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)
Dostarlimab (new therapeutic indication: primary advanced or recurrent endometrial cancer with dMMR/ MSI-H, combination with carboplatin and paclitaxel)

of 20 June 2024

At its session on 20 June 2024, 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 Dostarlimab in accordance with the resolution of 2 December 2021:

Dostarlimab

Resolution of: 20 June 2024
Entry into force on: 20 June 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 7 December 2023):

JEMPERLI is indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.

Therapeutic indication of the resolution (resolution of 20 June 2024):

See new therapeutic indication according to marketing authorisation.

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

a) Adult patients with microsatellite instability-high (MSI-H) or with mismatch repair deficient (dMMR) primary advanced endometrial cancer (stage III or IV) or with recurrence of endometrial cancer who:
   - have not yet received systemic therapy as postoperative or adjuvant therapy for treatment of the primary advanced disease,
   - have not yet received chemotherapy for treatment of the recurrence.

Appropriate comparator therapy:

- Carboplatin + paclitaxel

Extent and probability of the additional benefit of dostarlimab compared to the appropriate comparator therapy:

a1) Patients with primary advanced disease

An additional benefit is not proven.

a2) Patients with recurrent disease

Indication of a major additional benefit

Study results according to endpoints:[1]

a) Adult patients with microsatellite instability-high (MSI-H) or with mismatch repair deficient (dMMR) primary advanced endometrial cancer (stage III or IV) or with recurrence of endometrial cancer who:
   - have not yet received systemic therapy as postoperative or adjuvant therapy for treatment of the primary advanced disease,
   - have not yet received chemotherapy for treatment of the recurrence.

a1) Patients with primary advanced disease

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	There is no relevant difference for the benefit assessment.
Morbidity	↔	Advantage in the symptom scale of tingling/ numbness in FIGO stage IV. Overall, no relevant differences.
Health-related quality of life	↑	Advantages in the functional scales of social functioning and role functioning.
Side effects	↔	Disadvantage in severe AEs in FIGO stage III. In detail, advantages and disadvantages in the specific AEs. Overall, no relevant differences for the benefit assessment.
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		

a2) Patients with recurrent disease

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary

[1] Data from the dossier assessment of the IQWiG (A23-143) and from the addendum (A24-59), unless otherwise indicated.

Mortality	↑↑	Advantage in overall survival
Morbidity	↔	There are no relevant differences for the benefit assessment.
Health-related quality of life	↑	Advantages in the functional scales "social functioning" and "role functioning".
Side effects	↔	There are no relevant differences for the benefit assessment. In detail, advantages and disadvantages in the 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
∅: No data available.
n.a.: not assessable

RUBY study: Dostarlimab in combination with carboplatin and paclitaxel **vs** carboplatin + paclitaxel

Randomised, controlled, double-blind, multicentre phase III study

Data from the relevant sub-population with dMMR/ MSI-H advanced or recurrent endometrial cancer (2nd data cut-off from 22 September 2023)

Mortality

Endpoint	**Dostarlimab + carboplatin + paclitaxel**		**Carboplatin + paclitaxel**		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 (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Overall survival					
	53	n.r. 12 (22.6)	65	31.4 [20.3; n.c.] 35 (53.8)	0.32 [0.17; 0.63]; < 0.001
Effect modification by the "disease status at the baseline" characteristic					
Primary FIGO stage III	9	n.r. [2.4; n.c.] 3 (33.3)	14	n.r. [20.0; n.c.] 3 (21.4)	1.85 [0.37; 9.18][c]; 0.445[d]
Primary FIGO stage IV	17	n.r. [21.0; n.c.] 6 (35.3)	19	18.2 [11.6; n.c.] 11 (57.9)	0.53 [0.19; 1.43][c]; 0.201[d]
Recurrent	27	n.r. 3 (11.1)	32	24.0 [13.0; 42.2] 21 (65.6)	0.12 [0.04; 0.42][c]; < 0.001[d]
				Interaction[e]:	0.032

Morbidity

Endpoint	Dostarlimab + carboplatin + paclitaxel		Carboplatin + paclitaxel		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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS)[2]					
Assessment by principal investigator	53	n.a. [11.8; n.c.] 19 (35.8)	65	7.7 [5.6; 9.7] 47 (72.3)	0.28 [0.162; 0.495]; < 0.0001
Assessment by BICR	53	n.a. [n.c.; n.c.] 16 (30.2)	65	9.5 [7.0; 11.7] 37 (56.9)	0.29 [0.158; 0.543]; < 0.0001

