Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) Eftrenonacog alfa (reassessment of an orphan drug after exceeding the EUR 30 million turnover limit (haemophilia B))

of 1 February 2024

Contents

1. Legal basis

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

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

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

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

2. Key points of the resolution

The active ingredient eftrenonacog alfa (Alprolix) was listed for the first time on 15 June 2016 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Eftrenonacog alfa for the treatment and prevention of bleeding in patients with haemophilia B is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) number 141/2000 of the European Parliament and the Council of 16 December 1999.

At its session on 15 December 2016, the G-BA decided on the benefit assessment of eftrenonacog alfa in the therapeutic indication "Therapy and prevention of bleeding in patients with haemophilia B (congenital factor IX deficiency)" in accordance with Section 35a SGB V.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 30 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 2 February 2023, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 August 2023, due to exceeding the €30 million turnover limit within the period from December 2021 to November 2022. The pharmaceutical company has 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 6 VerfO on 28 July 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 November 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of eftrenonacog alfa compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of eftrenonacog alfa.

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

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

2.1.1 Approved therapeutic indication of Eftrenonacog alfa (Alprolix) according to the product information

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). Alprolix can be used with all age groups.

Therapeutic indication of the resolution (resolution of 1 February 2024):

See therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients of all age groups with haemophilia B

Appropriate comparator therapy for eftrenonacog alfa:

- recombinant or coagulation factor IX preparations derived from human blood plasma

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

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

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

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

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

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

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

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

on 1. Currently, various plasma-derived and recombinant coagulation factor IX products are approved for the treatment of haemophilia B:

- Recombinant factor IX products contain the genetically engineered human factor IX glycoprotein:

- Nonacog alfa and nonacog gamma differ in glycosylation, but both contain the natural human factor IX glycoprotein with the complete amino acid sequence
- Albutrepenonacog alfa is a recombinant fusion protein of the human factor IX glycoprotein and albumin
- Nonacog beta pegol is a recombinant human factor IX with a polyethylene glycol (PEG)
- Eftrenonacog alfa is a recombinant fusion protein of the human factor IX glycoprotein and the Fc domain of human IgG1

- Human plasma factor IX preparations[2] contain the human-identical factor IX glycoprotein obtained from cryoprecipitates. They are obtained from large human plasma pools and are approved for the treatment and prevention of haemophilia B.
- Combination preparations of coagulation factors II, VII, IX and X[3] are approved for the treatment of bleeding and for perioperative prevention in cases of hereditary deficiency of one of the vitamin K-dependent coagulation factors if no purified specific coagulation product is available.
- A human plasma fraction enriched with factor VIII inhibitor bypassing activity is approved for the treatment and prevention of bleeding in haemophilia B patients with FIX inhibitor.
- A recombinant blood coagulation factor VIIa preparation (active ingredient: eptacog alfa) is approved for the treatment of bleeding and prevention of bleeding associated with surgical or invasive procedures in, among others, patients with congenital haemophilia with inhibitors of coagulation factor IX. It is not approved for the permanent treatment of haemophilia B requiring replacement.

Etranacogene dezaparvovec is a gene therapy medicinal product that expresses human coagulation factor IX, which is approved for the treatment of severe and moderate haemophilia B in adult patients without a history of factor IX inhibitors. It is a non-replicating, recombinant vector based on the adeno-associated virus serotype 5 (AAV5), which contains a codon-optimised cDNA of the human coagulation factor IX variant R338L (FIX-Padua) under the control of a liver-specific promoter (LP1).

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

on 3. The G-BA has made the following resolutions on the early benefit assessment in the therapeutic indication "Haemophilia B": Albutrepenonacog alfa from 1 December 2016 and from 7 April 2022, eftrenonacog alfa from 15 December 2016, nonacog beta pegol from 19 April 2018 and etranacogene dezaparvovec from 19 October 2023.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V". The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

[2] Various proprietary medicinal products are available.
[3] Various proprietary medicinal products are available.

It is assumed that the patient population in the present indication is haemophilia patients requiring factor IX replacement.

