Gemeinsamer Bundesausschuss

Resolution

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: Carfilzomib (New therapeutic indication: Multiple myeloma, at least 1 prior therapy, combination with daratumumab and dexamethasone)

of 15 July 2021

At its session on 15 July 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 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 carfilzomib in accordance with the resolution of 15 February 2018:

Carfilzomib

Resolution of: 15 July 2021
Entry into force on: 15 July 2021
BAnz AT TT. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 17 December 2020):

Carfilzomib in combination with daratumumab and dexamethasone, with lenalidomide and dexamethasone, or with dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Therapeutic indication of the resolution (resolution of 15 July 2021):

Carfilzomib in combination with daratumumab and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

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

Adults with multiple myeloma who have received at least one prior therapy

Appropriate comparator therapy:

- Bortezomib in combination with pegylated liposomal doxorubicin

or

- Bortezomib in combination with dexamethasone

or

- Lenalidomide 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 carfilzomib in combination with daratumumab and dexamethasone compared with carfilzomib in combination with dexamethasone:

An additional benefit is not proven.

Study results according to endpoints:

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment
Morbidity	↔	No relevant difference for the benefit assessment
Health-related quality of life	↔	No relevant difference for the benefit assessment
Side effects	↔	No relevant differences for the benefit assessment, in detail for the specific AEs an advantage for the AE renal and urinary disorders and disadvantages for the AE diarrhoea and thrombocytopenia

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

CANDOR study: Carfilzomib + daratumumab + dexamethasone **vs** carfilzomib + dexamethasone [1,2]

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

Mortality

Endpoint	**Carfilzomib + daratumumab + dexamethasone**		**Carfilzomib + 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					
	312	n.a. 89 (28.5)	154	33.2 [33.2; n.c.] 51 (33.1)	0.76 [0.54; 1.07] 0.118

Morbidity

Endpoint	**Carfilzomib + daratumumab + dexamethasone**		**Carfilzomib + 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)[b]					
	312	n.c. [n.c.; n.c.] 111 (35.6)	154	15.8 [12.1; 33.2] 69 (44.8)	0.629 [0.465; 0.852] 0.0025
Disease symptoms - time to deterioration[c]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	281	2.8 [1.9; 2.9] 213 (75.8)	128	2.8 [1.9; 2.9] 91 (71.1)	0.98 [0.77; 1.25] 0.861

1 Data from the dossier assessment of the IQWiG (A21-08) and from the addendum (A21-70), unless otherwise indicated.

2 Data cut-off 15.06.2020

Endpoint	Carfilzomib + daratumumab + dexamethasone		Carfilzomib + 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]
Nausea and vomiting	281	12.9 [8.4; 16.1] 148 (52.7)	128	18.2 [14.0; n.c.] 51 (39.8)	1.31 [0.95; 1.80] 0.095
Pain	281	8.4 [5.6; 12.4] 167 (59.4)	128	4.9 [3.8; 8.4] 79 (61.7)	0.77 [0.59; 1.01] 0.050
Dyspnoea	281	3.8 [2.8; 5.6] 185 (65.8)	128	3.7 [2.1; 5.0] 86 (67.2)	0.83 [0.64; 1.07] 0.143
Insomnia	281	4.8 [3.7; 7.5] 172 (61.2)	128	3.8 [2.8; 6.6] 79 (61.7)	0.84 [0.64; 1.09] 0.176
Loss of appetite	281	9.4 [5.6; 12.2] 161 (57.3)	128	10.6 [4.9; 18.5] 62 (48.4)	1.05 [0.78; 1.41] 0.738
Constipation	281	22.8 [15.4; n.c.] 117 (41.6)	128	n.a. [10.0; n.c.] 45 (35.2)	1.06 [0.75; 1.49] 0.747
Diarrhoea	281	9.8 [7.5; 12.4] 162 (57.7)	128	15.2 [9.4; 24.3] 58 (45.3)	1.22 [0.90; 1.65] 0.186
Symptom scales of the EORTC QLQ-MY20[c]					
Symptoms of disease	278	2.8 [2.0; 4.7] 174 (62.6)	133	4.7 [2.8; 14.5] 74 (55.6)	1.11 [0.85; 1.46] 0.432
Side effects	278	n.a. 94 (33.8)	133	n.a. 34 (25.6)	1.27 [0.86; 1.89] 0.219
Health status					
EQ-5D VAS (time to deterioration)[d]					
7 points	278	3.8 [2.8; 6.6] 199 (71.6)	132	2.8 [1.9; 4.7] 96 (72.7)	0.80 [0.62; 1.02] 0.055

