Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Emicizumab (new therapeutic indication: Haemophilia A without inhibitors)

of 5 September 2019

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 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 shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient emicizumab 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 13 March 2019, emicizumab received the marketing authorisation for a new therapeutic indication as routine prophylaxis for severe haemophilia A without inhibitors classified as a major variation of type 2 according to Annex 2 number 2a to Regulation (EC) number 1234/2008 of the Commission from 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 December 2008, p. 7).

On 15 March 2019, 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 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 commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 17 June 2019 on the website of the G-BA (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 emicizumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company and the dossier assessment prepared by the IQWiG (IQWiG No. A19-26) as well as 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 was not used in the benefit assessment of emicizumab.

In the light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at 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 (Hemlibra®) in accordance with product information

Hemlibra® is indicated for routine prophylaxis of bleeding episodes in patients with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors. Hemlibra® can be used in all age groups.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors who are eligible for routine prophylaxis

- plasmatic or recombinant blood coagulation factor VIII products used as routine prophylaxis

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 according to 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 Federal Joint Committee 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. For the therapy of haemophilia A, medicinal products with the following active ingredients are currently approved:

- Recombinant factor VIII products contain the genetically engineered human factor VIII glycoprotein. Factor VIII glycoproteins differ in the length of their side chains, among other things.
  - Octocog alfa contains the natural human factor VIII glycoprotein with the complete amino acid sequence[1]. Rurioctocog alfa pegol, damoctocog alfa pegol, and turoctocog alfa pegol are each a pegylated, recombinant blood coagulation factor VIII octocog alfa. Moroctocog alfa has a shorter side chain than the natural factor VIII glycoprotein.
  - Turoctocog alfa has a shorter side chain than 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 sequence.
  - Efmoroctocog alfa has a shorter side chain than the natural factor VIII glycoprotein; it is covalently linked to the Fc domain of human immunoglobulin G1.
  - Lonoctocog alfa is a single-chain polypeptide with a shortened B domain, which allows a covalent connection of the heavy and light factor VIII chain.

  All products are approved for the treatment and prophylaxis of haemophilia A. The pegylated factor VIII products rurioctocog alfa pegol, damoctocog alfa pegol and turoctocog alfa pegol are authorised only for patients with haemophilia A from the age of 12 years.

- Human plasma factor VIII products[1] contain the human-identical factor VIII glycoprotein obtained from cryoprecipitates: They are derived from large human plasma pools and are approved for the treatment and prophylaxis of haemophilia A.
- A human plasma fraction enriched with factor VIII inhibitor bypassing activity is approved for the treatment and prophylaxis of bleeding in haemophilia A patients with factor VIII inhibitor.
- A recombinant blood coagulation factor VIIa product (active ingredient: eptacog alfa) is approved for the treatment of bleeding and the prophylaxis of bleeding associated with surgical or invasive procedures, including in patients with congenital haemophilia with inhibitors of blood coagulation factor VIII. It is not approved for the permanent treatment of moderate to severe haemophilia A requiring substitution.
- Emicizumab is a bi-specific antibody that combines the activated factors IX and X to replace the function of the missing activated factor VIII. Emicizumab is approved for the routine prophylaxis of patients with haemophilia A and factor VIII

[1] Different proprietary medicinal products available.

inhibitors as well as for the routine prophylaxis of bleeding in severe haemophilia A without factor VIII inhibitors.

On 2. Non-medicinal treatment is not considered an appropriate comparator therapy.

On 3. For the treatment of haemophilia patients, the guideline “Outpatient treatment in hospital according in accordance with Section 116b SGB V (Annex 2, No. 2: Diagnostics and care of patients with coagulation disorders (haemophilia)) must be considered.

In the therapeutic indication “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 (resolution of 20 September 2018)
- Rurioctocog alfa pegol (resolution of 1 November 2018)
- Damoctocog alfa pegol (resolution of 20 June 2019)

On 4. The general state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication. In the overall view of the evidence, the recombinant factor VIII products and those derived from human plasma are to be regarded as equivalent and are therefore equally suitable as appropriate comparator therapy. No evidence has been found that recombinant or human plasma-derived factor VIII products are generally preferable in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) with regard to therapeutic efficacy, the side effect profile (e.g. development of inhibitory haemophilia), or safety risk (e.g. infection risk). This also applies to recombinant factor VIII products with extended 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 in patients with existing factor VIII inhibitors and is therefore not an appropriate comparator therapy for the present therapeutic indication.