In summary, there is little evidence for the treatment of haemophilia B. No evidence-based data were found on the therapeutic efficacy or on the side-effect profile or safety risk that would lead to a preference for therapy with recombinant or factor IX preparations obtained from human plasma in the treatment of bleeding or treatment of haemophilia B. Direct comparator studies of plasma-derived and recombinant factor IX products are not available.

From the available G-BA resolutions on the benefit assessment of the low-frequency recombinant factor IX preparations (active ingredients nonacog beta pegol, albutrepenonacog alfa), it is also not possible to derive any statements on the comparative efficacy, safety and comparative side effect profile compared to other recombinant or plasma-derived factor IX products, as no comparator studies were available. A human plasma fraction enriched with factor VIII inhibitor bypassing activity is only approved for patients with existing factor IX inhibitors and is therefore not considered as an appropriate comparator therapy for the present therapeutic indication.

The active ingredient etranacogene dezaparvovec is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 23.02.2023). Based on the generally accepted state of medical knowledge, etranacogene dezaparvovec is not determined to be an appropriate comparator therapy for the present resolution.

In the overall view of the body of evidence, the recombinant and human plasma-derived factor IX preparations are to be regarded as equivalent and are therefore equally eligible as appropriate comparator therapy. The additional benefit can be proven compared to one of the therapy options mentioned; usually, this can be done within the framework of a single-comparator study.

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

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

2.1.3 Extent and probability of the additional benefit

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

For patients of all age groups with haemophilia B, the additional benefit of eftrenonacog alfa compared to the appropriate comparator therapy is not proven.

Justification:

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

Supportively, the pharmaceutical company presents the four single-arm, non-randomised, uncontrolled studies B-LONG, Kids B-LONG, PUPs B-LONG and B YOND with male patients with severe haemophilia B (defined by ≤ 2 I.U./dl endogenous factor IX activity).

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

Overall, on the basis of the studies presented, no additional benefit can be derived for patients of all age groups with haemophilia B compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the medicinal product Alprolix with the active ingredient eftrenonacog alfa due to the exceeding of the € 30 million turnover limit.

Alprolix (active ingredient eftrenonacog alfa) has been approved as an orphan drug and is used for the treatment and prevention of bleeding in patients with haemophilia B (congenital factor IX deficiency) in all age groups.

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

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

Supportively, the pharmaceutical company presents the four single-arm, non-randomised, uncontrolled studies B-LONG, Kids B-LONG, PUPs B-LONG and B YOND with male patients with severe haemophilia B (defined by ≤ 2 I.U./dl endogenous factor IX activity). The presented single-arm studies are unsuitable for the assessment of an additional benefit due to the lack of comparison with the appropriate comparator therapy.

In the overall assessment, the additional benefit of eftrenonacog alfa for patients of all age groups with haemophilia B compared to 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).

Analogous to the pharmaceutical company's approach, the G-BA bases the present resolution on the patient numbers stated in the resolution to amend the Pharmaceuticals Directive: Annex XII - Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V on albutrepenonacog alfa (exceeding € 50 million turnover limit: haemophilia B, congenital factor IX deficiency).

Both the upper and lower limit figures are subject to uncertainties due to the currently available annual reports of the German Haemophilia Registry (DHR) for 2019 and 2020 and may tend to be underestimated.

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 Alprolix (active ingredient: eftrenonacog alfa) at the following publicly accessible link (last access: 15 January 2024):

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

Treatment with eftrenonacog alfa should only be initiated and monitored by doctors experienced in treating patients with haemophilia B.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 January 2024).

