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 (New Therapeutic Indication: Multiple myeloma, at least 1 prior therapy, combination with carfilzomib 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. In Annex XII, the following information shall be added after No. 4 to the benefit assessment information on isatuximab in accordance with the resolution of 4 November 2021 for the therapeutic indication "[...] 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":

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.

New 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 carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

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

<u>Adults with multiple myeloma who have received at least one prior 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

- Elotuzumab in combination with lenalidomide 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 carfilzomib and dexamethasone compared with carfilzomib in combination with dexamethasone:

An additional benefit is not proven.

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	↔	No relevant difference for the benefit assessment.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↔	No difference relevant for the benefit assessment, in detail advantages and disadvantages for 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

IKEMA study

Study design: open-label, multicentre, RCT

Comparison: Isatuximab + carfilzomib + dexamethasone vs carfilzomib + dexamethasone

Data: Interim data cut-off from 7 February 2020

Mortality

Endpoint	Isatuximab + carfilzomib + dexamethasone		Carfilzomib + 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] p-value[a]
Overall survival					
	179	n.a. *31 (17.3)*	123	n.a. *25 (20.3)*	0.88 [0.52; 1.50] 0.644

(continuation)

[1] Data from the dossier assessment of the IQWiG (A21-60) and from the addendum (A21-123), unless otherwise indicated.

Morbidity

Endpoint	Isatuximab + carfilzomib + dexamethasone		Carfilzomib + 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] p-value[a] Absolute difference (AD)[b]
Progression-free survival (PFS)[c]					
Independent Review Committee	179	n.c. [n.c.; n.c.] *48 (26.8)*	123	19.15 [15.77; n.c.] *55 (44.7)*	0.53 [0.36; 0.79] 0.0016[d] AD: n.c.
Disease symptomatology - time to permanent deterioration[e,f]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	179	n.a. [20.7; n.c.] *69 (38.5)*	123	n.a. [20.6; n.c.] *47 (38.2)*	1.03 [0.71; 1.49] 0.891
Nausea and vomiting	179	n.a. *22 (12.3)*	123	n.a. *19 (15.4)*	0.75 [0.41; 1.39] 0.363
Pain	179	23.7 [22.6; n.c.] *56 (31.3)*	123	n. a. [23.1; n.c.] *34 (27.6)*	1.17 [0.76; 1.80] 0.465
Dyspnoea	179	n.a. *51 (28.5)*	123	24.0 [21.7; n.c.] *38 (30.9)*	0.89 [0.58; 1.36] 0.587
Insomnia	179	n.a. *40 (22.3)*	123	n.a. *29 (23.6)*	0.96 [0.59; 1.55] 0.858
Appetite loss	179	n.a. *36 (20.1)*	123	n.a. *22 (17.9)*	1.10 [0.65; 1.87] 0.727
Constipation	179	n.a. *24 (13.4)*	123	n.a. *15 (12.2)*	1.05 [0.55; 2.01] 0.878
Diarrhoea	179	n.a. *18 (10.1)*	123	26.4 [26.4; n.c.] *18 (14.6)*	0.68 [0.35; 1.33] 0.259

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Symptom scales of the EORTC QLQ-MY20					
Symptoms of disease	179	n.a. *39 (21.8)*	123	n. a. [23.1; n.c.] *29 (23.6)*	0.88 [0.54; 1.43] 0.601
Side effects	179	n.a. *47 (26.3)*	123	n. a. [24.0; n.c.] *34 (27.6)*	0.92 [0.59; 1.43] 0.700
Health status					
EQ-5D VAS - time to permanent deterioration[g,f]					
≥ 15 points	179	n.a. *31 (17.3)*	123	n.a. *23 (18.7)*	0.91 [0.53; 1.56] 0.730
≥ 10 points	179	24.4 [23.1; 25.6] *58 (32.4)*	123	n.a. *31 (25.2)*	1.24 [0.80; 1.93] 0.328
≥ 7 points	179	24.4 [23.1; n.c.] *50 (27.9)*	123	n.a. *29 (23.6)*	1.15 [0.73; 1.82] 0.555

Health-related quality of life

Endpoint	**Isatuximab + carfilzomib + dexamethasone**		**Carfilzomib + 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] p-value[a]
Health-related quality of life - time to permanent deterioration[g,f]					
Global health status and functional scales of the EORTC QLQ-C30					
Global health status	179	n.a. *56 (31.3)*	123	n.a. *35 (28.5)*	1.16 [0.76; 1.78] 0.494
Physical functioning	179	n.a. *53 (29.6)*	123	n.a. *32 (26.0)*	1.17 [0.75; 1.82] 0.490
Role functioning	179	n. a. [22.7; n.c.] *59 (33.0)*	123	n. a. [23.1; n.c.] *41 (33.3)*	1.02 [0.68; 1.52] 0.931
Emotional functioning	179	n.a. *34 (19.0)*	123	n.a. *20 (16.3)*	1.14 [0.65; 1.98] 0.647

