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 Pomalidomide (New Therapeutic Indication: Combination Therapy Multiple Myeloma)

of 5 December 2019

At its session on 5 December 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 pomalidomide in accordance with the resolution of 17 March 2016:

Pomalidomide

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

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

Imnovid in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

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

Adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide

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 lenalidomid and dexamethasone

or

- carfilzomib in combination with lenalidomid and dexamethasone

or

- carfilzomib in combination with dexamethasone

or

- daratumumab in combination with lenalidomid and dexamethasone

or

- daratumumab in combination with bortezomib and dexamethasone

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

An additional benefit is not proven.

Study results according to endpoints:[1]

Adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide

MM-007 study: Pomalidomide + bortezomib + dexamethasone **vs** bortezomib + dexamethasone

Mortality

Endpoint	**Pomalidomide + bortezomib + dexamethasone**		**Bortezomib + 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 (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	281	40.5 [29.8; n.c.] 116 (41.3)	278	30.5 [24.6; 35.9] 126 (45.3)	0.91 [0.70; 1.18] 0.476

Morbidity

Endpoint	**Pomalidomide + bortezomib + dexamethasone**		**Bortezomib + 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 (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS)[2]					
	281	11.70 [9.69; 14.59] 188 (66.9)	278	6.87 [5.62; 8.25] 198 (71.2)	0.58 [0.47; 0.71] < 0.001 AD=4.83 months
Symptomatology (EORTC-QLQ-C30 symptom scales)					
Fatigue	240	1.6 [1.4; 2.1] 204 (85.0)	209	1.7 [1.4; 2.1] 156 (74.6)	1.13 [0.92; 1.40] 0.241
Nausea and vomiting	240	10.6 [7.2; 14.8] 111 (46.3)	209	13.9 [11.0; n.c.] 76 (36.4)	1.05 [0.78; 1.41] 0.733
Pain	240	3.6	209	3.4	0.97

[1] Data from the dossier evaluation of the IQWiG (A19-50) and from the addendum (A19-91), unless otherwise indicated.

[2] Pomalidomide: Dossier of the pharmaceutical company, Module 4A of 6 June 2019

Endpoint	Pomalidomide + bortezomib + dexamethasone		Bortezomib + 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 (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
		[2.9; 5.7] 157 (65.4)		[2.8; 5.1] 120 (57.4)	[0.76; 1.23] 0.782
Dyspnoea	240	3.5 [2.8; 4.2] 156 (65.0)	209	3.5 [2.9; 4.9] 111 (53.1)	1.14 [0.89; 1.45] 0.310
Insomnia	240	4.5 [3.3; 6.1] 144 (60.0)	209	3.5 [2.8; 5.6] 113 (54.1)	0.94 [0.73; 1.20] 0.598
Loss of appetite	239	4.8 [3.8; 6.0] 144 (60.3)	209	6.5 [4.5; 9.3] 94 (45.0)	1.21 [0.93; 1.58] 0.152
Constipation	240	2.9 [2.2; 4.3] 154 (64.2)	209	3.7 [2.8; 5.4] 108 (51.7)	1.32 [1.03; 1.69] 0.030 AD=0.8 months
Diarrhoea	239	9.2 [6.0; 12.8] 118 (49.4)	209	6.8 [4.5; 9.9] 90 (43.1)	0.96 [0.72; 1.26] 0.752
Symptomatology (EORTC-QLQ-MY20 symptom scales)					
Disease symptoms	238	7.9 [5.5; 10.2] 123 (51.7)	207	11.0 [5.4; 15.2] 88 (42.5)	1.08 [0.82; 1.42] 0.598
Side effects	238	3.0 [2.4; 3.6] 175 (73.5)	207	3.0 [2.7; 3.6] 129 (62.3)	1.07 [0.85; 1.35] 0.548

