Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM -RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients in Accordance with Section 35a SGB V
Damoctocog alfa pegol

From 20 June 2019

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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 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 relevant date for the first placement on the (German) market of the active ingredient damoctocog alfa pegol in accordance with Chapter 5, Section 8, No. 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1. January 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, No. 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, No. 1 VerfO on 18 December 2018.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 April 2019, 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 damoctocog alfa pegol compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier evaluation prepared by the IQWiG, and the statements submitted in the written and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA 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 damoctocog alfa pegol.

In 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 damoctocog alfa pegol (Jivi®) in accordance with the product information

Treatment and prophylaxis of bleeding in previously treated patients 12 years of age and older with haemophilia A (congenital factor VIII deficiency).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients aged 12 and older with haemophilia A (congenital factor VIII deficiency)

- Recombinant or human plasma-derived blood coagulation factor VIII preparations.

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 practice 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, in principle, have a marketing authorisation for the therapeutic indication.
2. If a non-medical 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-drug 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.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

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

On 1. For the therapy of haemophilia A, drugs with the following active ingredients are currently approved:

- Recombinant factor VIII preparations 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[2]. Rurioctocog alfa pegol is the 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[2].
  - Efmoroctocog alfa has a shorter side chain than the natural factor VIII glycoprotein; this 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 preparations are approved for the treatment and prophylaxis of haemophilia A.

- Human plasma factor VIII preparations[2] 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 preparation (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 bispecific antibody that combines the activated factors IX and X to restore the function of the missing activated factor VIII. Emicizumab is approved for the routine prophylaxis of patients with haemophilia A and factor VIII inhibitors as well as for the routine prophylaxis of bleeding in severe haemophilia A without factor VIII inhibitors.

On 2. Non-drug 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

[2] Different proprietary medicinal products available.

benefit assessment of drugs 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)

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 preparations 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 preparations 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 preparations 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.

Emicizumab is another drug approved for use in this therapeutic indication. As of March 2019, the marketing authorisation also includes routine prophylaxis of bleeding in patients with severe haemophilia A without existing factor VIII inhibitors in addition to routine prophylaxis of bleeding in patients with existing factor VIII inhibitors. In addition to routine prophylaxis, the present therapeutic indication of Damoctocog alfa pegol includes the treatment on demand of bleeding and is not limited to severe haemophilia A. Regardless of the fact that emicizumab is only approved for a part of the indication to be evaluated here, at the time of the resolution emicizumab has only been available on the German market for a short time for the routine prophylaxis of bleeding for patients with severe haemophilia A without existing factor VIII inhibitors. The therapeutic value can therefore not 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 mandate.

2.1.3 Extent and probability of the additional benefit

<u>Patients aged 12 and older with haemophilia A (congenital factor VIII deficiency)</u>

In summary, the additional benefit of Damoctocog alfa pegol is assessed as follows:

For the treatment and prophylaxis of bleeding in patients aged 12 and older with haemophilia A (congenital factor VIII deficiency), the additional benefit compared to the appropriate comparator therapy is not proven.

Justification:

In the dossier for the assessment of the additional benefit of Damoctocog alfa pegol, the pharmaceutical company does not present any directly comparative studies compared to the appropriate comparator therapy. The two non-comparative registration studies (13024 and 13401) are presented as further investigations in the dossier.

Study 13024 is an open, four-arm, semi-randomised study comparing treatment on demand versus a prophylactic treatment (three different treatment regimens) with Damoctocog alfa pegol in previously treated adolescents (12 to < 18 years) and adult male patients (≥ 18 to 65 years) with severe haemophilia A.

In the single-arm, non-randomised Phase I study 13401, pretreated male patients with severe haemophilia A were investigated. The study investigated the pharmacokinetics of Damoctocog alfa pegol in two cohorts; after a single dose of octocog alfa, patients received Damoctocog alfa pegol in different treatment regimens over a period of 8 weeks.

The two studies submitted are the basis for the marketing authorisation. The studies cannot be considered by the G-BA because they do not permit comparison with the appropriate comparator therapy. An indirect comparison with the appropriate comparator therapy was not sought.

Summary:

The pharmaceutical company has not submitted any relevant data for the assessment of the additional benefit of Damoctocog alfa pegol. The G-BA considers the results presented to be generally unsuitable for deriving patient-relevant effects for the additional benefit of Damoctocog alfa pegol compared to 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 Jivi® with active ingredient Damoctocog alfa pegol.

