Gemeinsamer Bundesausschuss

Emicizumab

Resolution of: 20 September 2018
Entry into force on: 20 September 2018
Federal Gazette, BAnz AT 19 11 2019 B2

Valid until: unlimited

Resolution of: 17 October 2019
Entry into force on: 17 October 2019
Federal Gazette, BAnz AT 10 12 2019 B2

Therapeutic indication (according to the marketing authorisation of 23 March 2018):

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.

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

Patients with haemophilia A and factor VIII Inhibitors

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.

Extent and probability of the additional benefit compared to the 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:

Hint for a non-quantifiable 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:

An additional benefit is not proven.

Study results according to endpoints:

Patients with haemophilia A and factor VIII Inhibitors

a) Patients for whom a treatment on demand with a product with bypassing activity represents the patient-individual therapy:

Results of the HAVEN 1 study for the relevant sub-population: RCT of emicizumab prophylaxis vs treatment on demand with bypassing products at week 24

HAVEN 1 study **Endpoint category** **Endpoint**	**Emicizumab routine prophylaxis**		**Treatment on demand with bypassing products**		**Emicizumab vs treatment on demand with bypassing products**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p value**
Mortality					
Overall mortality	34	0 (0)	18	0 (0)	n.c.

HAVEN 1 study **Endpoint category** **Endpoint**	**Emicizumab routine prophylaxis**		**Treatment on demand with bypassing products**		**Emicizumab vs treatment on demand with bypassing products**
	N[a]	**ABR, MV [95% CI]**	**N[a]**	**ABR, MV [95% CI]**	**ABR ratio [95% CI]; p value**
Morbidity					
Annualised bleeding rate					
Bleedings treated	35	3.5 [0.83; 9.46][b]	18	26.2 [17.17; 38.37][b]	0.13 [0.06; 0.28]; < 0.001[c]
Joint bleedings	35	1.0 [0.03; 5.57][b]	18	8.1 [3.55; 15.95][b]	0.11 [0.03; 0.52]; 0.005[c]
All bleedings (additionally shown)	35	6.3 [2.37; 13.45][b]	18	30.8 [20.89; 43.76][b]	0.20 [0.10; 0.38]; < 0.001[c]
Target joint bleeding (additionally shown)	35	0.4 [0.00; 4.48][b]	18	6.2 [2.32; 13.34][b]	0.05 [0.01; 0.23]; < 0.001[c]

HAVEN 1 study Endpoint category Endpoint	Emicizumab routine prophylaxis			Treatment on demand with bypassing products			Emicizumab vs treatment on demand with bypassing products
	N[a]	Values at start of study MV (SD)	Change at week 25 MV[d] (SD)	N[a]	Values at start of study MV (SD)	Change at week 25 MV[d] (SD)	MD [95% CI]; p value[e]
Morbidity							
Health status (*EQ-5D VAS*)[f]	29	72.7 (20.3)	10.7 (17.2)[g]	16	78.4 (13.6)	−2.0 (15.0)[g]	9.72 [1.82; 17.62]; 0.017 *Hedges' g:* 0.74 [0.11; 1.37][h]
Health-related quality of life							
Haem-A-QoL [i, j]	25	38.1 (18.0)	−10.7 (14.1)[g]	14	45.1 (15.8)	2.5 (8.6)[g]	−14.01 [−22.45; −5.56]; 0.002 *Hedges' g:* −1.06 [−1.76; −0.36][h]
Physical health	25	52.41 (21.03)	−19.80 (21.82)[g]	14	57.19 (20.81)	0.36 (16.46)[g]	−21.55 [−35.22; −7.89]; 0.003 *Hedges' g:* −1.01 [−1.71; −0.32][h]
Feelings	25	18.51 (24.97)	−14.83 (4.09)	14	41.07 (30.59)	6.70 (5.46)	−21.52 [−35.38; −7.67]; 0.003 *Hedges' g:* −1.00 [−1.69; −0.30][h]
Self-orientation	25	28.65 (23.43)	−12.90 (3.49)	14	53.21 (19.96)	3.93 (4.82)	−16.83 [−28.92; −4.74]; 0.008 *Hedges' g:* −0.89 [−1.58; −0.21][h]

HAVEN 1 study Endpoint category Endpoint	Emicizumab routine prophylaxis			Treatment on demand with bypassing products			Emicizumab vs treatment on demand with bypassing products
	N[a]	Values at start of study MV (SD)	Change at week 25 MV[d] (SD)	N[a]	Values at start of study MV (SD)	Change at week 25 MV[d] (SD)	MD [95% CI]; p value[e]
Sport and recreation[k]	No usable data[k]						
Work and school	15	No usable data[k]					
Dealing with haemophilia	25	22.12 (25.05)	−3.67 (3.64)	14	30.36 (18.38)	6.86 (4.96)	−10.53 [−23.01; 1.96]; 0.096
Treatment	25	22.84 (22.94)	−10.64 (2.96)	14	47.32 (18.38)	4.32 (4.18)	−14.96 [−25.36; −4.56]; 0.006 *Hedges' g:* −0.92 [−1.61; −0.23][h]
Thoughts about the future	25	29.81 (22.43)	−15.71 (3.91)	14	51.79 (23.34)	0.33 (5.32)	−16.04 [−29.44; −2.63]; 0.021 *Hedges' g:* −0.77 [−1.45; −0.09][h]
Family planning	9	No usable data					
Relationships or partnership	25	20.51 (32.68)	−1.71 (4.13)	14	21.43 (19.53)	2.26 (5.60)	−3.98 [−18.10; 10.15] 0.571
Haemo-QoL SF[l]	No usable data[m]						