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Eftrenonacog alfa	Continuously, 1 x every 7 or 1 x every 10 days	52.1 - 36.5	1	52.1 - 36.5
Appropriate comparator therapy				
recombinant blood coagulation factor IX preparations				
Albutrepenonacog alfa	Continuously, 1 x every 7 days or every 10 to 14 days	52.1 or 26.1 – 36.5	1	52.1 or 26.1 – 36.5
Nonacog alfa	Continuously, 1 x every 3 to 4 days	91.3 - 121.7	1	91.3 - 121.7
Nonacog beta pegol	Continuously, 1 x every 7 days	52.1	1	52.1
Nonacog gamma	Continuously, 1 x every 3 to 4 days	91.3 - 121.7	1	91.3 - 121.7
Blood coagulation factor IX preparations derived from human blood plasma				
Human plasma-derived preparations[4]	Continuously, every 3 to 4 days	91.3 – 121.7	1	91.3 – 121.7

Consumption:

The theoretical annual consumption of eftrenonacog alfa and the active ingredients (factor IX preparations) of the appropriate comparator therapy required for the prevention of bleeding in patients with severe haemophilia B is presented. Treatment with human plasma preparations is only recommended from the age of 6.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies

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

from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Consumption is calculated per injection for the relevant age groups (children aged below 6 years, children aged 6 to below 12 years, adolescents aged 12 to below 18 years and adults) according to the respective product information.

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population"[5] as well as "Microcensus 2021 – body measurements of the population"[6] were applied. For body weight, the average weight of an adult male aged 18 years and over is therefore assumed to be 85.8 kg. For the underlying weight in the respective male age groups, the ranges were determined from 12 to under 18 years (47.6 kg - 74.6 kg), from 6 to under 12 years (24.0 kg - 42.7 kg) and from under 1 to under 6 years (7.8 kg - 21.0 kg).

The following dosage ranges are used for the cost calculation: For the calculation of the upper cost range, the dosage with the most frequent application and the highest body weight of the respective age group is used. For the calculation of the lower cost limit, the dosage with the largest interval and the lowest body weight of the respective age range is used. Shorter dosing intervals or higher doses may be generally required in some cases, especially in younger patients.

Since factor IX preparations can be stored only for a maximum of 8 hours after reconstitution, discarding must be taken into account, consequently the consumption per injection is presented. The consumption of vials and pre-filled syringes was optimised according to the packaging size on the basis of the weight-adjusted demand for factor IX I.U./ injection. For example, for an adult requiring 1708 I.U./ injection, this was composed of three vials each of 1,000 I.U., 500 I.U. and 250 I.U. of factor IX each.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Eftrenonacog alfa	50 – 100 I.U./kg	**Adults**			
		4,290 – 8,580 I.U.	2 x 2,000 I.U. + 1 x 500 I.U. - 2 x 3,000 I.U. + 1 x 2,000 I.U. + 1 x 500 I.U. + 1 x 250 I.U.	52.1 – 36.5	104.2 x 2,000 I.U. + 52.1 x 500 I.U. - 73.0 x 3,000 I.U. + 36.5 x 2,000 I.U. + 36.5 x 500 I.U. + 36.5 x 250 I.U.
		12 to < 18 years			

