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) and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Olaparib (new therapeutic indication: primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR), combination with durvalumab, maintenance treatment)

of 20 February 2025

At its session on 20 February 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. 5 to the information on the benefit assessment of Olaparib in accordance with the resolution of 21 September 2023:

Olaparib

Resolution of: 20 February 2025
Entry into force on: 20 February 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 12 August 2024):

Lynparza in combination with durvalumab is indicated for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.

Therapeutic indication of the resolution (resolution of 20 February 2025):

See new therapeutic indication according to marketing authorisation.

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

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) 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; maintenance treatment

Appropriate comparator therapy:

- Carboplatin + paclitaxel followed by monitoring wait-and-see approach

Extent and probability of the additional benefit of olaparib in combination with durvalumab in maintenance treatment after first-line treatment with durvalumab in combination with carboplatin and paclitaxel versus carboplatin + paclitaxel followed by the monitoring wait-and-see approach:

a) Patients with newly diagnosed disease:

Indication of a considerable additional benefit.

b) Patients with recurrent disease:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) 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; maintenance treatment

a) Patients with newly diagnosed disease:

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival.
Morbidity	↓	Disadvantages for dyspnoea, appetite loss, constipation and change in taste
Health-related quality of life	↔	There is no relevant difference for the benefit assessment.
Side effects	↔	There is no relevant difference for the benefit assessment. In detail, disadvantage in 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		

[1] Data from the dossier assessment of IQWiG on durvalumab (endometrial cancer, pMMR: A24-86), unless otherwise indicated.

b) Patients with recurrent 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	↓	Disadvantages for dyspnoea, nausea and vomiting, appetite loss, constipation and change in taste.
Health-related quality of life	↔	There is no relevant difference for the benefit assessment.
Side effects	↔	There is no relevant difference for the benefit assessment. In detail, disadvantage in 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		

DUO-E study: ongoing, three-arm, randomised, double-blind phase III study

- Carboplatin + paclitaxel, followed by placebo[2] (arm A) **vs**
- Durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + placebo (arm B) **vs**
- Durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + olaparib (arm C)

Relevant sub-population: Proficient mismatch repair (pMMR) patients (arm A vs arm C)

[2] The placebo comparison conducted in maintenance treatment in arm A of the DUO-E study adequately corresponds to the implementation of the monitoring wait-and-see approach in the appropriate comparator therapy.

Mortality

Endpoint	Olaparib + durvalumab[a]		Carboplatin + paclitaxel followed by placebo[b]		Intervention vs control
	N[c]	Median time to event in months [95% CI] *Patients with event n (%)*	N[c]	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[d] Absolute difference (AD)[e]
Overall survival					
	191	n.r. 46 (24.1)	192	25.9 [25.1; n.c.] 64 (33.3)	0.68 [0.46; 0.99] 0.044
Effect modification for the "disease status at baseline" characteristic					
Recurrent	99	n.r. 25 (25.3)	101	n.r. 26 (25.7)	1.04 [0.60; 1.81] 0.883
Newly diagnosed	92	n.r. 21 (22.8)	91	25.1 [17.4; n.c.] 38 (41.8)	0.45 [0.26; 0.77] 0.003
					Interaction: 0.033

