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: Daratumumab (reassessment due to new scientific knowledge: multiple myeloma, newly diagnosed, patients ineligible for autologous stem cell transplant, combination with lenalidomide and dexamethasone)

of 18 March 2022

At its session on 18 March 2022, 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 D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. The information on daratumumab in combination with lenalidomide and dexamethasone in the version of the resolution of 20 August 2020 (Federal Gazette, BAnz AT 08.10.2020 B4) is repealed.
2. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of daratumumab in accordance with the resolution of 3 February 2022:

Daratumumab

Resolution of: 18 March 2022
Entry into force on: 18 March 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 19 November 2019):

"Daratumumab is indicated in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisolone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant."

Therapeutic indication of the resolution (resolution of 18 March 2022):

Daratumumab is indicated in combination with lenalidomide and dexamethasone 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

<u>Adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant</u>

Appropriate comparator therapy:

- Daratumumab in combination with bortezomib, melphalan and prednisolone

or

- bortezomib in combination with melphalan and prednisone

or

- bortezomib in combination with lenalidomide and dexamethasone

or

- thalidomide in combination with melphalan and prednisone

or

- lenalidomide in combination with dexamethasone

or

- bortezomib in combination with cyclophosphamide and dexamethasone [only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Annex VI to Section K of the Pharmaceuticals Directive]

Extent and probability of the additional benefit of Daratumumab in combination with Lenalidomide and Dexamethasone compared to Lenalidomide and Dexamethasone:

Hint of a considerable additional benefit

Study results according to endpoints:

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival.
Morbidity	↑	Advantages in the endpoints of pain and dyspnoea
Health-related quality of life	↑	Advantages in the endpoints of physical functioning and social functioning
Side effects	↓	Disadvantage in the endpoint of severe AE (CTCAE grade ≥ 3), advantages and disadvantages in detail in particular specific AEs.
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		

MAIA study: Daratumumab + lenalidomide + dexamethasone **vs** lenalidomide + dexamethasone [1, 2]

Total population

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

[1] Data from the dossier assessment of the IQWiG (A21-126) and from the addendum (A22-27), unless otherwise indicated.
[2] Data cut-off from 19.02.2021

Mortality

Endpoint	Daratumumab + lenalidomide + dexamethasone		Lenalidomide + 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					
	368	n.a. 117 (31.8)	369	n.a. [55.69; n.c.] 156 (42.3)	0.68 [0.53; 0.86] 0.001

Morbidity

Endpoint	Daratumumab + lenalidomide + dexamethasone		Lenalidomide + 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]					
	368	n.a. [54.80; n.a.] 160 (43.5%)	369	34.43 [29.57; 39.16] 217 (58.8%)	0.54 [0.43; 0.66] < 0.0001
Disease symptomatology - time to deterioration[c]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	368	4.86 [4.70; 7.52] 237 (64.4)	369	4.80 [4.63; 7.49] 225 (61.0)	0.85 [0.71; 1.02] 0.086
Nausea and vomiting	368	38.70 [26.68; n.c.] 159 (43.2)	369	30.55 [21.32; 53.49] 145 (39.3)	0.92 [0.73; 1.16] 0.478
Pain	368	39.42 [27.20; 54.51] 164 (44.6)	369	17.97 [10.78; 27.27] 168 (45.5)	0.69 [0.56; 0.86] < 0.001 21.45 months
Dyspnoea	368	29.01 [21.22; 40.84] 185 (50.3)	369	15.74 [10.25; 22.08] 177 (48.0)	0.78 [0.63; 0.96] 0.019