At the time of the resolution on routine prophylaxis and treatment of bleeding for patients with haemophilia A, turoctocog alfa pegol was only available on the German market for a short time. Therefore, the therapeutic significance cannot yet be assessed, and the active ingredient cannot be considered as an appropriate comparator therapy.

It is assumed that the patient population in this indication is factor VIII haemophilia patients requiring substitution.

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

2.1.3 Extent and probability of the additional benefit

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

For patients with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors, the additional benefit for emicizumab as routine prophylaxis compared with the appropriate comparator therapy is not proven.

Justification:

In the dossier for the assessment of the additional benefit of emicizumab, the pharmaceutical company does not present any direct comparative studies compared to the appropriate comparator therapy. For patients with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors, an (intra-individual) before and after comparison was presented by the pharmaceutical company. Furthermore, the possibility of an adjusted, indirect comparison based on individual study arms from different studies was also examined in the dossier by the pharmaceutical company. In the overall view, the pharmaceutical company concluded that an indirect comparison was not possible because the patient populations were not comparable.

Adjusted, indirect comparison

From the perspective of the G-BA, the comparability of the relevant study populations is sufficient. The indirect comparison is thus used for the benefit assessment. The adjusted, indirect comparison performed by IQWiG for the comparison of routine prophylaxis with emicizumab with the appropriate comparator therapy of routine prophylaxis with factor VIII products was performed using a bridge comparator consisting of a treatment on demand with bypassing agents. This indirect comparison is based on the HAVEN 3 study for emicizumab and the SPINART study for routine prophylaxis with factor VIII products. These are described briefly below.

The HAVEN 3 study is an open, multi-centre, parallel group study with three randomised arms and one non-randomised arm. Adults and adolescents (≥ 12 years) with severe haemophilia A (factor VIII residual coagulation activity < 1%) were included in the study. Patients in the randomised part of the study had previously been treated with factor VIII products and were randomised 2:2:1 for routine prophylaxis with 1.5 mg emicizumab once per week (Arm A), routine prophylaxis with 3 mg emicizumab every 2 weeks (Arm B), or treatment on demand with factor VIII products (Arm C). The randomised part of the study was completed after 24 weeks. The primary endpoint of the study was the number of treated bleedings.

The SPINART study is a randomised, open, multi-centre, parallel group study comparing routine prophylaxis with recombinant factor VIII products (octocog alfa) with treatment on demand with recombinant factor VIII products (octocog alfa). Predominantly male patients aged 12 to 50 with severe haemophilia A (factor VIII residual coagulation activity < 1%) were included. Treatment in the routine prophylaxis arm included application of factor VIII products at a dose of 25 international units (IU) per kg body weight three times per week; dose adjustments were possible. The treatment on demand took place according to the recommendation of the investigator and in accordance with the product information. The primary endpoint of the study was the number of bleeding episodes after one year of treatment.

The two studies included in the indirect comparison were sufficiently similar to baseline with regard to patient characteristics as well as the annualised bleeding rates (ABR) of the bridge comparator. Regardless of this, the study duration differs between the two studies (HAVEN 3 study: 6 months; SPINART: 1 year [interim analysis] or 3 years [end of study]).

This affects the occurrence of AEs (AE rates of the potentially relevant studies in the bridge comparator arm: HAVEN 3 study: 33% of patients affected by AEs vs SPINART study: 69% of patients affects after 1 year and 88% after 3 years. The indirect comparison thus only permits statements for the bleeding rates evaluated on an annualised basis. Because the different study durations, no usable evaluation of adverse events is possible.

The results of the adjusted indirect comparison to bleeding events was used to estimate the differences in annualised bleeding rates. These show no statistically significant differences between routine prophylaxis with emicizumab and prophylaxis with a recombinant factor VIII product neither for all treated bleedings nor for treated joint bleedings. However, these data on bleeding rates only allow statements to be made on morbidity.

