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
Belantamab mafodotin (reassessment after the deadline: multiple myeloma, at least 4 prior therapies, monotherapy)

of 5 October 2023

At its session on 5 October 2023, 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 Belantamab mafodotin in the version of the resolution of 4 March 2021 (BAnz AT 16.04.2021 B5), last modified on 17 November 2022, is repealed.

2. Annex XII shall be amended in alphabetical order to include the active ingredient Belantamab mafodotin as follows:

Belantamab mafodotin

Resolution of: 5 October 2023
Entry into force on: 5 October 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 25 August 2020):

Blenrep is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

Therapeutic indication of the resolution (resolution of 5 October 2023):

Therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Belantamab mafodotin is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Adults with multiple myeloma, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy

Extent of the additional benefit and significance of the evidence of belantamab mafodotin:

The G-BA classifies the extent of the additional benefit of belantamab mafodotin to be assumed solely from a legal point of view according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V on the basis of the criteria in Section 5, paragraph 7 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as non-quantifiable taking into account the severity of the disease and the therapeutic objective in the treatment of the disease.

Study results according to endpoints:[1]

Adults with multiple myeloma, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	n.a.	The data are not assessable.
Side effects	↔	No relevant differences for the benefit assessment, in detail one disadvantage for corneal 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
∅: No data available.
n.a.: not assessable

DREAMM-3 study: Belantamab mafodotin vs pomalidomide/ dexamethasone, ongoing, open-label, randomised, multicentre phase III study, primary data cut-off from 12.09.2022

Relevant sub-population: sub-population tailored according to the approved therapeutic indication (5L+)

DREAMM-2 study: non-controlled phase 2 study of belantamab mafodotin, final data cut-off from 31.03.2022

Relevant sub-population: Treatment cohort in which belantamab mafodotin was used at the PI-compliant dose of 2.5 mg/kg BW

1 Data from the dossier assessment of the G-BA (published on 3. Juli 2023), unless otherwise indicated.

Mortality

Endpoint	**Belantamab mafodotin**		**Pomalidomide/ dexamethasone (Pom/Dex)**		Belantamab mafodotin vs Pom/Dex
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Overall survival					
DREAMM-3	29	9.5 [5.1; n.c.] 16 (55)	15	n.c. [9.5; n.c.] 4 (27)	2.02 [0.52; 7.85] 0.30
DREAMM-2	97	15.3 [9.9; 18.9] 70 (72)	-		

Morbidity

Endpoint	**Belantamab mafodotin**		**Pomalidomide/ dexamethasone (Pom/Dex)**		Belantamab mafodotin vs Pom/Dex
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS)[c]					
DREAMM-3	29	2.6 [1.4; 5.7] 20 (69)	15	9.3 [3.5; n.c.] 8 (53)	2.89 [0.91; 9.20] 0.063
DREAMM-2	97	2.8 [1.6; 3.6] 75 (77)	-		

Endpoint	Belantamab mafodotin		Pomalidomide/ dexamethasone (Pom/Dex)		Belantamab mafodotin vs Pom/Dex
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value Absolute difference (AD)[a]
Symptomatology (EORTC QLQ-C30 – deterioration by ≥ 10 points at week 4[d])					
Fatigue					
DREAMM-3	29	9 (39)	15	3 (27)	n.d.
Pain					
DREAMM-3	29	6 (26)	15	3 (25)	n.d.
Nausea and vomiting					
DREAMM-3	29	4 (18)	15	3 (25)	n.d.
Dyspnoea					
DREAMM-3	29	6 (26)	15	4 (33)	n.d.
Appetite loss					
DREAMM-3	29	6 (27)	15	2 (17)	n.d.
Insomnia					
DREAMM-3	29	5 (23)	15	2 (18)	n.d.
Constipation					
DREAMM-3	29	3 (14)	15	4 (33)	n.d.
Diarrhoea					
DREAMM-3	29	2 (9)	15	1 (8)	n.d.
Myeloma-specific symptomatology (EORTC QLQ-MY20/IL52 – deterioration by ≥ 10 points at week 4[d])					
Disease symptoms					
DREAMM-3	29	6 (27)	15	1 (8)	n.d.

