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 Mogamulizumab (Mycosis Fungoides, Sézary Syndrome)

of 3 December 2020

At its session on 3 December 2020 the Federal Joint Committee (G-BA) resolved to amend the 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. Annex XII shall be amended in alphabetical order to include the active ingredient mogamulizumab as follows:

Mogamulizumab

Resolution of: 3 December 2020
Entry into force on: 3 December 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 22 November 2018):

Poteligeo is indicated for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.

Therapeutic indication of the resolution (resolution of 3 December 2020):

See therapeutic indication according to marketing authorisation

1. Extent of the additional benefit and significance of the evidence

Mogamulizumab is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy

Extent of the additional benefit and significance of the evidence for mogamulizumab:

Hint for a non-quantifiable additional benefit because the scientific data does not allow quantification

Study results according to endpoints:[1]

MAVORIC study: Mogamulizumab vs vorinostat

Study design: open-label, randomised, Phase III

Data cut-offs: Data cut-off of 31 December 2016 (primary efficacy analysis), data cut-off of 2 March 2019 (end of study)

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No difference relevant for the benefit assessment compared with a non-approved comparator with limited healthcare relevance.
Morbidity	↔	No difference relevant for the benefit assessment compared with a non-approved comparator with limited healthcare relevance.
Health-related quality of life	↔	No difference relevant for the benefit assessment compared with a non-approved comparator with limited healthcare relevance.
Side effects	↑	Advantages in the endpoints severe AEs (CTCAE grade ≥ 3) and therapy discontinuation because of AEs compared with a non-approved comparator with limited healthcare relevance.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

[1] Data from the dossier assessment by the G-BA (published on 15 September 2020) as well as from the amendment unless indicated otherwise.

Mortality

Endpoint	Mogamulizumab		Vorinostat		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
Overall survival[b]					
	186	57.17 [43.27; n.a.] *64 (34.4)*	186	58.37 [45.67; n.a.] *67 (36.0)*	1.10 [0.78; 1.55] 0.580

Morbidity[c]

Progression-free survival (PFS)[d]					
Assessment by independent review	186	6.70 [5.63; 9.37] *110 (59.1)*	186	3.83 [3.00; 4.70] *122 (65.6)*	0.64 [0.49; 0.84] < 0.001 AD: 2.9 months
Complete response of the skin (mSWAT)					
Assessment by independent review	186	n.a. *8 (4.3)*	186	n.a. *2 (1.1)*	2.38 [0.49; 11.52] 0.267
Response of the skin (mSWAT)					
Assessment by independent review	186	7.60 [5.10; 9.40] *73 (39.2)*	186	22.43 [22.43; n.a.] *27 (14.5)*	2.33 [1.49; 3.64]; <0.001 AD: 14.8 months
Sensitivity analyses - BSA					
	186	8.20 [6.60; 18.00] *64* (34.4)	186	n.a. *23 (12.4)*	0.51 [0.31; 0.82]; 0.010 AD: n.c.
Complete response	186	1 (0.5)	186	1 (0.5)	-
Partial response	186	63 (33.9)	186	22 (11.8)	-

Endpoint	Mogamulizumab		Vorinostat		Intervention vs control
	N[e]	MV (SD)	N[e]	MV (SD)	Mean difference (MD) [95% CI] p value
Pruritus NRS[f]					
Baseline	180	6.2 (2.87)	180	6.3 (2.72)	-
Cycle 1	180	5.2 (2.74)	166	5.0 (2.82)	0.3 [−0.28; 0.81] 0.337

Endpoint	Mogamulizumab			Vorinostat			Intervention vs control
	N[e]	Value at Cycle 1 MV (SD)	Change from baseline to Cycle 1 MV [95% CI]	N[e]	Value at Cycle 1 MV (SD)	Change from baseline to Cycle 1 MV [95% CI]	Mean difference (MD) [95% CI] p value
Skindex-29 – Symptom domain[g]							
	156	51.3 (22.98)	−11.4 [−15.08; −7.80]	166	50.8 (21.12)	−10.3 [−13.95; −6.74]	−1.1 [−4.61; 2.41] 0.539
Health status (EQ-5D VAS[h])							
	167	64.8 (21.56)	2.8 [−0.88; 6.49]	169	60.9 (21.22)	−0.7 [−4.35; 3.01]	3.5 [−0.37; 7.31] 0.076

