REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

HEMLIBRA

30 mg/ml – 1 ml solution for injection x 1 vial

150 mg/ml – 0.4 ml solution for injection x 1 vial

150 mg/ml – 0.7 ml solution for injection x 1 vial

150 mg/ml – 1 ml solution for injection x 1 vial

Emicizumab

Therapeutic indications	Hemlibra is indicated for routine prophylaxis of bleeding episodes in patients with: ● haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors ● severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without factor VIII inhibitors.
Start- end of the procedure	21.06.2019-30.09.2019
Final decision	Inclusion in Annex № 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the National Health Insurance Fund (NHIF).

Summary of the report on the clinical and pharmacoeconomic evaluation of the health technology of the medicinal product Hemlibra

Health problem

Hemophilia A is an inherited disease from the group of rare diseases. It is caused by a deficiency or a defective structure of coagulation factor VIII as a result of a mutation in the gene of the corresponding coagulation factor located on the long arm of the X chromosome. The main clinical manifestations of the disease are the hemorrhages. **Factor VIII (FVIII) is an essential protein for the coagulation system. In the complete absence of the FVIII the cascade of biochemical reactions gets interrupted and a blood clot cannot form.**
Due to the fact that hemophilia A is transmitted by X-linked recessive inheritance, the majority (approximately 90%) of patients are male, women are carriers of the disease. The sons of hemophiliacs are always healthy and their daughters are always carriers. Depending on the degree of reduction of factor VIII, hemophilia A is divided into three forms:

- Severe form - factor VIII below 1%

- Moderate form - factor VIII between 1 and 5%

- Mild form - factor VIII between 6 and 40%

About one-third of patients have *de novo* mutations without a family history of the disease. Hemophilia A leads to a tendency to bleed throughout life and is a serious chronic disease that can be fatal. The final diagnosis is established by quantification of FVIII. The specific mutation responsible for hemophilia can be identified by DNA-based mutation analysis. The most common genetic defect in severe Hemophilia A is intron 22 inversion.

Epidemiological data

The incidence of hemophilia A is approximately 1 in 5,000 live male births or 1 in 10,000 live births. Approximately 30% of cases occur spontaneously, without a previous family history of hemophilia. In a global study for 2017 conducted in 116 countries, the World Federation of Hemophilia (WFH) identified 158,225 people with hemophilia A. According to the WFH report, about 45% of men with hemophilia A have severe form of the disease, and 5,948 patients are with hemophilia A and inhibitors.

