# Resolution

Gemeinsamer Bundesausschuss

## of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Olaparib (New Therapeutic Indication: Ovarian carcinoma, fallopian tube carcinoma or primary peritoneal carcinoma; maintenance treatment after first-line therapy; HRD-positive; combination with bevacizumab)

of 3 June 2021

At its session on 3 June 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 on 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 information on the benefit assessment of olaparib in accordance with the resolution of 16 January 2020:**

**Olaparib**

Resolution of: 3 June 2021
Entry into force on: 3 June 2021
BAnz AT TT. MM YYYY Bx

**New therapeutic indication (according to the marketing authorisation of 3 November 2020):**

Lynparza in combination with bevacizumab is indicated for the:

Maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapyin combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability.

**Therapeutic indication of the resolution (resolution of 3/6/2021):**

see therapeutic indication according to marketing authorisation.

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

Adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma who have a response (complete or partial) after completion of a platinum treatment as part of first-line chemotherapy regimen in combination with bevacizumab; disease associated with homologous recombination deficiency (defined by either a BRCA1/2-mutation and/or genomic instability); maintenance treatment:

**Appropriate comparator therapy:**

- Continuation of treatment with bevacizumab started with platinum treatment as part of first-line chemotherapy regimen.

**Extent and probability of additional benefit of olaparib in combination with bevacizumab compared with bevacizumab:**

An additional benefit is not proven.

**Study results according to endpoints:**

**Summary of results of relevant clinical endpoints**

| Endpoint category | Effect direction/ Risk of bias | Summary |
|---|---|---|
| Mortality | ↔ | no relevant difference for the benefit assessment |
| Morbidity | ↔ | Advantages in the endpoints Insomnia, Hormonal symptoms, Side effects of chemotherapy; Disadvantages in the endpoints Nausea and vomiting, Loss of appetite; overall, no predominant advantage or disadvantage |
| Health-related quality of life | ↔ | no relevant difference for the benefit assessment |
| Side effects | ↓ | Disadvantage in the endpoint Discontinuation due to AE as well as in detail predominantly disadvantages with specific AE |
| 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 a high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data<br>↔: no statistically significant or relevant difference<br>∅: There are no usable data for the benefit assessment.<br>n.a.: not assessable | | |

PAOLA-1 study: Olaparib + bevacizumab **vs** bevacizumab[1,2]

Study design: randomised, double-blind, two-armed

Relevant sub-population: Patients whose tumour is associated with a positive HRD status (BRCA 1/2-mutation and/or genomic instability) (approximately 48.0% of the study population)

[1] Data from the dossier assessment of the IQWiG (A20-111) and from the addendum (A21-55), unless otherwise indicated.
[2] Data cut-off 22.3.2020

**Mortality**

| **Endpoint** | **Olaparib + Bevacizumab** | | **Bevacizumab** | | Intervention vs Control |
|---|---|---|---|---|---|
| | N | Median time to the event in months [95% CI] *Patients with event n (%)* | N | Median time to to the event in Months [95% CI] *Patients with event n (%)* | HR [95% CI] p value Absolute difference (AD)[a] |
| **Overall survival** | | | | | |
| | 255 | n.a. 61 (23.9) | 132 | n.a. 42 (31.8) | 0,70 [0.47; 1.05] 0.078 |
| Effect modification by the "outcome of first-line therapy" feature | | | | | |
| NED (PDS)[b] | 92 | n.a. 8 (8.7) | 48 | n.a. 14 (29.2) | 0,26 [0.11; 0.61] 0,002 |
| NED/CR (IDS)[c] | 74 | n.a. 23 (31.1) | 38 | n.a. 11 (28.9) | 1,04 [0.52; 2.23] 0,904 |
| NED/CR (chemo)[d] | 40 | n.a. 9 (22.5) | 20 | n.a. 8 (40.0) | 0,54 [0.21; 1.45] 0,216 |
| PR[e] | 49 | 44,0 [32.3; n.c.] 21 (42.9) | 26 | n.a. 9 (34.6) | 1,13 [0.53; 2.60] 0,758 |
| | | | | Interaction: | 0.043 |
| NED (PDS)[b] + NED/CR (chemo)[d] | | | | | 0.36[f] 0.19 (0.68)[f] 0.002[f] |
| NED/CR (IDS)[c] + PR[e] | | | | | 1.08[f] 0,63 (1,85)[f] 0.778[f] |
| | | | | Interaction: | 0.010[g] |