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Cognitive functioning	179	n. a. [23.1; n.c.] *59 (33.0)*	123	n. a. [21.5; n.c.] *38 (30.9)*	1.13 [0.75; 1.71] 0.560
Social functioning	179	n.a. *60 (33.5)*	123	n. a. [24.0; n.c.] *39 (31.7)*	1.04 [0.70; 1.57] 0.832
Functional scales of the EORTC QLQ-MY20					
Body image	179	9.0 [6.5; 15.7] *102 (57.0)*	123	n.a. *30 (24.4)*	0.90 [0.56; 1.44] 0.653
Future prospects	179	10.6 [5.9; n.c.] *94 (52.5)*	123	n. a. [24.0; n.c.] *41 (33.3)*	0.83 [0.55; 1.26] 0.375

Side effects

Endpoint	**Isatuximab + carfilzomib + dexamethasone**		**Carfilzomib + 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] p-value[a]
Total adverse events (presented additionally)					
	177	0.2 [0.1; 0.2] *172 (97.2)*	122	0.4 [0.3; 0.6] *117 (95.9)*	-
Serious adverse events (SAE)					
	177	12.6 [9.3; 17.3] *105 (59.3)*	122	13.8 [9.2; 21.8] *70 (57.4)*	1.08 [0.80; 1.47] 0.616
Severe adverse events (CTCAE grade ≥ 3)					
	177	5.6 [4.5; 7.8] *136 (76.8)*	122	6.6 [4.6; 10.5] *82 (67.2)*	1.22 [0.93; 1.62] 0.154
Therapy discontinuations due to adverse events (≥ 1 active ingredient component)					
	177	n.a. *47 (26.6)*	122	n.a. 21 (17.2)	1.63 [0.97; 2.72] 0.062

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Specific adverse events					
Infusion-related reactions (PT, AEs)[h]	177	n.a. *79 (44.6)*	122	n.a. *4 (3.3)*	17.61 [6.43; 48.19] < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)	177	n.a. *49 (27.7)*	122	n.a. *16 (13.1)*	2.23 [1.26; 3.93] 0.005
Thrombocyto-penia (PT, severe AEs)	177	n.a. *4 (2.3)*	122	n.a. *10 (8.2)*	0.26 [0.08; 0.83] 0.015

[a] HR and CI based on stratified proportional hazards model; p-value based on stratified log-rank test. Stratification factors include the number of prior lines of therapy (1 vs > 1) and R-ISS stage (I or II vs III vs unclassified)
[b] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[c] Data from the dossier isatuximab Modul 4B of 07.05.2021
[d] Hazard ratio (incl. 95% CI and p-value) calculated using Cox proportional hazard model with the factors treatment, number of previous lines of therapy (1 vs > 1) and R-ISS stage (I or II vs III vs not classified) according to Interactive Response Technology
[e] Defined as an increase in score of at least 10 points compared to baseline (scale range 0–100)
[f] 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 includes patients whose deterioration occurred only at the last documented visit.
[g] Defined as a decrease in score of at least 10 points (for EORTC-QLQ-C30 and EORTC-MY20) or at least 7 points or 10 points or 15 points (EQ 5D VAS) compared to baseline (scale range 0-100)
[h] Operationalised as PT "infusion-related reaction"

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.c. = not calculable; n.a. = not achieved; PT = preferred term QLQ-C30 = Quality of Life Questionnaire Core 30; QLQ-MY20 = Quality of Life Questionnaire Multiple Myeloma 20; RCT = randomised controlled trial; R-ISS = Revised International Staging System; SOC = system organ class; VAS = visual analogue scale; vs = versus

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

Adults with multiple myeloma who have received at least one prior therapy

approx. 4,700 – 7,000 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: 18 August 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 multiple myeloma who have received at least one prior therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Isatuximab in combination with carfilzomib and dexamethasone	
Isatuximab	€ 163,513.84
Carfilzomib	€ 171,103.50
Dexamethasone	€ 58.42
Total	€ 334,675.76
Additionally required SHI services	€ 680.89 - € 683.93
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
Daratumumab in combination with lenalidomide and dexamethasone	
Daratumumab	€ 136,671.75 €
Lenalidomide	€ 102,100.96
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
Carfilzomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	6	78	€ 6,318
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	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1st – 2nd cycle: 4 from 3rd cycle: 2	30	€ 2,130

II. The resolution will enter into force on the day of its publication 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