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, first-line, ineligible for stem cell transplant, combination with bortezomib, lenalidomide and dexamethasone)

of 7 August 2025

At their session on 7 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 following information shall be added after No. 4 to the information on the benefit assessment of Isatuximab in accordance with the resolution of 4 November 2021:**

**Isatuximab**

Resolution of: 7 August 2025
Entry into force on: 7 August 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

**New therapeutic indication (according to the marketing authorisation of 20 January 2025):**

SARCLISA is indicated in combination with bortezomib, lenalidomide, and dexamethasone, 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 7 August 2025):**

See new therapeutic indication according to marketing authorisation.

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

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

**Appropriate comparator therapy:**

– Daratumumab in combination with lenalidomide and dexamethasone

or

– daratumumab in combination with bortezomib, melphalan and prednisone

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

– 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 isatuximab in combination with bortezomib, lenalidomide and dexamethasone compared to bortezomib, lenalidomide and dexamethasone:**

Hint for a minor additional benefit

**Study results according to endpoints:**[1]

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 | ↔ | No relevant difference for the benefit assessment |
| Morbidity | ↑ | Advantages particularly in the endpoints of dyspnoea, nausea and vomiting |
| Health-related quality of life | ↑ | Advantages in the endpoints of role functioning and future prospects |
| Side effects | ↔ | Overall, no relevant differences for the benefit assessment. In detail, advantages in the specific AEs: Metabolism and nutrition disorders, and respiratory, thoracic and mediastinal disorders |
| Explanations:<br>↑: statistically significant and relevant positive effect with low/unclear reliability of data<br>↓: statistically significant and relevant negative effect with low/unclear reliability of data<br>↑↑: statistically significant and relevant positive effect with high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data<br>↔: no statistically significant or relevant difference<br>∅: No data available.<br>n.a.: not assessable | | |

Open-label, randomised phase III IMROZ study

- Isatuximab + bortezomib + lenalidomide + dexamethasone (IsaVRd) vs bortezomib + lenalidomide + dexamethasone (VRd)
- 1st data cut-off for mortality, morbidity, health-related quality of life: 26.09.2023; for side effects: 03.10.2023
- Relevant sub-population: ASCT ineligibility according to EMA definition

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A25-20) unless otherwise indicated.

## Mortality

| Endpoint | Isatuximab + bortezomib + lenalidomide + dexamethasone[a] | | Bortezomib + lenalidomide + dexamethasone[b] | | Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs bortezomib + lenalidomide + dexamethasone[b] |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | HR [95% CI]<br>p value |
| **Overall survival** | | | | | |
| | 196 | n.r.<br>*57 (29.1)* | 136 | n.r. [63.6; n.c.]<br>*48 (35.3)* | 0.80 [0.55; 1.18]<br>0.256 |

## Morbidity

| Endpoint | Isatuximab + bortezomib + lenalidomide + dexamethasone[a] | | Bortezomib + lenalidomide + dexamethasone[b] | | Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs bortezomib + lenalidomide + dexamethasone[b] |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | HR [95% CI]<br>p value<br>Absolute difference (AD)[c] |
| **Progression-free survival (PFS) according to IRC[d]** | | | | | |
| | 196 | n.r.<br>*65 (33.2)* | 136 | 49.1<br>*57 (41.9)* | 0.65 [0.45; 0.93]<br>0.0173 |
| **Symptomatology (EORTC QLQ-C30 – time to 1st deterioration[e])** | | | | | |
| Fatigue | 196 | 2.9 [2.8; 4.2]<br>*143 (73.0)* | 136 | 2.8 [1.6; 2.9]<br>*106 (77.9)* | 0.81 [0.63; 1.04]<br>0.112 |
| Nausea and vomiting | 196 | 18.2 [12.4; 31.0]<br>*106 (54.1)* | 136 | 8.5 [6.8; 12.7]<br>*78 (57.4)* | 0.72 [0.54; 0.97]<br>0.031<br>AD: 9.7 months |
| Pain | 196 | 6.1 [4.4; 8.4]<br>*125 (63.8)* | 136 | 4.4 [2.9; 6.0]<br>*91 (66.9)* | 0.79 [0.60; 1.04]<br>0.089 |
| Dyspnoea | 196 | 11.2 [7.0; 16.3]<br>*114 (58.2)* | 136 | 3.6 [2.9; 6.6]<br>*91 (66.9)* | 0.61 [0.46; 0.80]<br>< 0.001 |