**Morbidity**

| Endpoint | Olaparib + Bevacizumab | | Bevacizumab | | Intervention vs Control |
|---|---|---|---|---|---|
| | N | Median time to to the event in Months [95% CI] *Patients with event n (%)* | N | Median time to to the event in Months [95% CI] *Patients with event n (%)* | HR [95% CI] p value Absolute difference (AD)[a] |
| **Progression-free survival 1 (PFS 1)[h]** | | | | | |
| | 255 | 42,6 [36.4; n.a.] 115 (45.1) | 132 | 17,6 [15.8; 20.3] 100 (75.8) | 0,39 [0.30; 0.51] <0.0001 25 months |
| **Disease symptoms - time to deterioration[i]** | | | | | |
| **Symptom scales of the EORTC QLQ-C30** | | | | | |
| Fatigue | 255 | 5,6 [3.1; 6.0] 199 (78.0) | 132 | 5,7 [5.5; 11.1] 98 (74.2) | 1,10 [0.86; 1.41] 0,482 |
| Nausea and Vomiting | 255 | 5,8 [5.6; 8.7] 178 (69.8) | 132 | 19,2 [12.7; 23.5] 70 (53.0) | 1,81 [1.37; 2.42] < 0.001 13.4 months |
| Pain | 255 | 5,8 [5.6; 8.3] 183 (71.8) | 132 | 5,6 [3.0; 8.1] 95 (72.0) | 0,92 [0.72; 1.19] 0,551 |
| Dyspnoea | 255 | 20,7 [16.0; 52.5] 125 (49.0) | 132 | 18,7 [12.3; 24.9] 67 (50.8) | 0,92 [0.68; 1.25] 0,580 |
| Insomnia | 255 | 11,3 [8.4; 14.0] 159 (62.4) | 132 | 8,3 [5.6; 11.1] 91 (68.9) | 0,73 [0.56; 0.95] 0,019 3.0 months |
| Loss of Appetite | 255 | 13,6 [11.1; 22.1] 146 (57.3) | 132 | 22,3 [16.6; 28.7] 65 (49.2) | 1,42 [1.06; 1.92] 0,023 8.7 months |
| Constipation | 255 | 19,9 [16.6; 23.4] 133 (52.2) | 132 | 19,7 [14.0; 22.3] 69 (52.3) | 1,03 [0.77; 1.39] 0,831 |
| Diarrhoea | 255 | 24,0 [16.6; 25.9] 124 (48.6) | 132 | 23,5 [19.9; 35.0] 58 (43.9) | 1,15 [0.84; 1.58] 0,409 |
| **Symptom scales of the EORTC QLQ-OV28** | | | | | |
| abdominal/ gastrointestinal | 255 | 11,1 [8.3; 14.0] | 132 | 8,3 [5.7; 11.3] | 0,88 [0.68; 1.15] |

| Endpoint | Olaparib + Bevacizumab | | Bevacizumab | | Intervention vs Control |
|---|---|---|---|---|---|
| | N | Median time to to the event in Months [95% CI] *Patients with event n (%)* | N | Median time to to the event in Months [95% CI] *Patients with event n (%)* | HR [95% CI] p value Absolute difference (AD)[a] |
| symptoms | | 169 (66.3) | | 89 (67.4) | 0,351 |
| peripheral neuropathy | 255 | 25,3 [18.6; n.c.] 114 (44.7) | 132 | 23 [12.7; n.c.] 58 (43.9) | 0,93 [0.68; 1.29] 0,654 |
| hormonal Symptoms | 255 | 19,1 [14.3; 24.2] 135 (52.9) | 132 | 11,3 [5.6; 19.1] 76 (57.6) | 0,75 [0.56; 0.996] 0.046 7.8 months |
| Chemotherapy side effects | 255 | 17,9 [12.0; 24.6] 135 (52.9) | 132 | 11,1 [8.3; 16.6] 82 (62.1) | 0,75 [0.57; 0.997] 0,045 6.8 months |
| individual questions[j] | 255 | 21,9 [16.6; 25.7] 127 (49.8) | 132 | 19,4 [16.4; n.c.] 64 (48.5) | 1,01 [0.75; 1.38] 0.954 |
| sexual function | no usable data available[k] | | | | |
| **health status** | | | | | |
| **EQ-5D VAS (time to deterioration)[l]** | | | | | |
| 15 points | 255 | 25.3 [17.5; n.c.] 116 (45.5) | 132 | 26.7 [19.9; n.c.] 58 (43.9) | 1,05 [0.77; 1.46] 0.749 |
| 10 points. | 255 | 11.1 [8.3; 13.9] 156 (61.2) | 132 | 16,4 [9.6; 21.9] 78 (59.1) | 1,15 [0.87; 1.52] 0,346 |
| 7 points. | 255 | 11,1 [8.3; 13.9] 156 (61.2) | 132 | 16,4 [9.6; 21.9] 78 (59.1) | 1,15 [0.88; 1.52] 0,333 |

