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 Turoctocog Alfa Pegol

of 6 February 2020

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 relevant date for the first placing on the market of the active ingredient turoctocog alfa pegol in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 August 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 30 July 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 November 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 turoctocog alfa pegol compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written 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 turoctocog alfa pegol.

In the light of the above and taking into account the statements 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 turoctocog alfa pegol (Esperoct®) in accordance with product information

Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).

2.1.2 Appropriate comparator therapy

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

Appropriate comparator therapy:

- Recombinant or human plasma-derived blood coagulation factor VIII products

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.

[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.

- Octocog alfa contains the natural human factor VIII glycoprotein with the complete amino acid sequence[2]. Rurioctocog alfa pegol and damoctocog alfa pegol, represent 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[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 products are approved for the treatment and prophylaxis of haemophilia A. The pegylated factor VIII products rurioctocog alfa pegol, and damoctocog alfa pegol are approved only for patients with haemophilia A from the age of 12 years.

- Human plasma factor VIII products[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 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 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:

[2] Different proprietary medicinal products 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 as well as 5 September 2019)
- 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.

Emicizumab is another medicinal product 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 turoctocog 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 contract.

2.1.3 Extent and probability of the additional benefit

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

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

Justification:

In the dossier for the assessment of the additional benefit of turoctocog alfa pegol, the pharmaceutical company does not present any directly comparative studies compared with the appropriate comparator therapy. As further investigations, the two non-comparative approval studies PATHFINDER2 and PATHFINDER3 were presented in the dossier, and before and after comparisons based on the PATHFINDER2 study were presented.

The PATHFINDER2 phase III study is an open-label, uncontrolled study with a parallel group design intended to compare treatment on demand with prophylactic treatment with turoctocog alfa pegol in pre-treated male patients aged 12 years and older with severe haemophilia A (factor VIII activity < 1%). In the main phase of the study, patients were either treated with 20 to 75 IU/kg as needed or received prophylaxis with 50 IU/kg turoctocog alfa pegol every 4 days or twice weekly. In the first extension phase, suitable patients were randomised to one of two dosing intervals for prophylaxis: the patients received either 75 IU/kg turoctocog alfa pegol every 7 days or 50 IU/kg turoctocog alfa pegol every 4 days. Patients in whom ≥ 2 bleedings occurred had to change back to the 4-day rhythm. In the second extension phase of the study, patients were able to switch between the 4-day and 7-day application interval depending on the frequency of their bleeding episodes.

The single-arm, non-comparative PATHFINDER3 phase III surgical study evaluated turoctocog alfa pegol in bleedingmanagement during surgical procedures. For this purpose, participants in the PATHFINDER2 study who had to undergo major surgery were included. The operations had to require several days of substitution with factor VIII products. The dose of turoctocog alfa pegol was selected on a patient-individual basis depending on the factor VIII activity level and the severity of surgery in accordance with the guidelines of the World Federation of Haemophilia (WFH). The treatment was performed before and up to 14 days after surgery.

For the PATHFINDER2 study, the pharmaceutical company limits statements on the derivation of the additional benefit to those patients who received prophylaxis; those patients receiving treatment on demand with turoctocog alfa pegol, who are also included in the therapeutic indication, are not considered. The pharmaceutical company presents the results of the PATHFINDER3 study only descriptively and does not aim for a comparison with the appropriate comparator therapy.

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.

Before and after comparison

The “before and after comparisons” presented to answer the question of the benefit assessment based on the PATHFINDER2 study are comparisons of the prophylactic study treatment with turoctocog alfa pegol with individual prophylactic treatment with other recombinant or human plasma-derived Factor VIII products received before the start of study. The pharmaceutical company also presents results for a *post hoc* sub-population of patients from OECD countries in order to address the transferability to the German health care context. The pharmaceutical company also states that the patients of this sub-population received long-term prophylaxis according to the requirements in the product

information both during the study and in previous therapy. Several before and after comparisons – for the entire sub-population as well as separately for adolescents and adults – are presented.

The comparisons are based on data from patients who had received individual prophylactic treatment with other recombinant or human plasma-derived factor VIII products before the start of study (before) and participated in the PATHFINDER2 study (after). Because of the strong methodological limitations, these comparisons cannot be considered for the question of benefit assessment. The comparability of the framework/setting (uncontrolled treatment before the study vs controlled study conditions in PATHFINDER2) cannot be taken for granted with sufficient certainty. The supplementary evaluations submitted for a sub-population treated in compliance with the marketing authorisation or product information do not increase the interpretability of the comparisons presented because an adequate therapy of patients with haemophilia A within the framework of the study was questionable. An interpretation of the bleeding rates observed before the start of the PATHFINDER2 study is not possible in the overall view. In addition, the pharmaceutical company carried out the before and after comparisons only selectively for endpoints of morbidity (annualised bleeding rate, health status) and quality of life but not for endpoints of side effects.

Accordingly, the before and after comparison cannot be considered for the question of benefit assessment.

