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 Elotuzumab (New Therapeutic Indication: Multiple Myeloma, Combination with Pomalidomide and Dexamethasone)

of 2 April 2020

On 2 April 2020, the Federal Joint Committee (G-BA) resolved by written statement 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 elotuzumab in accordance with the resolution of 1 December 2016:

Elotuzumab

Resolution of: 2 April 2020
Entry into force on: 2 April 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 23 August 2019):

Empliciti is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy (see sections 4.2 and 5.1).

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

Adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy

Appropriate comparator therapy:

- bortezomib in combination with dexamethasone

or

- lenalidomide in combination with dexamethasone

or

- pomalidomide in combination with dexamethasone

or

- elotuzumab in combination with lenalidomide and dexamethasone

or

- carfilzomib in combination with lenalidomide and dexamethasone

or

- carfilzomib in combination with dexamethasone

or

- daratumumab in combination with lenalidomide and dexamethasone

or

- daratumumab in combination with bortezomib and dexamethasone

Extent and probability of the additional benefit of elotuzumab compared with pomalidomide in combination with dexamethasone:

Hint for a considerable additional benefit

Study results according to endpoints:[1]

Adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy

Study ELOQUENT-3: Elotuzumab in combination with pomalidomide and dexamethasone vs pomalidomide in combination with dexamethasone (ongoing randomised controlled open Phase 2 study)

Mortality

Endpoint	Elotuzumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	60	n.a. [29.94; n.a.] 20 (33.3)	57	17.41 [13.83; n.a.] 28 (49.1)	0.54 [0.30; 0.96] 0.034 n.a.

Morbidity

Endpoint	Elotuzumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Intervention vs control
	N	Median time to event [95% CI] *Patients with event n (%)*	N	Median time to event [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS)[b]					
	60	10.22 [5.59; 15.31] 40 (66.7)	57	4.67 [2.83; 7.16] 50 (87.7)	0.499 [0.325; 0.765] 0.0011 5.55 months

[1] Data from the dossier evaluation of the IQWiG (A19-80) and the addendum (A20-12) unless otherwise indicated.

Endpoint	Elotuzumab + Pomalidomide + Dexamethasone			Pomalidomide + Dexamethasone			Intervention vs control
	N	Value start of study MV[c] (SD)	Change at the end of observation MV (SE)	N	Values at the start of study MV[c] (SD)	Change at the end of observation MV (SE)	MD [95% CI]; p value
Health status							
EQ-5D VAS[d]	54	65.5 (18.6)	−0.1 (2.6)	49	69.2 (20.9)	−2.2 (2.7)	2.1 [−3.2; 7.3]; 0.440
Severity of symptoms							
MDASI-MM Total Symptom Severity[e]	49	1.5 (1.4)	0.6 (0.2)	41	1.6 (1.4)	0.4 (0.2)	0.2 [−0.2; 0.6]; 0.233
Impairment of everyday life through symptoms							
MDASI-MM Symptom Interference[e]	49	2.5 (2.7)	0.9 (0.3)	41	2.1 (2.0)	0.7 (0.4)	0.2 [−0.5; 0.9]; 0.601

Health-related quality of life

There are no suitable data available.

Side effects[f]

Endpoint	Elotuzumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Intervention vs Control
	N	Median time to event [95% CI] *Patients with event n (%)*	N	Median time to event [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	60	0.23 [0.10; 0.26] 58 (96.7)	55	0.10 [0.03; 0.26] 53 (96.4)	
Serious adverse events (SAE)					
	60	9.20 [3.35; 17.31] 37 (61.7)	55	7.23 [3.32; n.a.] 28 (50.9)	0.99 [0.59; 1.65] 0.958

Endpoint	Elotuzumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Intervention vs Control
	N	Median time to event [95% CI] *Patients with event n (%)*	N	Median time to event [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Severe adverse events (CTCAE grade 3 or 4)					
Total	60	5.22 [0.76; 10.15] 39 (65.0)	55	0.72 [0.69; 1.87] 43 (78.2)	0.62 [0.40; 0.98] 0.040 4.5 months
2–3 lines of therapy	35	7.89 [1.54; n.a.] 20 (57.1)	35	0.72 [0.62; 1.41] 31 (88.6)	0.39 [0.22; 0.69] 0.001 7.17 months
≥ 4 lines of therapy	25	1.22 [0.53; 10.12] 19 (76.0)	20	2.40 [0.49; n.a.] 12 (60.0)	1.33 [0.65; 2.75] 0.433
Therapy discontinuation because of adverse events (≥ 1 active ingredient components)					
	60	n.a. [n.a; n.a.] 11 (18.3)	55	n.a. [n.a.; n.a.] 12 (21.8)	0.63 [0.27; 1.44] 0.270
Specific adverse events					
Neutropoenia (CTCAE grade 3–4)					
	60	n.a. 8 (13.3)	55	n.a. 16 (29.1)	0.41 [0.17; 0.97] 0.033 n.a.
Anaemia (CTCAE grade 3–4)					
	60	n.a. 6 (10.0)	55	n.a. 12 (21.8)	0.37 [0.14; 0.98] 0.038 n.a.