In the overall view, the usable data on bleeding events alone do not allow sufficient consideration of an additional benefit or minor benefit compared with the appropriate comparative therapy because no methodologically suitable evaluations for side effects are available within the framework of the adjusted indirect comparison. In addition, there is no usable data available for the quality of life category, for other morbidity endpoints, or for mortality.

Intraindividual comparison

The “before and after comparison” presented to answer the question of the benefit assessment is a comparison of routine prophylaxis with emicizumab and routine prophylaxis with factor VIII products for patients ≥ 18 years. This intra-individual comparison is based on data from patients who participated in both the prospective observational study BH29768 (“before”; non-interventional study (NIS)) and the pivotal study (“after”) HAVEN 3 (non-randomised arm D). Because of the strong methodological limitations, this intra-individual comparison cannot be considered for the question of benefit assessment. The study settings (uncontrolled treatment in NIS vs controlled study conditions in HAVEN 3) cannot be assessed as comparable with sufficient certainty. The supplementary evaluations presented on 22 “formally faithful to therapy” patients from the population of 44 patients do not increase the interpretability of the comparisons presented because an adequate therapy of patients with haemophilia A within the framework of the NIS was questionable. Among other things, the criteria chosen by the pharmaceutical company to define “formal adherence to therapy” for the factor VIII products used in the NIS are based on the lower limit of the dosage recommendation. An adequate routine prophylaxis with factor VIII products can thus not be assumed with sufficient certainty; a meaningful interpretation of the bleeding rates observed in the NIS is not possible in the overall view.

Accordingly, the intra-individual comparison cannot be considered for the question of benefit assessment.

Summary

It is not possible to weigh up an additional benefit or a minor benefit against the appropriate comparator therapy on the basis of the data presented. Thus, no additional benefit can be derived from the appropriate comparator therapy. The additional benefit compared to the appropriate comparator therapy is therefore not proven.

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 severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors in all age groups".

Recombinant or human plasma-derived blood coagulation factor VIII products in a prophylactic regime were determined as an appropriate comparator therapy by the G-BA.

The pharmaceutical company does not present direct comparative studies for emicizumab compared to the appropriate comparator therapy. The benefit assessment is based on the adjusted indirect comparison of routine prophylaxis with emicizumab (HAVEN 3 study) with the appropriate comparator therapy of routine prophylaxis with factor VIII products (SPINART study) using a bridge comparator. This shows no statistically significant differences between routine prophylaxis with emicizumab and the appropriate comparator therapy.

It is not possible to weigh up an additional benefit or a minor benefit against the appropriate comparator therapy on the basis of the data presented. Thus, no additional benefit can be derived from the appropriate comparator therapy.

Because of methodological limitations, the before and after comparison presented here is also not suitable for addressing the question of benefit assessment.

In the overall view, for emicizumab for the routine prophylaxis of bleeding events in patients with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors, an additional benefit compared with the appropriate comparator therapy is 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 will be based on the information from the dossier of the pharmaceutical company. These figures are based on figures from the German Haemophilia Register (Deutsches Hämophilieregister; DHR) and are subject to uncertainty. It cannot be assumed that all patients with haemophilia A in the German Haemophilia Register will be covered completely. However, the patient numbers also appear plausible in their magnitude against the background of previous resolutions[2] on haemophilia A (without age and severity restrictions).

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: 15 August 2019):

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

Treatment with emicizumab should be initiated and monitored by specialists experienced in the treatment of haemophilia.

[2] Resolution of 20 June 2017 on lonoctocog alfa, resolution of 16 June 2016 on efmoroctocog alfa, resolution of 7 May 2015 on simoctocog alfa, and resolution of 3 July 2014 on turoctocog alfa.

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide training material for medical personnel, patients/caregivers (patient passport and training material), and laboratory personnel. The training material contains specific information on the handling of thrombotic microangiopathy and thromboembolism, on the use of bypassing agents, and on 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: 15 August 2019).

