Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Emicizumab (new therapeutic indication: Haemophilia A without inhibitors)

of 5 September 2019

At its session on 5 September 2019, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of emicizumab in accordance with the resolution of 20 September 2018:

Emicizumab

Resolution of: 5 September 2019
Entry into force on: 5 September 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 13 March 2019):

Hemlibra® is indicated for routine prophylaxis of bleeding episodes in patients with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without 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 severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors who are eligible for routine prophylaxis

Appropriate comparator therapy:

plasmatic or recombinant blood coagulation factor VIII products used as routine prophylaxis

Extent and probability of the additional benefit compared to the appropriate comparator therapy:

The additional benefit is not proven.

Study results according to endpoints:[1]

Patients with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors who are eligible for routine prophylaxis

[1] Data from the dossier evaluation of the IQWiG (A19-26) unless otherwise indicated.

Indirect comparison of routine prophylaxis with emicizumab vs routine prophylaxis with recombinant factor VIII (octocog alfa) via bridge comparator (treatment on demand with FVIII products) using the HAVEN 3 (partially randomised, open RCT) and SPINART (open RCT) studies

Endpoint category **Endpoint** **Comparison** **Study**	**Routine prophylaxis with emicizumab (HAVEN 3) or routine prophylaxis with factor VIII products (SPINART)**		**Treatment on demand**		**Intervention vs control**
	N[a]	**MV [95% CI] or (SD)[b]**	**N[a]**	**MV [95% CI] or (SD)[b]**	**ABR ratio [95% CI] p value**
Mortality					
No deaths occurred.					
Morbidity					
Treated bleedings – annualised bleeding rate (ABR);					
Treated bleedings (1.5 mg emicizumab[c])					
HAVEN 3	36	1.5 [0.89; 2.47]	18	38.2 [22.86; 63.76]	0.04 [0.02; 0.08]; < 0.001
SPINART	42	2.2 (5.1)	42	36.9 (23.8)	0.07 [0.04; 0.12]
Indirect comparison via bridge comparator[d]: Routine prophylaxis with emicizumab vs routine prophylaxis with FVIII					0.61 [0.25; 1.47]; 0.268
Treated bleedings (3 mg emicizumab[e])					
HAVEN 3	35	1.3 [0.75; 2.25]	18	38.2 [22.86; 63.76]	0.03 [0.02; 0.07]; < 0.001
SPINART	42	2.2 (5.1)	42	36.9 (23.8)	0.07 [0.04; 0.12]
Indirect comparison via bridge comparator[d]: Routine prophylaxis with emicizumab vs routine prophylaxis with FVIII					0.46 [0.19; 1.11]; 0.085
Treated bleedings (1.5 and 3 mg emicizumab[f])					
HAVEN 3	71	1.4 (2.34)	18	38.2 [22.86; 63.76]	0.04 [0.02; 0.07]
SPINART	42	2.2 (5.1)	42	36.9 (23.8)	0.07 [0.04; 0.12]
Indirect comparison via bridge comparator[d]: Routine prophylaxis with emicizumab vs routine prophylaxis with FVIII					0.56 [0.23; 1.35]; 0.194

Endpoint category Endpoint Comparison Study	Routine prophylaxis with emicizumab (HAVEN 3) or routine prophylaxis with factor VIII products (SPINART)		Treatment on demand		Intervention vs control
	N[a]	MV [95% CI] or (SD)[b]	N[a]	MV [95% CI] or (SD)[b]	ABR ratio [95% CI] p value
Morbidity					
Joint bleedings – annualised bleeding rate (ABR);					
Joint bleedings (1.5 mg emicizumab[c])					
HAVEN 3	36	1.1 [0.59; 1.89]	18	26.5 [14.67; 47.79]	0.04 [0.02; 0.09]; < 0.001
SPINART	42	1.9 (4.7)	42	29.2 (20.6)	0.07 [0.03; 0.14]
Indirect comparison via bridge comparator[d]: Routine prophylaxis with emicizumab vs routine prophylaxis with FVIII					0.61 [0.21; 1.81]; 0.377
Joint bleedings (3 mg emicizumab[e])					
HAVEN 3	35	0.9 [0.44; 1.67]	18	26.5 [14.67; 47.79]	0.03 [0.02; 0.07]; < 0.001
SPINART	42	1.9 (4.7)]	42	29.2 (20.6)	0.07 [0.03; 0.14]
Indirect comparison via bridge comparator[d]: Routine prophylaxis with emicizumab vs routine prophylaxis with FVIII					0.46 [0.15; 1.38]; 0.166
Joint bleedings (1.5 and 3 mg emicizumab[f])					
HAVEN 3	71	1.0 (1.9)	18	26.5 [14.67; 47.79]	0.04 [0.02; 0.08]
SPINART	42	1.9 (4.7)	42	29.2 (20.6)	0.07 [0.03; 0.14]
Indirect comparison via bridge comparator[d]: Routine prophylaxis with emicizumab vs routine prophylaxis with FVIII					0.58 [0.19; 1.73]; 0.330
Health-related quality of life					
No usable data					
Side effects					
No usable data					