**Health-related quality of life**

| Endpoint | Olaparib + Bevacizumab | | Bevacizumab | | Intervention vs Control |
|---|---|---|---|---|---|
| | N | Median time to to the event in Months [95% CI] *Patients with event n (%)* | N | Median time to to the event in Months [95% CI] *Patients with event n (%)* | HR [95% CI] p value Absolute difference (AD)[a] |
| **Health-related quality of life - time to deterioration[m]** | | | | | |
| **Global health status and functional scales of the EORTC QLQ-C30** | | | | | |
| global health status | 255 | 16.6 [11.5; 21.8] 146 (57.3) | 132 | 13.8 [9.3; 17.2] 81 (61.4) | 0.85 [0.65; 1.12] 0.234 |
| Physical function | 255 | 20 [13.9; 52.5] 125 (49.0) | 132 | 16.4 [11.5; 22.4] 74 (56.1) | 0.85 [0.64; 1.14] 0,279 |
| Role function | 255 | 8,4 [5.8; 11.2] 167 (65.5) | 132 | 9,3 [6.1; 16.2] 82 (62.1) | 1,11 [0.85; 1.46] 0,450 |
| Cognitive function | 255 | 11,1 [8.5; 14.0] 174 (68.2) | 132 | 8,5 [5.9; 13.6] 85 (64.4) | 0,91 [0.70; 1.19] 0.484 |
| Emotional function | 255 | 13,8 [9.0; 19.3] 158 (62.0) | 132 | 11,1 [8.3; 13.8] 85 (64.4) | 0,93 [0.71; 1.22] 0,571 |
| Social function | 255 | 13,5 [8.6; 19.6] 148 (58.0) | 132 | 11,3 [8.5; 16.4] 81 (61.4) | 0,91 [0.69; 1.20] 0,471 |
| **Scales of the EORTC QLQ-OV28[i]** | | | | | |
| Body image | 255 | 21,9 [12.7; n.c.] 126 (49.4) | 132 | 18,7 [11.5; 25.1] 71 (53.8) | 0,93 [0.70; 1.26] 0,638 |
| Attitude towards disease/treatment | 255 | 12.2 [8.3; 24.1] 134 (52.5) | 132 | 17.5 [11.2; n.c.] 65 (49.2) | 1.15 [0.86; 1.57] 0.362 |

(continuation)

**Side effects**

| Endpoint | Olaparib + Bevacizumab | | Bevacizumab | | Intervention vs Control |
|---|---|---|---|---|---|
| | N | Median time to to the event in Months [95% CI] *Patients with event n (%)* | N | Median time to to the event in Months [95% CI] *Patients with event n (%)* | HR [95% CI] p value Absolute difference (AD)[a] |
| **Adverse events (AEs) presented additionally** | | | | | |
| | 255 | 0.2 [0.2; 0.3] 255 (100) | 131 | 0.3 [0.2; 0.7] 127 (96.9) | - |
| **Serious adverse events (SAE)** | | | | | |
| | 255 | n.a. 73 (28.6) | 131 | n.a. 45 (34.4) | 0.75 [0.52; 1.10] 0.133 |
| **Severe adverse events (CTCAE grade ≥ 3)** | | | | | |
| | 255 | 8.6 [5.6; 15.3] 147 (57.6) | 131 | 16.7 [6.6; n.c.] 65 (49.6) | 1.20 [0.90; 1.63] 0.221 |
| **Discontinuation due to AE** | | | | | |
| | 255 | n.a. 50 (19.6) | 131 | n.a. 8 (6.1) | 3.14 [1.57; 7.18] 0.002 |
| **Specific adverse events** | | | | | |
| myelodysplastic syndrome and acute myeloid leukaemia (PT, UE)[n, o] | 255 | n.a. 2 (0.8) | 131 | n.a. 2 (1.5) | 0.54 [0.06; 4.51] 0.531 |
| Pneumonitis (PT, AE)[n] | 255 | n.a. 3 (1.2) | 131 | n.a. 0 (0) | n.a. 0.195 |
| Nausea (PT, AE)[n] | 255 | 2.9 [0.8; 16.0] 144 (56.5) | 131 | n.a. 33 (25.2) | 3.10 [2.14; 4.63] < 0.001 |
| Anaemia (PT severe AE)[n] | 255 | n.a. 47 (18.4) | 131 | n.a. 1 (0.8) | 27.79 [6.08; 492.43] < 0.001 |
| Fatigue and asthenia (PT, severe AE)[n] | 255 | n.a. 17 (6.7) | 131 | n.a. 2 (1.5) | 4.54 [1.29; 28.70] 0.027 |
| Hypertonia (PT, severe AE)[n] | 255 | n.a. 50 (19.6) | 131 | n.a. 42 (32.1) | 0.52 [0.34; 0.79] 0.002 |