Health-related quality of life

Endpoint	**Belantamab mafodotin**		**Pomalidomide/ dexamethasone (Pom/Dex)**		Belantamab mafodotin vs Pom/Dex
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value Absolute difference (AD)[a]
EORTC QLQ-C30 – deterioration by ≥ 10 points at week 4[d]					
Global health status / Global quality of life					
DREAMM-3	29	8 (35)	15	4 (33)	n.d.
Physical functioning					
DREAMM-3	29	6 (26)	15	4 (33)	n.d.
Role functioning					
DREAMM-3	29	7 (30)	15	5 (42)	n.d.
Emotional functioning					
DREAMM-3	29	4 (17)	15	2 (17)	n.d.
Cognitive functioning					
DREAMM-3	29	5 (22)	15	4 (33)	n.d.
Social functioning					
DREAMM-3	29	7 (30)	15	3 (25)	n.d.

Side effects

Endpoint	**Belantamab mafodotin**		**Pomalidomide/ dexamethasone (Pom/Dex)**		Belantamab mafodotin vs Pom/Dex
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	HR [95% CI] p value[e] Absolute difference (AD)[a]
Adverse events in total					
DREAMM-3	29	28 (97)	14	13 (93)	
DREAMM-2	95	93 (98)	-		
Serious adverse events (SAE)					
DREAMM-3	29	13 (45)	14	5 (36)	2.18 [0.76; 6.29] 0.14
DREAMM-2	95	43 (45)	-		
Severe adverse events (CTCAE grade ≥ 3)					
DREAMM-3	29	20 (69)	14	11 (79)	0.90 [0.44; 1.85] 0.76
DREAMM-2	95	80 (84)	-		
Therapy discontinuation due to adverse events[f]					
DREAMM-3	29	1 (3)	14	2 (14)	0.31 [0.03; 3.52] 0.32
DREAMM-2	95	11 (12)	-		
Adverse events of special interest					
Subjects with at least one AESI regardless of severity grade					
Infusion-related reactions					
DREAMM-3	29	4 (14)	14	0 (0)	n.c. [n.c.; n.c.]
DREAMM-2	95	20 (21)	-		
Thrombocytopenia					
DREAMM-2	95	36 (38)	-		

Endpoint	Belantamab mafodotin		Pomalidomide/ dexamethasone (Pom/Dex)		Belantamab mafodotin vs Pom/Dex
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	HR [95% CI] p value[e] Absolute difference (AD)[a]
Neutropenia					
DREAMM-2	95	14 (15)	-		
Corneal events					
DREAMM-3	29	12 (41)	14	2 (14)	5.19 [1.13; 23.86] 0.02
DREAMM-2	95	68 (72)	-		
Eye examinations					
DREAMM-2					
Blurred vision	95	24 (25)	-		
Dry eye	95	17 (18)	-		
Subjects with ≥ 1 severe AESI ≥ CTCAE grade 3					
Infusion-related reactions					
DREAMM-3	29	1 (3)	14	0 (0)	n.c. [n.c.; n.c.]
DREAMM-2	95	3 (3)	-		
Thrombocytopenia					
DREAMM-3	29	8 (28)	14	2 (14)	2.11 [0.45; 9.94] 0.33
DREAMM-2	95	21 (22)	-		
Neutropenia					
DREAMM-2	95	10 (11)	-		
Corneal events					
DREAMM-3	29	6 (21)	14	0 (0)	n.c. [n.c.; n.c.]

Endpoint	Belantamab mafodotin		Pomalidomide/ dexamethasone (Pom/Dex)		Belantamab mafodotin vs Pom/Dex
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	HR [95% CI] p value[e] Absolute difference (AD)[a]
Eye examinations					
DREAMM-2					
Blurred vision	95	4 (4)	-		
Dry eye	95	2 (2)	-		
Keratopathy	95	29 (31)	-		
Subjects with ≥ 1 serious AESI					
Infusion-related reactions					
DREAMM-3	29	1 (3)	14	0 (0)	n.c. [n.c.; n.c.]
DREAMM-2	95	4 (4)	-		
Thrombocytopenia					
DREAMM-3	29	1 (3)	14	0 (0)	n.c. [n.c.; n.c.]
DREAMM-2	95	1 (1)	-		
Neutropenia					
DREAMM-2	95	0 (0)	-		
Corneal events					
DREAMM-3	29	0 (0)	14	0 (0)	n.c. [n.c.; n.c.]
Eye examinations					
DREAMM-2					
Blurred vision	95	0 (0)	-		
Dry eye	95	0 (0)	-		

