.	1 PSI	€ 2,931.72	€ 2.00	€ 281.38	€ 2,648.34
Octocog alfa 2000 I.U.	1 PSI	€ 1,973.69	€ 2.00	€ 187.59	€ 1,784.10
Octocog alfa 1000 I.U.	1 PSI	€ 999.49	€ 2.00	€ 93.79	€ 903.70
Octocog alfa 500 I.U.	1 PSI	€ 505.38	€ 2.00	€ 46.90	€ 456.48
Octocog alfa 250 I.U.	1 PSI	€ 258.35	€ 2.00	€ 23.45	€ 232.90
Rurioctocog alfa pegol 3000 I.U.	1 PSI	€ 2,177.72	€ 2.00	€ 207.57	€ 1,968.15
Rurioctocog alfa pegol 2000 I.U.	1 PSI	€ 1,469.20	€ 2.00	€ 138.38	€ 1,328.82

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
Rurioctocog alfa pegol 500 I.U.	1 PSI	€ 375.77	€ 2.00	€ 34.59	€ 339.18
Simoctocog alfa 1000 I.U.	1 PSI	€ 726.60	€ 2.00	€ 67.89	€ 656.71
Simoctocog alfa 500 I.U.	1 PSI	€ 368.95	€ 2.00	€ 33.95	€ 333.00
Simoctocog alfa 250 I.U.	1 PSI	€ 190.13	€ 2.00	€ 16.97	€ 171.16
Turoctocog alfa 1000 I.U.	1 PSI	€ 669.52	€ 2.00	€ 62.48	€ 605.04
Turoctocog alfa 500 I.U.	1 PSI	€ 340.40	€ 2.00	€ 31.24	€ 307.16
Turoctocog alfa 250 I.U.	1 PSI	€ 175.85	€ 2.00	€ 15.62	€ 158.23
Turoctocog alfa pegol 3000 I.U.	1 PSI	€ 2,206.43	€ 2.00	€ 210.38	€ 1,994.05
Turoctocog alfa pegol 1500 I.U.	1 PSI	€ 1,119.53	€ 2.00	€ 105.19	€ 1,012.34
Turoctocog alfa pegol 2000 I.U.	1 PSI	€ 1,488.95	€ 2.00	€ 140.25	€ 1,346.70
Turoctocog alfa pegol 1000 I.U.	1 PSI	€ 750.12	€ 2.00	€ 70.13	€ 677.99
Turoctocog alfa pegol 500 I.U.	1 PSI	€ 380.69	€ 2.00	€ 35.06	€ 343.63
Human plasma-derived preparations					
Von Willebrand factor / blood coagulation factor VIII 1500 I.U.	1 DSS	€ 926.19	€ 2.00	€ 86.82	€ 837.25
Von Willebrand factor / blood coagulation factor VIII 1000 I.U.	1 DSS	€ 621.10	€ 2.00	€ 57.88	€ 561.22
Von Willebrand factor / blood coagulation factor VIII 500 I.U.	1 DSS	€ 316.19	€ 2.00	€ 28.94	€ 285.25
Von Willebrand factor / blood coagulation factor VIII 250 I.U.	1 DSS	€ 163.73	€ 2.00	€ 14.47	€ 147.26
Abbreviations: 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 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 Emicizumab

According to Section 35a, paragraph 3, sentence 4, the G-BA designates 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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designated medicinal products are each an active ingredient that can be used in combination therapy with the assessed medicinal product on the basis of an open-label combination. This results from the fact that, on the one hand, the product information for the assessed medicinal product does not contain any information on combination therapies and, on the other, this product information does not contain any information that regularly contradicts a combination therapy with the assessed medicinal product.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the specifications in the product information for the designated medicinal products, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive, which serves search purposes.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 its session on 12 December 2017, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 17 February 2023, the pharmaceutical company submitted a dossier for the benefit assessment of emicizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 20 February 2023 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 emicizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 May 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 June 2023. The deadline for submitting written statements was 22 June 2023.

The oral hearing was held on 10 July 2023.

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 8 August 2023, and the proposed resolution was approved.

At its session on 17 August 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	20 December 2017	Determination of the appropriate comparator therapy
Working group Section 35a	4 July 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 July 2023	Conduct of the oral hearing,
Working group Section 35a	18 July 2023 1 August 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	8 August 2023	Concluding discussion of the draft resolution
Plenum	17 August 2023	Resolution on the amendment of Annex XII and the amendment of Annex XIIa Pharmaceuticals Directive

Berlin, 17 August 2023

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

Prof. Hecken