(continuation)

| Endpoint | Olaparib + Bevacizumab | | Bevacizumab | | Intervention vs Control |
|---|---|---|---|---|---|
| | N | *Patients with event n (%)* | N | *Patients with event n (%)* | RR [95% CI] p value |
| **Specific adverse events** | | | | | |
| myelodysplastic syndrome | 255 | 1 (0.4) | 131 | 1 (0.8) | 0.51 [0.03; 8.15] 0.637 |
| acute myeloid leukaemia | 255 | 2 (0.8) | 131 | 1 (0.8) | 1.03 [0.09; 11.23] 0.982 |

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[b] Patients without detectable tumour after primary surgery
[c] Patients without detectable tumour/with complete response after interval surgery
[d] Patients without detectable tumour/with complete response after chemotherapy
[e] patients with partial response
[f] IQWiG calculation; fixed-effect meta-analysis (inverse variance method)
[g] IQWiG's own calculation, Q-test
[h] Data from: Olaparib Module 4A dossier dated 30.11.2020
[i] Time to deterioration; defined as an increase in score of ≥ 10 points from baseline
[j] The individual questions included in this scale relate to the presence of Indigestion or heartburn, hair loss and altered sense of taste. According to the current scoring manual, this scale is no longer evaluated, but the individual questions are included in the evaluation of the other scales
[k] The pharmaceutical company did not submit any evaluations for the sexuality scale, as according to the scoring manual used, there is no scoring algorithm.
[l] Time to deterioration, defined as a decrease in score by ≥ 15, 10, and 7 points, respectively, in the comparison to baseline
[m] Time to deterioration; defined as a decrease in score by ≥ 10 points compared to baseline
[n] Follow-up until death or end of study
[o] discrepant data within module 4 A of the dossier; data for the endpoint MDS/ AML intervention vs. control n (%); HR [95% CI]; p: 2 (0.8) vs. 1 (0.8); 1.07 [0.10; 23.20]; 0.955

Abbreviations used:
AD = absolute difference; AML = acute myeloid leukaemia; BRCA = breast cancer susceptibility gene; CTCAE = Common Terminology Criteria for Adverse Events; CR = complete response; chemo = chemotherapy; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = European Quality of Life Questionnaire - 5 Dimensions; HR = hazard ratio; IDS = interval surgery; CI = confidence interval; MDS = myelodysplastic syndrome; N = number of patients evaluated; n = number of patients with (at least one) event; n. b. = not calculable; n. a. = not achieved; NED = no detectable tumour; QLQ-C30 = Quality of Life Questionnaire - Core 30; QLQ-OV28 = Quality of Life Questionnaire - Ovarian Cancer 28; PDS = primary surgery; PR = partial response; PT = preferred term; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation; SE = standard error; tBRCA = tumour-BRCA; VAS = visual analogue scale; vs = versus

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

Adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma who have a response (complete or

partial) after completion of a platinum treatment as part of first-line chemotherapy regimen in combination with bevacizumab; disease associated with homologous recombination deficiency (defined by either a BRCA1/2-mutation and/or genomic instability); maintenance treatment:

approx. 1030 patient

## 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: 2 March 2021):

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

Treatment with olaparib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in gynaecology and obstetrics, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with ovarian carcinoma.

Prior to initiating treatment with Lynparza and bevacizumab for first-line maintenance treatment of epithelial ovarian carcinoma (EOC), fallopian tube carcinoma (FTC), or primary peritoneal carcinoma (PPC), patients must have a confirmed or suspected harmful BRCA1/2-mutation and/or genomic instability as determined by a validated testing method.

## 4. Treatment costs

**Annual treatment costs:**

Adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma who have a response (complete or partial) after completion of a platinum treatment as part of first-line chemotherapy regimen in combination with bevacizumab; disease associated with homologous recombination deficiency (defined by either a BRCA1/2-mutation and/or genomic instability); maintenance treatment:

| Name of therapy | Annual treatment costs/patient |
|---|---|
| Medicinal product to be assessed: | |
| Olaparib | € 69,059,30 |
| Bevacizumab | € 63,626,29 |
| *Total:* | € 132,685,59 |
| Appropriate comparator therapy: | |
| Continuation of treatment with bevacizumab started with platinum treatment as part of first-line chemotherapy regimen. | |
| Bevacizumab | € 63,626,29 |

Cost after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 May 2021).

Costs for additionally required SHI services: not applicable

Other SHI services:

| Designation of therapy | Type of service | Costs/ unit | Number/ cycle | Number/ Patient/ Year | Costs Patient/ Year |
|---|---|---|---|---|---|
| Bevacizumab | Preparation of parenteral solutions with monoclonal antibodies | € 71 | 15.7 | 15.7 | € 1,114.70 |

## II. Entry into force

1. **The resolution will enter into force on the day of its publication on the internet on the G-BA website on 3 June 2021.**

2. **The period of validity of the resolution is limited to the 1st October 2022.**

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

Berlin, 3 June 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The chairman

Prof. Hecken