The present assessment refers to the therapeutic indication “Treatment and prophylaxis of bleeding in previously treated 12 years of age and older with haemophilia A (congenital factor VIII deficiency)”.

Recombinant or human plasma-derived blood coagulation factor VIII preparations were determined as an appropriate comparator therapy by the G-BA. The pharmaceutical company does not present comparative studies for Damoctocog alfa pegol compared to the appropriate comparator therapy. Thus, no appropriate treatment data are available to assess the additional benefit of Damoctocog alfa pegol for the treatment and prophylaxis of bleeding in previously treated 12 years of age and older with haemophilia A (congenital factor VIII deficiency). Therefore, in the overall view, no additional benefit is 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 information is based on the data of the pharmaceutical company from the dossier; this in turn is based on the previous resolution of the G-BA in the indication area haemophilia A from the age of 12 years from the year 2018[3].

[3] Resolution of 1 November 2018 concerning Rurioctocog alfa pegol.

2.3 Requirements for a quality-assured application

The requirements of 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 Jivi® (active ingredient: damoctocog alfa pegol) at the following publicly accessible link (last access: 29 April 2019):

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

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

2.4 Treatment costs

The treatment costs are based on the contents of the summary of product characteristics and the information listed in the LAUER-TAXE® (last revised: 01 June 2019).

Treatment duration:

Treatment duration in patients with severe haemophilia A (prophylaxis)[4]:

Designation of the therapy	Treatment mode[5]	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Damoctocog alfa pegol[6]	continuously Twice per week or every 5 days	73–104	1	73–104
Appropriate comparator therapy				
Recombinant blood coagulation factor VIII				
Rurioctocog alfa pegol	continuously, twice per week	104	1	104
Efmoroctocog alfa	continuously every 3 to 5 days	73–122	1	73–122
Lonoctocog alfa	continuously 2 to 3 times per week	104–156	1	104–156
Moroctocog alfa	continuously every 2 to 3 days	122–183	1	122–183
Octocog alfa[7]	continuously	104–156	1	104–156

[4] The costs of treatment on demand for haemophilia A patients with mild to moderate severity vary from patient to patient and are not shown. The consumption for prophylaxis in the presence of severe haemophilia A is presented and used as a basis for the cost calculation.

[5] In younger patients, shorter dosing intervals or higher doses may be required for individual patients.

[6] The summary of product characteristics 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 scheme with the largest consumption range (30 I.U. per kg body weight twice a week to 60 I.U. per kg body weight every 5 days) was used to determine the consumption. The consumption when using the other dosing schemes is within the calculated consumption range.

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

	2 to 3 times per week			
Simoctocog alfa[8]	continuously every 2 to 3 days	122–183	1	122–183
Turoctocog alfa[9]	continuously 3 x per week	156	1	156
Blood coagulation factor VIII derived from human plasma				
Human plasma preparations[10]	continuously every 2 to 3 days	122–183	1	122–183

Usage and consumption:

In patients with mild and moderate haemophilia A, the consumption of factor VIII preparations depends on the respective need and varies from patient to patient. For this reason, the consumption of patient-specific demand therapy cannot be determined.

The theoretical annual consumption of damoctocog alfa pegol and the active ingredients (factor VIII preparations) 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 (12 to under 18 years and adults) in accordance with the summary of product characteristics. 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 2017" is assumed[11]. For the underlying average weight (kg) in the respective male age group from 12 to under 18 years, the mean of the age group (61.8 kg) was used.

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

Because factor VIII preparations 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 pre-filled 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., respectively. 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 PFS)[12]

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

[9] The summary of product characteristics 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. The dosing scheme with the largest consumption range (20–50 I.U. factor VIII per kg body weight three times per week) was used to determine consumption. The consumption when using the other dosing schemes is within the calculated consumption range.