Health-related quality of life

Endpoint	Pomalidomide + bortezomib + dexamethasone		Bortezomib + 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 (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
EORTC-QLQ-C30 Functional scales					
Global health status	240	3.1 [2.3; 4.0] 159 (66.3)	209	3.4 [2.7; 4.2] 124 (59.3)	1.17 [0.92; 1.48] 0.206
Physical function	240	3.3 [2.8; 4.3] 163 (67.9)	209	3.6 [3.0; 4.8] 117 (56.0)	1.12 [0.88; 1.42] 0.365
Role function	240	2.8 [2.2; 3.0] 183 (76.3)	209	2.6 [2.1; 3.1] 141 (67.5)	1.00 [0.80; 1.25] 0.987
Cognitive function	240	3.6 [2.8; 5.1] 156 (65.0)	209	4.9 [3.2; 8.6] 104 (49.8)	1.22 [0.95; 1.57] 0.117
Emotional function	240	4.5 [3.5; 5.5] 156 (65.0)	209	5.1 [4.0; 7.8] 108 (51.7)	1.12 [0.87; 1.43] 0.371
Social function	240	2.8 [2.3; 3.5] 178 (74.2)	209	2.8 [2.1; 3.9] 131 (62.7)	1.12 [0.90; 1.41] 0.313
EORTC-QLQ-MY20 Functional scales					
Future perspectives	238	4.9 [3.1; 7.2] 143 (60.1)	207	4.4 [3.5; 7.0] 108 (52.2)	0.98 [0.76; 1.26] 0.861
Body image	238	5.0 [3.9; 8.1] 131 (55.0)	207	6.9 [4.2; 9.9] 101 (48.8)	0.98 [0.75; 1.27] 0.854

Side effects

Endpoint	Pomalidomide + bortezomib + dexamethasone		Bortezomib + 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 (%)	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	278	0.2 [0.1; 0.2] 278 (100.0)	270	0.3 [0.1; 0.3] 264 (97.8)	-
Serious adverse events (SAE)					
	278	6.3 [4.3; 10.5] 169 (60.8)	270	19.1 [6.1; n.c.] 116 (43.0)	1.28 [1.01; 1.63] 0.039 AD=12.8 months
Severe adverse events (CTCAE grade ≥ 3)					
	278	0.8 [0.7; 1.2] 258 (92.8)	270	1.7 [1.1; 2.2] 193 (71.5)	1.56 [1.30; 1.88] < 0.001 AD=0.9 months
Therapy discontinuation because of adverse events					
	278	37.3 [31.3; n.c.] 83 (29.9)	270	n.a. 52 (19.3)	1.27 [0.90; 1.80] 0.173
Specific adverse events[b]					
Peripheral neuropathy (SMQ, AE)	278	4.4 [3.6; 5.9] 154 (55.4)	270	5.8 [4.4; n.c.] 117 (43.3)	1.21 [0.95; 1.54] 0.115
Venous thromboembolic event (SMQ, AE)	278	n.a. 32 (11.5)	270	n.a. 7 (2.6)	3.27 [1.44; 7.44] 0.005
Neutropoenia (PT, severe AEs)	278	18.0 [14.3; 25.6] 126 (45.3)	270	n.a. 24 (8.9)	5.27 [3.40; 8.17] < 0.001
Cataracts (PT, AE)	278	48.6 [n.c.; n.c.] 18 (6.5)	270	n.a. 2 (0.7)	5.61 [1.28; 24.63] 0.022
Constipation (PT, AE)	278	36.8 [36.8; 53.2] 105 (37.8)	270	n.a. 66 (24.4)	1.53 [1.12; 2.08] 0.007
Stomatitis (PT,	278	n.a.	270	n.a.	15.70

AE)		17 (6.1)		1 (0.4)	[2.09; 117.9] 0.007
Peripheral oedema (PT, AE)	278	38.8 [24.1; n.c.] 99 (35.6)	270	n.a. 54 (20.0)	1.63 [1.17; 2.27] 0.004
Fever (PT, AE)	278	45.4 [n.c.; n.c.] 72 (25.9)	270	n.a. 33 (12.2)	1.73 [1.14; 2.62] 0.010
Muscle weakness (PT, AE)	278	n.a. 39 (14.0)	270	n.a. 13 (4.8)	2.58 [1.37; 4.84] 0.003
Tremor (PT, AE)	278	n.a. 31 (11.2)	270	n.a. 8 (3.0)	3.56 [1.64; 7.75] 0.001
Pulmonary embolism (PT, AE)	278	n.a. 11 (4.0)	270	n.a. 1 (0.4)	8.22 [1.05; 64.04] 0.044
Rash (PT, AE)	278	n.a. 29 (10.4)	270	n.a. 9 (3.3)	2.55 [1.20; 5.42] 0.015
Blood and lymphatic system disorders (SOC severe AE [CTCAE grade ≥ 3])	278	4.2 [1.8; 12.9] 163 (58.6)	270	n.a. [14.8; n.c.] 112 (41.5)	1.48 [1.16; 1.88] 0.002
Infections and infestations (SOC, SAE)	278	n.a. [18.3; n.c.] 98 (35.3)	270	n.a. [31.3; n.c.] 50 (18.5)	1.61 [1.14; 2.26] 0.007

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation

[b] Selection according to the methodology of the IQWiG; selection using events based on frequency and differences between treatment arms and taking into account patient relevance.

