Resolution

Gemeinsamer Bundesausschuss

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V - daratumumab (new therapeutic indication: newly diagnosed multiple myeloma)

of 22 March 2019

At its session on 22 March 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) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on 22 April 2019 (Federal Gazette, BAnz AT 03.05.2019 B3), as follows:

I. **In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of daratumumab in accordance with the resolution of 15 February 2018:**

Daratumumab

Resolution of: 22 March 2019
Entry into force on: 22 March 2019
BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 31.08.2018):

DARZALEX is indicated in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

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

Patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Appropriate comparator therapy:

A combination therapy according to the doctor's instructions.

Extent and probability of the additional benefit of daratumumab in combination with bortezomib, melphalan and prednisone over combination therapy according to the doctor's instructions:

Hint of a considerable additional benefit

Study results according to endpoints:[1]

Patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

ALCYONE study: daratumumab + bortezomib + melphalan + prednisone (D-VMP) **versus** bortezomib + melphalan + prednisone (VMP)
3. data cut-off, total population

Mortality

Endpoint	**Daratumumab + bortezomib + melphalan + prednisone**		**Bortezomib + melphalan + prednisone**		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 (%)*	Effect estimator [95% CI] p-value[a]
Overall survival					
	350	n.a. *59 (16.9)*	356	n.a. *83 (23.3)*	0.68 [0.49; 0.95] 0.023

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A18-66), unless otherwise indicated.

Morbidity

Progression-free survival (PFS)[b]					
	350	NA [32.16; NA] *134 (38.3)*	356	19.12 [17.91; 20.37] *223 (62.6)*	0.43 [0.35; 0.54] < 0.0001
EORTC QLQ-C30 - Symptom scales (time to deterioration ≥ 10 points)					
Fatigue					
	350	n.a. [21.2; n.c.] *127 (36.3)*	356	15.9 [9.3; 20.6] *147 (41.3)*	0.74 [0.58; 0.94] 0.015
Nausea and vomiting					
	350	n.a. *107 (30.6)*	356	n.a. [27.4; n.c.] *101 (28.4)*	0.90 [0.68; 1.18] 0.453
Pain					
	350	n.a. [25.1; n.c.] *116 (33.1)*	356	27.2 [18.0; n.c.] *121 (34.0)*	0.84 [0.65; 1.08] 0.174
Dyspnoea					
	350	31.3 [27.5; n.c.] *113 (32.3)*	356	33.6 [27.2; n.c.] *105 (29.5)*	0.96 [0.73; 1.25] 0.758
Insomnia					
	350	n.a. [21.6; n.c.] *124 (35.4)*	356	n.a. [18.0; n.c.] *119 (33.4)*	0.90 [0.70; 1.16] 0.422
Loss of appetite					
	350	n.a. [24.4; n.c.] *116 (33.1)*	356	34.6 [27.3; n.c.] *102 (28.7)*	1.05 [0.80; 1.38] 0.709
Constipation					
	350	33.7 [33.6; n.c.] *107 (30.6)*	356	29.0 [27.3; n.c.] *103 (28.9)*	0.90 [0.68; 1.18] 0.427
Diarrhoea					
	350	n.a. *95 (27.1)*	356	n.a. [27.4; n.c.] *91 (25.6)*	0.93 [0.69; 1.24] 0.606

Health status (EQ-5D VAS)							
		Values at start of study MV (SD)	Change in month 12 MV [95% CI]		Values at start of study MV (SD)	Change in month 12 MV [95% CI]	MD [95% CI] p-value
Mean change in month 12 compared to start of study[c]							
	n.d.	57.9 (20.2)	8.1 [6.1; 0.1]	n.d.	60.3 (20.6)	9.5 [7.4; 11.7]	-1.4 [-4.2; 1.3] 0.313
		Median time to event in months [95% CI] *Patients with event n (%)*			Median time to event in months [95% CI] *Patients with event n (%)*		Effect estimator [95% CI] p-value[a]
Deterioration ≥ 10 points[b]							
	350	NA [30.19; NA] *101 (28.9)*		356	NA [24.61; NA] *108 (30.3)*		0.78 [0.59; 1.02] 0.0730
Deterioration ≥ 7 points[b]							
	350	NA [27.66; NA] *111 (31.7)*		356	25.10 [21.88; NA] *118 (33.1)*		0.78 [0.60; 1.02] 0.0688

Health-related quality of life

EORTC QLQ-C30 - Functional scales (time to deterioration ≥ 10 points)					
General health status					
	350	n.a. [30.1; n.c.] *98 (28.0)*	356	n.a. [25.1; n.c.] *105 (29.5)*	0.80 [0.61; 1.06] 0.124
Role functioning					
	350	28.1 [21.8; n.c.] *129 (36.9)*	356	24.6 [12.2; n.c.] *129 (36.2)*	0.89 [0.70; 1.14] 0.371
Emotional functioning					
	350	36.3 [n.c.; n.c.] *90 (25.7)*	356	32.5 [28.8; n.c.] *85 (23.9)*	0.92 [0.68; 1.24] 0.576
Physical functioning					
	350	36.3 [30.2; 36.3] *99 (28.3)*	356	29.0 [23.3; n.c.] *108 (30.3)*	0.78 [0.59; 1.04] 0.089