HAVEN 1 study Endpoint category Endpoint	Emicizumab routine prophylaxis		Treatment on demand with bypassing products		Emicizumab vs treatment on demand with bypassing products
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p value
Side effects					
AE (additionally shown)	34	29 (85.3)[n]	18	9 (50.0)[n]	---
SAE	34	4 (11.8)[n]	18	4 (22.2)[n]	0.53 [0.15; 1.87]; 0.401[o]
Discontinuation because of AE	34	2 (5.9)	18	0 (0)	- [p]; 0.400[o]
Thromboembolic events	34	1 (2.9)	18	1 (5.6)	0.53 [0.04; 7.97]; 0.735[o]
Thrombotic microangiopathy	34	1 (2.9)	18	0 (0)	– [p]; 0.568[o]
Reaction at the injection site (PT)	34	8 (23.5)	18	0 (0)	9.23 [0.56; 151.30][q] 0.025[o]

a: Number of patients included in the evaluation to calculate the effect; values at the start of study may be based on other patient numbers.
b: Observed ABR (effect and CI or quartile) from study report
c: Effect, confidence interval, and p value: Generalised linear model with negative binomially distributed target variable – stratified by number of bleedings before study enrolment – data from study report
d: Result from ANCOVA, unless otherwise stated
e: Effect, confidence interval, and p value: ANCOVA of changes from start of study to end of study; adjusted for baseline values and interaction of baseline values and treatment.
f: The VAS of the EQ-5D measures the subjective health status of the patients and can have a value range from 0 to 100. Higher values mean a better health status.
g: Values of observed population at end of study, mean (standard deviation)
h: Own calculation of the IQWiG
i: The Haem-A-QoL is a disease-specific questionnaire to assess the health-related quality of life of haemophilia patients. It consists of 46 items in 10 domains; the mean value of these forms an overall 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.
j: For patients ≥ 18 years, the disease-specific Haem-A-QoL questionnaire was used. In the HAVEN 1 study, 31 patients in the intervention arm and 16 patients in the comparator arm were ≥ 18 years.
k: For this domain, values are available for less than 70% of adult patients. The study documents do not indicate whether the missing values are due to patients not answering the questions in this domain or whether they have indicated that these questions do not apply to them (answer option: “not applicable”).
l: For patients < 18 years, the Haemo-QoL SF questionnaire was used.
m: In agreement with the estimation of the pharmaceutical company, the data are not presented because the proportion of patients < 18 years was too low (4 patients in the intervention arm and 2 patients in the comparator arm).
n: Serious bleeding is included (MedDRA SMQ bleeding N/n: 34/1 vs 18/2), non-serious bleeding was not recorded as AEs
o: Own calculation of the IQWiG, unconditional exact test (CSZ method according to Martín Andrés A. et al, Computat Stat Data Anal 1994; 17 (5): 555–574)
p: No representation of effect estimation and CI because not informative

q: Own calculation of the IQWiG, asymptotic Discrepancy between p value (exact) and confidence interval (asymptotic) because of different calculation methods.

ABR: annualised bleed rate; ANCOVA: covariance analysis; EQ-5D: European Quality of Life-5 Dimensions; Haem-A-QoL: Haemophilia-specific quality of life questionnaire; Haemo-QoL-SF: Haemophilia-specific quality of life questionnaire Short Form; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; MV: mean value; n: number of patients with (at least one) event; n.c.: not calculable; N: number of patients evaluated; RCT: Randomised Controlled Trial; RR: Relative Risk; SD: standard deviation; SE: standard error; SQQ: standardised MedDRA query; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus

b) Patients for whom a therapy other than a treatment on demand is the patient-individual therapy:

No relevant data are available.

2. Number of patients or demarcation of patient groups eligible for treatment

Patients with haemophilia A and factor VIII Inhibitors

Approx. 100 patients

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 (risk of misinterpretation).

4. Treatment costs

Annual treatment costs[1]:

Patients with haemophilia A and factor VIII Inhibitors

[1] The prices of the appropriate comparator therapy are not subject to the Pharmaceutical Price Ordinance (AMPreisV).

Designation of the therapy	Annual treatment costs per patient	
Medicinal product to be assessed		
Emicizumab[2, 3] (Hemlibra®)	Adults 12 – < 18 years 6 – < 12 years < 6 years	€ 741,647.92 € 520,020.80 – 596,785.28 € 298,392.64 – € 520,020.80 € 150,640.36 – € 298,392.64
Appropriate comparator therapy		
Human plasma fraction enriched with factor VIII inhibitor bypassing activity		
Product with bypassing activity (Feiba®)	different for each individual patient	

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2018

Costs for additionally required SHI services: not applicable

[2] The costs represent the continuous administration in the maintenance phase.

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