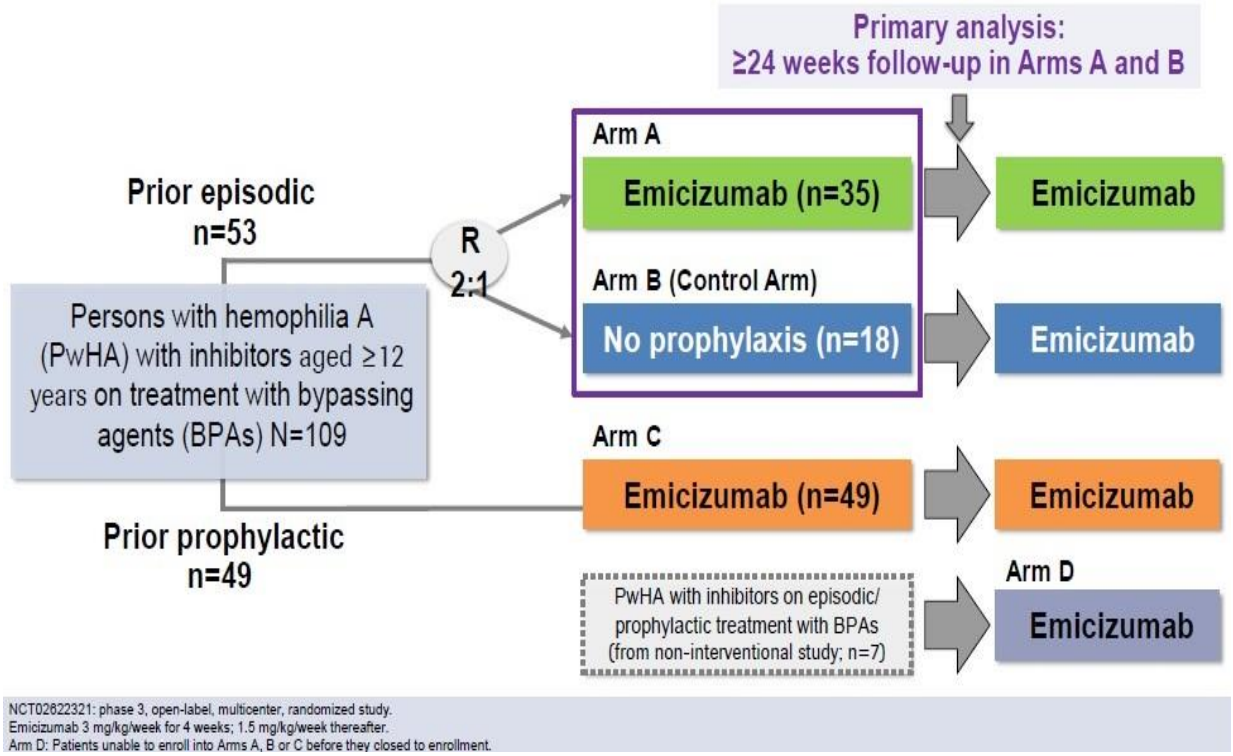
The number of patients with hemophilia A, hemophilia B, Von Willebrand disease and other rare coagulopathies in Bulgaria is about 600. Patients with hemophilia A are about 93%, and about 72% of patients have moderate and severe Hemophilia A and respectively need routine prophylaxis. Although hemophilia A is a rare disease, it has a significant social and economic burden on those affected and health systems. Complications associated with spontaneous and prolonged bleeding lead to increased morbidity in patients with haemophilia A, especially in patients with severe disease. Hemarthrosis - the most typical manifestation, most often in the knee, ankle and elbow joints. Soft tissue and muscle hematomas – most often after trauma, hematuria, epistaxis, gingivorrhagia, etc. The incidence of bleeding in children is higher than in adult patients. In patients with FVIII inhibitors for whom FVIII treatment remains ineffective, the severity of the disease is even greater than in patients without inhibitors.

Hemophilia A usually is not immediately life-threatening for patients in developed countries. Studies show that mortality in the haemophilia population is approximately twice that of the general population, with even higher mortality rates associated with severe haemophilia and the presence of inhibitors than in mild or moderate hemophilia. Uncommonly, but with potentially fatal consequences, patients with haemophilia A may develop intracranial or severe gastrointestinal bleeding. In patients with inhibitors is reported significantly higher mortality (up to 70% increased risk of death) than patients with haemophilia A without inhibitors.

Efficacy data

Clinical trial HAVEN 1 (BH29884)

The study evaluated prophylactic treatment with Emicizumab at a loading dose of 3 mg/kg/week for 4 weeks, followed by a maintenance dose of 1.5 mg/kg/week. The study had four therapeutic arms and patients were assigned based on their previous treatment with bypass products.



NIS - non-interventional study; R - randomization; 24-w BR - 24-week bleeding rate before enrollment in the study.

a) The first efficacy analysis is performed after all randomized patients (i.e., those assigned to Arm A or B) reach 24 weeks of the study or withdraw.

b) Patients participating in NIS BH29768 who have previously been treated sporadically with bypass products but cannot be included in arms A and B of the HAVEN 1 study prior to closure of randomization in them are included in arm D. Patients who previously were treated with prophylaxis with bypass products and which could not be included in arm C may also be included in arm D.

The sample size in HAVEN 1 is based on clinical and statistical indicators that reflect the limited number of haemophilia A patients with inhibitors and the desire to collect sufficient data to evaluate the safety and efficacy of Emicizumab. It was found that a sample size of 45 patients, assuming a randomization ratio of 2:1 (30 patients with prophylaxis in arm A and 15 patients without prophylaxis in Bcontrol), would achieve a power of more than 95% to detect a 78% reduction in bleeding during the efficacy period.