Treatment duration in patients with severe haemophilia A (prophylaxis):

Designation of the therapy	Treatment mode[3]	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Emicizumab[4]	continuous, every week/ every 2 weeks/ every 4 weeks	13–52	1	13–52
Appropriate comparator therapy				
Recombinant blood coagulation factor VIII				
Rurioctocog alfa pegol[5]	continuous, 2 x per week	104	1	104
Efmoroctocog alfa	continuous every 3 to 5 days	73–122	1	73–122
Lonoctocog alfa	continuous, 2 to 3 times per week	104–156	1	104–156
Moroctocog alfa	continuous, every 2 to 3 days	122–183	1	122–183
Octocog alfa[6]	≥ 12 years: continuous, 2 to 3 times per week;	104–156	1	104–156

[3] In younger patients, patient-individual shorter dosing intervals or higher doses may be required.

[4] The costs represent the continuous administration in the maintenance phase. The product information on emicizumab includes various therapy regimens: 1.5 mg per kg body weight every week, 3 mg per kg body weight every 2 weeks, or 6 mg per kg body weight every 4 weeks. In the determination of consumption, a range from application every 4 weeks to application every week was formed, taking into account discards.

[5] Rurioctocog alfa pegol is authorised only from 12 years of age.

[6] Cost representation based on the information provided in the product information for Kovaltry®. Further proprietary medicinal products are available.

Designation of the therapy	Treatment mode[3]	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
	< 12 years: continuous, 2 to 3 times per week or every 2 days	104–183	1	104–183
Simoctocog alfa[7]	continuous, every 2 to 3 days	122–183	1	122–183
Turoctocog alfa[8]	continuous, every 2 days, every 3 days 3 or 2 times per week	104–183	1	104–183
Damoctocog alfa pegol[9]	continuous, twice per week or every 5 days or every 7 days	52–104	1	52–104
Blood coagulation factor VIII derived from human plasma				
Human plasma products[10]	continuous, every 2 to 3 days	122–183	1	122–183

Usage and consumption:

The theoretical annual consumption of emicizumab and the active ingredients (factor VIII products) of the appropriate comparator therapy required for the prophylaxis of bleeding in patients with severe haemophilia A are presented. Consumption is calculated per injection for the relevant age groups (under 1 to under 6 years, 6 to under 12 years, 12 to under 18 years, and adults) in accordance with the product information. In principle, the G-BA does not base the calculation of the consumption of weight-dependent medicinal products to be dispensed on indication-specific average weights. Therefore, for the body weight, the mean weight of a male adult (85.0 kg) according to the official representative statistic “Microcensus

[7] Cost representation based on the information provided in the product information for Nuwiq®. Further proprietary medicinal products are available.

[8] The product information for turoctocog alfa provides for various therapy schemes: Either 20–40 I.U. per kg body weight every 2 days, 20–50 I.U. per kg body weight three times per week, or 40–60 I.E. per kg body weight every 3 days or twice per week. For children and adolescents under 12 years, a dosage of 25–50 I.U. per kg body weight every two days or 25–60 I.U. per kg body weight three times per week is recommended. To determine consumption, the dosing scheme with the largest consumption range (20 to 50 I.U. factor VIII per kg body weight three times per week for patients 12 years and older and 25 to 60 I.U. per kg body weight three times per week for patients under 12 years) was used. The consumption when using the other dosing schemes is within the calculated consumption range.

[9] The product information for damoctocog alfa pegol provides for various therapy schemes: Either 45–60 I.U. per kg body weight every 5 days, 60 I.U. per kg body weight every 7 days, or 30–40 I.U. per kg body weight twice a week. The dosing schemes with the largest consumption range (60 I.U. per kg body weight every 7 days to 60 I.U. per kg body weight every 5 days) were used to determine the consumption. The consumption when using the other dosing schemes is within the calculated consumption range. Damoctocog alfa pegol is authorised only from 12 years of age.

[10] Cost representation based on the information provided in the product information for Fanhdi®. Further proprietary medicinal products are available.

2017" is assumed[11]. For the underlying average weight (kg) in the respective male age group, the mean value of the age group was used: from 12 to under 18 years of age, this is 61,8 kg; from 6 to under 12 years, 32.7 kg; and from under 1 year to under 6 years, 15.1 kg.

Damoctocog alfa pegol and rurioctocog alfa pegol are authorised only from 12 years of age.