Endpoint	Dostarlimab + carboplatin + paclitaxel		Carboplatin + paclitaxel		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 (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Symptomatology (EORTC QLQ-C30; time to first deterioration)[f]					
Fatigue	53	2.3 [1.6; 4.0] 41 (77.4)	65	1.4 [1.0; 2.8] 52 (80.0)	0.84 [0.55; 1.28]; 0.410
Nausea and vomiting	53	5.8 [2.8; 14.9] 36 (67.9)	65	4.5 [2.6; 11.3] 41 (63.1)	0.87 [0.54; 1.38]; 0.539
Pain	53	11.5 [2.8; 27.1] 31 (58.5)	65	3.3 [2.2; 4.9] 47 (72.3)	0.64 [0.40; 1.03]; 0.058
Dyspnoea	53	4.4 [2.6; 17.7] 35 (66.0)	65	3.7 [2.1; 10.6] 42 (64.6)	0.90 [0.56; 1.45]; 0.661
Insomnia	53	7.5 [2.1; n.c.] 29 (54.7)	65	4.2 [2.8; n.c.] 36 (55.4)	0.96 [0.59; 1.57]; 0.862
Appetite loss	53	19.8 [5.6; n.c.] 25 (47.2)	65	8.5 [2.8; 27.6] 39 (60.0)	0.68 [0.41; 1.14]; 0.144
Constipation	53	2.8 [1.0; 33.8] 32 (60.4)	65	3.9 [2.1; 5.8] 44 (67.7)	0.87 [0.54; 1.40]; 0.518

[2] Data on dostarlimab from module 4 of the pharmaceutical company from 18.12.2023 at the 1st data cut-off

Diarrhoea	53	4.6 [2.4; 14.9] 36 (67.9)	65	5.7 [3.7; 28.5] 37 (56.9)	1.18 [0.73; 1.89]; 0.503
Symptomatology (EORTC QLQ-EN24 – time to first deterioration)[f]					
Lymphoedema	53	2.8 [2.1; 4.4] 39 (73.6)	65	2.8 [1.7; 3.5] 50 (76.9)	0.87 [0.56; 1.33]; 0.518
Urological symptoms	53	n.r. [7.2; n.c.] 22 (41.5)	65	3.8 [2.1; n.c.] 36 (55.4)	0.60 [0.35; 1.04]; 0.068
Gastrointestinal symptoms	53	26.7 [4.4; n.c.] 24 (45.3)	65	11.7 [6.5; n.c.] 33 (50.8)	0.91 [0.53; 1.56]; 0.736
Sexual/ vaginal problems	No usable data available[g]				
Back and pelvic pain	53	21.6 [8.8; n.c.] 23 (43.4)	65	24.0 [4.6; n.c.] 32 (49.2)	0.82 [0.48; 1.41]; 0.473
Feeling of tingling/ numbness	53	1.5 [1.0; 2.1] 45 (84.9)	65	1.4 [0.9; 2.1] 56 (86.2)	0.88 [0.58; 1.32]; 0.509
Effect modification by the “disease status at the baseline“ characteristic					
Primary FIGO stage III	9	1.4 [0.7; 2.1] 9 (100)	14	1.2 [0.8; 2.1] 12 (85.7)	1.03 [0.43; 2.45][c]; 0.950[d]
Primary FIGO stage IV	17	3.5 [2.1; 7.2] 11 (64.7)	19	0.8 [0.7; 2.1] 18 (94.7)	0.34 [0.16; 0.75][c]; 0.005[d] AD: + 2.7 months
Recurrent	27	1.0 [0.8; 2.1] 25 (92.6)	32	1.8 [1.4; 2.3] 26 (81.3)	1.35 [0.77; 2.36][c]; 0.317[d]
				Interaction[e]:	0.016
Muscular pain	53	1.4 [0.9; 3.5] 43 (81.1)	65	2.1 [1.4; 2.9] 50 (76.9)	1.15 [0.76; 1.75]; 0.556
Hair loss	53	0.8 [0.7; 0.8] 47 (88.7)	65	0.8 [0.7; 0.8] 61 (93.8)	1.15 [0.77; 1.71]; 0.574
Change of taste	53	2.2 [0.9; 3.5] 37 (69.8)	65	2.2 [1.4; 3.0] 48 (73.8)	0.90 [0.58; 1.40]; 0.609
Health status (EQ-5D VAS – time to first deterioration)[h]					
	53	n.r. 15 (28.3)	65	16.3 [4.2; n.c.] 29 (44.6)	0.54 [0.28; 1.02]; 0.055

