Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V:

Elotuzumab (reassessment after the deadline: multiple myeloma, at least 2 prior therapies, combination with Pomalidomide and Dexamethasone)

of 16 December 2021

At its session on 16 December 2021, 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 by the publication of the resolution of DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. The information on elotuzumab in the version of the resolution of 2 April 2020 (Federal Gazette, BAnz AT 18.06.2020 B4) is repealed.
2. 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: 16 December 2021
Entry into force on: 16 December 2021
Federal Gazette, BAnz AT DD. MM YYYY Bx

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

Elotuzumab 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.

Therapeutic indication of the resolution (resolution of 16 December 2021):

see therapeutic indication according to marketing authorisation

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 pegylated liposomal doxorubicin

or

- 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 in combination with Pomalidomide and Dexamethasone compared with Pomalidomide in combination with Dexamethasone:

Hint of a considerable additional benefit

Study results according to endpoints:

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	↔	No relevant difference for the benefit assessment
Health-related quality of life	∅	No data available
Side effects	↑	Advantage in the endpoint severe AEs (CTCAE grade 3 or 4)
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		

ELOQUENT-3 study: Elotuzumab + pomalidomide + dexamethasone **vs** pomalidomide + dexamethasone [1,2]

Study design: randomised, open-label, two-armed

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-90) unless otherwise indicated.
[2] Data cut-off of 22.02.2021

Mortality

Endpoint	Elotuzumab + Pomalidomide + Dexamethasone		Pomalidomide + Dexamethasone		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 (%)*	HR [95% CI] p-value Absolute difference (AD)[a]
Overall survival					
	60	29.80 [22.87; 45.67] 37 (61.7)	57	17.41 [13.83; 27.70] 41 (71.9)	0.59 [0.37; 0.93] 0.022 12.39 months
Effect modification by the characteristic "prior stem cell transplant"					
yes	31	26.64 [18.04; 34.14] 23 (74.2)	33	27.70 [13.83; 37.13] 21 (63.6)	1.05 [0.58; 1.90] 0.865
no	29	48.59 [15.70; n.c.] 14 (48.3)	24	14.62 [6.80; 16.89] 20 (83.3)	0.33 [0.16; 0.67] 0.001 33.97 months
					Interaction: 0.008

Morbidity

Endpoint	Elotuzumab + Pomalidomide + Dexamethasone		Pomalidomide + Dexamethasone		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 (%)*	HR [95% CI] p-value Absolute difference (AD)[a]
Progression-free survival (PFS)					
No data available.					
Symptom severity – time to initial deterioration[b]					
MDASI-MM total symptom severity					
	60	24.90 [6.31; n.c.]	57	16.43 [7.43; 34.37]	0.995 [0.50; 1.99]

Endpoint	Elotuzumab + Pomalidomide + Dexamethasone		Pomalidomide + Dexamethasone		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 (%)*	HR [95% CI] p-value Absolute difference (AD)[a]
		23 (38.3)		16 (28.1)	0.989
Impairment of daily life due to symptoms - time to initial deterioration[b]					
MDASI-MM symptom interference					
	60	4.70 [2.83; 11.10] 32 (53.3)	57	4.67 [1.91; 32.92] 22 (38.6)	1.18 [0.66; 2.11] 0.576
Health status					
EQ-5D VAS (time to initial deterioration)[c]					
≥ 7 points	60	2.8 [1.9; 5.6] 39 (65.0)	57	1.1 [1.0; 2.8] 36 (63.2)	0.73 [0.45; 1.21] 0.220
≥ 10 points	60	2.8 [1.9; 5.6] 39 (65.0)	57	1.1 [1.0; 2.9] 35 (61.4)	0.79 [0.48; 1.30] 0.362
≥ 15 points	60	6.51 [2.79; n.c.] 29 (48.3)	57	3.75 [1.91; n.c.] 25 (43.9)	0.95 [0.53; 1.70] 0.871

Health-related quality of life

Endpoint not surveyed

Side effects[d]

Endpoint	Elotuzumab + Pomalidomide + Dexamethasone		Pomalidomide + Dexamethasone		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 (%)*	HR [95% CI] p-value Absolute difference (AD)[a]
Adverse events (AEs) 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] 41 (68.3)	55	7.23 [3.32; 40.25] 29 (52.7)	0.98 [0.59; 1.63] 0.936
Severe adverse events (CTCAE grade ≥ 3)					
	60	3.19 [0.72; 10.12] 43 (71.7)	55	0.72 [0.69; 2.00] 44 (80.0)	0.62 [0.40; 0.97] 0.036 2.47 months
Discontinuation due to AEs [e,f]					
	60	n.a. [n.c.; n.c.] 11 (18.3)	55	n.a. [40.25; n.c.] 12 (21.8)	0.66 [0.29; 1.52] 0.326