a: Number of patients included in the evaluation to calculate the effect estimate; values may be based on other patient numbers.
b: The ABR is based on bleeding events observed over 6 months in the HAVEN 3 study and over 12 months in the SPINART study.
c: ABR for the emicizumab arm is based on patients who were treated with 1.5 mg of emicizumab once per week.
d: Indirect comparison according to Bucher [12]; own calculation
e: ABR for the emicizumab arm is based on patients who were treated with 3 mg of emicizumab every two weeks.
f: ABR for the emicizumab arm is based on the pooled data of patients who were treated with 1.5 mg of emicizumab oncer per week and patients who were treated with 3 mg every 2 weeks.

ABR: annualised bleeding rate; FVIII: factor VIII; CI: confidence interval; MV mean value; N: Number of patients evaluated; SD: Standard deviation

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

Patients with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors who are eligible for routine prophylaxis

Approx. 2,000 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: 15 August 2019):

https://www.ema.europa.eu/documents/product-information/hemlibra-epar-product-information_de.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 card 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:

Patients with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors who are eligible for routine prophylaxis

Designation of the therapy	Annual treatment costs/patient	
Medicinal product to be assessed:		
Emicizumab[2]	Adults	€ 617,547.58 – € 656,592.04
	12 – <18 years	€ 454,843.87 – € 509,078.44
	6 – <12 years	€ 254,539.22 – € 292,140.16
	< 6 years	€ 127,269.61 – € 147,513.60
Appropriate comparator therapy:		
Recombinant blood coagulation factor VIII		
Damoctocog alfa pegol	Adults	€ 484,056.30 – € 679,540.58
	12 – <18 years	€ 345,754.50 – € 485,386.13
Rurioctocog alfa pegol	Adults	€ 390,710.32 – € 474,433.96
	12 – <18 years	€ 279,078.80 – € 362,802.44
Efmoroctocog alfa	Adults	€ 184,120.97 – € 786,367.47
	12 – <18 years	€ 143,205.20 – € 581,228.13
	6 – <12 years	€ 81,831.54 – € 307,709.01
	< 6 years	€ 40,915.77 – € 136,759.56
Lonoctocog alfa	Adults	€ 200,986.24 – € 732,164.16
	12 – <18 years	€ 143,561.60 – € 559,890.24
	6 – <12 years	€ 114,849.28 – € 301,479.36
	< 6 years	€ 57,424.64 – € 172,273.92
Moroctocog alfa	Adults	€ 246,443.05 – € 739,329.15

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

Designation of the therapy	Annual treatment costs/patient	
	12 – <18 years	€ 176,030.75 – € 528,092.25
	6 – <12 years	€ 105,618.45 – € 316,855.35
	< 6 years	€ 70,412.30 – € 158,427.68
Octocog alfa[3]	Adults	€ 237,718.21 – € 713,154.62
	12 – <18 years	€ 169,798.72 – € 509,396.16
	6 – <12 years	€ 101,879.23 – € 418,292.62
	< 6 years	€ 67,919.49 – € 239,024.35
Simoctocog alfa[4]	Adults	€ 222,306.88 – € 666,920.63
	12 – <18 years	€ 158,790.63 – € 476,371.88
	6 – <12 years	€ 95,274.38 – € 285,823.13
	< 6 years	€ 63,516.25 – € 142,911.56
Turoctocog alfa	Adults	€ 269,642.10 – € 654,845.10
	12 – <18 years	€ 192,601.50 – € 500,763.90
	6 – <12 years	€ 154,081.20 – € 308,162.40
	< 6 years	€ 77,040.60 – € 154,081.20
Blood coagulation factor VIII derived from human plasma		
Human plasma products[5]	Adults	€ 210,873.95 – € 632,621.85
	12 – <18 years	€ 150,624.25 –

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

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

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

Designation of the therapy	Annual treatment costs/patient	
		€ 451,872.75
	6 – <12 years	€ 90,374.55 – € 271,123.65
	< 6 years	€ 60,249.70 – € 135,561.83

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2019)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 5 September 2019.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de .

Berlin, 5 September 2019

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

Prof Hecken