Endpoint	Carfilzomib + daratumumab + dexamethasone		Carfilzomib + 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]
10 points	278	6.6 [3.8; 10.3] 175 (62.9)	132	4.7 [2.8; 7.5] 90 (68.2)	0.77 [0.59; 0.99] 0.037 1.9 months
15 points	278	17.1 [11.0; 22.7] 138 (49.6)	132	8.4 [4.7; 17.1] 72 (54.5)	0.71 [0.53; 0.94] 0.016 8.7 months

Health-related quality of life

Endpoint	Carfilzomib + daratumumab + dexamethasone		Carfilzomib + 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]
Health-related quality of life - time to deterioration[e]					
Global health status and functional scales of the EORTC QLQ-C30					
Global health status	281	6.5 [4.7; 10.9] 172 (61.2)	128	4.0 [2.8; 7.5] 78 (60.9)	0.83 [0.63; 1.08] 0.146
Physical function	281	6.2 [4.7; 9.6] 177 (63.0)	128	4.7 [3.1; 5.8] 81 (63.3)	0.86 [0.66; 1.12] 0.238
Role function	281	2.8 [1.9; 3.8] 212 (75.4)	128	2.8 [1.9; 3.8] 92 (71.9)	0.94 [0.74; 1.20] 0.612
Emotional function	281	8.7 [6.6; 14.5] 159 (56.6)	128	10.8 [6.6; 21.7] 58 (45.3)	1.10 [0.82; 1.49] 0.514

Endpoint	Carfilzomib + daratumumab + dexamethasone		Carfilzomib + 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]
Cognitive function	281	5.2 [3.8; 7.5] 195 (69.4)	128	4.7 [2.9; 7.5] 81 (63.3)	0.93 [0.72; 1.21] 0.599
Social function	281	3.8 [2.8; 4.7] 183 (65.1)	128	2.8 [1.9; 4.0] 95 (74.2)	0.76 [0.59; 0.97] 0.021 1.0 months
Functional scales of the EORTC QLQ-MY20					
Body image	278	10.3 [7.6; 17.1] 149 (53.6)	133	5.6 [3.8; 13.3] 74 (55.6)	0.85 [0.64; 1.12] 0.238
Future prospects	278	7.5 [5.2; 12.1] 168 (60.4)	133	7.5 [4.7; 14.0] 77 (57.9)	0.93 [0.71; 1.22] 0.600

Side effects

Endpoint	Carfilzomib + daratumumab + dexamethasone		Carfilzomib + 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[f]					
	308	0.3 [0.2; 0.3] 307 (99.7)	153	0.5 [0.3; 0.5] 148 (96.7)	-
Serious adverse events (SAE)[f]					
	308	10.4 [8.5; 13.7] 192 (62.3)	153	13.2 [7.6; 28.7] 75 (49.0)	1.16 [0.89; 1.51] 0.279
Severe adverse events (CTCAE grade ≥ 3)[f]					
	308	1.7 [1.1; 2.5] 267 (86.7)	153	2.6 [1.9; 3.5] 116 (75.8)	1.22 [0.98; 1.51] 0.080

Endpoint	Carfilzomib + daratumumab + dexamethasone		Carfilzomib + 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]
Discontinuation due to AE					
Discontinuation of ≥ 1 component	308	n.a. 85 (27.6)	153	33.2 [n.d.] 38 (24.8)	0.93 [0.63; 1.36] 0.702
Specific adverse events					
Infusion-related reactions	no usable data available[g]				
Diarrhoea (PT, AE)	308	n.a. [22.5; n.c.] 110 (35.7)		n.a. 26 (17.0)	2.02 [1.32; 3.09] 0.001
Renal and urinary disorders (SOC, severe AE)	308	n.a. 15 (4.9)		n.a. 14 (9.2)	0.47 [0.23; 0.98] 0.040
Thrombocytopenia (PT, severe AE)	308	n.a. 76 (24.7)		n.a. 25 (16.3)	1.57 [1.00; 2.47] 0.049

