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: Isatuximab (Multiple myeloma, at least 2 prior therapies, combination with pomalidomide and dexamethasone)

of 4 November 2021

At its session on 4 November 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 by the publication of the resolution of DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient isatuximab as follows:

Isatuximab

Resolution of: 4 November 2021
Entry into force on: 4 November 2021
BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 30 May 2020):

Sarclisa is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy.

Therapeutic indication (according to the marketing authorisation of 15 April 2021):

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

Therapeutic indication of the resolution (resolution of 4 November 2021):

Sarclisa is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy.

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

<u>Adults with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy</u>

Appropriate comparator therapy:

- Bortezomib in combination with pegylated liposomal doxorubicin

or

- Bortezomib in combination with dexamethasone

or

- Lenalidomide in combination with dexamethasone

or

- Pomalidomide in combination with dexamethasone

or

- Elotuzumab in combination with lenalidomide and dexamethasone

or

- Elotuzumab in combination with pomalidomide 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 isatuximab in combination with pomalidomide and dexamethasone compared with pomalidomide in combination with dexamethasone:

Hint for a minor additional benefit

Study results according to endpoints: [1]

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	↑	Advantages in the symptom scales pain and diarrhoea
Health-related quality of life	↑	Advantages in global health status and function scale role functioning
Side effects	↓	Disadvantage in the endpoint severe adverse events (CTCAE grade ≥ 3) and in the detail of specific adverse events

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

ICARIA-MM study

Study design: open-label, multicentre, RCT

Comparison: Isatuximab + pomalidomide + dexamethasone vs pomalidomide + dexamethasone

Data: Data cut-offs 1 October 2020 (mortality, side effects) and 11 October 2018 (morbidity, health-related quality of life)

Mortality

Endpoint	Isatuximab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		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					
	154	24.6 [20.3; 31.3] *93 (60.4)*	153	17.7 [14.4; 26.2] *105 (68.6)*	0.76 [0.57; 1.01] 0.056

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[1] Data from the dossier assessment of the IQWiG (A21-61) and from the addendum (A21-124), unless otherwise indicated.

Morbidity

Endpoint	**Isatuximab + pomalidomide + dexamethasone**		**Pomalidomide + 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 [95% CI][a] p-value[b] Absolute difference (AD)[c]
Progression-free survival (PFS)[d]					
Independent Review Committee	154	11.53 [8.94; 13.90] *73 (47.4)*	153	6.47 [4.47; 8.28] *89 (58.2)*	0.60 [0.44; 0.81] 0.0012[e] AD: + 5.06 months
Disease symptomatology – time to permanent deterioration[f, g]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	154	15.7 [11.7; n.c.] *59 (38.3)*	153	n.a. [9.3; n.c.] *58 (37.9)*	0.88 [0.61; 1.26] 0.474
Nausea and vomiting	154	n.a. *19 (12.3)*	153	n.a. *18 (11.8)*	0.92 [0.48; 1.77] 0.811
Pain	154	n.a. *34 (22.1)*	153	n.a. *48 (31.4)*	0.61 [0.39; 0.95] 0.026 AD: n.c.
Dyspnoea	154	n.a. [15.7; n.c.] *44 (28.6)*	153	n.a. *38 (24.8)*	1.03 [0.66; 1.59] 0.908
Insomnia	154	n.a. *30 (19.5)*	154	n.a. *22 (14.4)*	1.26 [0.73; 2.19] 0.408
Appetite loss	154	n.a. *32 (20.8)*	153	n.a. *26 (17.9)*	1.11 [0.66; 1.87] 0.682
Constipation	154	n.a. *25 (16.2)*	153	n.a. *31 (20.3)*	0.69 [0.40; 1.16] 0.158
Diarrhoea	154	n.a. *9 (5.8)*	153	n.a. *19 (12.4)*	0.41 [0.18; 0.90] 0.022 AD: n.c.

