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 According to Section 35a SGB V – Emicizumab

of 20 September 2018

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 emicizumab in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 April 2018. 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, number 1 VerfO on 27 March 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 2 July 2018, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of emicizumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional

benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of emicizumab.

In the light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at the following assessment:

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

2.1.1 Approved therapeutic indication of emicizumab (Hemlibra®) in accordance with product information

Hemlibra® is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A and factor VIII inhibitors. Hemlibra® can be used in all age groups.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for emicizumab as routine prophylaxis for the prevention of bleeding or the reduction of the frequency of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) and factor VIII inhibitors is:

- a patient-individual therapy taking into account factors such as the inhibitor titre, bleeding events, bleeding risk, and tolerability using a product with bypassing activity (human plasma fraction enriched with factor VIII inhibitor bypassing activity)

The marketing authorisations of the respective medicinal products must be observed.

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.

[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. Various authorised plasmatic or recombinant factor VIII preparations are available for the prophylaxis of bleeding, and a human plasma fraction (FEIBA®) enriched with factor VIII inhibitor bypassing activity is approved for routine prophylaxis as well as for treatment on demand. NovoSeven, on the other hand, is not approved for routine prophylaxis but rather only for the "prophylaxis of bleeding in connection with surgical or invasive procedures"; for this reason, only FEIBA® as a basically approved bypassing product can be considered as an appropriate comparator therapy.

On 2. Within the framework of statutory health insurance, non-medicinal treatments for the prophylaxis of bleeding in haemophilia A patients with inhibitors are not considered an appropriate comparator therapy.

On 3. For the treatment of haemophilia A with inhibitors, the G-BA has not passed any resolutions on the benefit assessment of medicinal products with new active ingredients according to 35a SGB V. Accordingly, the G-BA did not find any patient-relevant additional benefit for any medicinal product in this indication.

On 4. The generally accepted state of medical knowledge was illustrated by systematic research for guidelines and 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 in accordance with Section 35a SGB V". This results in a body of evidence for haemophilia A patients with factor VIII inhibitors that is limited in the overall level of evidence. It is generally assumed that the patient population in this indication is factor VIII haemophilia patients requiring substitution.

In everyday care, patient-individual factors such as the inhibitor titre, bleeding events, bleeding risk, tolerability, or a response to previous treatments, including immunotolerance induction with factor VIII preparations are decisive for the individual therapy assessment of the physician.

As a rule, patients with haemophilia A and inhibitors first undergo immunotolerance induction with factor VIII products. An exclusively higher dosage of factor VIII products with existing inhibitors is generally not a suitable therapy option because the inhibitors eliminate the factor VIII administered and thus neutralise the desired coagulating effect. However, after a successful immunotolerance induction, no or significantly fewer inhibitory antibodies against factor VIII are formed in the blood so that prophylaxis with factor VIII products can be resumed. Only after failure of this therapy and/or in the presence of a high inhibitor titre are patients eligible for therapy with a product with bypassing activity (activated prothrombin complex).

Even if permanent prophylaxis with a product with bypassing activity is generally indicated in the relevant therapeutic indication, as part of routine prophylaxis, it is possible to switch from long-term prophylaxis with FEIBA® to treatment on demand with FEIBA® on demand both in alternation depending on patient-individual criteria such as inhibitor titre, bleeding events, bleeding risk, and tolerability.

The efficacy of a therapy with bypassing products is not the same for all patients in the indication area. Accordingly, there are patients for whom regular permanent prophylaxis is out of the question. Irrespective of a decision on the suitable patient-individual prophylaxis, it

must be possible for all patients to receive regular treatment on demand for bleeding events ("rescue therapy").

In summary, against the background of the authorised therapy options for the treatment of haemophilia A with inhibitors for all age groups, a patient-individual therapy using a product with bypassing activity (human plasma fraction enriched with factor VIII inhibitor bypassing activity) depending on factors such as the inhibitor titre, bleeding events, bleeding risk, and tolerability is considered appropriate.

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

2.1.3 Extent and probability of the additional benefit

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

Comments regarding the change of the appropriate comparator therapy

A deviation from the originally determined appropriate comparator therapy after the oral hearing, which is also supported by the comments of the medical societies on the therapy situation of patients with haemophilia A and inhibitors, is regarded as justified. As a rule, patients with haemophilia A and inhibitors initially undergo immunotolerance induction with factor VIII products. Thus, solely higher doses of factor VIII products with existing inhibitors are generally not a suitable therapy option.