[5] Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de

[6] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
		2,380 I.U. - 7,460 I.U.	1 x 2,000 I.U. + 1 x 500 I.U. 2 x 3,000 I.U. + 1 x 1,000 I.U. + 1 x 500 I.U.	52.1 36.5	52.1 x 2,000 I.U. + 52.1 x 500 I.U. 73.0 x 3,000 I.U. + 36.5 x 1,000 I.U. + 36.5 x 500 I.U.
	50 – 60 I.U./kg	**6 to < 12 years**			
		1,200 I.U. 2,562 I.U.	1 x 1,000 I.U. + 1 x 250 I.U. 1 x 2,000 I.U. + 1 x 500 I.U. 1 x 250 I.U.	52.1 52.1	52.1 x 1,000 I.U. + 52.1 x 250 I.U. 52.1 x 2,000 I.U. + 52.1 x 500 I.U. + 52.1 x 250 I.U.
		0 to < 6 years			
		390 I.U. 1,260 I.U.	1 x 500 I.U. 1 x 1,000 I.U. + 1 x 500 I.U.	52.1 52.1	52.1 x 500 I.U. 52.1 x 1,000 I.U. + 52.1 x 500 I.U.
Appropriate comparator therapy					
recombinant blood coagulation factor IX preparations					
Albutrepenon acog alfa	35 – 50 I.U. /kg	**Adults**			
		3,003 I.U. – 4,290 I.U.	1 x 2,000 I.U. + 1 x 1,000 I.U. + 1 x 250 I.U. - 2 x 2,000 I.U. + 1 x 500 I.U.	52.1	52.1 x 2,000 I.U. + 52.1 x 1,000 I.U. + 52.1 x 250 I.U. - 104.2 x 2,000 I.U. + 52.1 x 500 I.U.
		12 to < 18 years			
		1,666 I.U. 3,730 I.U.	1 x 1,000 I.U. + 1 x 500 I.U. + 1 x 250 I.U. 1 x 3,500 I.U. + 1 x 250 I.U.	52.1 52.1	52.1 x 1,000 I.U. + 52.1 x 500 I.U. + 52.1 x 250 I.U. 52.1 x 3,500 I.U. + 52.1 x 250 I.U.
	75 I.U.	**Adults**			
		6,435 I.U.	1 x 3,500 I.U. + 1 x 2,000 I.U. + 1 x 1,000 I.U.	26.1 – 36.5	26.1 x 3,500 I.U. + 26.1 x 2,000 I.U. + 26.1 x 1,000 I.U. - 36.5 x 3,500 I.U. + 36.5 x 2,000 I.U. + 36.5 x 1,000 I.U.
		12 to < 18 years			