A significant and clinically significant reduction in bleeding frequency was observed for treatment-requiring, bleeding episodes and for all bleeding episodes in the HAVEN 1 study, in a randomized comparison of prophylactic treatment with Emicizumab versus non-prophylactic treatment, and an intra-individual comparison of patients from non-interventional study (NIS)

(BH29768) who were on prophylactic treatment with bypass products and switched to prophylactic treatment with Emicizumab.

The study reached the primary endpoint for reducing the incidence of bleeding (treated bleeding episodes) in prophylactic treatment with Emicizumab compared to episodic treatment. Prophylactic treatment with Emicizumab resulted in a statistically significant ($p < 0.0001$) and clinically significant 87% reduction in bleed rate for treated episodes (Annualised Bleed Rate (ABR) = 2.9) compared to episodic treatment (ABR = 23.3). A total of 22 of 35 patients (63%) in prophylactic treatment had 0 treated bleeding episodes while on prophylactic therapy with Emicizumab compared with 1 of 18 patients (6%) in episodic treatment.

All bleeding-related secondary endpoints were also reached in the study, showing a sustained and clinically significant reduction in bleed rates in patients with Emicizumab prophylaxis compared to those without prophylaxis.

An updated efficacy analysis was performed in the HAVEN 1 study, which provided data with a median efficacy period of 60.29 weeks (range: 0.1-94.3) for 113 patients. In general, the results of the updated efficacy analysis are consistent with those of the primary analysis. The longer time to evaluate efficacy, taking into account ABR results from 12-week intervals, showed an improvement (decrease in ABR) over time of the effect of prophylactic treatment with Emicizumab, resulting in better bleeding control.

Endpoint	Primary Analysis CCOD = 25 October 2016	Updated Analysis CCOD = 08 September 2017
	n=104[a]	n=113
Treated Bleeds		
ABR[b] (95% CI)	4.6 (2.74; 7.57)	2.7 (1.64; 4.35
Mean ABR (95% CI)	4.7 (1.47; 11.27)	2.8 (0.53; 8.45)
Median ABR (IQR)	0.0 (0.00;3.55)	0.0 (0.00;1.46)

The calculated mean ABR values for the treated bleeding episodes determined at the last 12 weeks decreased to week 12 (first interval) and the improvement was maintained after week 48; median values remain 0. Descriptive analysis of the number of bleeding episodes and ABR shows that most patients have 0-3

bleeding episodes for "all bleeds", "treated bleeds", "treated joint bleeds", and "treated target joint bleeds."

Clinical trial HAVEN 2: main clinical trial in children (BH29992)

Patients were treated with a loading weekly dose of 3 mg/kg for the first 4 weeks, followed by a maintenance dose of 1.5 mg/kg/week for 52 weeks. In case of suboptimal efficacy, the dose may be titrated according to protocol criteria.

Efficacy results are based on data from 23 patients <12 years of age treated for at least 12 weeks (as the study aims to examine the effect of treatment based on age <12). The median duration of efficacy follow-up for these patients was 38.1 weeks (range: 12.7 - 41.6). Baseline efficacy data indicate that bleeding is well controlled during prophylactic treatment with Emicizumab. The ABR value for treated bleeds was 0.2 (95% CI: 0.06; 0.62). No ABR value was calculated for treated target joint bleeds from the NB regression model because no cases of treated target joint bleeds were reported. At the end of the clinical data collection, 20 of 23 patients (87.0%) had 0 treated bleeds (ABR = 0) during prophylactic treatment with Emicizumab.

An interim analysis of intra-patient comparison showed that weekly prophylaxis with Emicizumab resulted in a clinically meaningful (99%) reduction in treated bleed rate after at least 12 weeks of treatment compared to the bleed rate determined in the NIS prior to enrollment in HAVEN 2.