In principle, shorter dosing intervals or higher doses may be required in some cases, especially with younger patients.

Because factor VIII products can only be stored for a maximum of 24 h after reconstitution, a discard must be taken into account; as a result, the consumption per injection is shown.

The consumption of vials or prefilled syringes was divided into package sizes on the basis of the weight-adjusted demand for I.E. factor VIII/injection. For example, for an adult with a need for 1,686 I.E./injection, this was composed of three vials with 1,000 I.U., 500 I.U., and 250 I.U. factor VIII.

Designation of the therapy	Dosage (I.U. per kg BW)	Dose/patient/treatment day (I.U.)[11]	Consumption by potency (I.U.) per treatment day	Treatment days/patient/year	Annual average consumption by potency (vialor PS)[12]
Medicinal product to be assessed					
Emicizumab	1.5 mg – 6 mg	Adults	Adults	13–52	Adults
		510 mg	3 x 150 mg 1 x 60 mg to		39 x 150 mg 13 x 60 mg to
		127.5 mg	1 x 105 mg 1 x 30 mg		52 x 105 mg 52 x 30 mg
		12 – <18 years	12 – <18 years		12 – <18 years
		370.8 mg	3 x 105 mg 1 x 60 mg to		39 x 105 mg 13 x 60 mg to
		92.7 mg	1 x 105 mg		52 x 105 mg
		6 – < 12 years	6 – < 12 years		6 – < 12 years
		196.2 mg	2 x 105 mg to		26 x 105 mg to

[11] Statistisches Bundesamt [German Federal Office for Statistics] Microcensus 2017: Fragen zur Gesundheit; Körpermaße der Bevölkerung 2017 [Questions about health; body measurements of the 2017 population] [online]. 2 August 2018 [Accessed: 11 September 2018]. URL: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

[12] The annual average consumption of vials or prefilled syringes was based on the most economical units of the I.U. required per injection.

Designation of the therapy	Dosage (I.U. per kg BW)	Dose/patient/treatment day (I.U.)[11]	Consumption by potency (I.U.) per treatment day	Treatment days/patient/year	Annual average consumption by potency (vialor PS)[12]
		49.05 mg	1 x 60 mg		52 x 60 mg
		< 6 years	< 6 years		< 6 years
		90.6 mg	1 x 105 mg to		13 x 105 mg to
		22.65 mg	1 x 30 mg		52 x 30 mg
Appropriate comparator therapy					
Recombinant blood coagulation factor VIII					
Rurioctocog alfa pegol	40 × 50 I.U.	Adults	Adults	104	Adults
		3,400–4,250	1 x 2,000 1 x 1,000 1 x 500 to 2 x 2,000 1 x 250		104 x 2,000–1,000 104 x 500 104 x to 208 x 2,000–250 104 x
		12 – <18 years	12 – <18 years		12 – <18 years
		2,472–3,090	1 x 2,000 1 x 500 to 1 x 2,000 1 x 1,000 1 x 250		104 x 2,000–500 104 x to 104 x 2,000–1,000 104 x 250 104 x
Efmoroctocog alfa	25–65 I.U.	Adults	Adults	73–122	Adults
		2,125–5,525	1 x 2,000 1 x 250 to 1 x 3,000 1 x 2,000 1 x 500 1 x 250		73 x 2,000 73 x 250 to 122 x 3,000–2,000 122 x 500–250 122 x

Designation of the therapy	Dosage (I.U. per kg BW)	Dose/patient/treatment day (I.U.)[11]	Consumption by potency (I.U.) per treatment day	Treatment days/patient/year	Annual average consumption by potency (vialor PS)[12]
					122 x
		12 – <18 years	12 – <18 years		12 – <18 years
		1,545–4,017	1 x 1,000 1 x 500 1 x 250 to 2 x 2,000 1 x 250		73 x 1,000 73 x 500 73 x 250 to 244 x 2,000 250 122 x
		6 – < 12 years	6 – < 12 years		6 – < 12 years
		817.5–2125	1 x 1,000 to 1 x 2,000 1 x 250		73 x 1,000 to 122 x 2,000 250 122 x
		< 6 years	< 6 years		< 6 years
		377.5–981.5	1 x 500 to 1 x 1,000		73 x 500 to 1222 x 1,000
Lonoctocog alfa	20–50 I.U.	Adults	Adults	104–156	Adults
		1,700–4,250	1 x 1,500 1 x 250 to 2 x 2,000 1x 250		104 x 1,500 250 104 x to 312 x 2,000 250 156 x
		12 – <18 years	12 – <18 years		12 – <18 years
		1,236–3,090	1 x 1,000 1 x 250 to 1 x 3,000 1 x 250		104 x 1,000 250 104 x to 156 x 3,000 250