Morbidity

Progression-free survival (PFS)					
	191	15.0 [12.4; 18.0] 108 (56.5)	192	9.7 [9.2; 10.1] 148 (77.1)	0.57 [0.44; 0.73] < 0.0001 AD: +5.3 months
Symptomatology (time to 1st deterioration)					
EORTC QLQ-C30[f]					
Fatigue	163	1.3 [0.8; 1.4] 127 (66.5)	149	1.4 [1.3; 2.0] 122 (63.5)	0.98 [0.76; 1.26] 0.859
Nausea and vomiting	163	2.8 [2.2; 3.5] 110 (57.6)	149	6.0 [3.6; 9.6] 81 (42.2)	1.60 [1.20; 2.15] 0.002 AD: -3.2 months
Effect modification for the "disease status at baseline" characteristic					
Recurrent	99	2.8 [1.4; 4.1] 63 (63.6)	101	7.0 [3.6; n.c.] 39 (38.6)	2.16 [1.45; 3.25] < 0.001 AD: -4.2 months
Newly diagnosed	92	3.4 [2.7; 5.1] 47 (51.1)	91	5.2 [2.1; 9.6] 42 (46.2)	1.17 [0.77; 1.78] 0.473
					Interaction: 0.036
Pain	163	3.5 [2.1; 6.0] 98 (51.3)	149	2.8 [2.1; 4.1] 100 (52.1)	0.81 [0.61; 1.08] 0.153
Dyspnoea	163	2.9 [2.1; 4.2] 103 (53.9)	149	4.2 [3.4; 8.7] 81 (42.2)	1.37 [1.02; 1.84] 0.037

					AD: -1.3 months
Insomnia	163	5.1 [3.4; 17.0] 78 (40.8)	149	9.0 [3.5; 15.1] 71 (37.0)	1.05 [0.76; 1.46] 0.744
Appetite loss	163	3.4 [2.7; 4.2] 110 (57.6)	149	7.7 [4.1; 14.4] 73 (38.0)	1.74 [1.29; 2.35]; < 0.001 AD: -3.3 months
Constipation	163	3.5 [2.1; 6.0] 97 (50.8)	149	9.7 [3.5; n.c.] 68 (35.4)	1.52 [1.12; 2.09] 0.008 AD: -6.3 months
Diarrhoea	163	6.1 [4.1; 12.5] 80 (41.9)	149	5.1 [3.5; 8.8] 79 (41.1)	0.93 [0.68; 1.28] 0.657
EORTC QLQ-EN24[f]					
Lymphoedema	156	2.0 [1.4; 2.2] 115 (60.2)	148	2.1 [1.5; 2.9] 101 (52.6)	1.33 [1.01; 1.74] 0.051
Urological symptoms	156	7.0 [4.1; 14.2] 73 (38.2)	148	9.6 [6.0; n.c.] 66 (34.4)	1.13 [0.81; 1.58] 0.482
Gastrointestinal symptoms	156	4.2 [2.8; 13.3] 78 (40.8)	148	9.6 [6.8; 18.2] 66 (34.4)	1.33 [0.95; 1.85] 0.094
Sexual/ vaginal problems	No suitable data[g]				
Back and pelvic pain	156	15.1 [7.8; n.c.] 63 (33.0)	148	10.5 [6.9; 17.9] 63 (32.8)	1.02 [0.71; 1.45] 0.929
Tingling/ numbness	156	1.4 [0.8; 1.4] 120 (62.8)	148	1.4 [0.9; 1.4] 117 (60.9)	0.94 [0.72; 1.22] 0.605
Muscular pain	156	2.1 [1.4; 2.8] 110 (57.6)	148	1.9 [1.4; 2.2] 109 (56.8)	0.86 [0.66; 1.13] 0.272
Hair loss	156	0.7 [n.c.] 148 (77.5)	148	0.7 [n.c.] 141 (73.4)	1.03 [0.81; 1.30] 0.827
Change in taste	156	1.4 [1.4; 2.2] 118 (61.8)	148	2.1 [1.4; 4.2] 87 (45.3)	1.55 [1.17; 2.06] 0.003 AD: -0.5 months
PGIS[h]	156	4.1 [3.4; 9.7] 80 (41.9)	147	8.7 [4.2; 16.1] 69 (35.9)	1.19 [0.86; 1.65] 0.282
Health status (time to 1st deterioration)					
EQ-5D VAS[j]	156	4.1 [3.4; 9.7] 80 (41.9)	147	8.7 [4.2; 16.1] 69 (35.9)	1.19 [0.86; 1.65] 0.282
PGIC	No suitable data[i]				