| Endpoint | Isatuximab + bortezomib + lenalidomide + dexamethasone[a] | | Bortezomib + lenalidomide + dexamethasone[b] | | Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs bortezomib + lenalidomide + dexamethasone[b] |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | HR [95% CI]<br>p value<br>Absolute difference (AD)[c] |
| | | | | | AD: 7.6 months |
| Insomnia | 196 | 4.3 [2.9; 6.9]<br>*122 (62.2)* | 136 | 2.9 [2.8; 4.3]<br>*86 (63.2)* | 0.84 [0.64; 1.12]<br>0.239 |
| Appetite loss | 196 | 7.4 [5.8; 9.7]<br>*119 (60.7)* | 136 | 5.7 [4.2; 7.0]<br>*93 (68.4)* | 0.75 [0.57; 0.99]<br>0.046<br>AD: 1.7 months |
| Constipation | 196 | 5.6 [3.1; 10.7]<br>*114 (58.2)* | 136 | 3.2 [2.6; 5.6]<br>*81 (59.6)* | 0.87 [0.66; 1.16]<br>0.365 |
| Diarrhoea | 196 | 9.0 [6.8; 13.6]<br>*132 (67.3)* | 136 | 5.8 [4.5; 7.6]<br>*95 (69.9)* | 0.77 [0.59; 1.00]<br>0.051 |
| **Symptomatology (EORTC QLQ-MY20 – time to 1st deterioration[e])** | | | | | |
| Symptoms of disease | 196 | 11.4 [7.4; 20.4]<br>*111 (56.6)* | 136 | 12.2 [6.1; 25.1]<br>*76 (55.9)* | 1.05 [0.78; 1.40]<br>0.765 |
| Side effects | 196 | 4.5 [4.1; 6.9]<br>*128 (65.3)* | 135 | 4.2 [2.9; 6.1]<br>*95 (70.4)* | 0.82 [0.62; 1.07]<br>0.137 |
| **Health status (EQ-5D VAS) – time to 1st deterioration[f])** | | | | | |
| | 196 | 17.0 [8.5; 38.2]<br>*97 (49.5)* | 136 | 7.1 [4.7; 27.3]<br>*75 (55.1)* | 0.78 [0.57; 1.05]<br>0.104 |

**Health-related quality of life**

| Endpoint | Isatuximab + bortezomib + lenalidomide + dexamethasone[a] | | Bortezomib + lenalidomide + dexamethasone[b] | | Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs bortezomib + lenalidomide + dexamethasone[b] |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | HR [95% CI]<br>p value<br>Absolute difference (AD)[c] |
| **EORTC QLQ-C30 – time to 1st deterioration[g]** | | | | | |
| Global health status | 196 | 6.6 [4.2; 11.1]<br>*119 (60.7)* | 136 | 4.2 [2.9; 5.8]<br>*88 (64.7)* | 0.79 [0.60; 1.05]<br>0.106 |
| Physical functioning | 196 | 5.6 [4.2; 6.9]<br>*123 (62.8)* | 136 | 4.3 [2.9; 5.7]<br>*94 (69.1)* | 0.77 [0.59; 1.02]<br>0.069 |
| Role functioning | 196 | 4.4 [3.0; 6.1]<br>*126 (64.3)* | 136 | 2.9 [1.7; 4.3]<br>*93 (68.4)* | 0.76 [0.58; 0.99]<br>0.048<br>AD: 1.5 months |
| Emotional functioning | 196 | 9.5 [7.1; 19.5]<br>*113 (57.7)* | 136 | 7.5 [4.3; 23.4]<br>*75 (55.1)* | 0.90 [0.67; 1.21]<br>0.488 |
| Cognitive functioning | 196 | 5.8 [4.2; 8.4]<br>*138 (70.4)* | 136 | 4.5 [2.9; 6.8]<br>*100 (73.5)* | 0.80 [0.61; 1.04]<br>0.09 |
| Social functioning | 196 | 4.2 [2.8; 4.4]<br>*142 (72.4)* | 136 | 2.8 [2.8; 3.0]<br>*96 (70.6)* | 0.85 [0.65; 1.11]<br>0.245 |
| **EORTC QLQ-MY20 – time to 1st deterioration[g]** | | | | | |
| Future prospects | 196 | 7.9 [5.7; 18.5]<br>*110 (56.1)* | 136 | 3.3 [2.9; 6.6]<br>*87 (64.0)* | 0.74 [0.56; 0.99]<br>0.046<br>AD: 4.6 months |
| Body image | 196 | 6.6 [4.3; 17.2]<br>*118 (60.2)* | 136 | 4.3 [3.3; 9.3]<br>*92 (67.6)* | 0.81 [0.61; 1.06]<br>0.126 |

