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 after the deadline: systemic light chain (AL) amyloidosis, first-line, combination with cyclophosphamide, bortezomib and dexamethasone)

of 21 August 2025

At their session on 21 August 2025, 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. In Annex XII, the information on the benefit assessment of Daratumumab in the version of the resolution of 20 January 2022 (BAnz AT 14.03.2022 B4) shall be amended as follows:

1. After the information

"Resolution of: 20 January 2022
Entry into force on: 20 January 2022
BAnz AT 14.03.2022 B4", the following information is inserted:

"Resolution of: 21 August 2025
Entry into force on: 21 August 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx“

2. In the heading "Therapeutic indication of the resolution (resolution of 20 January 2022): see new therapeutic indication according to the marketing authorisation.", the information "Resolution" is replaced by "Resolutions" and the information "and of 21 August 2025" is inserted after "20 January 2022".

3. Number 1. "Additional benefit of the medicinal product in relation to the appropriate comparator therapy" shall be amended as follows:

a) The information before the heading "Study results by endpoint" shall be amended as follows:

aa) The information "Adults with newly diagnosed systemic light chain (AL) amyloidosis Appropriate comparator therapy: a patient-individual therapy taking into account general condition, comorbidity and organ damage Extent and probability of the additional benefit of daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone compared with the appropriate comparator therapy" is deleted.

bb) After the information "a1) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy", the following information shall be inserted:

"**Appropriate comparator therapy:**

– Bortezomib in combination with cyclophosphamide and dexamethasone

Extent and probability of the additional benefit of daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone compared to bortezomib, cyclophosphamide and dexamethasone"

cc) After the information "Hint for a", the information "minor" is replaced by the information "considerable".

dd) After the information "a2) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom therapy other than bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy", the following information

"Appropriate comparator therapy

– A patient-individual therapy, taking into account general condition, comorbidity and organ damage"

shall be inserted.

b) The information after the heading "Study results by endpoints[1]" shall be amended as follows:

aa) In footnote [1], the information "(A21-100)" is replaced by the information "(A25-40)" after the information "Data from the IQWIG dossier assessment".

bb) The information "Adults with newly diagnosed systemic light chain (AL) amyloidosis" is deleted.

cc) The information under the heading "a1) Adults with newly diagnosed systemic light chain (AL) amyloidosis, for whom bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy" shall be replaced by the following information:

"Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival.
Morbidity	↑	Advantage especially in the endpoint of severe organ damage, also advantage in the dyspnoea symptom scale.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↔	Overall, no relevant differences for the benefit assessment. In detail, in specific AEs, an advantage in hypokalaemia and a disadvantage in skin and subcutaneous tissue disorders.
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 ∅: No data available. n.a.: not assessable		

ANDROMEDA study: Daratumumab + cyclophosphamide + bortezomib + dexamethasone versus cyclophosphamide + bortezomib + dexamethasone (VCd)

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

Mortality[1]

Endpoint	Daratumumab + VCd		VCd		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI][a] p value[b] Absolute difference (AD)[c]
Overall survival					
	195	n.r. 47 (24.1)	193	n.r. 67 (34.7)	0.62 [0.42; 0.90] 0.011

Morbidity[2]

Endpoint	Daratumumab + VCd		VCd		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 [95% CI][a] p value[b] Absolute difference (AD)[c]
Severe organ damage					
	195	n.r. 3 (1.5)	193	n.r. 11 (5.7)	0.22 [0.06; 0.79] 0.011
Endpoint component: clinical manifestation of heart failure[d]	195	n.r. 1 (0.5)[e]	193	n.r. 1 (0.5)[e]	_
Endpoint component: clinical manifestation of kidney failure[f]	195	n.r. 2[g] (1.0)[e]	193	n.r. 10 (5.2)[e]	_
Symptomatology (EORTC QLQ-C30 symptom scales)[h; i]					
Fatigue	195	2.14 [1.94; 3.71] 122 (62.6)	193	1.94 [1.87; 2.83] 128 (66.3)	0.81 [0.63; 1.04] 0.100
Nausea and vomiting	195	29.21 [9.43; n.c.]	193	40.80 [4.83; n.c.]	0.87 [0.64; 1.19]

