Resolution

Gemeinsamer Bundesausschuss

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: High-Grade Epithelial Ovarian Cancer, Fallopian Tube Cancer or Primary Peritoneal Cancer, BRCA Mutation, Maintenance Treatment)

of 16 January 2020

At its session on 16 January 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 6 December 2018:

Olaparib

Resolution of: 16 January 2020
Entry into force on: 16 January 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 12 June 2019):

Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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.

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

Adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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

Appropriate comparator therapy:

- Monitoring wait-and-see approach

Extent and probability of the additional benefit of olaparib compared with the monitoring wait-and-see approach:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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

SOLO1 study: Olaparib **vs** placebo

Mortality

Endpoint	**Olaparib**		**Placebo**		**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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	260	n.a. 55 (21.2)	131	n.a. 27 (20.6)	0.95 [0.60; 1.53] 0.890

Morbidity

Endpoint	**Olaparib**		**Placebo**		**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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS1)[2]					
	260	n.a. [no data available] 102 (39.2)	131	13.8 [no data available] 96 (73.3)	0.30 [0.23; 0.41] < 0.0001 AD = n.c.
Health status (EQ-5D VAS) – time to first deterioration					
MID 7	260	18.4 [no data available] 140 (53.8)	131	15.6 [no data available] 79 (60.3)	0.99 [0.75; 1.31] 0.888
MID 10	260	19.4 [no data available] 137 (52.7)	131	15.6 [no data available] 79 (60.3)	0.95 [0.72; 1.25] 0.647

(Continuation)

[1] Data from the dossier evaluation of the IQWiG (A19-56) unless otherwise indicated.
[2] Olaparib: Dossier of the pharmaceutical company, Module 4A of 8 July 2019

Endpoint	Olaparib		Placebo		Intervention vs Control
	N[b]	Values at start of study MV (SD) Change after 24 months MV (SE)	N[b]	Values at start of study MV (SD) Change after 24 months MV (SE)	Mean difference [95% CI] p value
Health status (EQ-5D VAS)[d] (presented as a supplement)					
	237	77.1 (15.40) 1.85 (0.66)	127	80.4 (13.09) 2.06 (0.95)	−0.21 [−2.49; 2.07]; 0.854

Health-related quality of life

Endpoint	Olaparib		Placebo		Intervention vs Control
	N[b]	Values at start of study MV (SD) Change after 24 months MV[c] (SE)	N[b]	Values at start of study MV (SD) Change after 24 months MV[c] (SE)	Mean difference [95% CI] p value[c] Hedges' g
FACT-O total score[d]					
	238	113.46 (18.23) −0.56 (0.73)	124	115.83 (18.57) 2.11 (1.06)	−2.67 [−5.20; −0.14] 0.038 −0.23 [−0.45; −0.02]
FACT-O sub-scales (presented additionally)					
Physical well-being	no data available				
Social well-being					
Emotional well-being					
Functional well-being					
Additional concerns					

Side effects

Endpoint	Olaparib		Placebo		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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Adverse events (presented additionally)					
	260	0.1 [no data available] 256 (98.5)	130	0.3 [no data available] 120 (92.3)	-
Serious adverse events (SAE)					
	260	n.a. [no data available] 54 (20.8)	130	n.a. [no data available] 16 (12.3)	1.58 [0.93; 2.87] 0.099
Severe adverse events (CTCAE grade ≥ 3)					
	260	42.1 [no data available] 102 (39.2)	130	n.a. [no data available] 24 (18.5)	2.30 [1.50; 3.68] 0.002
Therapy discontinuation because of adverse events					
	260	n.a. [no data available] 30 (11.5)	130	n.a. [no data available] 3 (2.3)	4.86 [1.73; 20.30] 0.004
Specific adverse events[e]					
Myelodysplastic syndrome (PT, AE) and myeloproliferative neoplasms (PT, AE)	260	n.a. [no data available] 1 (0.4)	130	n.a. [no data available] 0 (0)	n.c.
Acute myeloid leukaemia (PT, AEs)	260	n.a. [no data available] 2 (0.8)	130	n.a. [no data available] 0 (0)	n.c.
Pneumonitis (PT, AEs)	260	n.a. [no data available] 5 (1.9)	130	n.a. [no data available] 0 (0)	n.c.
Anaemia (PT, severe AE (CTCAE grade ≥ 3))	260	n.a. [no data available] 55 (21.2)	130	n.a. [no data available] 2 (1.5)	15.42 [4.80; 94.13] < 0.001
Taste disorder (PT, AEs)	260	n.a. [no data available] 68 (26.2)	130	n.a. [no data available] 5 (3.8)	7.45 [3.32; 21.27] < 0.001

Endpoint	Olaparib		Placebo		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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Dyspnoea (PT, AEs)	260	n.a. [no data available] 39 (15.0)	130	n.a. [no data available] 7 (5.4)	2.49 [1.18; 6.10] 0.029
Nausea (PT, AEs)	260	0.3 [no data available] 201 (77.3)	130	n.a. [no data available] 49 (37.7)	3.31 [2.44; 4.58] < 0.001
Stomatitis (PT, AEs)	260	n.a. [no data available] 23 (8.8)	130	n.a. [no data available] 3 (2.3)	3.62 [1.26; 15.30] 0.025
Vomiting (PT, AEs)	260	n.a. [no data available] 104 (40.0)	130	n.a. [no data available] 19 (14.6)	3.08 [1.94; 5.18] < 0.001
Muscle spasms (PT, AEs)	260	n.a. [no data available] 17 (6.5)	130	n.a. [no data available] 1 (0.8)	7.61 [1.55; 137.23] 0.021
Asthenia (PT, AEs)	260	n.a. [no data available] 63 (24.2)	130	n.a. [no data available] 16 (12.3)	2.06 [1.22; 3.68] 0.008
Mucosa inflammation (PT, AEs)	260	n.a. [no data available] 17 (6.5)	130	n.a. [no data available] 1 (0.8)	7.69 [1.57; 138.62] 0.022

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Number of patients included in the evaluation to calculate the effect estimate; values at the start of study may be based on other patient numbers.
[c] MMRM evaluation adjusted for treatment, round, and value at baseline as well as interaction terms for treatment and round, value at baseline, and round
[d] A positive change from start of study to end of study means an improvement; a positive effect estimate means an advantage for the intervention.
[e] Selection in accordance with IQWiG methodology; selection based on those identified in the study Events based on frequency and differences between treatment arms and taking into account patient relevance.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; CI = confidence interval; MID = minimal important difference; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Effect direction/ Risk of bias	Summary
Mortality	↔	No difference relevant for the benefit assessment
Morbidity	↔	No differences relevant for the benefit assessment
Health-related quality of life	↔	No differences relevant for the benefit assessment
Side effects	↓↓	Disadvantages in the endpoints severe AE (CTCAE grade ≥ 3), therapy discontinuation because of AE, and in individual specific AE

Explanations:
↑, ↓: statistically significant and relevant positive or negative effect with high or unclear risk of bias
↑↑, ↓↓: statistically significant and relevant positive or negative effect with low risk of bias
↔: no relevant difference
∅: no data available
n.r.: not ratable

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

approx. 70–325 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: 8 November 2019):

https://www.ema.europa.eu/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 cancer.

Before starting treatment with Lynparza for first-line maintenance treatment of high-grade epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC), mutations in the breast cancer susceptibility genes (BRCA) 1 or 2 that are harmful or

suspected of being harmful to patients must have been confirmed in the germ line and/or tumour using a validated test method.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Olaparib	€ 82,740.68
Appropriate comparator therapy:	
Monitoring wait-and-see approach	not quantifiable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 December 2019

Costs for additionally required SHI services: not applicable

II. Entry into force

1. **The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 16 January 2020.**

2. **The period of validity of the resolution is limited to 1 April 2024.**

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

Berlin, 16 January 2020

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

Prof. Hecken