Endpoint	Belantamab mafodotin		Pomalidomide/ dexamethasone (Pom/Dex)		Belantamab mafodotin vs Pom/Dex
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	HR [95% CI] p value[e] Absolute difference (AD)[a]
Keratopathy	95	2 (2)	-		
Ocular toxicity (OSDI - deterioration by ≥ 15% of the scale range at week 4[d])					
Total score					
DREAMM-3	29	2 (9)	14	2 (17)	n.d.
Ocular symptoms					
DREAMM-3	29	2 (9)	14	0 (0)	n.d.
Visual function					
DREAMM-3	29	2 (9)	14	3 (25)	n.d.
Environmental triggers					
DREAMM-3	29	5 (26)	14	1 (10)	n.d.
Ocular toxicity (OSDI – mean change by week 4 compared to baseline)					
DREAMM-2	**Belantamab mafodotin**				
	N	**MV (SD)**			
Total score	77	3.4 (17.7)	-		
Ocular symptoms	77	7.6 (19.7)	-		
Visual function	77	1.8 (20.6)	-		
Environmental triggers	74	2.2 (17.3)	-		

a Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b Cox proportional hazards model stratified by ISS stage (I/II; III), pretreatment with anti-CD38 antibody therapy (Yes; No) and CRF reported number of previous lines of therapy (4; 5; 6; ...). p value based on two-sided stratified log-rank test.
c From the dossier of the pharmaceutical company
d Subjects with missing values were not included in the responder analysis. Percentages of deterioration therefore do not refer to the ITT sub-population 5 L+, but to those with values at baseline and week 4
e Unstratified Cox proportional hazards model; p value based on unstratified log-rank test
f Study participants received study medication until the occurrence of disease progression, withdrawal of informed consent, death, the occurrence of unacceptable toxicities, lost to follow-up or study termination, whichever occurred earlier. These possible therapy discontinuation reasons that may occur prior to potential discontinuation due to AEs thus represent a competing event, which is why the reliability and interpretability of the results is limited.

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; HR = hazard ratio; n.d.: no data available; CI = confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; OSDI = Ocular Surface Disease Index; (S)AE = (serious) adverse event; vs = versus

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

Adults with multiple myeloma, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy

Approx. 570 to 1,130 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 Blenrep (active ingredient: belantamab mafodotin) at the following publicly accessible link (last access: 28 June 2023):

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

Treatment with belantamab mafodotin 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 measures to risk minimisation, the pharmaceutical company should provide training materials for all healthcare professionals prescribing, dispensing and administering belantamab mafodotin and to patients receiving belantamab mafodotin.

The training material for medical professionals includes a guideline for corneal side effects and a guideline for eye examination. The guideline for corneal side effects contains information on the safety risk of these side effects and on appropriate risk minimisation measures. The guideline for eye examination also contains instructions to facilitate communication between the patient's treating physician and ophthalmologist.

The patient training material includes a guideline regarding corneal side effects for patients, a patient card and a pharmacy card for eye drops. The guideline informs patients that corneal side effects can occur during treatment with belantamab mafodotin and also contains information about the prescribed eye examinations and measures to be taken upon occurrence of the corneal side effects. The patient card, which shows that the patient is being treated with belantamab mafodotin and contains the contact information of the haematologist/ oncologist and the ophthalmologist, should be presented to the healthcare professional during follow-up examinations. Presentation of the pharmacy card for eye drops to the pharmacy is to ensure receipt and correct use of eye drops containing preservative-free tear substitute.

This medicinal product was approved under "conditional marketing authorisation". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

Adults with multiple myeloma, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy

Designation of the therapy	Annual treatment costs/ patient
Belantamab mafodotin	€ 180,391.72

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 01 September 2023

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Belantamab mafodotin	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	1	17.4	€ 1740

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:

Adults with multiple myeloma, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and

an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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 5 October 2023.

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

Berlin, 5 October 2023

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

Prof. Hecken