Efficacy in patients ≤ 2 years of age

In the second interim analysis, efficacy was assessed in 59 pediatric patients <12 years of age who received weekly prophylactic treatment with Emicizumab for at least 12 weeks. 38 patients aged 6 to <12 years were included; 17 patients aged 2 to <6 years and 4 patients <2 years of age, with the main aim of the study being to investigate the effect of treatment in patients <12 years of age. The frequency of bleeding on an annual basis and the proportion of patients with zero bleeding episodes were calculated for 59 patients. The median follow-up time for these patients was 29.6 weeks (range: 18.4-63).

Summary of efficacy (primary analysis)

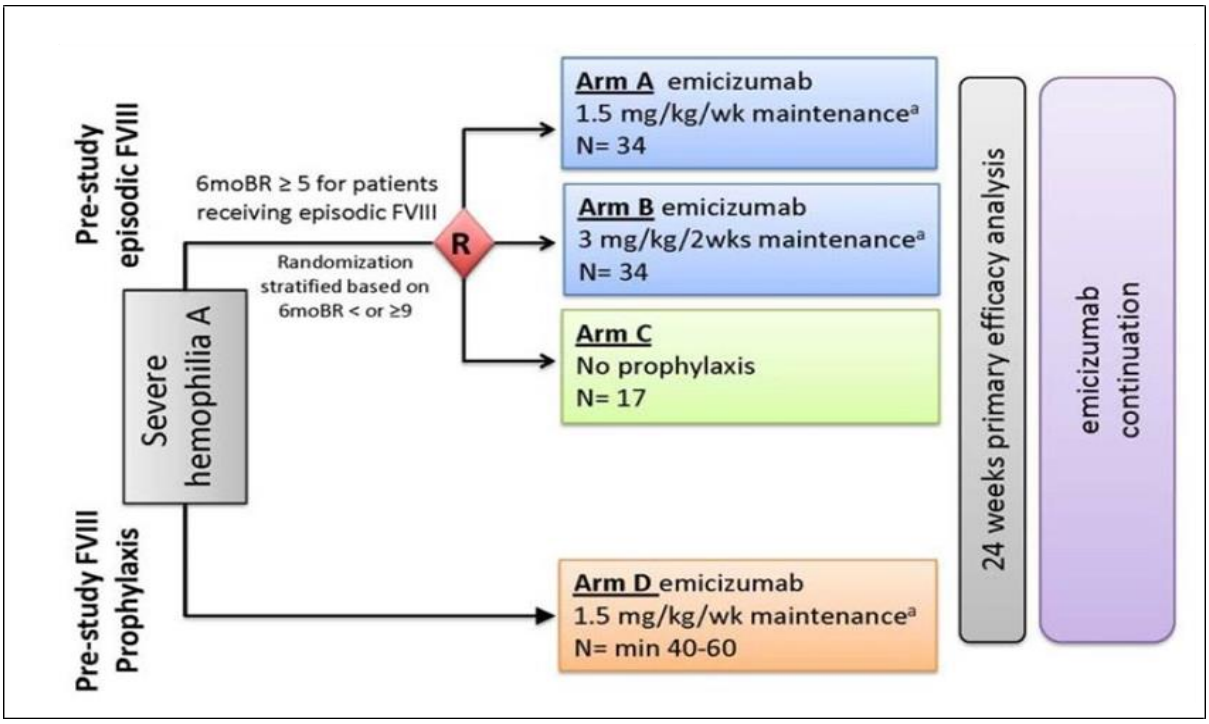
Prophylactic treatment with Emicizumab using the following maintenance dose regimens of 1.5 mg/kg QW, 3 mg/kg Q2W and 6 mg/kg Q4W provides clinically relevant efficacy in the prophylaxis of bleeding episodes in children with haemophilia A with FVIII inhibitors.

- QW-arm: ABR 0.3, 76.9% (n = 50/65) with 0 treated bleeds, 100% with 0-3 bleeds
- Q2W- arm: ABR 0.2, 90% (n = 9/10) with 0 treated bleeds, 100% with 0-3 bleeds
- Q4W- arm: ABR 2.2, 60% (n = 6/10) with 0 treated bleeds, 100% with 0-3 bleeds
- Total: ABR 0.4, 76.5% (n = 65/85) with 0 treated bleeds, 100% with 0-3 bleeds

The median ABR is 0 for all endpoints except all bleeds in arms QW and Q2W.
None of the patients had > 3 treated bleeds, treated joint bleeds, treated spontaneous bleeds or treated target joint bleeds.
Comparison between patients (QW, n = 18) showed a clinically significant reduction of 99% in the incidence of bleeding during prophylactic treatment with Emicizumab compared to previous prophylactic/episodic treatment with bypass products.

Clinical trial HAVEN-3 (BH30071)

Patients with previous episodic FVIII treatment were randomized in a 2:2:1 ratio in arms A, B, and C, those with previous FVIII prophylactic treatment were included in arm D.



2wks - every 2 weeks; 6moBR – 6 months bleed rate; BR – bleed rate; FVIII - coagulation factor VIII; min - minimum; mo - month; R - randomization; wk - weeks. All patients receive Hemlibra loading dose of 3 mg/kg/week for 4 weeks before starting maintenance therapy.

This randomized comparison of prophylactic treatment with Emicizumab with episodic rather than prophylactic treatment with FVIII concentrate is considered clinically relevant for the following reasons: first, patients with episodic treatment comprise a significant proportion of patients in the general hemophilia A patient population.

The medians of the efficacy period in the HAVEN 3 study for the different therapeutic arms were as follows:

- Arm A (1.5 mg/kg QW): 30 weeks (range: 17-50 weeks)
- Arm B (3 mg/kg Q2W): 31 weeks (range: 7-51 weeks)
- Ccontrol arm (without prophylaxis): 24 weeks (range: 14-25 weeks) and 8 weeks (range: 0.3-26 weeks) after Emicizumab prophylaxis
- Arm D (1.5 mg/kg QW): 33 weeks (range: 18-49 weeks)

The primary endpoint was the number of treated bleeds (i.e., the number of bleeding episodes over time treated with coagulation factor). Secondary endpoints included all bleeds, treated joint bleeds, treated spontaneous bleeds, treated target joint bleeds.

The primary endpoint and all secondary endpoints related to the frequency of bleeding have been reached. The results demonstrate reliable and sustained, clinically significant results from prophylactic treatment with Emicizumab on the prevention of bleeding episodes in patients with haemophilia A.

Prophylactic treatment with Emicizumab versus episodic treatment with FVIII

Patients on prophylactic treatment with Emicizumab (arm A with a maintenance dose of 1.5 mg/kg QW and arm B with a dose of 3 mg/kg Q2W) had a significantly lower bleed rate than patients on episodic treatment with FVIII (episodic treatment with concentrate of FVIII) (arm Ccontrol).

Prophylactic treatment with Emicizumab versus previous prophylactic treatment with FVIII

Prophylactic administration of Emicizumab reduced bleeding by 68% in patients with previous FVIII prophylaxis.
In the HAVEN 3 clinical trial, subgroup analyzes were performed on subgroups determined by baseline age, race, bleed rate within 24 weeks prior to study enrollment (<9 vs. ≥9), and the presence or absence of affected target joints. Prophylactic treatment with Emicizumab resulted in a sustained reduction in the incidence of treated bleeding episodes in all subgroups studied.
Prophylactic treatment with Emicizumab compared with episodic treatment with FVIII resulted in a sustained reduction in bleed rates in all subgroups for both treatment regimens (1.5 mg/kg QW and 3 mg/kg Q2W). These results are consistent with the overall effect of Emicizumab, further supporting the efficacy results.