Health-related quality of life

Endpoint	Dostarlimab + carboplatin + paclitaxel		Carboplatin + paclitaxel		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 (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
EORTC QLQ-C30 – time to first deterioration[f]					
Global health status	53	12.9 [4.0; n.c.] 29 (54.7)	65	4.2 [2.0; 9.0] 48 (73.8)	0.63 [0.39; 1.02]; 0.055
Physical functioning	53	4.0 [2.1; 23.5] 32 (60.4)	65	3.7 [2.1; 10.8] 42 (64.6)	0.93 [0.58; 1.49]; 0.759
Role functioning	53	4.4 [2.3; 30.4] 31 (58.5)	65	2.5 [1.4; 4.4] 48 (73.8)	0.61 [0.38; 0.98]; 0.040 AD: + 1.9 months
Emotional functioning	53	20.5 [3.5; n.c.] 27 (50.9)	65	13.9 [4.2; 27.7] 35 (53.8)	0.83 [0.50; 1.40]; 0.478
Cognitive functioning	53	4.0 [2.3; 8.8] 34 (64.2)	65	2.9 [2.1; 4.1] 48 (73.8)	0.70 [0.44; 1.11]; 0.119
Social functioning	53	4.2 [2.5; n.c.] 28 (52.8)	65	2.8 [1.5; 8.8] 48 (73.8)	0.57 [0.35; 0.92]; 0.020 AD: + 1.4 months
EORTC QLQ-EN24 – time to first deterioration[f]					
Libido	53	n.r. 10 (18.9)	65	n.r. 17 (26.2)	0.63 [0.29; 1.38]; 0.242
Sexual activity	53	n.r. 6 (11.3)	65	n.r. 5 (7.7)	1.22 [0.37; 4.01]; 0.738
Sexual pleasure	No usable data available[i]				
Negative body image[j]	53	1.4 [0.8; 4.0] 32 (60.4)	65	1.4 [0.9; 1.4] 52 (80.0)	0.70 [0.45; 1.10]; 0.126

Side effects[k]

Endpoint	Dostarlimab + carboplatin + paclitaxel		Carboplatin + paclitaxel		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	52	0.1 [0.0; 0.1] 52 (100)	65	0.1 [0.0; 0.1] 65 (100)	-
Serious adverse events (SAE)					
	52	n.r. [23.8; n.c.] 17 (32.7)	65	26.4 [13.5; n.c.] 21 (32.3)	0.86 [0.44; 1.66]; 0.633
Severe adverse events (CTCAE grade 3 or 4)					
	52	3.2 [1.4; 5.2] 39 (75.0)	65	3.4 [1.9; 9.9] 43 (66.2)	1.22 [0.77; 1.91]; 0.402
Effect modification by the "disease status at the baseline" characteristic					
Primary FIGO stage III	9	4.1 [0.0; 4.6] 8 (88.9)	14	16.5 [2.6; n.c.] 7 (50.0)	5.40 [1.57; 18.53][c]; 0.003[d]
Primary FIGO stage IV	16	4.1 [0.3; 11.3] 12 (75.0)	19	2.4 [0.7; 4.5] 15 (78.9)	0.82 [0.37; 1.79][c]; 0.605[d]
Recurrent	27	2.7 [1.0; 25.6] 19 (70.4)	32	2.3 [1.4; 9.9] 21 (65.6)	0.91 [0.48; 1.74][c]; 0.763[d]
				Interaction[e]:	0.031
Therapy discontinuation due to adverse events[l]					
	52	n.r. 10 (19.2)	65	n.r. 11 (16.9)	0.86 [0.34; 2.17]; 0.751
Specific adverse events					
Immune-mediated AEs (presented additionally)[m]	52	2.8 [0.7; 4.6] 39 (75.0)	65	25,8 [2,1; n.c.] 26 (40.0)	-
Immune-mediated SAEs[m]	52	n.r. 3 (5.8)	65	n.r. 2 (3.1)	1.53 [0.24; 9.81]; 0.652
Immune-mediated severe AEs[m]	52	n.r. [31.8; n.c.] 12 (23.1)	65	n.r. 0	n.d.[n]
Infusion-related reactions	No usable data available				

Urinary tract infections (PT, AEs)	52	n.r. 4 (7.7)	65	n.r. [13.3; n.c.] 16 (24.6)	0.25 [0.08; 0.78]; 0.010

[a] Data on absolute difference (AD) only in the case of statistically significant difference; own calculation
[b] Effect and CI: Cox proportional hazards model; p value: log-rank test. In each case, stratified according to previous pelvic radiotherapy (yes vs no) and disease status at the start of study (primary FIGO stage III vs primary FIGO stage IV vs recurrent)
[c] Effect and CI: Cox proportional hazards model, stratified by previous pelvic radiotherapy (yes vs no) and disease status at the start of study (primary FIGO stage III vs primary FIGO stage IV vs recurrent)
[d] p value: Log-rank test, stratified by previous pelvic radiotherapy (yes vs no) and disease status at the start of study (primary FIGO stage III vs primary FIGO stage IV vs recurrent)
[e] p value of the interaction term of the stratified Cox proportional hazards model
[f] An increase in score by ≥ 10 points compared to the baseline is considered a clinically relevant deterioration (scale range 0 to 100).
[g] 81% of the patients had no value at baseline and were therefore not included in the analysis.
[h] A decrease in score by ≥ 15 points compared to the baseline is considered a clinically relevant deterioration (scale range 0 to 100).
[i] 82% of the patients had no value at baseline and were therefore not included in the analysis.
[j] In deviation from the pharmaceutical company's recommendation, this scale was not assigned to symptomatology, but to health-related quality of life.
[k] According to the study protocol, events due to progression of the underlying disease should not be reported as AEs. However, 2 (3.1%) patients with event for the PT "Cancer pain" from the SOC "Benign, malignant and non-specific neoplasms (including cysts and polyps)" were documented among AEs in the control arm.
[l] Discontinuation of at least 1 active ingredient component
[m] Operationalisation was based on an a priori defined list of preferred terms (PTs), whereby only immune-mediated AEs with a CTCAE grade ≥ 2 could be assessed as being immune-mediated.
[n] The pharmaceutical company provides no information on HR (including 95% CI) and p value.

Abbreviations used:
AD = absolute difference; BICR = Blinded Independent Central Review; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; FIGO = International Federation of Gynaecology and Obstetrics; HR = hazard ratio; CI = confidence interval; n.d.: no data available; N = number of evaluated patients; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PT = preferred term; QLQ-C30 = Quality of Life Questionnaire − Core 30; QLQ-EN24 = Quality of Life Questionnaire − Endometrial Cancer Module 24; VAS = visual analogue scale; vs = versus

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

Adult patients with microsatellite instability-high (MSI-H) or with mismatch repair deficient (dMMR) primary advanced endometrial cancer (stage III or IV) or with recurrence of endometrial cancer who:

- have not yet received systemic therapy as postoperative or adjuvant therapy for treatment of the primary advanced disease,
- have not yet received chemotherapy for treatment of the recurrence.

Approx. 590 to 1,520 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 Jemperli (active ingredient: dostarlimab) at the following publicly accessible link (last access: 11 June 2024):

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

Treatment with dostarlimab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with endometrial cancer.

All doctors prescribing Jemperli must inform patients about the patient card and explain what to do in case of symptoms of immune-mediated side effects. The doctor provides each patient with a patient card.

The dMMR/MSI-H tumour status should be determined using a validated investigation method.

4. Treatment costs

Annual treatment costs:

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

a) Adult patients with microsatellite instability-high (MSI-H) or with mismatch repair deficient (dMMR) primary advanced endometrial cancer (stage III or IV) or with recurrence of endometrial cancer who:
   - have not yet received systemic therapy as postoperative or adjuvant therapy for treatment of the primary advanced disease,
   - have not yet received chemotherapy for treatment of the recurrence.

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Dostarlimab + carboplatin + paclitaxel	
Dostarlimab	€ 48,524.60
Carboplatin	€ 1,899.90
Paclitaxel	€ 5,357.82
Total	€ 55,782.32
Appropriate comparator therapy:	
Carboplatin + paclitaxel	
Carboplatin	€ 6,860.99
Paclitaxel	€ 15,537.68
Total	€ 22,398.67

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 June 2024)

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
Medicinal product to be assessed:					
Dostarlimab + carboplatin + paclitaxel					
Dostarlimab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	11.7	€ 1,170
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	6	€ 600
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	6	€ 600
Appropriate comparator therapy:					
Carboplatin + paclitaxel					
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 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:

a) Adult patients with microsatellite instability-high (MSI-H) or with mismatch repair deficient (dMMR) primary advanced endometrial cancer (stage III or IV) or with recurrence of endometrial cancer who:
   - have not yet received systemic therapy as postoperative or adjuvant therapy for treatment of the primary advanced disease,
   - have not yet received chemotherapy for treatment of the recurrence.

- 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 20 June 2024.

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

Berlin, 20 June 2024

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

Prof. Hecken