[A] Absolute difference (AD) is given only in the case of a statistically significant difference; own calculation
[b] Data from: Dossier on carfilzomib Module 4A dated 13.01.2021
[c] Time to deterioration; defined as an increase in score of at least 10 points compared to start of the study
[d] Time to deterioration, defined as a decrease in score by at least 7, 10, and 15 points, respectively, compared to start of the study
[e] Time to deterioration; defined as a decrease in score of at least 10 points compared to start of the study
[f] Overall rate excluding AEs attributed to progression of the underlying disease, defined as the PTs "plasma cell myeloma" (referred to as multiple myeloma by the pharmaceutical company) and "plasmocytoma."
[g] Various operationalisations for the endpoint were submitted by the pharmaceutical company, but no usable data exist for any of the submitted operationalisations

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = European Quality of Life Questionnaire - 5 Dimensions; HR = hazard ratio; n. d = no data; 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; PT = preferred term QLQ-C30 = Quality of Life Questionnaire Core 30; QLQ-MY20 = Quality of Life Questionnaire Multiple Myeloma 20; RCT = randomised controlled trial; SOC = system organ class; 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

Adults with multiple myeloma who have received at least one prior therapy

approx. 4,700 to 7,000 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 Kyprolis (active ingredient: carfilzomib) at the following publicly accessible link (last access: 24 March 2021):

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

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

4. Treatment costs

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

Adults with multiple myeloma who have received at least one prior therapy

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Carfilzomib in combination with daratumumab and dexamethasone	
Carfilzomib	€ 171,103.50 €
Daratumumab	€ 136,671.75 €
Dexamethasone	€ 174.12
Total	€ 307,949.37
Additionally required SHI services	€ 425.82 - € 426.49
Appropriate comparator therapy:	
Carfilzomib in combination with lenalidomide and dexamethasone	
Carfilzomib	€ 90,826.28
Lenalidomide	€ 101,593.57
Dexamethasone	€ 193.43
Total	€ 192,613.28
Additionally required SHI services	€ 106.40

Designation of the therapy	Annual treatment costs/patient
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)	€ 20,196.80
Total	€ 51,839.04
Lenalidomide in combination with dexamethasone	
Lenalidomide	€ 101,593.57
Dexamethasone	€ 312.46
Total	€ 101,906.03
Additionally required SHI services	€ 106.40
Elotuzumab in combination with lenalidomide and dexamethasone	
Elotuzumab	€ 88,211.40
Lenalidomide	€ 101,593.57
Dexamethasone	€ 185.69
Total	€ 189,990.66
Additionally required SHI services	€ 345.69 - € 346.56
Daratumumab in combination with lenalidomide and dexamethasone	
Daratumumab	€ 136,671.75 €
Lenalidomide	€ 101,593.57
Dexamethasone	€ 107.87

Designation of the therapy	Annual treatment costs/patient
Total	€ 238,373.19
Additionally required SHI services	€ 577.44 - € 578.11
Daratumumab 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	€ 384.86 - € 385.47

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2021)

Other SHI services:

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Carfilzomib	Surcharge for the preparation of a parenteral preparation containing cytostatic agents	€ 81	6	78	€ 6,318
Daratumumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	Cycle 1-2: 4 cycle: 36 2 From cycle 7 onwards: 1	23	€ 1,633
Appropriate comparator therapy:					
Bortezomib	Surcharge for the preparation of a	€ 81	4	16 - 32	€ 1,296 € 2,592

	parenteral preparation containing cytostatic agents				
Carfilzomib (in combination with lenalidomide and dexamethasone)	Surcharge for the preparation of a parenteral preparation containing cytostatic agents	€ 81	1. 12th cycle 6 from 13th cycle 4	76	€ 6,156
Carfilzomib (in combination with dexamethasone)	Surcharge for the preparation 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: once a week 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: Once every 7 days Week 10 - 24: every 21 days From week 25: once every 28 days	21	€ 1,491
Doxorubicin (pegylated, liposomal)	Surcharge for the preparation of a parenteral preparation containing cytostatic agents	€ 81	Day 4 21 days cycle	8	€ 648

Elotuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1. 2nd cycle 4 From 3rd cycle 2	30	€ 2,130

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 15 July 2021.

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

Berlin, 15 July 2021

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

Prof. Hecken