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
		3,570 I.U.	1 x 3,500 I.U. + 1 x 250 I.U.	26.1	26.1 x 3,500 I.U. + 26.1 x 250 I.U.
		5,595 I.U.	1 x 3,500 I.U. + 1 x 2,000 I.U. + 1 x 250 I.U.	36.5	36.5 x 3,500 I.U. + 36.5 x 2,000 I.U. + 36.5 x 250 I.U.
	35 – 50 I.U. /kg	**6 to < 12 years**			
		840 I.U.	1 x 1,000 I.U.	52.1	52.1 x 1,000 I.U.
		2,135 I.U.	1 x 2,000 I.U. + 1 x 250 I.U.	52.1	52.1 x 2,000 I.U. + 52.1 x 250 I.U.
		0 to < 6 years			
		273 I.U.	1 x 500 I.U.	52.1	52.1 x 500 I.U.
		1,050 I.U.	1 x 1,000 I.U. + 1 x 250 I.U.	52.1	52.1 x 1,000 I.U. + 52.1 x 250 I.U.
Nonacog alfa	40 I.U./kg	**Adults**			
		3,432 I.U.	1 x 3,000 I.U. + 1 x 500 I.U.	91.3 – 121.7	91.3 x 3,000 I.U. + 91.3 x 500 I.U. - 121.7 x 3,000 I.U. + 121.7 x 500 I.U.
		12 to < 18 years			
		1,904 I.U.	1 x 2,000 I.U.	91.3	91.3 x 2,000 I.U.
		2,984 I.U.	1 x 3,000 I.U.	121.7	121.7 x 3,000 I.U.
		6 to < 12 years			
		960 I.U.	1 x 1,000 I.U.	91.3	91.3 x 1,000 I.U.
		1,708 I.U.	1 x 1,000 I.U. + 1 x 500 I.U. + 1 x 250 I.U.	121.7	121.7 x 1,000 I.U. + 121.7 x 500 I.U. + 121.7 x 250 I.U.
		0 to < 6 years			
		312 I.U.	1 x 500 I.U.	91.3	91.3 x 500 I.U.
		840 I.U.	1 x 1,000 I.U.	121.7	121.7 x 1,000 I.U.
Nonacog beta pegol	40 I.U. /kg	**Adults**			
		3,432 I.U.	1 x 2,000 I.U. + 1 x 1,000 I.U. + 1 x 500 I.U.	52.1	52.1 x 2,000 I.U. + 52.1 x 1,000 I.U. + 52.1 x 500 I.U.
		12 to < 18 years			
		1,904 I.U.	1 x 2,000 I.U.	52.1	52.1 x 2,000 I.U.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
		2,984 I.U.	1 x 2,000 I.U. 1 x 1,000 I.U.	52.1	52.1 x 2,000 I.U. + 52.1 x 1,000 I.U.
		6 to < 12 years			
		960 I.U.	1 x 1,000 I.U.	52.1	52.1 x 1,000 I.U.
		1,708 I.U.	1 x 2,000 I.U.	52.1	52.1 x 2,000 I.U.
		0 to < 6 years			
		312 I.U.	1 x 500 I.U.	52.1	52.1 x 500 I.U.
		840 I.U.	1 x 1,000 I.U.	52.1	52.1 x 1,000 I.U.
Nonacog gamma	40 - 60 I.U./kg	**Adults**			
		3,432 I.U. - 5,148 I.U.	1 x 3,000 I.U. + 1 x 500 I.U. - 1 x 3,000 I.U. + 1 x 2,000 I.U. + 1 x 250 I.U.	91.3 – 121.7	91.3 x 3,000 I.U. + 91.3 x 500 I.U. - 121.7 x 3,000 I.U. + 121.7 x 2,000 I.U. + 121.7 x 250 I.U.
		12 to < 18 years			
		1,904 I.U.	1 x 2,000 I.U.	91.3	91.3 x 2,000 I.U.
		4,476 I.U.	1 x 3,000 I.U. + 1 x 1,000 I.U. + 1 x 500 I.U.	121.7	121.7 x 3,000 I.U. + 121.7 x 1,000 I.U. + 121.7 x 500 I.U.
	40 - 80 I.U./kg	**6 to < 12 years**			
		960 I.U.	1 x 1,000 I.U.	91.3	91.3 x 1,000 I.U.
		3,416 I.U.	1 x 3,000 I.U. + 1 x 500 I.U.	121.7	121.7 x 3,000 I.U. + 121.7 x 500 I.U.
		0 to < 6 years			
		312 I.U.	1 x 500 I.U.	91.3	91.3 x 500 I.U.
		1,680 I.U.	1 x 1,000 I.U. 1 x 500 I.U. + 1 x 250 I.U.	121.7	121.7 x 1,000 I.U. + 121.7 x 500 I.U. + 121.7 x 250 I.U.
Coagulation factor IX preparations derived from human blood plasma					
Human plasma-derived preparations[7]	20 I.U. /kg – 40 I.U. /kg	**Adults**			
		1,716 I.U.	2 x 1,000 I.U.	91.3	182.6 x 1,000 I.U.
		3,432 I.U.	3 x 1,000 I.U. + 1 x 500 I.U.	121.7	365.1 x 1,000 I.U. + 121.7 x 500 I.U.

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
		12 to < 18 years			
		952 I.U.	1 x 1,000 I.U.	91.3	91.3 x 1,000 I.U.
		2,984 I.U.	3 x 1,000 I.U.	121.7	365.1 x 1,000 I.U.
		6 to < 12 years			
		480 I.U.	1 x 500 I.U.	91.3	91.3 x 500 I.U.
		1,708 I.U.	2 x 1,000 I.U.	121.7	243.4 x 1,000 I.U.

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Eftrenonacog alfa 250 I.U.	1 PSI	€ 474.38	€ 2.00	€ 0.00	€ 472.38
Eftrenonacog alfa 500 I.U.	1 PSI	€ 937.42	€ 2.00	€ 0.00	€ 935.42
Eftrenonacog alfa 1,000 I.U.	1 PSI	€ 1,853.31	€ 2.00	€ 0.00	€ 1,851.31
Eftrenonacog alfa 2,000 I.U.	1 PSI	€ 3,648.96	€ 2.00	€ 0.00	€ 3,646.96
Eftrenonacog alfa 3,000 I.U.	1 PSI	€ 5,444.61	€ 2.00	€ 0.00	€ 5,442.61
Appropriate comparator therapy					
recombinant blood coagulation factor IX preparations					
Albutrepenonacog alfa 250 I.U.	1 PSI	€ 457.97	€ 2.00	€ 24.73	€ 431.24
Albutrepenonacog alfa 500 I.U.	1 PSI	€ 904.64	€ 2.00	€ 49.46	€ 853.18
Albutrepenonacog alfa 1,000 I.U.	1 PSI	€ 1,789.72	€ 2.00	€ 98.92	€ 1,688.80
Albutrepenonacog alfa 2,000 I.U.	1 PSI	€ 3,521.78	€ 2.00	€ 197.84	€ 3,321.94
Albutrepenonacog alfa 3,500 I.U.	1 PSI	€ 6,119.88	€ 2.00	€ 346.22	€ 5,771.66