Therefore, only products with bypassing activity (human plasma fraction enriched with factor VIII inhibitor bypassing activity) in a patient-individual therapy regime – depending on factors such as the inhibitor titre, bleeding events, bleeding risk, and tolerability – can be considered as an appropriate comparator therapy.

a) Patients with haemophilia A and factor VIII inhibitors for whom the sole treatment on demand with bypassing products represents a patient-individual therapy

   For patients with haemophilia A and factor VIII inhibitors for whom the sole treatment on demand with bypassing products represents a patient-individual therapy, there is a hint for a non-quantifiable additional benefit for emicizumab as routine prophylaxis compared with the appropriate comparator therapy of a single treatment on demand with bypassing preparations.

Justification:

The benefit assessment is based, among other things, on the directly comparative HAVEN 1 authorisation study. This is an open, actively controlled, multi-centre Phase III study that, within its randomised part, compares emicizumab as routine prophylaxis with treatment on demand with bypassing products in adults and adolescents (≥ 12 years) with haemophilia A and factor VIII inhibitors over a period of 6 months. Pre-treated patients (adults and adolescents ≥ 12 years) with congenital haemophilia A and inhibitors and high titre factor

VIII inhibitors (≥ 5 Bethesda units (BE)) in their medical history were included. The patients in the randomised part of the study (total n=53) had previously been treated with bypassing products and were randomised at a ratio of 2:1 to long-term prophylaxis with emicizumab (Arm A, n = 35) or treatment on demand with bypassing products (Arm B, n = 18). In addition to these randomised arms, the study also included two other non-randomised arms in which the patients were treated prophylactically with emicizumab. Because of the lack of randomisation, these are not relevant for the question of benefit assessment.

Extent and probability of the additional benefit for patient population a)

Mortality

In the HAVEN 1 study, no events occurred in the mortality category at Week 25.

Morbidity

In the present assessment, morbidity is represented by annualised bleeding rates and health status (*EQ-5D-VAS*).

Annualised bleeding rates

Depending on the extent and frequency, bleeding is patient-relevant. The *annualised bleeding rate* (ABR) morbidity endpoint was the primary endpoint in the HAVEN 1 study. Results are available for total ABR ("all bleedings") as well as annualised rates of treated bleedings, joint haemorrhages, and target joint haemorrhages. The target joints were defined as large joints (e.g. hip, elbow, hand, shoulder, knee, and ankle joints) in which at least three bleedings occurred (in the same joint) over a period of 24 weeks prior to the start of study. For the benefit assessment, the comparison of bleeding rates between emicizumab prophylaxis and treatment on demand with bypassing products is taken into account. For all bleeding rates collected, there is a statistically significant ABR ratio in favour of prophylaxis with emicizumab. Under emicizumab prophylaxis, the annualised bleeding rates for both treated bleeding and joint bleeding are significantly reduced compared with treatment on demand with bypassing products [ABR ratio (treated bleeding) 0.13 [95% CI 0.06; 0.28]; p value < 0.001; ABR ratio (joint bleeding) 0.11 [0.03; 0.52]; p = 0.005].

In the comparator arm, the bleeding rate can be regarded as an expression of the severity of the disease because of the short half-life of a treatment on demand. In contrast to the treatment on demand with bypassing products alone, there is a positive effect in favour of long-term prophylaxis with emicizumab.

Health status using EQ-5D VAS

In the HAVEN 1 study, the health status of the patients was assessed using EQ-5D VAS. The mean change in *EQ-5D VAS* from start of study to treatment week 25 is patient-relevant and used for assessment. There is a statistically significant advantage in favour of emicizumab prophylaxis compared to treatment on demand with bypassing products (MD 9.72 [1.82; 17.62]; p value = 0.017). The effect cannot be classified as clinically relevant

because the 95% confidence interval of the standardised mean difference is not completely outside the irrelevance range of −0.2 to 0.2 (Hedges' g: 0.74 [95% CI 0.11; 1.37]).

Health-related quality of life

Haem-A-QoL, Haemo-QoL SF

In the HAVEN 1 study, the disease-specific quality of life was assessed using the *Haem-A-QoL* questionnaire for patients aged 18 years and older (n = 47) and the *Haemo-QoL SF* for patients under 18 years (n = 6).