[1] Data cut-off from 15.11.2024
[2] Data cut-off from 17.04.2024

Endpoint	Daratumumab + VCd		VCd		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 [95% CI][a] p value[b] Absolute difference (AD)[c]
		82 (42.1)		78 (40.4)	0.390
Pain	195	3.98 [2.86; 7.42] 130 (66.7)	193	3.81 [2.86; 5.16] 106 (54.9)	1.09 [0.84; 1.42] 0.516
Dyspnoea	195	29.04 [12.98; n.c.] 84 (43.1)	193	3.81 [2.79; 6.37] 95 (49.2)	0.71 [0.53; 0.97] 0.029 AD = 25.2 months
Insomnia	195	4.67 [3.02; 18.69] 107 (54.9)	193	4.60 [2.89; 15.80] 99 (51.3)	1.00 [0.76; 1.33] 0.984
Appetite loss	195	9.27 [4.47; 22.64] 99 (50.8)	193	5.78 [3.75; 15.84] 93 (48.2)	0.92 [0.69; 1.23] 0.580
Constipation	195	n.r. 56 (28.7)	193	n.r. 51 (26.4)	1.01 [0.75; 1.34] 0.969
Diarrhoea	195	7.85 [4.67; 49.74] 99 (50.8)	193	6.44 [3.81; 14.65] 93 (48.2)	0.92 [0.68; 1.23] 0.565
Symptomatology (EORTC QLQ individual items[j])[h; i]					
Tingling in hands and feet	195	13.08 [8.77; 60.06] 87 (44.6)	193	11.07 [4.73; 29.93] 88 (45.6)	0.83 [0.62; 1.13] 0.236
Fullness in the abdomen/ stomach	195	3.88 [2.23; 9.27] 114 (58.5)	193	2.86 [1.94; 3.75] 113 (58.5)	0.89 [0.68; 1.16] 0.382
Swelling of the legs or ankles	195	7.20 [3.06; 34.14] 96 (49.2)	193	4.63 [2.89; 28.58] 92 (47.7)	0.99 [0.74; 1.32] 0.932
Health status (EQ-5D VAS)[i; k]					

Endpoint	Daratumumab + VCd		VCd		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 [95% CI][a] p value[b] Absolute difference (AD)[c]
	195	17.61 [4.96; 59.17] 90 (46.2)	193	6.24 [3.75; n.c.] 86 (44.6)	0.93 [0.68; 1.26] 0.627

Health-related quality of life[3]

Endpoint	Daratumumab + VCd		VCd		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 [95% CI][a] p value[b] Absolute difference (AD)[c]
EORTC QLQ-C30 functional scales[i; l]					
Global health status	195	4.70 [2.96; 7.42] 107 (54.9)	193	2.89 [2.37; 3.78] 114 (59.1)	0.82 [0.63; 1.08] 0.158
Physical functioning	195	4.73 [2.83; 17.02] 112 (57.4)	193	3.75 [2.83; 4.76] 109 (56.5)	0.86 [0.66; 1.13] 0.279
Role functioning[m]	195	2.69 [1.94; 4.60] 122 (62.6)	193	2.83 [1.97; 3.68] 122 (63.2)	0.88 [0.68; 1.13] 0.315
Emotional functioning	195	47.70 [16.69; n.c.] 76 (39.0)	193	12.22 [4.21; 58.58] 82 (42.5)	0.78 [0.57; 1.08] 0.135
Cognitive functioning	195	5.58 [4.14; 9.23] 114 (58.5)	193	3.81 [2.83; 4.76] 111 (57.5)	0.85 [0.65; 1.11] 0.222
Social functioning	195	2.79 [1.94; 3.09] 125 (64.1)	193	2.86 [1.97; 3.75] 114 (59.1)	1.09 [0.84; 1.41] 0.521
SF-36[i; n]					

[3] Data cut-off from 17.04.2024

Endpoint	Daratumumab + VCd		VCd		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 [95% CI][a] p value[b] Absolute difference (AD)[c]
Physical Component Summary (PCS) score					
	195	64.39 [32.23; n.c.] 74 (37.9)	193	24.21 [4.73; 59.70] 79 (40.9)	0.77 [0.55; 1.06] 0.106
Mental Component Summary (MCS) score					
	195	14.92 [8.12; 54.87] 88 (45.1)	193	28.62 [6.21; n.c.] 78 (40.4)	1.04 [0.77; 1.42] 0.788

Side effects[4]

Endpoint	Daratumumab + VCd		VCd		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 [95% CI][a] p value[b] Absolute difference (AD)[c]
Total adverse events (presented additionally)					
	193	0.10 [0.07; 0.13] 190 (98.4)	188	0.18 [0.10; 0.26] 185 (98.4)	–
Serious adverse events (SAE)					
	193	n.r. [9.43; n.c.] 91 (47.2)	188	n.r. 68 (36.2)	1.01 [0.73; 1.41] 0.934
Severe adverse events (CTCAE grade ≥ 3)					
	193	3.61 [2.40; 4.86] 126 (65.3)	188	3.48 [2.53; 4.40] 114 (60.6)	1.01 [0.78; 1.32] 0.909
Therapy discontinuation due to adverse events°					
	193	n.r.	188	n.r.	1.04

[4] Data cut-off from 15.11.2024

Endpoint	Daratumumab + VCd		VCd		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 [95% CI][a] p value[b] Absolute difference (AD)[c]
		22 (11.4)		17 (9.0)	[0.54; 2.01] 0.895
Specific adverse events					
Peripheral neuropathies (HLT, AEs [CTCAE grade ≥ 2])	193	n.r. 28 (14.5)	188	n.r. 20 (10.6)	0.98 [0.54; 1.78] 0.943
Skin and subcutaneous tissue disorders (SOC, AEs)	193	14.85 [6.5; n.c.] 97 (50.3)	188	n.r. 42 (22.3)	2.00 [1.37; 2.92] < 0.001
Hypokalaemia (PT, severe AEs [CTCAE grade ≥ 3])	193	n.r. 4 (2.1)	188	n.r. 10 (5.3)	0.27 [0.07; 0.997] 0.0495