**Side effects**[h]

| Endpoint | Isatuximab + bortezomib + lenalidomide + dexamethasone[a] | | Bortezomib + lenalidomide + dexamethasone[b] | | Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs bortezomib + lenalidomide + dexamethasone[b] |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | HR [95% CI]<br>p value |
| **Total adverse events (presented additionally)** | | | | | |
| | 195 | 0.2 [0.1; 0.3]<br>*194 (99.5)* | 136 | 0.2 [0.1; 0.3]<br>*134 (98.5)* | - |
| **Serious adverse events (SAEs)** | | | | | |
| | 195 | 12.2 [8.4; 24.3]<br>*139 (71.3)* | 136 | 5.3 [2.5; 11.6]<br>*100 (73.5)* | 0.79 [0.61; 1.03]<br>0.078 |
| **Severe adverse events (CTCAE grade ≥ 3)** | | | | | |
| | 195 | 2.0 [1.4; 2.9]<br>*176 (90.3)* | 136 | 1.5 [0.9; 2.3]<br>*117 (86.0)* | 0.95 [0.75; 1.20]<br>0.685 |
| **Discontinuation due to AEs (at least one active ingredient component)**[i] | | | | | |
| | 195 | n.r. [43.63; n.r.]<br>*87 (44.6)* | 136 | 52.17 [30.62; n.r.]<br>*60 (44.1)* | 0.90 [0.65; 1.26]<br>0.5421 |
| **Specific adverse events** | | | | | |
| Infusion-related reactions | No suitable data | | | | |
| Peripheral neuropathy (SMQ, severe AEs)[i] | 195 | n.r. [n.r.; n.r.]<br>17 (8.7) | 136 | n.r. [n.r.; n.r.]<br>10 (7.4) | 1.19 [0.54; 2.60]<br>0.6650 |
| Metabolism and nutrition disorders (SOC, severe AEs) | 195 | n.r.<br>*13 (6.7)* | 136 | n.r. [62.2; n.c.]<br>*22 (16.2)* | 0.36 [0.18; 0.71]<br>0.002 |
| Respiratory, thoracic and mediastinal disorders (SOC, severe AEs) | 195 | n.r.<br>*15 (7.7)* | 136 | n.r.<br>*20 (14.7)* | 0.45 [0.23; 0.89]<br>0.018 |

| Endpoint | Isatuximab + bortezomib + lenalidomide + dexamethasone[a] | | Bortezomib + lenalidomide + dexamethasone[b] | | Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs bortezomib + lenalidomide + dexamethasone[b] |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | HR [95% CI]<br>p value |

a. Followed by therapy with isatuximab + lenalidomide + dexamethasone in the maintenance phase (from cycle 5)
b. Followed by therapy with lenalidomide + dexamethasone in the maintenance phase (from cycle 5)
c. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
d. Information provided by the pharmaceutical company in the dossier
e. An increase in EORTC QLQ-C30 and EORTC-QLQ-MY20 scores by ≥ 10 points compared to the start of the study is considered as clinically relevant deterioration (scale range: 0 to 100).
f. A decrease in EQ-5D VAS score by ≥ 15 points compared to the start of study is considered as clinically relevant deterioration (scale range: 0 to 100).
g. A decrease in EORTC QLQ-C30 and EORTC-QLQ-MY20 scores by ≥ 10 points compared to the start of study is considered as clinically relevant deterioration (scale range: 0 to 100).
h. Exclusive PTs Malignant neoplasm progression, Bone metastases, Plasma cell leukaemia and Plasma cell myeloma
i. Information provided by the pharmaceutical company in the analyses submitted in the written statement procedure