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

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

approx. 3060 to 3450 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 Imnovid (active ingredient: pomalidomide at the following publicly accessible link (last access: 16 October 2019):

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

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

Pomalidomide should not be taken during pregnancy.

The prescribing doctor must inform the patient about the expected teratogenic risk and the strict contraceptive measures as described in the contraceptive programme and provide the patient with the appropriate patient information brochure, a patient card (therapy passport), and/or similar materials in accordance with the nationally implemented patient card system. The training material for medical professionals includes instructions on prophylaxis and the handling of the side effects potentially caused by pomalidomide, in particular thromboembolic events, cytopoenia, and infections.

Treatment with pomalidomide should be discontinued if the disease progresses.

4. Treatment costs

Annual treatment costs[3]:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Pomalidomide in combination with bortezomib and dexamethasone	
Pomalidomide	€ 103,077.23
Bortezomib	€ 56,312.50
Dexamethasone	€ 233.56
Total	€ 159,623.29
Appropriate comparator therapy:	
Carfilzomib in combination with lenalidomid and dexamethasone	
Carfilzomib	€ 90,821.60

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

Designation of the therapy	Annual treatment costs/patient
Lenalidomide	€ 100,191.65
Dexamethasone	€ 193.37
Total	€ 191,206.62
Carfilzomib in combination with dexamethasone	
Carfilzomib	€ 171,085.02
Dexamethasone	€ 242.90
Total	€ 171,327.92
Bortezomib in combination with dexamethasone	
Bortezomib	€ 18,020.00 – € 36,040.00
Dexamethasone	€ 103.96 – € 168.76
Total	€ 18,123.96 – € 36,208.76
Bortezomib in combination with pegylated, liposomal doxorubicin	
Bortezomib	€ 36,040.00
Doxorubicin (pegylated, liposomal)	€ 19,924.08
Total	€ 55,964.08
Lenalidomide in combination with dexamethasone	
Lenalidomide	€ 100,191.65
Dexamethasone	€ 312.36
Total	€ 100,504.01
Elotuzumab in combination with lenalidomid and dexamethasone	
Elotuzumab	€ 88,207.80
Lenalidomide	€ 100,191.65
Dexamethasone	€ 185.61
Total	€ 188,585.06
Additionally required SHI services	€ 237.78 – € 238.65
Daratumumab in combination with lenalidomid and dexamethasone	
Daratumumab	€ 139,870.82
Lenalidomide	€ 100,191.65
Dexamethasone	€ 193.37
Total	€ 240,255.84
Additionally required SHI services	€ 295.76 – € 296.40
Daratumumab in combination with bortezomib and dexamethasone	
Daratumumab	€ 127,708.14
Bortezomib	€ 36,040.00
Dexamethasone	€ 168.76
Total	€ 163,916.90

Designation of the therapy	Annual treatment costs/patient
Additionally required SHI services	€ 295.76 – € 296.40

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

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Bortezomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	Cycle 1–8: 4 From Cycle 9: 2	50	€ 4,050
Appropriate comparator therapy:					
Bortezomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4	16 – 32	€ 1,296 – € 2,592
Carfilzomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1st –12th Cycle 6 From 13th Cycle 4	76	€ 6,156
Daratumumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	Week 1–8: 1 × a week Week 9–24: every 2 weeks From week 25: every 4 weeks	23	€ 1,633
Doxorubicin (pegylated, liposomal)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	8	€ 648
Elotuzumab	Surcharge for the preparation of a parenteral solution containing	€ 71	1st –2nd Cycle 4 From 3rd Cycle 2	30	€ 2,130

	monoclonal antibodies				

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 December 2019.

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

Berlin, 5 December 2019

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

Prof Hecken