Cognitive functioning					
	350	17.5 [9.1; 24.1] *154 (44.0)*	356	16.6 [11.3; 23.6] *146 (41.0)*	1.02 [0.81; 1.29] 0.863
Social functioning					
	350	n.a. [20.3; n.c.] *125 (35.7)*	356	25.4 [17.1; n.c.] *120 (33.7)*	0.95 [0.74; 1.22] 0.675

Side effects

Endpoint	**Daratumumab + bortezomib + melphalan + prednisone**		**Bortezomib + melphalan + prednisone**		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 (%)*	Effect estimator [95% CI] p-value[a]
Total adverse events (presented additionally)					
	346	0.2 [0.1; 0.3] *335 (96.8)*	354	0.3 [0.3; 0.3] *342 (96.6)*	-
Serious adverse events (SAE)					
	346	n.a. [23.5; n.c.] *151 (43.6)*	354	n.a. *115 (32.5)*	1.20 [0.93; 1.54] 0.154
Severe adverse events (CTCAE grade ≥ 3)					
	346	0.6 [0.5; 1.0] *274 (79.2)*	354	1.0 [0.7; 1.1] *276 (78.0)*	1.07 [0.90; 1.27] 0.432
Therapy discontinuation due to adverse events					
of all active ingredient component					
	346	n.a. *22 (6.4)*	354	n.a. *33 (9.3)*	0.48 [0.26; 0.86] 0.013
of any active ingredient component					
	No data available				
Specific adverse events					
Infections and infestations (SAEs)					
	346	n.a. *83 (24.0)*	354	n.a. *42 (11.9)*	1.85 [1.27; 2.71] 0.001

Vascular disorders (severe AEs [CTCAE grade ≥ 3])					
	346	n.a. *20 (5.8)*	354	n.a. *8 (2.3)*	2.38 [1.04; 5.44] 0.040
Peripheral neuropathy (AEs)					
	346	n.a. *110 (31.8)*	354	n.a. *133 (37.6)*	0.75 [0.58; 0.96] 0.025
Respiratory, thoracic and mediastinal disorders (AEs)					
	346	n.a. [31.1; n.c.] *140 (40.5)*	354	n.a. *74 (20.9)*	1.91 [1.43; 2.55] < 0.001

[a]: HR, CI and p-value: Cox proportional hazards model stratified by factors of ISS stage (I vs II vs III), region (Europe vs other) and age (< 75 years vs ≥ 75 years)
[b]: Information from the dossier of the pharmaceutical company
[c]: MMRM evaluations were available only for the 1st data cut-off. Patients with one value at start of study and at least another value thereafter were included in the analysis.

Abbreviations used:
CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: Hazard Ratio; ISS: International Staging System; n.d.: no data available; CI: Confidence Interval; n: number of patients with (at least 1) event; N: number of patients evaluated; NA: not assessable; n.c.: not calculable; n.a. = not achieved; QLQ-C30: Quality of Life Questionnaire Core 30; RCT: randomised controlled trial; SAE: serious adverse event; AE: adverse event; vs.: versus

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

Patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

approx. 3,380 to 3,900 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 Darzalex® (active ingredient: daratumumab) at the following publicly accessible link (last access: 13 February 2019):

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

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

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient identification card. The training material for medical professionals and blood banks contains instructions on how to manage the risk of daratumumab interfering with blood typing (indirect antihuman globulin test or indirect Coombs test). Interference with blood typing induced by daratumumab may persist for up to 6 months after the last infusion of the medicinal product; therefore, medical professionals should advise patients to carry their patient identification card with them for up to 6 months after the end of the treatment.

4. Treatment costs

Annual treatment costs: [2]

Patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Daratumumab	€ 133,789.48
Bortezomib	€ 61,495.20
Melphalan	€ 573.26
Prednisone	€ 51.52
Total	€ 195,909.46
additionally required SHI services	€ 295.24 – € 295.87
Appropriate comparator therapy:[a]	
Bortezomib + melphalan + prednisone	
Bortezomib	€ 79,943.76
Melphalan	€ 573.26
Prednisone	€ 64.51
Total	€ 80,581.53
Thalidomide + melphalan + prednisone	
Thalidomide	€ 25,355.70
Melphalan	€ 627.34
Prednisone	€ 132.75
Total	€ 26,115.79

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

Lenalidomide + dexamethasone	
Lenalidomide	€ 98,712.64
Dexamethasone	€ 178.83
Total	€ 98,891.47
[a] In addition to the combination therapies listed, the triple combination of bortezomib + lenalidomide + dexamethasone also represents a suitable comparator for the present benefit assessment in the context of combination therapy according to the doctor's instructions. This triple combination is not approved in the present therapeutic indication and therefore, the costs are not represented.	

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 March 2019)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Daratumumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	6 / 1 2 / 8	22	€ 1562
Bortezomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	8 / 1 4 / 8	40	€ 3240
Appropriate comparator therapy: [a]					
bortezomib in combination with melphalan and prednisone					
Bortezomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	8 / 4 4 / 5	52	€ 4212
[a] In addition to the combination therapies listed, the triple combination of bortezomib + lenalidomide + dexamethasone also represents a suitable comparator for the present benefit assessment in the context of combination therapy according to the doctor's instructions. This triple combination is not approved in the present therapeutic indication and therefore, the costs are not represented.					

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 22 March 2019.**
2. **The period of validity of the resolution is limited to 1 March 2022.**

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

Berlin, 22 March 2019

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

Prof. Hecken