Summary:

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

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

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

The pharmaceutical company does not present any direct comparative studies for turoctocog alfa pegol compared with the appropriate comparator therapy. Because of methodological limitations, the before and after comparisons presented here are also not suitable for addressing the question of benefit assessment. Thus, no suitable data are available to assess the additional benefit of turoctocog alfa pegol for the treatment and prophylaxis of bleeding in previously treated patients 12 years of age and older with haemophilia A (congenital factor VIII deficiency). Therefore, in the overall view, an additional benefit 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 information is based on the data of the pharmaceutical company from the dossier; this in turn is based on the previous resolutions of the G-BA in the indication area haemophilia A from the age of 12 years[3].

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 Esperoct® (active ingredient: turoctocog alfa pegol) at the following publicly accessible link (last access: 19 December 2019):

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

Treatment with turoctocog 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 product information and the information listed in the LAUER-TAXE® (last revised: 15 January 2020).

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				
Turoctocog alfa pegol	continuously, every 4 days	91	1	91
Appropriate comparator therapy				
Recombinant blood coagulation factor VIII				
Damoctocog alfa pegol[6]	continuously, twice per week or	52–104	1	52–104

[3] Resolution of 1 November 2018 concerning rurioctocog alfa pegol, resolution of 20 June 2019 concerning damoctocog alfa pegol.

[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, patient-individual shorter dosing intervals or higher doses may be required.

[6] 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

	every 5 days or every 7 days			
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 2 to 3 times per week	104–156	1	104–156
Rurioctocog alfa pegol	continuously, 2 × per week	104	1	104
Simoctocog alfa[8]	continuously every 2 to 3 days	122–183	1	122–183
Turoctocog alfa[9]	continuously 3 × per week	156	1	156
Blood coagulation factor VIII derived from human plasma				
Human plasma products[10]	continuously every 2 to 3 days	122–183	1	122–183

Usage and consumption:

The theoretical annual consumption of turoctocog alfa pegol 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. Turoctocog alfa, damoctocog alfa pegol, and rurioctocog alfa pegol are approved only from 12 years of age.

Consumption is calculated per injection for the relevant age groups (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 2017” is

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.

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

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

[9] The product information for turoctocog alfa provides for various therapy schemes: Either 20–40 I.U. per kg body weight every two days, 20–50 I.U. per kg body weight three times per week, or 40–60 I.U. per kg body weight every three 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 product information for Fanhdi®. Further proprietary medicinal products are available.

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.

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.U. factor VIII/injection. For example, for an adult with a need for 1,686 I.U./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 (vial orPS)[12]
Medicinal product to be assessed					
Turoctocog alfa pegol	50–75 I.U.	Adults	Adults		Adults
		4,250–6,375	1 × 3,000 1 × 1,500 to 2 × 3,000 1 × 500	91	91 × 3,000 91 × 1,500 to 181 × 3,000 91 × 500
		12 – <18 years	12 – <18 years		12 – <18 years
		3,090–4,635	1 × 3,000 1 × 500 to 1 × 3,000 1 × 2,000		91 × 3,000 91 × 500 to 91 × 3,000 91 × 2,000
Appropriate comparator therapy					
Recombinant blood coagulation factor VIII					
Damoctocog alfa pegol[6]	60 I.U.	Adults	Adults	52–73	Adults
		5,100	1 × 3,000 1 × 2,000 1 × 250 to 1 × 3,000 1 × 2,000 1 × 250		52 × 3,000 52 × 2,000 52 × 250 to 73 × 3,000 73 × 2,000 73 × 250

[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: 09/12/2019]. URL: www.gbe-bund.de

[12] The mean annual 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 (vial orPS)[12]
		12 – <18 years	12 – <18 years		12 – <18 years
		3,708	1 × 3,000 1 × 500 1 × 250 to 1 × 3,000 1 × 500 1 × 250		52 × 3,000 52 × 500 52 × 250 to 73 × 3,000 73 × 500 73 × 250
Efmoroctocog alfa	25–65 I.U.	Adults	Adults	73–122	Adults
		2,125 – 5,525	1 × 2,000 1 × 250 to 1 × 3,000 1 × 2,000 1 × 500 1 × 250		73 × 2,000 73 × 250 to 122 × 3,000 122 × 2,000 122 × 500 122 × 250
		12 – <18 years	12 – <18 years		12 – <18 years
		1,545 – 4,017	1 × 1,000 1 × 500 1 × 250 to 1 × 4,000 1 × 250		73 × 1,000 73 × 500 73 × 250 to 122 × 4,000 122 × 250
Lonoctocog alfa	20–50 I.U.	Adults	Adults	104–156	Adults
		1,700 – 4,250	1 × 1,500 1 × 250 to 2 × 2,000 1 × 250		104 × 1,500 104 × 250 to 312 × 2,000 156 × 250
		12 – <18 years	12 – <18 years		12 – <18 years
		1,236 – 3,090	1 × 1,000 1 × 250 to 1 × 3,000 1 × 250		104 × 1,000 104 × 250 to 156 × 3,000 156 × 250
Moroctocog alfa	20–40 I.U.	Adults	Adults	122–183	Adults
		1,700 – 3,400	1 × 1,000 1 × 500 1 × 250 to 1 × 3,000		122 × 1,000 122 × 500 122 × 250 to 183 × 3,000