Endpoint	Daratumumab + lenalidomide + dexamethasone		Lenalidomide + 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]
					13.27 months
Insomnia	368	16.92 [10.15; 29.18] 196 (53.3)	369	16.46 [10.19; 27.76] 171 (46.3)	0.94 [0.77; 1.16] 0.588
Appetite loss	368	40.28 [27.66; n.c.] 162 (44.0)	369	26.02 [11.53; 32.26] 161 (43.6)	0.81 [0.65; 1.01] 0.056
Constipation	368	21.68 [10.48; 33.77] 180 (48.9)	369	16.13 [7.72; 26.74] 173 (46.9)	0.84 [0.68; 1.04] 0.117
Diarrhoea	368	15.70 [10.25; 16.33] 235 (63.9)	369	10.64 [9.96; 15.97] 211 (57.2)	0.95 [0.79; 1.15] 0.627
Health status					
EQ-5D VAS (time to deterioration)[d]					
≥ 7 points	368	17.41 [10.15; 26.97] 198 (53.8)	369	10.28 [7.52; 17.02] 191 (51.8)	0.82 [0.67; 1.01] 0.062
≥ 10 points	368	22.60 [15.70; 33.54] 186 (50.5)	369	15.70 [9.27; 24.31] 178 (48.2)	0.84 [0.68; 1.03] 0.101
≥ 15 points	368	53.26 [39.23; n.c.] 146 (39.7)	369	39.62 [30.09; 53.49] 127 (34.4)	0.92 [0.72; 1.17] 0.477

Health-related quality of life

Endpoint	**Daratumumab + lenalidomide + dexamethasone**		**Lenalidomide + 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[c]					
Global health status and functional scales of the EORTC QLQ-C30					
Global health status	368	26.78 [17.51; 39.79] 182 (49.5)	369	21.26 [11.37; 28.68] 167 (45.3)	0.87 [0.71; 1.08] 0.213
Physical functioning	368	45.47 [27.76; n.c.] 162 (44.0)	369	21.52 [12.75; 33.51] 165 (44.7)	0.77 [0.62; 0.96] 0.022 23.95 months
Role functioning	368	10.22 [7.33; 18.17] 209 (56.8)	369	10.19 [6.80; 15.70] 193 (52.3)	0.92 [0.76; 1.12] 0.411
Emotional functioning	368	46.09 [32.59; n.c.] 156 (42.4)	369	32.23 [16.53; 45.60] 144 (39.0)	0.84 [0.67; 1.06] 0.146
Cognitive functioning	368	7.98 [7.42; 15.70] 237 (64.4)	369	10.15 [7.52; 11.56] 200 (54.2)	0.95 [0.78; 1.14] 0.565
Social functioning	368	10.68 [7.49; 21.19] 209 (56.8)	369	7.52 [4.83; 10.41] 203 (55.0)	0.82 [0.67; 0.99] 0.045 3.16 months

Side effects

Endpoint	**Daratumumab + lenalidomide + dexamethasone**		**Lenalidomide + 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)					
	364	0.03 [n.c.] 364 (100)	365	0.20 [0.13; 0.26] 363 (99.5)	-
Serious adverse events (SAE)					
	364	12.85 [7.56; 16.46] 281 (77.2)	365	9.82 [7.62; 12.71] 257 (70.4)	0.93 [0.79; 1.11] 0.434
Severe adverse events (CTCAE grade ≥ 3)					
	364	0.72 [0.69; 1.08] 350 (96.2)	365	1.91 [1.64; 2.86] 324 (88.8)	1.37 [1.17; 1.60] < 0.001 1.19 months
Discontinuation due to AEs[e]					
	364	40.44 [32.46; 48.16] 176 (48.4)	365	48.10 [37.88; n.c.] 131 (35.9)	1.18 [0.94; 1.48] 0.162
Specific adverse events					
Reaction in connection with an infusion	Evaluation unsuitable[f]				
Chills (PT, AE)	364	n.a. 49 (13.5)	365	n.a. 6 (1.6)	8.07 [3.46; 18.86] < 0.001
Respiratory, thoracic and mediastinal disorders (SOC, AE)[g]	364	4.63 [2.79; 7.29] 267 (73.4)	365	19.38 [12.71; 31.31] 179 (49.0)	1.82 [1.50; 2.20] < 0.001 14.75 months
Infections and infestations (SOC, SAE)	364	n.a. [45.60; n.c.] 149 (40.9)	365	n.a. 98 (26.8)	1.32 [1.02; 1.71] 0.036
Neutropoenia (PT, severe AE)	364	23.75 [12.95; 39.49] 197 (54.1)	365	n.a. [40.41; n.c.] 135 (37.0)	1.60 [1.28; 1.99] < 0.001

Endpoint	Daratumumab + lenalidomide + dexamethasone		Lenalidomide + 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]
Anaemia (PT, severe AE)	364	n.a. 61 (16.8)	365	n.a. 79 (21.6)	0.61 [0.43; 0.85] 0.004
Skin and subcutaneous tissue disorders (SOC, severe AE)	364	n.a. 20 (5.5)	365	n.a. 35 (9.6)	0.51 [0.29; 0.88] 0.016