Designation of the therapy	Dosage (I.U. per kg BW)	Dose/patient/treatment day (I.U.)[11]	Consumption by potency (I.U.) per treatment day	Treatment days/patient/year	Annual average consumption by potency (vialor PS)[12]
					156 x
	30–50 I.U.	6 – < 12 years	6 – < 12 years		6 – < 12 years
		981–1635	1 x 1,000 1 x to 1 x 1,500 250		104 1,000 x to 1,500 156 250 x 156 x
		< 6 years	< 6 years		< 6 years
		453–755	1 x 500 to 1 x 1,000		104 500 x to 1,000 156 x
Moroctocog alfa	20–40 I.U.	Adults	Adults	122–183	Adults
		1,700–3,400	1 x 1,000 1 x 500 1 x 250 to 1 x 3,000 1 x 500		122 1,000 x 500 122 250 x 122 x to 183 3,000 x 500 183 x
		12 – <18 years	12 – <18 years		12 – <18 years
		1,236–2,472	1 x 1,000 1 x 250 to 1 x 2,000 1 x 500		122 1,000 x 250 122 x to 183 2,000 x 500 183 x
		6 – < 12 years	6 – < 12 years		6 – < 12 years
		654–1,308	1 x 500 1x 250		122 500 x 250

Designation of the therapy	Dosage (I.U. per kg BW)	Dose/patient/treatment day (I.U.)[11]	Consumption by potency (I.U.) per treatment day	Treatment days/patient/year	Annual average consumption by potency (vialor PS)[12]
			to 1x 1,000 1x 500		122 to x 1,000 500 183 x 183 x
		< 6 years	< 6 years		< 6 years
		302–604	1 x 500 to 1x 500 1x 250		122 500 x to 500 183 250 x 183 x
Octocog alfa[6]	20–40 I.U.	Adults	Adults	104–156	Adults
		1,700–3,400	1 x 1,000 1 x 500 1 x 250 to 1 x 3,000 1 x 500		104 1,000 x 500 104 250 x 104 x to 156 3,000 x 500 156 x
		12 – <18 years	12 – <18 years		12 – <18 years
		1,236–2,472	1 x 1,000 1 x 250 to 1 x 2,000 1 x 500		104 1,000 x 250 104 x to 156 2,000 x 500 156 x
	20–50 I.U.	6 – < 12 years	6 – < 12 years	104–183	6 – < 12 years
		654–1635	1 x 500 1x 250		104 500 x 250

Designation of the therapy	Dosage (I.U. per kg BW)	Dose/patient/treatment day (I.U.)[11]	Consumption by potency (I.U.) per treatment day	Treatment days/patient/year	Annual average consumption by potency (vialor PS)[12]
			to 1x 1,000 1x 500 1 x 250		104 to x 1,000 500 183 250 x 183 x 183 x
		< 6 years	< 6 years		< 6 years
		302–755	1 x 500 to 1x 1,000		122 500 x to 1,000 183 x