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Nonacog alfa 250 I.U.	1 DSS	€ 287.30	€ 2.00	€ 15.28	€ 270.02
Nonacog alfa 500 I.U.	1 DSS	€ 563.25	€ 2.00	€ 30.56	€ 530.69
Nonacog alfa 1,000 I.U.	1 DSS	€ 1,115.18	€ 2.00	€ 61.12	€ 1,052.06
Nonacog alfa 2,000 I.U.	1 DSS	€ 2,197.97	€ 2.00	€ 122.23	€ 2,073.74
Nonacog alfa 3,000 I.U.	1 DSS	€ 3,268.12	€ 2.00	€ 183.35	€ 3,082.77
Nonacog beta pegol 500 I.U.	1 PSI	€ 958.37	€ 2.00	€ 52.43	€ 903.94
Nonacog beta pegol 1,000 I.U.	1 PSI	€ 1,893.91	€ 2.00	€ 104.87	€ 1,787.04
Nonacog beta pegol 2,000 I.U.	1 PSI	€ 3,730.15	€ 2.00	€ 209.74	€ 3,518.41
Nonacog gamma 250 I.U.	1 PSI	€ 280.29	€ 2.00	€ 14.89	€ 263.40
Nonacog gamma 500 I.U.	1 PSI	€ 549.27	€ 2.00	€ 29.78	€ 517.49
Nonacog gamma 1,000 I.U.	1 PSI	€ 1,087.26	€ 2.00	€ 59.57	€ 1,025.69
Nonacog gamma 2,000 I.U.	1 PSI	€ 2,143.79	€ 2.00	€ 119.14	€ 2,022.65
Nonacog gamma 3,000 I.U.	1 PSI	€ 3,186.84	€ 2.00	€ 178.71	€ 3006.13
Blood coagulation factor IX preparations derived from human blood plasma					
ALPHANINE 500 I.U.	1 DSS	€ 463.30	€ 2.00	€ 25.03	€ 436.27
ALPHANINE 1,000 I.U.	1 DSS	€ 915.30	€ 2.00	€ 50.05	€ 863.25
Abbreviations: PSI = powder and solvent for solution for injection; DSS = dry substance with solvent					

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Costs for additionally required SHI services:

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

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

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

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

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

Basic principles of the assessed medicinal product

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

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

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

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

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

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

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or

- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient:

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

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

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

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

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

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

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

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same

combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

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

Exception to the designation

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

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

Legal effects of the designation

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

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Patients of all age groups with haemophilia B

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 20 December 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 July 2023 the pharmaceutical company submitted a dossier for the benefit assessment of eftrenonacog alfa to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 6 VerfO.

By letter dated 1 August 2023 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 eftrenonacog alfa.

The dossier assessment by the IQWiG was submitted to the G-BA on 18 October 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2023. The deadline for submitting statements was 22 November 2023.

The oral hearing was held on 11 December 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 23 January 2024, and the proposed resolution was approved.

At its session on 1 February 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	20 December 2022	Determination of the appropriate comparator therapy
Working group Section 35a	5 December 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	11 December 2023	Conduct of the oral hearing, if necessary: Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	19 December 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	23 January 2024	Concluding discussion of the draft resolution
Plenum	1 February 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 1 February 2024

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

Prof. Hecken