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation if calculable
[b] Data from the dossier of the pharmaceutical company
[c] unless indicated otherwise, MMRM evaluation of the ITT population
[d] Higher values on the scale indicate a better health status; a positive group difference indicates an advantage for elotuzumab
[e] Higher values on the scale correspond to a higher severity of symptoms or impairment; a negative group difference means an advantage for elotuzumab
[f] Survey was conducted until 60 days after end of treatment; the following PTs representing multiple myeloma progression were not included in the evaluation: Progression of a malignant neoplasia, bone metastases, plasma cell leukaemia, plasma cell myeloma

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HR: hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least

one) event; n.c. = not calculable; n.a. = not achieved; vs = versus; SAE = serious adverse event; AE = adverse event; EQ-5D = European Quality of Life-5 Dimensions; MD = mean difference; MDASI-MM = M. D. Anderson Symptom Inventory – Multiple Myeloma; MMRM = mixed model with repeated measurements; MV = mean value, SD = standard deviation, VAS = visual analogue scale

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	↔	No differences relevant for the benefit assessment
Health-related quality of life	∅	no data available
Side effects	↑	Advantages for individual endpoints in the endpoint category side effects

Explanations:
↑, ↓: statistically significant and relevant positive or negative effect with high or unclear risk of bias
↑↑, ↓↓: statistically significant and relevant positive or negative effect with low risk of bias
↔: no relevant difference
∅: no data available
n.a.: not assessable

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

Adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy

approx. 2,500 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 Empliciti® (active ingredient: elotuzumab) at the following publicly accessible link (last access: 18 November 2019):

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

Treatment with elotuzumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with multiple myeloma.

4. Treatment costs

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

Annual treatment costs:

Adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Elotuzumab	€ 88,211.40
Pomalidomide	€ 118,236.43
Dexamethasone	€ 202.51
Total:	€ 206,650.34
Additionally required SHI services	€ 196.43
Appropriate comparator therapy:	
Bortezomib in combination with dexamethasone	
Bortezomib	€ 18,020.96 – 36,041.92
Dexamethasone	€ 74.78 – 149.56
Total:	€ 18,095.74 – 36,191.48
Lenalidomide in combination with dexamethasone	
Lenalidomide	€ 100,192.43
Dexamethasone	€ 312.46
Total:	€ 100,504.89
Pomalidomide in combination with dexamethasone	
Pomalidomide	€ 118,236.43
Dexamethasone	€ 178.89
Total:	€ 118,415.32
Elotuzumab in combination with lenalidomide and dexamethasone	
Elotuzumab	€ 88,211.40
Lenalidomide	€ 100,192.43
Dexamethasone	€ 179.54
Total:	€ 188,583.37
Additionally required SHI services	€ 310.15
Carfilzomib in combination with lenalidomide and dexamethasone	
Carfilzomib	€ 90,826.28
Lenalidomide	€ 100,192.43
Dexamethasone	€ 178.89

Designation of the therapy	Annual treatment costs/patient
Total:	€ 191,197.60
Carfilzomib in combination with dexamethasone	
Carfilzomib	€ 171,103.50
Dexamethasone	€ 243.03
Total:	€ 171,346.53
Daratumumab in combination with lenalidomide and dexamethasone	
Daratumumab	€ 139,876.34
Lenalidomide	€ 100,192.43
Dexamethasone	€ 107.87
Total:	€ 240,176.64
Additionally required SHI services	€ 201.85 – 203.42
Daratumumab in combination with bortezomib and dexamethasone	
Daratumumab	€ 127,713.18
Bortezomib	€ 36,041.92
Dexamethasone	€ 123.85
Total:	€ 163,878.95
Additionally required SHI services	€ 201.85 – 203.42

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

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Elotuzumab in combination with pomalidomide and dexamethasone					
Elotuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1–4	19	€ 1,349
Bortezomib in combination with dexamethasone					
Bortezomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4–6	16–32	€ 1,296 – 2,592
Elotuzumab in combination with lenalidomide and dexamethasone					
Elotuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	2–4	30	€ 2,130
Carfilzomib in combination with lenalidomide and dexamethasone					
Carfilzomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2–6	76	€ 6,156
Carfilzomib in combination with dexamethasone					
Carfilzomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	6	78	€ 6,318
Daratumumab in combination with lenalidomide and dexamethasone					
Daratumumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1–4	23	€1,633
Daratumumab in combination with bortezomib and dexamethasone					
Daratumumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1–3	23	€1,491

II. Entry into force

1. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 2 April 2020.

2. The period of validity of the resolution is limited to 1 July 2021.

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

Berlin, 2 April 2020

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

Prof. Hecken