Endpoint	Mogamulizumab		Vorinostat		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
Health status (EQ-5D VAS[h]) – time to deterioration/improvement					
No usable data					

Health-related quality of life[c]

Endpoint	Mogamulizumab		Vorinostat		Intervention vs control
	N[e]	Change from baseline MV (SD)	N[e]	Change from baseline MV (SD)	Mean difference (MD) [95% CI] p value
ItchyQoL[i]					
Total score – Cycle 1	159	−0.4 (0.07)	165	−0.4 (0.07)	0.0 [−0.12; 0.15] 0.830
Total score – Cycle 2	145	−0.5 (0.07)	142	−0.4 (0.07)	−0.2 [−0.31; 0.01] 0.059
ItchyQoL domains:					
Emotion – Cycle 1	162	−0.4 (0.09)	169	−0.3 (0.09)	−0.1 [−0.24; 0.11] 0.446
Function – Cycle 1	166	−0.3 (0.09)	166	−0.4 (0.09)	0.1 [−0.07; 0.28] 0.248
Symptoms – Cycle 1	168	−0.3 (0.08)	167	−0.4 (0.08)	0.1 [−0.08; 0.25] 0.298

Endpoint	Mogamulizumab			Vorinostat			Intervention vs control
	N[e]	Value at Cycle 1 MV (SD)	Change from baseline to Cycle 1 MV [95% CI]	N[e]	Value at Cycle 1 MV (SD)	Change from baseline to Cycle 1 MV [95% CI]	Mean difference (MD) [95% CI] p value
Skindex-29[i]							
Total score	156	44.9 (23.12)	−9.2 [−12.44; −6.02]	166	43.8 (21.14)	−6.7 [−9.88; −3.51]	−2.5 [−5.65; 0.58] 0.110

(Continuation)

Skindex-29 domains:							
Emotion	156	43.9 (26.31)	−9.7 [−13.41; −5.98]	165	42.7 (25.52)	−6.0 [−9.64; −2.29]	−3.7 [−7.39; −0.08] 0.046 Hedges' g [95% CI]: −0.270 [0.49; -0.05]
Function	156	39.6 (26.24)	−6.8 [−10.40; −3,11]	165	38.1 (24.16)	−4.3 [−7.94; −0.71]	−2.4 [−6.04; 1.18] 0.186

Endpoint	**Mogamulizumab**		**Vorinostat**		**Intervention vs control**
	N[e]	MV (SD)	N[e]	MV (SD)	Mean difference (MD) [95% CI] p value
FACT-G total score[j]					
Baseline	177	70.9 (16.87)	184	73.9 (16.94)	-
Cycle 1	156	74.1 (16.99)	172	72.8 (16.12)	3.6 [1.44; 5.81] 0.001 Hedges' g [95% CI]: 0.386 [0.17; 0.60]
FACT-G sub-scales (presented additionally):					
Physical well-being:					
Baseline	180	19.7 (5.97)	185	20.3 (5.56)	-
Cycle 1	166	20.7 (5.76)	173	18.9 (5.77)	2.1 [1.11; 3.07] < 0.001 Hedges' g [95% CI]: 0.464 [0.25; 0.68]
Social/familiar well-being:					
Baseline	181	21.0 (5.81)	185	21.8 (5.66)	-
Cycle 1	167	21.3 (5.39)	173	21.6 (5.38)	0.3 [−0.56; 1.26] 0.455

(Continuation)

Mental well-being:					
Baseline	180	15.5 (4.91)	185	15.8 (4.91)	-
Cycle 1	165	16.5 (4.66)	174	16.1 (5.03)	0.6 [−0.20; 1.36] 0.142
Functionality:					
Baseline	179	14.7 (6.54)	185	15.8 (6.34)	-
Cycle 1	165	15.7 (6.76)	173	15.9 (5.94)	0.5 [−0.60; 1.51] 0.397

Endpoint	**Mogamulizumab**		**Vorinostat**		**Intervention vs control**
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
FACT-G – time to improvement/deterioration					
No usable data					