Designation of the therapy	Dosage (I.U. per kg BW)	Dose/patient/treatment day (I.U.)[11]	Consumption by potency (I.U.) per treatment day	Treatment days/patient/year	Annual average consumption by potency (vial or PS)[12]
Simoctocog alfa[7]	20–40 I.U.	Adults	Adults	122 - 183	Adults
		1,700–3,400	1 x 1,000 1 x 500 1 x 250 to 1 x 3,000 1 x 500		122 x 1,000 122 x 500 122 x 250 to 183 x 3,000 183 x 500
		12 – <18 years	12 – <18 years		12 – <18 years
		1,236–2,472	1 x 1,000 1 x 250 to 1 x 2,500		122 x 1,000 122 x 250 to 183 x 2,500
		6 – < 12 years	6 – < 12 years		6 – < 12 years
		654–1,308	1 x 500 1x 250 to 1x 1,000 1x 500		122 x 500 122 x 250 to 183 x 1,000 183 x 500
		< 6 years	< 6 years		< 6 years
		302–604	1 x 500 to 1x 500 1x 250		122 x 500 to 156 x 500 156 x 250
Turoctocog alfa[8]	20–50 I.U.	Adults	Adults	156	Adults
		1,700–4,250	1 x 1,500 1 x 250 to 2 x 2,000 1x 250		156 x 1,500 156 x 250 to 312 x 2,000 156 x 250
		12 – <18 years	12 – <18 years		12 – <18 years
		1,236–3,090	1 x 1,000 1 x 250 to 1 x 3,000 1 x 250		156 x 1,000 156 x 250 to 156 x 3,000 156 x 250
	25–60 I.U.	6 – < 12 years	6 – < 12 years		6 – < 12 years

Designation of the therapy	Dosage (I.U. per kg BW)	Dose/patient/treatment day (I.U.)[11]	Consumption by potency (I.U.) per treatment day	Treatment days/patient/year	Annual average consumption by potency (vial or PS)[12]
		817.5–1,962	1 x 500 1 x to 1 x 2,000		156 x 1,000 to 156 x 2,000
		<u>< 6 years</u>	<u>< 6 years</u>		<u>< 6 years</u>
		377.5–906	1 x 500 to 1 x 1,000		156 x 500 to 156 x 1,000
Damoctocog alfa pegol[9]	60 I.U.	<u>Adults</u>	<u>Adults</u>	52–73	<u>Adults</u>
		5,100	1 x 3,000 1 x 2,000 1 x 250 to 1 x 3,000 1 x 2,000 1 x 250		52 x 3,000 52 x 2,000 52 x 250 to 73 x 3,000 73 x 2,000 73 x 250
		<u>12 – <18 years</u>	<u>12 – <18 years</u>		<u>12 – <18 years</u>
		3,708	1 x 3,000 1 x 500 1 x 250 to 1 x 3,000 1 x 500 1 x 250		52 x 3,000 52 x 500 52 x 250 to 73 x 3,000 73 x 500 73 x 250

Designation of the therapy	Dosage (I.U. per kg BW)	Dose/patient/treatment day (I.U.) [11]	Consumption by potency (I.U.) per treatment day	Treatment days/patient/year	Annual average consumption by potency (vial or PS)[12]
Blood coagulation factor VIII derived from human plasma					
Human plasma products[10]	20 × 40 I.U.	Adults	Adults	122–183	Adults
		1,700–3,400	1 x 1,500 1 x 250 to 2 x 1,500 1 x 500		122 x 1,500 122 x 250 to 366 x 1,500 183 x 500
		12 – <18 years	12 – <18 years		12 – <18 years
		1,236–2,472	1 x 1,000 1 x 250 to 1 x 1,500 1 x 1,000		122 x 1,000 122 x 250 to 183 x 1,500 183 x 1,000
		6 – < 12 years	6 – < 12 years		6 – < 12 years
		654–1,308	1 x 500 1x 250 to 1x 1,000 1x 500		122 x 500 122 x 250 to 183 x 1,000 183 x 500
		< 6 years	< 6 years		< 6 years
		302–604	1 x 500 to 1x 500 1x 250		122 x 500 to 183 x 500 183 x 250
PS = prefilled syringes					