The *Haem-A-QoL* is a disease-specific questionnaire to assess the health-related quality of life of haemophilia patients and consists of 46 items in 10 domains, the mean of which is used to calculate a total score. The domains as well as the total score represent a value range from 0 to 100. Lower values mean a better health-related quality of life.

For the overall *Haem-A-QoL* score, a statistically significant effect can be derived in favour of emicizumab prophylaxis compared with treatment on demand with bypassing products (MD −14,01 [−22,45; −5,56]; p value = 0.002). In addition, the five *Haem-A-QoL* domains "physical health", "feelings", "attitude towards oneself", "treatment", and "thoughts about the future" each show a statistically significant advantage in favour of emicizumab prophylaxis compared with treatment on demand with bypassing products. The effects can be classified as clinically relevant, since the 95% confidence interval of the standardised mean value differences is completely outside the irrelevance range of −0.2 to 0.2 for both the *Haem-A-QoL* total score (*Hedges' g*: −1.06 [95% CI −1.76; −0.36]) and for four of the five statistically significant domains of the *Haem-A-QoL* mentioned above (with the exception of the domain "Thoughts about the future"). However, on the basis of this evaluation alone (Hedges' g), the clinically relevant advantage cannot be quantified with sufficient certainty.

For the domains "dealing with haemophilia" and "relationships and partnership", there are no statistically significant group differences between intervention and control. For the remaining three of the 10 domains of *Haem-A-QoL*, less than 70% of the patients had values available. Thus, no usable data could be depicted for these domains because of a lack of information on missing values.

The age-specific questionnaire *Haemo-QoL SF* used to assess the quality of life of patients under 18 years of age did not provide any usable data because the proportion of patients in this age group within the study arms relevant for the benefit assessment was too small (4 patients in the intervention arm, 2 patients in the comparator arm).

Overall, there is a statistically significant, clinically relevant effect in favour of emicizumab for the health-related quality of life, the extent of which cannot be quantified.

Side effects

SAE, discontinuation because of AE

For the patient-relevant endpoints SAE and discontinuation because of AE, there are no statistically significant differences between emicizumab prophylaxis and comparative treatment with bypassing products in the on-demand regime.

Thromboembolic events, thrombotic microangiopathy, reaction at the injection site

For the patient-relevant endpoints "thromboembolic events" and "thrombotic microangiopathy", there are also no statistically significant advantages or disadvantages of prophylaxis with emicizumab compared with treatment on demand with bypassing products. During the weekly subcutaneous therapy with emicizumab, events of the preferred term (PT) "reactions at the injection site" occurred statistically significantly more frequently than during treatment with bypassing preparations, which were administered i.v. according to the individual needs of the patient. The "reactions at the injection site" are not to be classified as serious AEs.

Overall assessment for patient population a)

For the benefit assessment of the active ingredient emicizumab for the routine prophylaxis of bleeding in the case of haemophilia A and factor VIII inhibitors for whom the sole treatment on demand with bypassing products is a patient-individual therapy, the results of the randomised, double-blind HAVEN 1 RCT are available. Results on mortality, morbidity, quality of life and side effects are available for this study.

In the endpoint category morbidity, for the endpoint annualised bleeding rates, especially for treated bleeding and joint haemorrhages, there are statistically significant, positive effects in favour of emicizumab prophylaxis compared with treatment on demand with bypassing products. Advantages are seen in the ABR which are assessed as non-quantifiable, in particular because of uncertainties regarding the appropriateness of the therapy regimes used (prophylaxis vs treatment on demand). In addition, no clinical relevance can be derived for the statistically significant benefit for emicizumab in the patient-relevant endpoint of health status.

In the quality of life category, the overall Haem-A-QoL score as well as individual domains of *Haem-A-QoL* show statistically significant, clinically relevant advantages under emicizumab prophylaxis over treatment on demand with bypassing products. The extent of the benefits is non-quantifiable.

In the category of side effects, there are neither advantages nor disadvantages for emicizumab compared with treatment on demand with bypassing products for the total rates of SAE or discontinuations because of AE. For "reactions at the injection site", there is a statistically significant disadvantage for emicizumab compared with control intervention with bypassing products. However, this is not considered serious. But the small number of patients in the HAVEN 1 study currently does not allow a final assessment of the side effect profile of emicizumab. Furthermore, long-term data on the safety and immunogenicity of emicizumab are lacking.