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[b] Data from: Dossier on daratumumab Module 4A dated 30.09.2021
[c] Time to first deterioration defined as increase (symptomatology) or decrease (health-related quality of life) in score by ≥ 10 points compared to the start of the study (scale range 0 to 100) and including death due to disease progression.
[d] Time to first deterioration defined as decrease in score by ≥ 7, ≥ 10 or ≥ 15 points compared to the start of the study (scale range 0 to 100) and including death due to disease progression.
[e] Operationalised as discontinuation of at least 1 active ingredient component
[f] The evaluation submitted by the pharmaceutical company is not suitable, but the events underlying the endpoint are additionally recorded via the specific AEs.
[g] Included therein are the PTs cough, dyspnoea, oropharyngeal pain, rhinorrhoea, wheezing, pharyngeal irritation and bronchospasm, among others

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D VAS = visual analogue scale of the European Quality of Life - 5 Dimensions; 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; PT = preferred term; SOC = system organ class; VAS = visual analogue scale; vs = versus

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

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

approx. 3,470 – 3,670 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: 4 January 2022):

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

Treatment with daratumumab 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:

Adults 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	€ 133,585.38
+ lenalidomide	€ 46,454.98
+ dexamethasone	€ 186.23
Total:	€ 180,226.59
Additionally required SHI costs	€ 333.38 - € 334.05
Appropriate comparator therapy:	
Daratumumab in combination with bortezomib, melphalan and prednisolone	
Daratumumab	€ 123,711.68
Bortezomib	€ 37,653.55
Melphalan	€ 313.39
Prednisone	€ 71.28
Total:	€ 161,749.90
Additionally required SHI costs	€ 293.09 - € 293.72

Designation of the therapy	Annual treatment costs/ patient
Bortezomib in combination with melphalan and prednisone	
Bortezomib	€ 49,426.37
Melphalan	€ 313.39
Prednisone	€ 95.04
Total:	€ 49,834.79
Bortezomib in combination with lenalidomide and dexamethasone	
Induction	
Bortezomib	€ 31,134.72
Lenalidomide	€ 19,058.45
Dexamethasone	€ 153.68
Follow-up treatment	
Lenalidomide	€ 25,014.22
Dexamethasone	€ 104.29
Total:	€ 75,465.36
Additionally required SHI costs	€ 106.40
Thalidomide in combination with melphalan and prednisone	
Thalidomide	€ 25,324.74
Melphalan	€ 348.21
Prednisone	€ 128.95
Total:	€ 25,801.91
Lenalidomide in combination with dexamethasone	
Lenalidomide	€ 46,454.98
Dexamethasone	€ 195.13
Total:	€ 46,650.11
Additionally required SHI costs	€ 106.40
Bortezomib in combination with cyclophosphamide and dexamethasone	
Bortezomib	€ 67,718.02
Cyclophosphamide	€ 1,144.40

Designation of the therapy	Annual treatment costs/ patient
Dexamethasone	€ 518.46
Total:	€ 69,380.88

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 March 2022)

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					
Daratumumab (in combination with lenalidomide and dexamethasone)	Daratumumab: Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	23	€ 1,633.00
Appropriate comparator therapy					
Daratumumab (in combination with bortezomib, melphalan and prednisolone)	Bortezomib: Surcharge for production of a parenteral preparation containing cytostatic agents Daratumumab: Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 81 € 71	4 – 8 2 - 6	38.7 21.3	€ 3,134.70 € 1,512.30
Bortezomib (in combination with melphalan and prednisone)	Bortezomib: Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4 - 8	50.8	€ 4,114.80

Bortezomib (in combination with lenalidomide and dexamethasone)	Bortezomib: Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4	32	€ 2,592.00
Bortezomib in combination with cyclophosphamide and dexamethasone	Bortezomib: Surcharge for production of a parenteral preparation containing cytostatic agents Cyclophosphamide: Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81 € 81	4 1	69.6 17.4	€ 5,637.60 € 1,409.40

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 18 March 2022.

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

Berlin, 18 March 2022

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

Prof. Hecken