Abbreviations used:
AD: absolute difference; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; IRC: Independent Review Committee; CI: confidence interval; n: number of patients with (at least 1) event; N: number of patients evaluated; n.c.: not calculable; n.r. = not reached; QLQ-C30: Quality of Life Questionnaire − Core 30; QLQ-MY20: Quality of Life Questionnaire – Myeloma Module 20; RCT: randomised controlled trial; R-ISS: Revised International Staging System; SOC: system organ class; SAE: serious adverse event; AE: adverse event; 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. 3,450 to 3,680 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: 24 June 2025):

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 European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient identification card). The training material contains in particular information and warnings 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

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

**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: | |
| Isatuximab in combination with bortezomib, lenalidomide and dexamethasone | |
| Isatuximab | € 69,257.44 |
| Bortezomib | € 5,610.88 |
| Lenalidomide | € 440.59 |
| Dexamethasone | € 365.21 |
| Total: | € 75,674.12 |
| Additionally required SHI costs | € 10.49 |
| Appropriate comparator therapy: | |
| Daratumumab in combination with lenalidomide and dexamethasone | |
| Daratumumab | € 133,586.30 |
| Lenalidomide | € 464.40 |
| Dexamethasone | € 108.03 |

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| Total: | € 134,158.73 |
| Additionally required SHI costs | € 261.25 – € 264.55 |
| Daratumumab in combination with bortezomib, melphalan and prednisone | |
| Daratumumab | € 124,293.34 |
| Bortezomib | € 6,803.19 |
| Melphalan | € 313.64 |
| Prednisone | € 73.19 |
| Total: | € 131,483.36 |
| Additionally required SHI costs | € 214.21 – € 217.28 |
| Bortezomib in combination with melphalan and prednisone | |
| Bortezomib | € 8,907.27 |
| Melphalan | € 313.64 |
| Prednisone | € 97.59 |
| Total: | € 9,318.50 |
| Bortezomib in combination with lenalidomide and dexamethasone | |
| *Induction* | |
| Bortezomib | € 5,610.88 |
| Lenalidomide | € 190.52 |
| Dexamethasone | € 169.43 |
| *Follow-up treatment* | |
| Lenalidomide | € 250.06 |
| Dexamethasone | € 104.31 |
| Total: | € 6,325.20 |
| Additionally required SHI costs | € 10.49 |
| Thalidomide in combination with melphalan and prednisone | |
| Thalidomide | € 15,011.72 |
| Melphalan | € 348.49 |
| Prednisone | € 134.10 |
| Total: | € 15,494.31 |
| Additionally required SHI costs | € 10.49 |

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| 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) | |
| Bortezomib | € 12,203.66 |
| Cyclophosphamide | € 775.75 |
| Dexamethasone | € 518.55 |
| Total: | € 13,497.96 |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 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 | | | | | |
| Isatuximab in combination with bortezomib, lenalidomide and dexamethasone | | | | | |
| Isatuximab | Surcharge for the preparation of a parenteral solution containing monoclonal antibodies | € 100 | 2 – 5 | 28.0 | € 2,800 |
| Bortezomib | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 8 | 32.0 | € 3,200 |
| Appropriate comparator therapy | | | | | |
| Daratumumab in combination with bortezomib, melphalan and prednisone | | | | | |
| Bortezomib | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 4 – 8 | 38.8 | € 3,880 |
| Bortezomib in combination with melphalan and prednisone | | | | | |
| Bortezomib | Surcharge for production of a parenteral preparation | € 100 | 4 – 8 | 50.8 | € 5,080 |

| Designation of the therapy | Type of service | Costs/ unit | Number/ cycle | Number/ patient/ year | Costs/ patient/ year |
|---|---|---|---|---|---|
| | containing cytostatic agents | | | | |
| Bortezomib in combination with lenalidomide and dexamethasone | | | | | |
| Bortezomib | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 4 | 32.0 | € 3,200 |
| 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) | | | | | |
| Bortezomib | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 4 | 69.6 | € 6,960 |
| Cyclophosphamide | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1 | € 1,740 | € 1,740 |

## 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:

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

– No medicinal product with new active ingredients that can be used in a combination therapy and 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 7 August 2025.**

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

Berlin, 7 August 2025

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

Prof. Hecken