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 orPS)[12]
			1 × 500		183 × 500
		12 – <18 years	12 – <18 years		12 – <18 years
		1,236 – 2,472	1 × 1,000 1 × 250 to 1 × 2,000 1 × 500		122 × 1,000 122 × 250 to 183 × 2,000 183 × 500
Octocog alfa[7]	20–40 I.U.	Adults	Adults	104–156	Adults
		1,700 – 3,400	1 × 1,000 1 × 500 1 × 250 to 1 × 3,000 1 × 500		104 × 1,000 104 × 500 104 × 250 to 156 × 3,000 156 × 500
		12 – <18 years	12 – <18 years		12 – <18 years
		1,236 – 2,472	1 × 1,000 1 × 250 to 1 × 2,000 1 × 500		104 × 1,000 104 × 250 to 156 × 2,000 156 × 500
Rurioctocog alfa pegol	40–50 I.U.	Adults	Adults	104	Adults
		3,400 – 4,250	1 × 2,000 1 × 1,000 1 × 500		104 × 2,000– 104 × 1,000 104 × 500
			to		to
			2 × 2,000 1x 250		208 × 2,000 104 × 250
		12 – <18 years	12 – <18 years		12 – <18 years
		2,472 – 3,090	1 × 2,000 1x 500		104 × 2,000 104 × 500
			to		to
			1 × 2,000 1 × 1,000 1 × 250		104 × 2,000 104 × 1,000 104 × 250
Simoctocog alfa[8]	20–40 I.U.	Adults	Adults	122–183	Adults
		1,700 – 3,400	1 × 1,000 1 × 500 1 × 250 to 1 × 3,000 1 × 500		122 × 1,000 122 × 500 122 × 250 to 183 × 3,000 183 × 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 orPS)[12]
		12 – <18 years	12 – <18 years		12 – <18 years
		1,236 – 2,472	1 × 1,000 1 × 250 to 1 × 2,500		122 × 1,000 122 × 250 to 183 × 2,500
Turoctocog alfa[9]	20–50 I.U.	Adults	Adults	156	Adults
		1,700 – 4,250	1 × 1,500 1 × 250 to 2 × 2,000 1x 250		156 × 1,500 156 × 250 to 312 × 2,000 156 × 250
		12 – <18 years	12 – <18 years		12 – <18 years
		1,236 – 3,090	1 × 1,000 1 × 250 to 1 × 3,000 1 × 250		156 × 1,000 156 × 250 to 156 × 3,000 156 × 250
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 × 1,500 1 × 250 to 2 × 1,500 1 × 500		122 × 1,500 122 × 250 to 366 × 1,500 183 × 500
		12 – <18 years	12 – <18 years		12 – <18 years
		1,236 – 2,472	1 × 1,000 1 × 250 to 1 × 1,500 1 × 1,000		122 × 1,000 122 × 250 to 183 × 1,500 183 × 1,000
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 (manufacturer's selling price plus value added tax)
Medicinal product to be assessed		
Turoctocog alfa pegol	500 I.U. 1,000 I.U. 1,500 I.U. 2,000 I.U. 3,000 I.U.	€ 714.00 € 1,428.00 € 2,142.00 € 2,856.00 € 4,284.00
Appropriate comparator therapy		
Recombinant blood coagulation factor VIII		
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
Efmoroctocog alfa	250 I.U. 500 I.U. 1,000 I.U. 1,500 I.U. 2,000 I.U. 3,000 I.U. 4,000 I.U.	€ 280.25 € 560.49 € 1,120.98 € 1,681.47 € 2,241.96 € 3,362.94 € 4,483.92
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.	€ 268.35 € 536.69 € 1,073.38 € 2,146.76
Simoctocog alfa	250 I.U. 500 I.U. 1,000 I.U.	€ 260.31 € 520.63 € 1,041.25

Designation of the therapy	Package size	Costs (manufacturer's selling price plus value added tax)
	2,000 I.U. 2,500 I.U. 3,000 I.U. 4,000 I.U.	€ 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 January 2020

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 6 November 2018.

On 30 July 2019, the pharmaceutical company submitted a dossier for the benefit assessment of turoctocog alfa pegol to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 31 July 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 turoctocog alfa pegol.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 October 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1 November 2019. The deadline for submitting written statements was 22 November 2019.

The oral hearing was held on 9 December 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 28 January 2020, and the proposed resolution was approved.

At its session on 6 February 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	6 November 2018	Determination of the appropriate comparator therapy
Working group Section 35a	3 December 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	9 December 2019	Conduct of the oral hearing
Working group Section 35a	17 December 2019 21 January 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	28 January 2020	Concluding consultation of the proposed resolution
Plenum	6 February 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 6 February 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken