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: Breast Cancer; HER2 negative)

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 8 April 2019):

Lynparza is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2 mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments.

Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

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

Adult patients with HER2-negative, locally advanced or metastatic breast cancer with BRCA1/2 mutations in the germ line; after prior therapy with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting or ineligible for these treatments

Appropriate comparator therapy:

capecitabine or vinorelbine or eribulin or possibly an anthracycline- or taxane-containing therapy

Extent and probability of the additional benefit of olaparib compared with chemotherapy according to the doctor's instructions (capecitabine, vinorelbine, or eribulin):

hint for a minor additional benefit

Study results according to endpoints:

Adult patients with HER2-negative, locally advanced or metastatic breast cancer with BRCA1/2 mutations in the germ line; after prior therapy with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting or ineligible for these treatments

OlympiAD study: Olaparib vs capecitabine or vinorelbine or eribulin [1,2]

Study design: randomised, open, two-armed

[1] Data from the dossier evaluation of the IQWiG (A19-57) and the addendum (A19-97) unless otherwise indicated.
[2] Data cut-off 25 September 2017

Mortality

Endpoint	**Olaparib**		**Chemotherapy according to the doctor's instructions[a]**		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)[b]
Overall survival					
	205	19.25 [17.15; 21.55] 130 (63.4)	97	17.12 [13.86; 21.85] 62 (63.9)	0.90 [0.66; 1.23] 0.513
Effect modification by the feature "Previous chemotherapy of metastatic breast cancer"					
Yes	146	18.8 [16.3; 20.4] 100 (68.5)	69	17.2 [13.5; 27.2] 41 (59.4)	1.13 [0.79; 1.64] 0.519
No	59	22.6 [17.8; n.c.] 30 (50.8)	28	14.7 [11.0; 21.3] 21 (75.0)	0.51 [0.29; 0.90] 0.013 7.9 months
				Interaction:	0.0215

Morbidity

Endpoint	**Olaparib**		**Chemotherapy according to the doctor's instructions[a]**		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)[b]
Progression-free survival (PFS)[c]					
	205	7.0 [5.68; 8.31][d] 163 (79.5)	97	4.2 [2.79; 4.27][d] 71 (73.2)	0.58 [0.43; 0.80] 0.0009 2.8 months
Disease symptomatology					
Symptom scales of the EORTC QLQ-C30					
No usable data					

(Continuation)

Health-related quality of life

Endpoint	Olaparib		Chemotherapy according to the doctor's instructions[a]		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)[b]
Health-related quality of life					
Global health status and functional scales of the EORTC QLQ-C30					
No usable data					

(Continuation)

Side effects

Endpoint	Olaparib		Chemotherapy according to the doctor's instructions[a]		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]
Adverse events (AE) (presented additionally)					
	205	0.2 [no data available] 200 (97.6)	91	0.2 [no data available] 87 (95.6)	-
Serious adverse events (SAE)					
	205	n.a. [no data available] 34 (16.6)	91	n.a. [no data available] 15 (16.5)	0.55 [0.28; 1.11] 0.098
Severe adverse events (CTCAE grade ≥3)					
	205	n.a. [no data available] 78 (38.0)	91	n.a. [no data available] 45 (49.5)	0.45 [0.29; 0.69] < 0.001
Discontinuation because of AEs					
	205	n.a. [no data available] 10 (4.9)	91	22.3 [no data available] 7 (7.7)	0.29 [0.09; 0.95] 0.042
Specific adverse events					
Hand-foot syndrome (PT, AE)	205	n.a. [no data available] 1 (0.5)	91	n.a. [no data available] 19 (20.9)	0.02 [0.01; 0.07] < 0.001
Anaemia (PT, severe AE	205	n.a. [no data available]	91	n.a. [no data available]	2.22 [1.05; 4.69]

(CTCAE grade ≥ 3))		32 (15.6)		4 (4.4)	0.037
Neutropoenia (PT, severe AE (CTCAE grade ≥ 3))	205	n.a. [no data available] 11 (5.4)	91	n.a. [no data available] 12 (13.2)	0.32 [0.13; 0.79]; 0.014
Vascular disorders (SOC, severe AE (CTCAE grade ≥ 3))	205	n.a. [no data available] 2 (1.0)	91	n.a. [no data available] 5 (5.5)	0.03 [0.00; 0.22]; < 0.001
Nausea (PT, AE)	205	1.6 [no data available] 119 (58.0)	91	14.5 [no data available] 32 (35.2)	1.69 [1.20; 2.37]; 0.003 12.9 months
Alopecia (PT, AE)	205	n.a. [no data available] 7 (3.4)	91	n.a. [no data available] 12 (13.2)	0.12 [0.04; 0.34]; < 0.001
General disorders and administration site conditions (SOC, AE)	205	7.9 [no data available] 106 (51.7)	91	1.5 [no data available] 56 (61.5)	0.58 [0.40; 0.83]; 0.003 6.4 months

[a] Capecitabine or vinorelbine or eribulin according to the doctor's instructions
[b] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[c] Data from: dossier on olaparib Module 4A from 8 July 2019, data cut-off of 9 December 2016
Abbreviations used:
[d] Data from: European Medicines Agency. Assessment report: Lynparza. 28 February 2019, page 45
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; QLQ-C30: Quality of Life Questionnaire – Cancer 30); PT: preferred term; SOC: system organ class; SAE: serious adverse event; AE: adverse event; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Effect direction/ Risk of bias	Summary
Mortality	↔	No difference in overall survival in the study population relevant for the benefit assessment
Morbidity	n.r.	No data suitable for the benefit assessment
Health-related quality of life	n.r.	No data suitable for the benefit assessment
Side effects	↑	Advantages in the endpoints severe AE (CTCAE grade 3 or 4) and discontinuation because of AE and predominantly advantages 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

Adult patients with HER2-negative, locally advanced or metastatic breast cancer with BRCA1/2 mutations in the germ line; after prior therapy with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting or ineligible for these treatments

460 to 710 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: 11 September 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 locally advanced or metastatic breast cancer.

Before initiating Lynparza therapy in patients with breast cancer susceptibility gene (gBRCA1/2)-mutated, human epidermal growth factor receptor 2 (HER2)-negative, metastatic breast cancer, a damaging or suspected damaging gBRCA1/2 mutation must be confirmed in the germ line. The gBRCA1/2 mutation status should be detected by an experienced laboratory using a validated test method. Data for the clinical validation of a BRCA1/2 test in tumour tissue are currently not available for breast cancer.

4. Treatment costs

Annual treatment costs:

Adult patients with HER2-negative, locally advanced or metastatic breast cancer with BRCA1/2 mutations in the germ line; after prior therapy with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting or ineligible for these treatments

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Olaparib	€ 82,740.68
Appropriate comparator therapy:	
Capecitabine	€ 2,392.42
Vinorelbine	€ 7,048.03 – 8,496.18
Eribulin	€ 38,970.46
Anthracycline- or taxane-containing therapy	
Docetaxel	€ 23,511.17
Doxorubicin	€ 2,081.25 – 3,120.59
Pegylated liposomal doxorubicin (PLD)	€ 41,719.08
Epirubicin	€ 4,587.00 – 5,130.56
Paclitaxel Additionally required SHI services Total:	€ 18,753.21 € 148.19 € 18,901.40
nab-paclitaxel	€ 31,819.75

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

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Vinorelbine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	52	€ 4,212
Eribulin	Surcharge for production of a parenteral preparation	€ 81	2	34	€ 2,754

	containing cytostatic agents				
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Doxorubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	5–11	€ 405 – 891
Pegylated liposomal doxorubicin (PLD)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	13	€ 1,053
Epirubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	10–16	€ 810 – 1,296
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
nab-paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377

II. 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.

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