Health-related quality of life

EORTC QLQ-C30[k,l]					
Global health status	163	3.5 [2.7; 5.1] 96 (50.3)	149	3.4 [2.1; 4.2] 97 (50.5)	0.94 [0.71; 1.25] 0.707
Physical functioning	163	2.8 [2.2; 3.5] 103 (53.9)	149	2.9 [2.1; 3.6] 98 (51.0)	0.96 [0.73; 1.27] 0.812
Role functioning	163	2.1 [1.4; 2.7] 116 (60.7)	149	1.6 [1.4; 2.1] 115 (59.9)	0.92 [0.71; 1.20] 0.557
Emotional functioning	163	6.0 [3.5; 13.4] 77 (40.3)	149	15.2 [7.1; n.c.] 61 (31.8)	1.24 [0.89; 1.74] 0.209
Cognitive functioning	163	2.7 [2.1; 2.9] 111 (58.1)	149	3.4 [2.2; 4.3] 94 (49.0)	1.23 [0.93; 1.62] 0.153
Social functioning	163	2.2 [1.6; 2.9] 107 (56.0)	149	2.8 [2.1; 3.6] 92 (47.9)	1.17 [0.88; 1.55] 0.288
EORTC QLQ-EN24[k]					
Libido[l]	156	n.r. 36 (18.8)	148	n.r. 34 (17.7)	1.01 [0.63; 1.62] 0.983
Sexual activity[l]	156	n.r. 25 (13.1)	148	n.r. 33 (17.2)	0.68 [0.40; 1.14] 0.147
Sexual pleasure[k]	No suitable data[g]				
Negative body image[f, m]	156	1.4 [1.0; 1.5] 117 (61.3)	148	1.4 [1.4; 2.1] 100 (52.1)	1.27 [0.97; 1.67] 0.080

Side effects

Endpoint	Olaparib + durvalumab[a]		Carboplatin + paclitaxel followed by placebo[b]		Intervention vs control
	N[c]	Median time to event in months [95% CI] *Patients with event n (%)*	N[c]	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[d] Absolute difference (AD)[e]
Total adverse events (presented additionally)[n]					
	191	0.1 [0.1; 0.1] 190 (99.5)	190	0.1 [0.1; 0.1] 190 (100)	–
Serious adverse events (SAE)					
	191	24.7 [24.7; n.c.] 69 (36.1)	190	n.r. 58 (30.5)	1.14 [0.80; 1.62] 0.470
Severe adverse events (CTCAE grade 3 or 4)					
	191	3.4 [2.3; 6.2] 129 (67.5)	190	5.3 [3.1; 12.2] 104 (54.7)	1.28 [0.99; 1.66] 0.063
Therapy discontinuation due to adverse events					
	191	n.r. 47 (24.6)	190	n.r. 37 (19.5)	1.19 [0.78; 1.85] 0.418
Specific adverse events					
PRO-CTCAE	No suitable data[i]				
Immune-mediated AEs (presented additionally)	No suitable data[i]				
Immune-mediated SAEs	No suitable data[i]				
Immune-mediated severe AEs[o]	No suitable data[i]				
MDS/ AML (SAEs)[o]	191	n.r. 0 (0)	190	n.r. 0 (0)	–
Pneumonitis (severe AEs [o])[p]	191	n.r. 3 (1.6)	190	n.r. 0 (0)	n.c.; 0.112
Anaemia (PT, severe AEs[o])	191	n.r. 46 (24.1)	190	n.r. 24 (12.6)	1.96 [1.21; 3.26] 0.007

[a] After first-line therapy with durvalumab in combination with carboplatin and paclitaxel

[b] The placebo comparison conducted in maintenance treatment in arm A of the DUO-E study adequately corresponds to the implementation of the monitoring wait-and-see approach in the appropriate comparator therapy.

[c] For the endpoints of morbidity and health-related quality of life: The information provided by the pharmaceutical company on the patients included in the time-to-event analyses is implausible when compared with the MMRM analyses. The number of patients who were included in the MMRM analyses for the change from the start of the study at a minimum of one time point was specified. Only these patients can contribute data to the time-to-event analysis.