In the overall view, in the population depicted here for patients for whom the sole treatment on demand with bypassing products is the patient-individual therapy, in the endpoint categories morbidity and quality of life, there are exclusively positive non-quantifiable effects for emicizumab compared with the appropriate comparator therapy. These are not called into question by the results of the side effects category.

As a result, on the basis of the criteria in Section 5, paragraph 7 of the AM-NutzenV, the G-BA classifies the extent of the additional benefit for emicizumab for the routine prophylaxis of

bleeding in haemophilia A and factor VIII inhibitors as non-quantifiable compared with treatment on demand with bypassing products for patients for whom the sole treatment on demand with bypassing products represents a patient-individual therapy. Thus, on the basis of the submitted data, it is not possible to quantitatively assess the extent of the effect or the additional benefit into one of the three categories 'low', 'considerable' or 'substantial'.

Reliability of data (probability of additional benefit) for patient population a)

The HAVEN 1 study is a randomised, double-blind Phase III study for the assessment of the additional benefit.

In the context of the German health care system, it can be assumed that the treatment on demand with bypassing products alone only represents the patient-individual therapy with bypassing activity (human plasma fraction enriched with factor VIII inhibitor bypassing activity) to a limited extent depending on factors such as the inhibitor titre, bleeding events, and bleeding risk. The decision against routine prophylaxis and for treatment on demand with bypassing products should be made based on patient-individual criteria such as the inhibitor titre, bleeding events, bleeding risk, or tolerability. The data presented by the pharmaceutical company for the HAVEN 1 study show that only a small proportion of patients opted for treatment on demand with a bypassing product for reasons of efficacy or tolerability. The majority of patients in the control arm decided against prophylaxis with a bypassing product for other reasons. It is therefore questionable to what extent the patient-individual therapy has been used regularly in the control arm. There are therefore significant uncertainties regarding the transferability of the study results to the German health care context.

According to the baseline criteria, the sub-population of the HAVEN 1 study relevant and depicted for the benefit assessment included both patients who had already undergone immunotolerance induction and patients who had not yet received ITT. It therefore remains unclear to what extent the patients included actually represent those patients for whom a patient-individual therapy using a product with bypassing activity is appropriate depending on factors such as inhibitor titre, bleeding events, and efficacy because ITT (in parallel or prior to treatment with bypassing products) may be an option for at least some patients. Also, only patients with a high inhibitor titre (≥ 5 BE) were included in the HAVEN 1 study.

In the overall view, the uncertainties described justify a classification of the reliability of data as a hint for an additional benefit.

b) Patients with haemophilia A and factor VIII inhibitors for whom a therapy other than the sole treatment on demand with bypassing products represents a patient-individual therapy

For patients with haemophilia A and factor VIII inhibitors for whom a therapy other than the sole treatment on demand with bypassing products represents a patient-individual therapy, the additional benefit for emicizumab as routine prophylaxis compared with the appropriate comparator therapy is not proven.

Justification:

For patients with haemophilia A and factor VIII inhibitors for whom a therapy other than the sole treatment on demand represents the patient-individual therapy, the pharmaceutical

company performed an adjusted, indirect comparison of emicizumab with FEIBA® as well as two (intra-individual) before-and-after comparisons. Furthermore, a non-adjusted indirect comparison based on individual study arms from different studies was also presented. In addition to the strong methodological limitations of a non-adjusted comparison based on single study arms, this could also not be taken into account because of the lack of comparability of the relevant study populations.

The adjusted, indirect comparison presented for the comparison of routine prophylaxis with emicizumab with the appropriate comparator therapy of routine prophylaxis with bypassing products (here: FEIBA®) was performed using a bridge comparator consisting of treatment on demand with bypassing agents. This indirect comparison is based on the HAVEN 1 study for emicizumab (see patient population a) and the PROOF and ProFEIBA studies for routine prophylaxis with bypassing products.

Because of methodological limitations, the indirect adjusted comparison is also not used for the benefit assessment. In particular, the similarity of the three studies included in the indirect comparison – among others with regard to patient characteristics at baseline, baseline bleeding risk, and unclear operationalisation of the collected endpoints to the annualised bleeding rates (treated vs all bleedings) – was insufficient.