Side effects[b]

Endpoint	**Mogamulizumab**		**Vorinostat**		**Intervention vs control**
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
Adverse events in total (presented additionally)					
	184	0.08 [0.03; 0.27] *180 (97.8)*	186	0.13 [0.10; 0.17] *185 (99.5)*	–
Serious adverse events (SAE)					
	184	20.63 [11.70; 37.07] *76 (41.3)*	186	n.a. *48 (25.8)*	1.03 [0.71; 1.50] 0.952

Severe adverse events (CTCAE grade ≥ 3)					
	184	16.80 [8.87; 20.63] *86 (46.7)*	186	5.67 [3.53; n.a.] *88 (47.3)*	0.63 [0.46; 0.86] 0.003 AD: 11.13 months
Therapy discontinuation because of adverse events					
	184	53.50 [28.03; 61.10] *40 (21.7)*	186	n.a. *44 (23.7)*	0.49 [0.31; 0.77] 0.002 AD: n.c.
Severe AE (CTCAE grade ≥ 3) with incidence ≥ 5% and SAE with incidence ≥ 10% each with statistically significant differences between the treatment arms					
Blood and lymphatic system disorders (SOC CTCAE grade ≥ 3)	184	no data available *3 (1.6)*	186	no data available *19 (10.2)*	0.10 [0.03; 0.36] < 0.001 AD: n.c.
Thrombocytopenia (PT, CTCAE grade ≥ 3)	184	no data available *0 (0)*	186	no data available *13 (7)*	0.00 [0.00; n.c.] < 0.001 AD: n.c.
Gastrointestinal disorders (SOC CTCAE grade ≥ 3)	184	no data available *4 (2.2)*	186	no data available *17 (9.1)*	0.17 [0.06; 0.51] < 0.001 AD: n.c.
General disorders and administration site conditions (SOC, CTCAE grade ≥ 3)	184	no data available *8 (4.3)*	186	no data available *17 (9.1)*	0.36 [0.15; 0.84] 0.013 AD: n.c.
Fatigue (PT, CTCAE grade ≥ 3)	184	no data available *3 (1.6)*	186	no data available *11 (5.9)*	0.21 [0.06; 0.76] 0.013 AD: n.c.

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Data cut-off of 2 March 2019
[c] Data cut-off of 31 December 2016
[d] Data from the dossier on mogamulizumab Module 4A of 10 June 2020
[e] Individuals in the evaluation
[f] The NRS scale for pruritus assessment uses a numbered scale from 0 to 10 to measure pruritus itching; 10 indicates the worst imaginable itching and 0 no itching.
[g] Higher scores are associated with more severe skin symptomatology.
[h] Values between 0 (worst possible health status) and 100 (best possible health status)
[i] A higher value in the total score reflects a worse health-related quality of life.
[j] The total score (0–108) is derived from the answers of all sub-scales. A higher value represents a better quality of life.

Abbreviations used:
AD = absolute difference; BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D = European Quality of Life Questionnaire 5 Dimensions; FACT-G = Functional Assessment of Cancer Therapy − General; HR = hazard ratio; CI = confidence

interval; MD = mean difference; mSWAT = Modified Severity Weighted Assessment Tool; MV = mean value; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; NRS = numeric rating scale; PFS = progression-free survival; QoL = Quality of Life; SD = standard deviation; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus

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

approx. 310–460 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 Poteligeo (active ingredient: mogamulizumab) at the following publicly accessible link (last access: 26 October 2020):

https://www.ema.europa.eu/documents/product-information/poteligeo-epar-product-information_de.pdf

Treatment with mogamulizumab may be initiated and monitored only by specialists in internal medicine, haematology, and oncology, specialists in skin and venereal diseases, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with mycosis fungoides or Sézary syndrome.

4. Treatment costs

Annual treatment costs:

The annual treatment costs shown refer to the first year of treatment.

Designation of the therapy	Annual treatment costs/patient
Mogamulizumab	€ 199,227.84

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 November 2020

Costs for additionally required SHI services: not applicable

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Mogamulizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1st cycle: 4; 2nd –13th cycle: 2	28	€ 1,988

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 3 December 2020.

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

Berlin, 3 December 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken