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
Olaparib (Reassessment after the deadline: ovarian, fallopian tube or primary peritoneal cancer; maintenance treatment after first-line therapy; HRD-positive; combination with bevacizumab)

of 20 April 2023

At its session on 20 April 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 Olaparib in the version of the resolution of 3 June 2021 (BAnz AT 23.07.2021 B3), last modified on 15 September 2022, is repealed.

2. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Olaparib in the version of the resolution of 16 February 2023:

Olaparib

Resolution of: 20 April 2023
Entry into force on: 20 April 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 03 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 chemotherapy in 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 20 April 2023):

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 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 chemotherapy in 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); maintenance therapy

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:

Hint for a considerable additional benefit

Study results according to endpoints:[1]

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 chemotherapy in 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); maintenance therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival.
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 differences for the benefit assessment.
Side effects	↓	Disadvantages in the endpoint discontinuation due to AEs. In detail, mainly disadvantages 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		

PAOLA-1 study: Olaparib + bevacizumab vs bevacizumab

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

Relevant sub-population: Patients whose tumour is associated with a positive HRD status (BRCA1/2-mutation and/or genomic instability)

Data cut-offs used:

- 22 March 2020 (morbidity, health-related quality of life, side effects)
- 22 March 2022 (overall survival, side effects)

[1] Data from the dossier evaluation of the Institute for Quality and Efficiency in Health Care (IQWiG) (A22-117) unless otherwise indicated.

Mortality

Endpoint	Olaparib + bevacizumab		Bevacizumab		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[a] Absolute difference (AD)[b]
Overall survival[c]					
	255	75.2 [73.3; n.c.] *93 (36.5)*	132	57.3 [51.6; n.c.] *69 (52.3)*	0.68 [0.50; 0.94] 0.017 AD = + 17.9 months
Effect modification by the characteristic "outcome of first-line therapy"					
NED (PDS)	92	n.r. *15 (16.3)*	48	n.r. *21 (43.8)*	0.29 [0.15; 0.57] < 0.001[d]
NED / CR (IDS)	74	73.3 [45.0; n.c.] *34 (45.9)*	38	57.3 [45.2; n.c.] *20 (52.6)*	0.88 [0.51; 1.55] 0.641[d]
NED / CR (chemo)	40	n.r. *15 (37.5)*	20	56.9 [31.8; 66.4] *12 (60.0)*	0.56 [0.26; 1.23] 0.146[d]
PR	49	50.4 [32.3; n.c.] *29 (59.2)*	26	43.0 [25.2; n.c.] *16 (61.5)*	0.88 [0.48; 1.66] 0.679[d]
				Interaction:	0.050[e]
NED (PDS) + NED / CR (chemo)					0.38 [0.23; 0.64] < 0.001[f]
NED / CR (IDS) + PR					0.88 [0.58; 1.33] 0.545[f]
				Interaction:	0.013[g]

Morbidity

Endpoint	Olaparib + bevacizumab		Bevacizumab		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[a] Absolute difference (AD)[b]
Progression-free survival 1 (PFS 1)[c,h]					
	255	46.9 [36.4; 65.7] *136 (53.3)*	132	17.6 [15.8; 20.3] *104 (78.8)*	0.42 [0.32; 0.55] <0.0001 AD = + 29.3 months

Endpoint	Olaparib + bevacizumab		Bevacizumab		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[a] Absolute difference (AD)[b]
Symptomatology (EORTC QLQ-C30)[i, j]					
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
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
Appetite loss	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
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
Symptomatology (EORTC QLQ-OV28)[i, j]					
Abdominal/ gastrointestinal symptoms	255	11.1 [8.3; 14.0] *169 (66.3)*	132	8.3 [5.7; 11.3] *89 (67.4)*	0.88 [0.68; 1.15] 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
Side effects of chemotherapy	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
Individual questions[k]	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

Endpoint	Olaparib + bevacizumab		Bevacizumab		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[a] Absolute difference (AD)[b]
Health status (EQ-5D VAS)[i, l]					
	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

Health-related quality of life

Endpoint	Olaparib + bevacizumab		Bevacizumab		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[a] Absolute difference (AD)[b]
EORTC QLQ-C30[j, m]					
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 functioning	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 functioning	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
Emotional functioning	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
Cognitive functioning	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
Social functioning	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
EORTC QLQ-OV28[i, j]					
Sexual functioning	No usable data available[n]				
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

Side effects

Endpoint	Olaparib + bevacizumab		Bevacizumab		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[a]
Total adverse events (presented additionally)[i]					
	255	0.2 [0.2; 0.3] *255 (100)*	131	0.3 [0.2; 0.7] *127 (96.9)*	-
Serious adverse events (SAE)[i]					
	255	n.r. *73 (28.6)*	131	n.r. *45 (34.4)*	0.75 [0.52; 1.10] 0.133
Severe adverse events (CTCAE grade ≥ 3)[i]					
	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
Therapy discontinuation due to adverse events[i]					
	255	n.r. *50 (19.6)*	131	n.r. *8 (6.1)*	3.14 [1.57; 7.18] 0.002
Specific adverse events[i]					
Nausea (PT, AE)	255	2.9 [0.8; 14.5]; *144 (56.5)*	131	n.r. *30 (22.9)*	3.38 [2.30; 5.13] < 0.001
Anaemia (PT, severe AE°)	255	n.r. *47 (18.4)*	131	n.r. *1 (0.8)*	27.85 [6.08; 493.74] < 0.001
Fatigue (PT, severe AE°)	255	n.r. *14 (5.5)*	131	n.r. *0 (0)*	n.c. 0.007
Hypertension (PT, severe AE°)	255	n.r. *45 (17.6)*	131	n.r. *42 (32.1)*	0.47 [0.30; 0.72] < 0.001
Specific adverse events[c]					
Myelodysplastic syndrome (PT, SAE)[p, q]	255	*1 (0.4)*	131	*3 (2.3)*	RR: 0.17 [0.02; 1.63] 0.085[r]
Acute myeloid leukaemia (PT, SAE)[p, q]	255	*4 (1.6)*	131	*1 (0.8)*	RR: 2.05 [0.23; 18.20] 0.616[r]
Pneumonitis	Data unusable				

[a] HR and CI: Cox proportional hazards model; p value: Log-rank test; each stratified by outcome of first-line therapy and tBRCA mutational status.
[b] Data on absolute difference (AD) only in the case of statistically significant difference; own calculation.

Endpoint	Olaparib + bevacizumab		Bevacizumab		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[a]

[c] Data cut-off of 22 March 2022.
[d] HR, CI and p value: Cox proportional hazards model; unstratified.
[e] Cox proportional hazards model with corresponding interaction term; unstratified.
[f] IQWiG calculation; fixed-effect meta-analysis (inverse variance method).
[g] IQWiG calculation; Q-test.
[h] Data from: Dossier on olaparib module 4A dated 28 October 2022.
[i] Data cut-off of 22 March 2020.
[j] Time to first clinically relevant deterioration; an increase in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
[k] The individual questions included in this scale refer 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 go into the evaluation of the other scales.
[l] Time to first clinically relevant deterioration; a decrease in score by ≥ 15 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
[m] Time to first clinically relevant deterioration; a decrease in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
[n] The pharmaceutical company did not submit any evaluations for the sexual functioning scale, as no evaluation algorithm is available according to the scoring manual used by it.
[o] Operationalised as CTCAE grade ≥ 3.
[p] Follow-up until death or final analysis.
[q] The pharmaceutical company describes these events in module 4A as AE. According to information in the study report, all events that occurred in the total study population are SAEs (exception: 1 event was recorded as AE).
[r] IQWiG calculation, unconditional exact test (CSZ method according to Martín Andrés A, Silva Mato A. Choosing the optimal unconditional test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.)

Abbreviations used:
AD = absolute difference; BRCA = breast cancer susceptibility gene; chemo = chemotherapy; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; IDS = interval debulking surgery; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; NED = no detectable tumour; PDS = primary surgery; PR = partial response; PT = preferred term; QLQ-C30 = Quality of Life Questionnaire - Core 30; QLQ-OV28 = Quality of Life Questionnaire - Ovarian Cancer 28; RR = relative risk; SAE = serious adverse event; tBRCA = tumour-BRCA; AE = adverse event; 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, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in 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); maintenance therapy

approx. 1,030 - 1,250 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: 13 April 2023):

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 gynaecology and obstetrics, and other specialists participating in the Oncology Agreement, all of whom 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

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

Annual treatment costs:

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 chemotherapy in 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); maintenance therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Olaparib	€ 58,205.77
Bevacizumab	€ 60,992.15
Total:	€ 119,197.91
Appropriate comparator therapy:	
Continuation of treatment with bevacizumab started with platinum treatment as part of first-line chemotherapy regimen.	
Bevacizumab	€ 60,992.15

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 01 April 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
Bevacizumab	Preparation of parenteral solutions with monoclonal antibodies	€ 100	15.7	15.7	€ 1,570.00

5. 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 Olaparib

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients which, on the basis of the marketing authorisation under Medicinal Products Act, can be used in a combination therapy with olaparib as 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 chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status:

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 chemotherapy in 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); maintenance therapy

- No active ingredient that can be used in a combination therapy that 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.

I. **The resolution will enter into force on the day of its publication on the website of the G-BA on 20 April 2023.**

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

Berlin, 20 April 2023

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

Prof. Hecken