[d] HR and CI: Cox model with proportional hazards; p value: log-rank test; for all analyses except for the operationalisations on side effects, the calculations were stratified by disease status (newly diagnosed vs recurrent) and region (Asia vs rest of the world).

[e] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation

[f] An increase by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 100).

[g] No suitable data available, as a maximum of 29 vs 25 patients (15% vs 13%) had a baseline value and another value in the course of the study.

[h] An increase by ≥ 1 point compared to the start of the study is considered a clinically relevant deterioration (range of values from "no symptoms" to "very severe"; the scale was converted by the pharmaceutical company into numerical values from 1 ["no symptoms"] to 6 ["very severe"] for the analyses).

[i] No suitable data available; for justification, see section I 4.1 of the present dossier assessment.

[j] A decrease by ≥ 15 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 100).

[k] Time to 1st deterioration.

[l] A decrease by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 100).

[m] In deviation from the pharmaceutical company's indication, this scale is not assigned to symptomatology, but to health-related quality of life.

[n] Events to be assigned to the progression of the underlying disease were not collected as AEs according to the study protocol

[o] Operationalised as CTCAE grade ≥ 3.

[p] The operationalisation of the AEs of special interest collected in the study is considered; for explanations, see section I 4.1 of this dossier assessment.

Abbreviations used:
AD = absolute difference; AML = acute myeloid leukaemia; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; CI = confidence interval; MDS = myelodysplastic syndrome; MMRM = mixed model for repeated measures; N = number of patients contributing data to the analysis; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not achieved; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; pMMR = proficient mismatch repair; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PT = preferred term; PC = pharmaceutical company; QLQ-C30 = Quality of Life Questionnaire-Core 30; QLQ-EN24 = Quality of Life Questionnaire - Endometrial Cancer Module 24; RCT = randomised controlled trial; 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

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) 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; maintenance treatment

Approx. 780 to 1,430 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 Lynparza (active ingredient: olaparib) at the following publicly accessible link (last access: 6 January 2025):

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

Treatment with olaparib 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.

4. Treatment costs

Annual treatment costs:

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

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) 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; maintenance treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Durvalumab in combination with carboplatin and paclitaxel	
Durvalumab	€ 17,845.36 – € 26,768.04
Carboplatin	€ 1,268.44 – € 2,370.00
Paclitaxel	€ 3,573.72 – € 5,360.58
Maintenance treatment with olaparib and durvalumab	
Olaparib	€ 38,349.68 – € 45,088.96
Durvalumab	€ 50,655.24 – € 59,594.40
Total	€ 123,503.54 – € 127,370.88
Appropriate comparator therapy:	
Carboplatin + paclitaxel	
Carboplatin	€ 6,873.00
Paclitaxel	€ 15,545.68
Total	€ 22,418.68

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2025)

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:					
Durvalumab in combination with carboplatin and paclitaxel					
Durvalumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	4 – 6	€ 400 – € 600
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4 – 6	€ 400 – € 600

Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4 – 6	€ 400 – € 600
Maintenance treatment with durvalumab and olaparib					
Durvalumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	8.5 – 10.0	€ 850 – € 1,000
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:

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) 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; maintenance treatment

The following medicinal products with new active ingredients that can be used in a combination therapy with olaparib in the therapeutic indication of the resolution on the basis of the marketing authorisation under Medicinal Products Act are named (active ingredients and invented names) in accordance with Section 35a, paragraph 3, sentence 4 SGB V:

- Durvalumab (Imfinzi)

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. **In Annex XIIa of the Pharmaceuticals Directive, the following information shall be added in alphabetical order:**

"Active ingredient of the assessed medicinal product

Olaparib

Resolution according to Section 35a paragraph 3 SGB V from

20 February 2025

Therapeutic indication of the resolution

Lynparza in combination with durvalumab is indicated for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.

Patient group

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) 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; maintenance treatment

Naming of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V (active ingredients and invented names[2])

Durvalumab (Imfinzi)

Period of validity of the designation (since... or from... to)

Since 20 February 2025

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.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 20 February 2025.

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

Berlin, 20 February 2025

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

Prof. Hecken