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Symptom scales of the EORTC QLQ-MY20[f]					
Symptoms of disease	154	n.a. *24 (15.6)*	153	n.a. *33 (21.6)*	0.61 [0.36; 1.03] 0.062
Side effects	154	n.a. *28 (18.2)*	153	n.a. *30 (19.6)*	0.80 [0.48; 1.35] 0.406
Health status					
EQ-5D VAS – Time to permanent deterioration[g, h]					
≥ 15 points	154	n.a. *29 (18.8)*	153	n.a. *32 (20.9)*	0.79 [0.48; 1.30] 0.351
≥ 10 points	154	n.a. [15.5; n.c.] *44 (28.6)*	153	n.a. *45 (29.4)*	0.81 [0.53; 1.22] 0.310
≥ 7 points	154	n.a. [15.5; n.c.] *49 (31.8)*	153	n.a. [12.0; n.c.] *54 (35.3)*	0.74 [0.50; 1.09] 0.127

Health-related quality of life

Endpoint	**Isatuximab + pomalidomide + dexamethasone**		**Pomalidomide + 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 [95% CI][a] p-value[b] Absolute difference (AD)[c]
Health-related quality of life – time to permanent deterioration[g, h]					
Global health status and functional scales of the EORTC QLQ-C30					
Global health status	154	n.a. *44 (28.6)*	153	n.a. *55 (35.9)*	0.65 [0.43; 0.96] 0.030 AD: n.c.
Physical functioning	154	n.a. *46 (29.9)*	153	n.a. [14.7; n.c.] *48 (31.4)*	0.80 [0.53; 1.20] 0.275

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Role functioning	154	n.a. *37 (24.0)*	153	n.a. [9.5; n.c.] *60 (39.2)*	0.50 [0.33; 0.76] 0.001 AD: n.c.
Emotional functioning	154	n.a. *31 (20.1)*	153	n.a. *28 (18.3)*	0.95 [0.57; 1.59] 0.859
Cognitive functioning	154	n.a. *37 (24.0)*	153	n.a. *37 (24.2)*	0.91 [0.58; 1.44] 0.696
Social functioning	154	n.a. [14.8; n.c.] *46 (29.9)*	153	n.a. *52 (34.0)*	0.78 [0.52; 1.16] 0.211
Functional scales of the EORTC QLQ-MY20					
Body image	154	n.a. *23 (14.9)*	153	n.a. *22 (14.4)*	0.93 [0.52; 1.67] 0.802
Future prospects	154	n.a. *34 (22.1)*	153	n.a. [13.2; n.c.] *42 (27.5)*	0.71 [0.45; 1.11] 0.129

Side effects

Endpoint	**Isatuximab + pomalidomide + dexamethasone**		**Pomalidomide + 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 [95% CI][a] p-value[b] Absolute difference (AD)[c]
Total adverse events (presented additionally)					
	152	0.2 [0.2; 0.2] *151 (99.3)*	149	0.3 [0.3; 0.5] *146 (98.0)*	-
Serious adverse events (SAE)					
	152	6.0 [2.8; 9.8] *111 (73.0)*	149	6.6 [3.8; 14.9] *90 (60.4)*	1.27 [0.96; 1.68] 0.097

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Severe adverse events (CTCAE grade ≥ 3)					
	152	0.9 [0.8; 1.1] *138 (90.8)*	149	1.6 [1.0; 2.8] *112 (75.2)*	1.50 [1.17; 1.94] 0.002 AD: - 0.7 months
Therapy discontinuations due to adverse events (≥ 1 active ingredient component)					
	152	n.a. *32 (21.1)*	149	n.a. *25 (16.8)*	1.20 [0.71; 2.03] 0.491
Specific adverse events					
Blood and lymphatic system disorders (SOC, severe AE)	152	0.7 [0.6; 0.8] *94 (61.8)*	149	1.0 [0.8; 1.9] *63 (42.3)*	1.68 [1.22; 2.31] 0.001 AD: - 0.3 months
Bronchitis (PT, AE)	152	12.5 [4.5; n.c.] 41 (27.0)	149	n.a. [27.2; n.c.] 17 (11.4)	2.43 [1.38; 4.28] 0.002 AD: n.c.
Infusion-related reactions	*No usable data available*				

[a] Cox proportional hazards model stratified by age (< 75 years vs ≥ 75 years) and number of prior therapies (2 or 3 vs > 3) according to Interactive Response Technology
[b] Log-rank test stratified by age (< 75 years vs ≥ 75 years) and number of prior therapies (2 or 3 vs > 3) according to Interactive Response Technology
[c] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[d] Data from the dossier isatuximab Modul 4A of 7 May 2021
[e] Hazard ratio (incl. 95% CI and p-value) calculated using Cox proportional hazard model with the factors treatment, age (< 75 years vs ≥ 75 years), number of previous lines of therapy (2 or 3 vs > 3) according to Interactive Response Technology
[f] Defined as an increase in score of at least 10 points compared to baseline (scale range 0–100)
[g] Permanent deterioration was operationalised as a change by at least the response threshold without subsequent improvement (to a change from baseline < response threshold). The evaluation also includes patients whose deterioration did not occur until the last documented visit.
[h] Defined as a decrease in score of at least 7 points or 10 points or 15 points compared to baseline (scale range 0-100).