Clinical trial HAVEN 4 (BO39182)

The median duration of the follow-up period for 41 patients was 25.6 weeks (range: 24.1-29.4). By the time of a Clinical Cut-off date (CCOD) for the primary analysis, all patients had a follow-up period of > 24 weeks. The main conclusions about efficacy are the following:

- Prophylactic treatment with Emicizumab 6 mg/kg Q4W demonstrated adequate bleeding control, as evidenced by consistently low ABR values for all bleeding-related endpoints (ABR = 2.4 for treated bleeding episodes). These results are consistent with the efficacy results in the QW (HAVEN 1, HAVEN 3) and Q2W (HAVEN 3) dose regimens.
- Most of the patients (56.1%) had 0 treated bleeding episodes and almost all patients (90.2%) had 0-3 treated bleeding episodes.

Studies with data from real practice

Non-interventional study BH29768

In cohort A, Health-Related Quality of Life (HRQoL) results and health status showed little variability. The overall values for Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) during the study were similar for adult patients receiving prophylactic and episodic treatment with bypassing agents (BPAs). In adolescents, lower Haemo-QoL-SF values (representing a better quality of life HRQoL) were observed in those receiving a prophylactic regimen. Little variability in the physical health subscale was observed in adult patients receiving episodic or prophylactic regimens with BPAs. Slightly greater variability was observed in adolescents. HRQoL and health status in patients with haemophilia A with inhibitors observed in this study are consistent with those in the literature. These results are to be expected as patients continue to receive the treatment they received before enrollment in the study and there was no intervention that would affect HRQoL or health status. The values for EQ-5D-5L Index Utility Score (IUS) and visual analogue scale (VAS) are lower during bleeding and scheduled visits, indicating that bleeding episodes have a clinically significant effect on patients' health status. Regarding patients with FVIII inhibitors, those receiving episodic treatment with BPAs had a markedly lower quality of life (HRQoL) than those receiving prophylactic treatment. At week 1, the Haem-A-QoL questionnaire was completed by 92% (34/37) of patients (≥18 years of age) in the episodic treatment group and by 95% (41/43) in the prophylactic treatment group. Adult patients have higher mean values (worse HRQoL) in the domains for physical health and sports & leisure.

Safety data

The most common serious adverse reactions (ADRs) reported in clinical trials with Emicizumab were thrombotic microangiopathy (TMA) and thrombotic events, including cavernous sinus thrombosis (CST) and superficial vein thrombosis contemporaneous with skin necrosis.
The most common ADRs reported in ≥ 10% of patients treated with at least one dose of Emicizumab were injection site reactions (19%), headache (15%) and arthralgia (10%).
A total of four patients (2.1%) in clinical trials receiving Emicizumab prophylaxis discontinued treatment due to ADR (TMA, skin necrosis, superficial thrombophlebitis and injection site reaction).

Comparators data

For the treatment of haemophilia A, the use of virus-inactivated plasma or recombinant FVIII concentrates is recommended, preferably over cryoprecipitates or fresh frozen plasma for reasons of quality and safety. At an inhibitor level > 5 BU, factor substitution is ineffective. Therefore, rFVIIa and aPCC bypass products are recommended as comparators. For the analysis were selected the following comparators applicable to routine prevention of hemophilia A in Bulgaria, which could be partially or completely displaced with the introduction of the new technology:

- Hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors

- Feiba (aPCC)

- Severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without factor VIII inhibitors

- Elocta (efmoroctocog alfa)

- Adynovi (rurioctocog alfa pegol)

- Covaltry (octocog alfa)

- Cogenate (octocog alfa)

- Advate (octocog alfa)

- NovoEight (turoctocog alfa)

- Nuwiq (simoctocog alfa)

- ReFacto AF (moroctocog alfa)

The choice of comparators includes aPCC in inhibitory hemophilia and recombinant factor VIII different generation for prophylaxis in patients with haemophilia A without inhibitor. Plasma coagulation factors are excluded as comparators in connection with the current practice in the country to provide prophylactic treatment of children under 18 years of age with recombinant factors and complies with the requirements of the NHIF in the treatment of congenital coagulopathies in outpatient care.
Hemlibra has an innovative mechanism of action, improved efficacy and an acceptable safety profile compared to the standard of treatment with FVIII concentrate and bypass products.