The before and after comparison presented to answer the question of the benefit assessment is a comparison of routine prophylaxis with emicizumab and routine prophylaxis with bypassing products. A before-and-after comparison was performed for patients ≥ 12 years and for patients < 12 years. These intra-individual comparisons are based on data from patients who participated in both the observational study BH29768 (“before”) and one of the pivotal studies (“after”) – either HAVEN 1 (Arm C, patients ≥ 12 years) or HAVEN 2 (patients < 12 years).

Because of strong methodological limitations, these intra-individual comparisons cannot be considered for the question of benefit assessment. In the overall view, the bleeding rates observed in the non-interventional observational study BH29768 (NIS) cannot be interpreted meaningfully because the study was uncontrolled, particularly with regard to the application regimes of FEIBA® prophylaxis. The comparability of bleeding rates under different study conditions (uncontrolled treatment in NIS vs controlled study conditions in HAVEN 1 or HAVEN 2) can therefore not be assessed with sufficient certainty.

Further possible uncertainties exist because of unexplained drop-outs of patients prior to the transition from the BH29768 study to one of the HAVEN studies. Without sufficient explanation of the reasons that led to these patients not being further treated in the HAVEN studies, the data basis cannot be evaluated. Furthermore, for the patients who ultimately moved from the NIS to the HAVEN studies, there is no information on the length of the observation period in the NIS study. Even the evaluations of “formally therapy-faithful” patients submitted in addition to the statement do not increase the interpretability of the comparisons submitted. In addition, the written statement presented only selective evaluations for a few endpoints.

Because of the methodological limitations described, neither the intra-individual comparisons nor the adjusted, indirect comparison can be taken into account for the question of the benefit assessment.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI). The resolution will be based on the information from the dossier of the pharmaceutical company. These figures are based on figures from the German Haemophilia Register (Deutsches Hämophilieregister; DHR) and are subject to uncertainty. It cannot be assumed that all patients with haemophilia A in the German Haemophilia Register will be covered completely. It is also unclear which proportion of patients with haemophilia A and inhibitors is suitable for routine prophylaxis.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Hemlibra® (active ingredient: emicizumab) at the following publicly accessible link (last access: 5 September 2018):

http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/004406/WC500244743.pdf

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

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 September 2018).

Treatment period:

In patients with severe haemophilia A and inhibitors:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)
Medicinal product to be assessed			
Emicizumab[2]	continuously, 1 ×	52	1

[2] In the case of acute bleeding during routine prophylaxis with emicizumab, treatment on demand with products with bypassing activity may be used.

(Hemlibra®)	weekly		
Appropriate comparator therapy			
Human plasma fraction enriched with factor VIII inhibitor bypassing activity			
Product with bypassing activity (FEIBA®)	different for each individual patient		

Usage and consumption:

In patients with haemophilia A and inhibitors, the use of human plasma fraction enriched with factor VIII inhibitor bypassing activity 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 emicizumab and the active ingredients of the appropriate comparator therapy (activated prothrombin complex/bypassing product FEIBA) required for the routine prophylaxis of bleeding events in patients with haemophilia A and factor VIII inhibitors are presented. Consumption is calculated per injection for the relevant age groups (< 6 years, 6 to < 12 years, 12 to < 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[3]) according to the official representative statistic “Microcensus 2017” is assumed. Because of different body weights and the resulting discards, there are large differences in the treatment costs of children and adolescents within the age groups considered. For the calculation of the annual treatment costs, average body weights of 7.8 kg (for patients < 1 year), 21 kg (for patients from 5 to < 6 years), 24 kg (for patients from 6 years), 42.7 kg (for patients from 11 to < 12 years), 47.6 kg (for patients from 12 years), and 73.2 kg (for patients from 17 to < 18 years) are used for the respective male age group under 18 years.

For emicizumab, a subcutaneously applied maintenance dose of 1.5 mg/kg body weight once a week for all age groups is used in accordance with the product information. The initial dose is not taken into account for the cost calculation. It should be noted that different concentrations of Hemlibra® (30 mg/ml and 150 mg/ml) must not be combined when preparing the total volume for use. In the case of acute bleeding during routine prophylaxis with emicizumab, treatment on demand with products with bypassing activity may be used.

The human plasma fraction FEIBA® enriched with factor VIII inhibitor bypassing activity in a variable dosage regime can be considered as an appropriate comparator therapy. This differs from patient to patient and is therefore not depicted. In the case of acute bleeding, the routine prophylaxis with emicizumab may also include treatment on demand with products

[3] Statistisches Bundesamt [German Federal Office for statistics]. Microcensus 2017: Questions on health; body measurements of the population 2017 [online]. 2 August 2018 [Accessed: 8 August 2018]. URL: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

with bypassing activity. For both the medicinal product to be assessed and the appropriate comparator therapy, this occurs to varying degrees depending on the individual patient.