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

[11] Statistisches Bundesamt [German Federal Office for Statistics] Microcensus 2017: Questions on health; body measurements of the population 2017 [on-line]. 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 pre-filled syringes was based on the most economical unitisation 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 PFS)[12]
Medicinal product to be assessed					
Damoctocog alfa pegol [6]	30–60 I.U.	Adults	Adults	73–104	Adults
		2,550–5,100	1 x 2,000 1 x 500 1 x 250 to 1 x 3,000 1 x 2,000 1 x 250		104 x 2,000 104 x 500 104 x 250 to 73 x 3,000 73 x 2,000 73 x 250
		12 – <18 years	12 – <18 years		12 – <18 years
		1,854 –3,708	1 x 2,000 to 1 x 3,000 1 x 500 1 x 250		104 x 2,000 to 73 x 3,000 73 x 500 73 x 250
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		104 x 2,000– 104 x 1,000 104 x 500
			to		to
			2 x 2,000 1 x 250		208 x 2,000 104 x 250
		12 – <18 years	12 – <18 years		12 – <18 years
		2,472–3,090	1 x 2,000 1x 500		104 x 2,000 104 x 500
			to		to
			1 x 2,000 1 x 1,000 1 x 250		104 x 2,000 104 x 1,000 104 x 250
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 3,000 122 x 2,000 122 x 500 122 x 250
		12 – <18 years	12 – <18 years		12 – <18 years
		1,545–4,017	1 x 1,000 1 x 500		73 x 1,000 73 x 500

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 PFS)[12]
			1 x 250 to 2 x 2,000 1 x 250		73 x 250 to 244 x 2,000 122 x 250
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 1,500 104 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		104 x 1,000 104 x 250 to 156 x 3,000 156 x 250
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 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 2,000 1 x 500		122 x 1,000 122 x 250 to 183 x 2,000 183 x 500
Octocog alfa[7]	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 x 1,000 104 x 500 104 x 250 to 156 x 3,000 156 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 2,000 1 x 500		104 x 1,000 104 x 250 to 156 x 2,000 156 x 500

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 PFS)[12]
Simoctocog alfa[8]	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
Turoctocog alfa[9]	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

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 PFS)[12]
Blood coagulation factor VIII derived from human plasma					
Human plasma preparations[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
PFS = pre-filled syringes					

Costs:

Factor VIII preparations 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 preparations 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 preparations 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 economic efficiency principle, the costs of factor VIII preparations were determined on the basis of direct marketing (manufacturer's sales prices plus value added tax). The price of the least expensive preparation in the corresponding potency is indicated.

Costs of the medicinal product:

Designation of the therapy	Package size	Cost (manufacturer's selling price plus value added tax)
Medicinal product to be assessed		
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
Appropriate comparator therapy		
Recombinant blood coagulation factor VIII		
Efmoroctocog alfa	250 I.U. 500 I.U. 1,000 I.U.	€ 280.25 € 560.49 € 1,120.98

Designation of the therapy	Package size	Cost (manufacturer's selling price plus value added tax)
	1,500 I.U. 2,000 I.U. 3,000 I.U.	€ 1,681.47 € 2,241.96 € 3,362.94
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. 3,000 I.U.	€ 326.54 € 653.07 € 1,306.14 € 2,612.29 € 3,918.43
Rurioctocog alfa pegol	250 I.U. 500 I.U. 1,000 I.U. 2,000 I.U.	€ 348.08 € 696.15 € 1,392.30 € 2,784.60
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
Human plasma preparations	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: 01 June 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 drug to be evaluated and the appropriate comparator therapy according to the summary of product characteristics, the costs incurred for this must be taken into account as costs for additional SHI services required.

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 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 additional SHI services required had 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

In a letter dated 03 May 2017, received on 04 May 2017, the pharmaceutical company requested consultation in accordance with Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) on, among other things, the question of appropriate comparator therapy. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its meeting on 11 July 2017. The consultation meeting took place on 14 July 2017.

On 18 December 2018, the pharmaceutical company submitted a dossier for the benefit assessment of damoctocog alfa pegol to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

By letter dated 18 December 2018 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 damoctocog alfa pegol.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 March 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 01 April 2019. The deadline for submitting written statements was 23 April 2019.

The oral hearing was held on 06 May 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 meetings.

The evaluation of the written statements received and the oral hearing was discussed at the meeting of the subcommittee on 11 June 2019, and the proposed resolution was approved.

At its meeting on 20 June 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Meeting	Date	Subject of consultation
Subcommittee Medicinal products	11 July 2017	Determination of the appropriate comparator therapy

Working group Section 35a	29 April 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 May 2019	Conduct of the oral hearing
Working group Section 35a	15 May 2019 5 June 2019	Consultation on the dossier assessment by the IQWiG and the evaluation of the written statement procedure
Subcommittee Medicinal products	12 June 2019	Concluding discussion of the proposed resolution
Plenum	20 June 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 June 2019

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

Prof. Hecken