Pharmacoeconomic indicators

Published assessments of health technology performed by state institutions for the purposes of another national health care system

For the health technology, 4 positive evaluations have been published for different healthcare systems and one evaluation for the healthcare system in Sweden, which limits reimbursement only to a subgroup of patients whose inhibitory development has not been eliminated by repeated immune tolerance induction (ITI) therapy.

Applied analysis

The applied pharmacoeconomic analysis is of the cost-benefit type and is consistent with the point of view of the paying institution - NHIF. The study, which was used as a basis for cost-benefit analysis, included an assessment of patients' health status using Euro-Qol 5D, and the main measure of outcome was the quality-adjusted life year (QALY). The health benefits for patients in the applied model in both indications were measured as quality-adjusted life years (QALYs).
The choice of comparators is consistent with the requirements of the NHIF in the treatment of congenital coagulopathies in outpatient care, pharmaco-therapeutic guidelines for medical hematology, local clinical practice for the treatment of patients with hemophilia A (with and without factor VIII inhibitors) and therapeutic indications (for prophylaxis or administration if necessary) in accordance with the approved summary of product characteristics.

• in patients with haemophilia A, with factor VIII inhibitors - Feiba (aPCC)

• in patients with haemophilia A, without factor VIII inhibitors - ELOCTA (efmoroctocog alfa), ADYNOVI (rurioctocog alfa pegol), Kovaltry (octocog alfa), Advate (octocog alfa).

Nuwiq, NovoEight and ReFacto AF are not present in the developed model, as there are no comparative data with them compared to Hemlibra.
The time horizon and the evidence for therapeutic results are based on the HAVEN 1 study - for patients with haemophilia A with factor VIII inhibitors and HAVEN 3 - for patients with haemophilia without inhibitors. Based on equivalent results obtained with respect to Life Years Gained (LYG) and the absence of a statistically significant difference in utility between the comparators, a cost-minimization analysis was applied. Modeling has been performed with no bleeding-related condition in patients with haemophilia without factor VIII inhibitors.

The results of the cost-benefit and cost-minimization analyzes show that the introduction of Hemlibra into the health insurance system leads to cost savings in haemophilia A patients with inhibitors and to additional costs in haemophilia A patients without inhibitors.
The sensitivity analysis performed by Monte Carlo simulation confirms the main results.

Emicizumab is an entirely new approach in the prevention of haemophilia A. Emicizumab is the first humanized bispecific monoclonal antibody that has no structural link or homology to factor VIII and therefore does not induce or enhance the development of direct factor VIII inhibitors.

Costs for the assessed health technology

The costs included in the model are the direct costs of drug therapy, ADR control costs, costs of hospitalization in clinical pathway 244 and costs of arthroplasty in clinical pathway 217.2, related to the application of the applied health technology and the costs of treatment with selected comparators.

Budgetary impact

The analysis of the budgetary impact was conducted from the point of view of the paying public institution - NHIF with a time horizon of 5 years. The target population in the budgetary impact analysis was selected on the basis of the applied epidemiological model and the number of patients was presented cumulatively taking into account the specifics of the disease and the duration of

prophylaxis. The estimated number of patients is 16 for the first year and increases to 38 by the fifth year, and the budget of the paying institution is expected to increase for a five-year period.
Sensitivity analysis was performed using a Tornado chart, varying the change in the number of patients, the cost of the applied health technology and the cost of treatment with comparators. The main uncertain data that have the greatest impact on the budget is the cost of treatment with Hemlimbra and the cost of treatment with the comparators.

Conclusion

Hemlimbra is the first and only health technology to date that shows significantly higher efficacy in routine prophylaxis compared to recombinant FVIII or bypass agents that are indicated for routine prophylaxis. Routine prophylaxis with Hemlibra significantly reduces the frequency of bleeding. Hemlibra is associated with a more convenient route of administration - subcutaneously and a better regimen than the alternatives used in current clinical practice and has a good tolerability and acceptable safety profile. The inclusion of Hemlimbra in the PDL will lead to an increase in the budget, without taking into account risk-sharing agreements and patient access schemes.