Because both FEIBA® and emicizumab can only be stored for a limited period of time after reconstitution, a discard must be taken into account; as a result, the consumption per injection is shown. However, it should be taken into consideration that the package sizes of emicizumab available result in a particularly high level of discard, especially among children.

The consumption of vials or prefilled syringes was divided into pack sizes based on the weight-adjusted demand. For example, for a patient requiring 109.8 mg emicizumab per treatment, the emicizumab was composed of two 150 mg/ml (0.4 ml) vials.

Designation of the therapy	Dose per kg/BW	Dose/patient/treatment day [mean body weight[3]]	Consumption by potency per treatment day	Treatment days/patient/year	Annually consumption by potency
Medicinal product to be assessed					
Emicizumab[2] (Hemlibra®)	1.5 mg	Adults 127.5 mg [85 kg]	Adults 1x 150 mg/ml (1ml)	52	Adults 52
		12 – < 18 years 71.4 – 109.8 mg [47.6– 73.2 kg]	12 – < 18 years 1 × 150 mg/ml (0.7 ml) – 2 × 150 mg/ml (0.4 ml)	52	12 – < 18 years 52–104
		6 – < 12 years 36 – 64.05 mg [24 – 42.7 kg]	6 – < 12 years 1 × 150 mg/ml (0.4 ml) – 1x 150 mg/ml (0.7 ml)	52	6 – < 12 years 52
		< 6 years 11.7 – 31.5 mg [7.8 – 21 kg]	< 6 years 1 × 30 mg/ml (1 ml) – 1 × 150 mg/ml (0.4 ml)	52	< 6 years 52
Appropriate comparator therapy					
Human plasma fraction enriched with factor VIII inhibitor bypassing activity					
Product with bypassing activity (FEIBA®)	50–100 U.	different for each individual patient			
U. = unit					

Costs:

Human plasma fraction enriched with factor VIII inhibitor bypassing activity is 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 human plasma fraction enriched with factor-VIII-inhibitor-bypassing activity 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[4]	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Emicizumab[2] (Hemlibra®)	30 mg/ml (1ml)	€ 3,070.80	€ 1.77	€ 172.10	€ 2,896.93
	150 mg/ml (0.4 ml)	€ 6,084.29	€ 1.77	€ 344.20	€ 5,738.32
	150 mg/ml (0.7 ml)	€ 10,604.52	€ 1.77	€ 602.35	€ 10,000.40
	150 mg/ml (1ml)	€ 15,124.73	€ 1.77	€ 860.50	€ 14,262.46

Designation of the therapy	Package size[4]	Costs (by potency)[5]
Appropriate comparator therapy		
Human plasma fraction enriched with factor VIII inhibitor bypassing activity		
Product with bypassing activity (FEIBA®)	500 U.	€ 803.25
	1,000 U.	€ 1,606.50

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 September 2018

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.

[4] for all active ingredients, the quantity per pack is 1 vial.
[5] The prices are made up of the manufacturer's selling price plus value-added tax.

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

In a letter dated 12 October 2017, received on 12 October 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 session on 12 December 2017. The consultation meeting took place on 20 December 2017.

On 27 March 2018, the pharmaceutical company submitted a dossier for the benefit assessment of emicizumab to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

By letter dated 29 March 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 emicizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 June 2018, and the written statement procedure was initiated with publication on the website of the G-BA on 2 July 2018. The deadline for submitting written statements was 23 July 2018.

The oral hearing was held on 6 August 2018.

By letter dated 6 August 2018, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 29 August 2018.

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 11 September 2018, and the proposed resolution was approved.

At its session on 20 September 2018, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	12 December 2017	Determination of the appropriate comparator therapy
Working group Section 35a	31 July 2018	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	6 August 2018	Conduct of the oral hearing; commissioning of the IQWiG with supplementary assessment of documents
Working group Section 35a	14 August 2018 28 August 2018 4 September 2018	Consultation on the dossier evaluation of the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal product	11 September 2018	Concluding discussion of the proposed resolution
Plenum	20 September 2018	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 September 2018

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

Prof Hecken