Costs:

factor VIII products are mainly sold directly to the treating doctor or haemophilia centre. This practice is based on an exception in the AMG (Section 47, paragraph 1, sentence 2a). At the same time factor VIII products can be excluded from the price ranges and prices of pharmacies in accordance with Section 1, paragraph 3, Nos. 3 and 6 of the Pharmaceutical Price Ordinance (AMPreisV). Thus, there is no manufacturer rebate for these products according to Section 130a SGB V. This was confirmed in a recent ruling of the Federal Social Court (B 6 KA 18/14 R). Because, according to the current judgement, the choice of the more cost-effective of several legally permissible routes of supply for medicinal products also falls under the obligation of care providers to derive the principle of economic efficiency, the costs of factor VIII products were determined on the basis of direct marketing (manufacturer's sales prices plus value added tax). The price of the least expensive product in the corresponding potency is indicated.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy wholesale 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/1 ml	€ 3,007.03	€ 1.77	€ 168.46	€ 2,836.80
	60 mg/0.4 ml	€ 5,956.77	€ 1.77	€ 336.92	€ 5,618.08
	105 mg/0.7 ml	€ 10,381.35	€ 1.77	€ 589.61	€ 9,789.97
	150 mg/1 ml	€ 14,805.93	€ 1.77	€ 842.30	€ 13,961.86

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 August 2019

Designation of the therapy	Package size	Cost (manufacturer's selling price plus value added tax)
Appropriate comparator therapy		
Recombinant blood coagulation factor VIII		
Efmoroctocog alfa	250 I.U. 500 I.U. 1,000 I.U. 1,500 I.U. 2,000 I.U. 3,000 I.U.	€ 280.25 € 560.49 € 1,120.98 € 1,681.47 € 2,241.96 € 3,362.94
Damoctocog alfa pegol	250 I.U. 500 I.U. 1,000 I.U. 2,000 I.U. 3,000 I.U.	€ 443.28 € 886.55 € 1,773.10 € 3,546.20 € 5,319.30
Lonoctocog alfa	250 I.U. 500 I.U. 1,000 I.U. 1,500 I.U. 2,000 I.U. 3,000 I.U.	€ 276.08 € 552.16 € 1,104.32 € 1,656.48 € 2,208.64 € 3,312.96
Moroctocog alfa	250 I.U. 500 I.U. 1,000 I.U. 2,000 I.U. 3,000 I.U.	€ 288.58 € 577.15 € 1,154.30 € 2,308.60 € 3,462.90
Octocog alfa	250 I.U. 500 I.U. 1,000 I.U. 2,000 I.U.	€ 326.54 € 653.07 € 1,306.14 € 2,612.29

Designation of the therapy	Package size	Cost (manufacturer's selling price plus value added tax)
	3,000 I.U.	€ 3,918.43
Rurioctocog alfa pegol	250 I.U. 500 I.U. 1,000 I.U. 2,000 I.U.	€ 268.35 € 536.69 € 1,073.38 € 2,146.76
Simoctocog alfa	250 I.U. 500 I.U. 1,000 I.U. 2,000 I.U. 2,500 I.U. 3,000 I.U. 4,000 I.U.	€ 260.31 € 520.63 € 1,041.25 € 2,082.50 € 2,603.13 € 3,123.75 € 4,165.00
Turoctocog alfa	250 I.U. 500 I.U. 1,000 I.U. 1,500 I.U. 2,000 I.U. 3,000 I.U.	€ 246.93 € 493.85 € 987.70 € 1,481.55 € 1,975.40 € 2,963.10
Blood coagulation factor VIII derived from human plasma		
Human plasma products	250 I.U. 500 I.U. 1,000 I.U. 1,500 I.U.	€ 246.93 € 493.85 € 987.70 € 1,481.55

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 August 2019

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 standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services have to be taken into account.

3. Bureaucratic costs

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 8 March 2016.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 9 April 2019.

On 15 June 2019, 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 15 March 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 13 June 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 17 June 2019. The deadline for submitting written statements was 8 July 2019.

The oral hearing was held on 23 July 2019.

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 were discussed at the session of the subcommittee on 27 August 2019, and the proposed resolution was approved.

At its session on 5 September 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	8 March 2016	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	9 April 2019	Redefinition of the appropriate comparator therapy
Working group Section 35a	16 July 2019	Information on written statements received; preparation of the oral hearing

Subcommittee Medicinal product	23 July 2019	Conduct of the oral hearing
Working group Section 35a	30 July 2019 13 August 2019 20 August 2019	Consultation on the dossier evaluation of the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal product	27 August 2019	Concluding discussion of the proposed resolution
Plenum	5 September 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 5 September 2019

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

Prof Hecken