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] Time to initial deterioration; defined as an increase in score by ≥ 1.5 points from baseline (corresponds to 15% of the scale range [scale range 0-10])
[c] Time to initial deterioration, defined as a decrease in score by ≥ 7, ≥ 10 and ≥ 15 points, respectively, from baseline (corresponds to 7%, 10% and 15% of the scale range [scale range 0–100])
[d] Assessment was conducted up to 60 days after the end of treatment; following PTs which represent a progression of multiple myeloma were not included in the evaluation: malignant neoplasm progression, bone metastases, plasma cell leukaemia, plasma cell myeloma.
[e] Discontinuation of ≥ 1 active ingredient component
[f] There are unexplained minor discrepancies between the 3 data cut-offs of the ELOQUENT-3 study in the data on discontinuations due to AEs at the SOC and PT level. It is not assumed that these discrepancies have relevant effects.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D = European Quality of Life Questionnaire - 5 Dimensions; HR = hazard ratio; CI = confidence interval; MDASI-MM = M. D. Anderson Symptom Inventory - Multiple Myeloma; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; VAS = visual analogue scale; vs = versus

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 August 2021):

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

Treatment with elotuzumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology experienced in treating patients with multiple myeloma.

4. Treatment costs

Annual treatment costs:

The annual treatment costs shown refer to the first year of 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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Elotuzumab in combination with pomalidomide and dexamethasone	
Elotuzumab	€ 88,211.40
Pomalidomide	€ 111,052.89
Dexamethasone	€ 188.52
Total	€ 199,452.81
Additionally required SHI services	€ 151.70 - € 152.25

Designation of the therapy	Annual treatment costs/ patient
Appropriate comparator therapy:	
Carfilzomib in combination with lenalidomide and dexamethasone	
Carfilzomib	€ 90,826.28
Lenalidomide	€ 102,100.96
Dexamethasone	€ 193.43
Total	€ 193,120.67
Additionally required SHI services	€ 106.40
Carfilzomib in combination with dexamethasone	
Carfilzomib	€ 171,103.50
Dexamethasone	€ 243.03
Total	€ 171,346.53
Additionally required SHI services	€ 106.40
Bortezomib in combination with dexamethasone	
Bortezomib	€ 15,821.12 - € 31,642.24
Dexamethasone	€ 104.08 - € 168.88
Total	€ 15,925.20 - € 31,811.12
Bortezomib in combination with pegylated liposomal doxorubicin	
Bortezomib	€ 31,642.24
Doxorubicin (pegylated, liposomal)	€ 18,769.76
Total	€ 50,412.00
Lenalidomide in combination with dexamethasone	
Lenalidomide	€ 102,100.96
Dexamethasone	€ 312.46
Total	102,413.42
Additionally required SHI services	€ 106.40
Elotuzumab in combination with lenalidomide and dexamethasone	
Elotuzumab	€ 88,211.40
Lenalidomide	€ 102,100.96

Designation of the therapy	Annual treatment costs/ patient
Dexamethasone	€ 185.69
Total	€ 190,498.05
Additionally required SHI services	€ 345.93 - € 346.80
Pomalidomide in combination with dexamethasone	
Pomalidomide	€ 111,052.89
Dexamethasone	€ 193.43
Total	€ 111,246.32
Daratumumab in combination with lenalidomide and dexamethasone	
Daratumumab	€ 136,671.75
Lenalidomide	€ 102,100.96
Dexamethasone	€ 107.87
Total	€ 238,880.58
Additionally required SHI services	€ 448.13 - € 448.80
Ddaratumumab in combination with bortezomib and dexamethasone	
Daratumumab	€ 124,787.25
Bortezomib	€ 31,642.24
Dexamethasone	€ 147.21
Total	€ 156,576.70
Additionally required SHI services	€ 385.03 - € 385.64

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 December 2021)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Elotuzumab (in combination with pomalidomide and dexamethasone)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1st - 2nd cycle: 4 From 3rd cycle: 1	19	€ 1,349
Appropriate comparator therapy:					
Bortezomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4	16 - 32	€ 1,296 - € 2,592
Carfilzomib (in combination with lenalidomide and dexamethasone)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1st - 12th cycle: 6 From 13th cycle: 4	76	€ 6,156
Carfilzomib (in combination with dexamethasone)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	6	78	€ 6,318
Daratumumab (in combination with lenalidomide and dexamethasone)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	Week 1 - 8: 1 x weekly Week 9 - 24: every 2 weeks From week 25: every 4 weeks	23	€ 1,633

Daratumumab (in combination with bortezomib and dexamethasone)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	Week 1 - 9: 1 x every 7 days Week 10 - 24: every 21 days From week 25: every 28 days	21	€ 1,491
Doxorubicin (pegylated, liposomal)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	Day 4 21-day cycle	8	€ 648
Elotuzumab (in combination with lenalidomide and dexamethasone)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1st - 2nd cycle: 4 From 3rd cycle: 2	30	€ 2,130

3. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 December 2021.

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

Berlin, 16 December 2021

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

Prof. Hecken