[a] Hazard ratio (including 95%CI): was calculated using the Cox proportional hazards model with the stratification factors of cardiac stage at baseline (Mayo stage I vs Mayo stage II vs Mayo stage IIIa), countries that typically offer transplantation to patients with AL amyloidosis (list A: yes vs list B: no), renal function status at baseline (CrCl < 60 ml/min vs CrCl ≥ 60 ml/min)

[b] p value: calculated with log-rank test stratified by cardiac stage at baseline (Mayo stage I vs Mayo stage II vs Mayo stage IIIa), countries that typically offer transplantation to patients with AL amyloidosis (list A: yes vs list B: no), renal function status at baseline (CrCl < 60 ml/min vs CrCl ≥ 60 ml/min).

[c] Information on absolute difference (AD) only in case of statistically significant difference; own calculation

[d] Defined as the need for a heart transplant, a left ventricular assist device or an intra-aortic balloon pump

[e] Calculation by IQWiG

[f] Defined as the development of end-stage renal disease (need for haemodialysis or kidney transplantation)

[g] The dossier contains discrepant information in Module 4A and Module 5; shown here: figures from Module 5.

[h] Time to 1st deterioration, defined as an increase by ≥ 10 points compared to baseline on a scale of 0 to 100 points

[i] Evaluation is only carried out for study participants with a baseline value and at least one progression value; study participants without a baseline value or without a progression value are censored at the time of randomisation; patients who have died as a result of disease progression are not evaluated as patients with an event in deviation from the SAP

[j] Individual items from the disease-specific modules EORTC-QLQ-MY20 (tingling in hands and feet), EORTC QLQ-OV28 (fullness in the abdomen/ stomach) and EORTC QLQ-PR25 (swelling of the legs or ankles)

[k] Time to 1st deterioration; defined as a decrease by ≥ 15 points compared to the baseline value on a scale of 0 to 100 points

[l] Time to 1st deterioration; defined as a decrease by ≥ 10 points compared to the baseline value on a scale of 0 to 100 points

[m] The dossier contains partially discrepant data in Module 4 A and Module 5; the figures from Module 5 are shown

Endpoint	Daratumumab + VCd		VCd		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 [95% CI][a] p value[b] Absolute difference (AD)[c]
[n] Time to 1st deterioration; defined as a decrease in the PCS by ≥ 9.4 points or the MCS by ≥ 9.6 points compared to the baseline value on a scale of 7.3 to 70.1 (PCS) and 5.8 to 69.9 (MCS); determined using the normative sample from 2009[5]; no responder analyses are available for subscales of the SF-36v2 [o] Discontinuation of at least one active ingredient component Abbreviations used: AD = absolute difference; AL = amyloidogenic, free light chains; CrCl = creatinine clearance; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; HLT = high level term; HR = hazard ratio; CI = confidence interval; MY20 = Multiple Myeloma 20; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; OV28 = Ovarian Cancer 28; PR25 = Prostate Cancer 20; PT = preferred term; QLQ-C30 = Quality of Life Questionnaire - Core 30; RCT = randomised controlled trial; SAP = statistical analysis plan; SF-36 = Short Form-36 Health Survey; SOC = system organ class; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; VCd = bortezomib in combination with cyclophosphamide and dexamethasone					

"

4. In Number 4. "Treatment costs", the information after the heading "Annual treatment costs:" shall be amended as follows:

a) The information "Adults with newly diagnosed systemic light chain (AL) amyloidosis" is deleted.

b) After the information "The annual treatment costs shown refer to the first year of treatment", the following information shall be inserted:

"

a1) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone	
Daratumumab	€ 133,586.30

[5] Maruish ME. User's manual for the SF-36v2 Health Survey (3rd edition). Lincoln, RI: Quality Metric Incorporated. 2011.

Designation of the therapy	Annual treatment costs/ patient
+ bortezomib	€ 4,208.16
+ cyclophosphamide	€ 37.41
+ dexamethasone	€ 44.52
Total	€ 137,876.39
Appropriate comparator therapy:	
Bortezomib in combination with cyclophosphamide and dexamethasone	
Bortezomib	€ 4,208.16 - € 5,807.04
+ cyclophosphamide	€ 37.41
+ dexamethasone	€ 124.34
Total	€ 4,369.91 - € 5,968.79

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 August 2025)

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 bortezomib, cyclophosphamide and dexamethasone					
Bortezomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	4	24.0	€ 2,400
Appropriate comparator therapy					
Bortezomib in combination with cyclophosphamide and dexamethasone					
Bortezomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	4	24.0	€ 2,400

a2) Adults with newly diagnosed systemic light-chain (AL) amyloidosis for whom therapy other than bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy"

5. After Number 4. "Treatment costs", the following Number 5. shall be inserted:

"5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

a1) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 21 August 2025.

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

Berlin, 21 August 2025

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

Prof. Hecken