Abbreviations used:
CI = confidence interval; 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; N = number of patients evaluated; n = number of patients with (at least one) event; n.a. = not achieved; n.c. = not calculable; n.d. = no data; 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; VAS = visual analogue scale; vs = versus

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

Adults with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy

approx. 2,500 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 Sarclisa (active ingredient: isatuximab) at the following publicly accessible link (last access: 7 October 2021):

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

Treatment with isatuximab 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 EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient identification card. The training material for healthcare professionals and blood banks contains instructions on how to manage the risk of isatuximab interfering with blood typing (indirect antihuman globulin test or indirect Coombs test). Isatuximab-induced interference with blood typing may persist for approximately 6 months after the last infusion of the medicinal product; therefore, healthcare professionals should advise patients to carry their patient identification card with them until 6 months after the end of treatment.

4. Treatment costs

Annual treatment costs:

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

Adults with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Isatuximab in combination with pomalidomide and dexamethasone	
Isatuximab	€ 163,513.84
Pomalidomide	€ 111,052.89
Dexamethasone	€ 89.28
Total	€ 274,656.01
Additionally required SHI services	€ 250.79 - € 253.83
Appropriate comparator therapy:	
Carfilzomib in combination with lenalidomide and dexamethasone	
Carfilzomib	€ 90,826.28
Lenalidomide	€ 102,100.96
Dexamethasone	€ 193.43
Total	€ 193,120.67
Additionally required SHI services	€ 106.40
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

Designation of the therapy	Annual treatment costs/patient
Bortezomib in combination with pegylated liposomal doxorubicin	
Bortezomib	€ 31,642.24
Doxorubicin (pegylated, liposomal)	€ 18,769.76
Total	€ 50,412.00
Lenalidomide in combination with dexamethasone	
Lenalidomide	€ 102,100.96
Dexamethasone	€ 312.46
Total	102 413.42
Additionally required SHI services	€ 106.40
Elotuzumab in combination with lenalidomide and dexamethasone	
Elotuzumab	€ 88,211.40
Lenalidomide	€ 102,100.96
Dexamethasone	€ 185.69
Total	€ 190,498.05
Additionally required SHI services	€ 345.93 - € 346.80
Elotuzumab in combination with pomalidomide and dexamethasone	
Elotuzumab	€ 88,211.40
Pomalidomide	€ 111,052.89
Dexamethasone	€ 188.52
Total	€ 199,452.81
Additionally required SHI services	€ 151.70 - € 152.25
Pomalidomide in combination with dexamethasone	
Pomalidomide	€ 111,052.89
Dexamethasone	€ 193.43
Total	€ 111,246.32
Daratumumab in combination with lenalidomide and dexamethasone	
Daratumumab	€ 136,671.75 €
Lenalidomide	€ 102,100.96

Designation of the therapy	Annual treatment costs/patient
Dexamethasone	€ 107.87
Total	€ 238,880.58
Additionally required SHI services	€ 448.13 - € 448.80
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	€ 385.03 - € 385.64

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 October 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:					
Isatuximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	Cycle 1: 4 from cycle 2: 2	28	€ 1,988
Appropriate comparator therapy:					
Bortezomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4	16 - 32	€ 1,296 € 2,592
Carfilzomib (in combination with lenalidomide and dexamethasone)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1st – 12th cycle: 6 from 13th cycle: 4	76	€ 6,156

Carfilzomib (in combination with dexamethasone)	Surcharge for production 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: 1 x weekly 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: 1 x every 7 days Week 10 - 24: every 21 days from week 25: once every 28 days	21	€ 1,491
Doxorubicin (pegylated, liposomal)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	Day 4 21-days cycle	8	€ 648
Elotuzumab (in combination with lenalidomide and dexamethasone)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1st – 2nd cycle: 4 from 3rd cycle: 2	30	€ 2,130
Elotuzumab (in combination with pomalidomide and dexamethasone)	Surcharge for the preparation of a parenteral solution containing	€ 71	1st – 2nd cycle: 4 from 3rd cycle: 1	19	€ 1,349

	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 4 November 2021.

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

Berlin, 4 November 2021

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

Prof. Hecken