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 (new therapeutic indication: breast cancer, HER2-, BRCA1/2-mutation, pretreated, high risk of recurrence, adjuvant treatment, monotherapy or combination with endocrine therapy)

of 16 February 2023

At its session on 16 February 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. 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 3 June 2021 last amended on 15 September 2022:

Olaparib

Resolution of: 16 February 2023
Entry into force on: 16 February 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 22 August 2022):

Lynparza is indicated as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.

Therapeutic indication of the resolution (resolution of 16 February 2023):

See new therapeutic indication according to marketing authorisation.

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

Adults with germline BRCA-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy; adjuvant therapy

Appropriate comparator therapy:

- Monitoring wait-and-see approach

Extent and probability of the additional benefit of olaparib as monotherapy or in combination with endocrine therapy versus monitoring wait-and-see approach:

Indication of a minor additional benefit

Study results according to endpoints:[1]

Adults with germline BRCA-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy; adjuvant 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 prevention of recurrences.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↓↓	Disadvantages in the endpoints of severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs. In detail, 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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

OlympiA study:

- Double-blind, parallel, randomised controlled trial
- Olaparib **vs** placebo
- Overall, about 90% of hormone receptor-positive patients have also received adjuvant endocrine therapy
- Data cut-off from 12.07.2021

Mortality

Endpoint	Olaparib		Placebo		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					
	921	n.r. [n.c.] *75 (8.1)*	915	n.r. [n.c.] *109 (11.9)*	0.68 [0.50; 0.91]; 0.009[c]

[1] Data from the dossier assessment of the IQWiG (A22-89) and from the addendum (A23-02), unless otherwise indicated.

Morbidity

Endpoint	**Olaparib**		**Placebo**		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value Absolute difference (AD)[b]
Recurrences					
Recurrence rate[d]	921	*138 (15.0)*	915	*210 (23.0)*	0.65 [0.54; 0.79]; < 0.001 AD = 8.0%
Ipsilateral invasive recurrence	921	*9 (1.0)*	915	*12 (1.3)*	–
Locoregional invasive recurrence	921	*9 (1.0)*	915	*18 (2.0)*	–
Distant recurrence	921	*88 (9.6)*	915	*135 (14.8)*	–
Contralateral invasive recurrence	921	*15 (1.6)*	915	*18 (2.0)*	–
Secondary primary tumour (not breast cancer)	921	*11 (1.2)*	915	*23 (2.5)*	–
Ductal carcinoma in situ	921	*4 (0.4)*		*4 (0.4)*	
Death from any cause	921	*2 (0.2)*	915	*0 (0)*	–
	N	Median time to event [95% CI] *Patients with event n (%)*	N	Median time to event [95% CI] *Patients with event n (%)*	HR [95% CI] p value[a] Absolute difference (AD)[b]
Disease-free survival	921	n.r. [n.c.] *138 (15.0)*	915	n.r. [n.c.] *210 (23.0)*	0.64 [0.51; 0.79]; < 0.001[c]

Endpoint	Olaparib			Placebo			Intervention vs control
	N[e]	Values at the start of the study MV (SD)	Mean change in the course of study MV (SE)	N[e]	Values at the start of the study MV (SD)	Mean change in the course of study MV (SE)	MD [95% CI]; p value[f]; SMD [95% CI]
Symptomatology (EORTC QLQ-C30)[g]							
Fatigue	772	29.30 (22.63)	0.10 (0.57)	774	29.10 (21.35)	-1.88 (0.57)	1.98 [0.41; 3.55]; 0.014; 0.13 [0.03; 0.23]
Nausea and vomiting	772	2.94 (8.49)	3.76 (0.30)	774	3.36 (10.08)	0.86 (0.30)	2.90 [< 2.07; 3.74]; < 0.001; 0.35 [0.25; 0.45]
Pain	772	20.60 (23.94)	-1.76 (0.58)	775	20.75 (23.51)	-2.01 (0.58)	0.26 [-1.34; 1.86]; 0.752 –
Dyspnoea	769	13.48 (21.56)	0.66 (0.52)	770	12.25 (20.29)	-0.74 (0.52)	1.41 [-0.03; 2.84]; 0.055 –
Insomnia	771	27.15 (28.18)	0.03 (0.74)	773	28.76 (29.62)	-0.40 (0.74)	0.44 [-1.61; 2.48]; 0.677 –
Loss of appetite	771	8.21 (18.03)	1.96 (0.46)	772	8.03 (17.93)	-0.63 (0.46)	2.60 [< 1.33; 3.86]; < 0.001; 0.20 [0.11; 0.31]
Constipation	769	9.67 (19.48)	2.52 (0.53)	772	9.67 (19.91)	0.39 (0.52)	2.13 [0.67; 3.59]; 0.004; 0.15 [0.05; 0.25]
Diarrhoea	769	5.77 (15.02)	0.88 (0.42)	772	6.00 (15.18)	0.74 (0.41)	0.14 [-1.01; 1.30]; 0.806 –
Symptomatology (FACIT fatigue)[h]							
Fatigue scale	766	40.27 (9.67)	-0.02 (0.23)	773	40.43 (8.88)	0.79 (0.23)	-0.80 [-1.45; -0.16]; 0.015; -0.12 [-0.23; -0.03]

Health-related quality of life

Endpoint	Olaparib			Placebo			Intervention vs control
	N[e]	Values at the start of the study MV (SD)	Mean change in the course of study MV (SE)	N[e]	Values at the start of the study MV (SD)	Mean change in the course of study MV (SE)	MD [95% CI]; p value[f]; SMD [95% CI]
EORTC QLQ-C30[i]							
Global health status	768	70.64 (19.31)	1.62 (0.51)	773	70.20 (19.07)	3.45 (0.50)	-1.83 [-3.23; -0.43]; 0.011; -0.13 [-0.23; -0.03]
Physical functioning	772	86.32 (14.55)	0.82 (0.35)	774	86.40 (14.43)	1.68 (0.35)	-0.86 [-1.83; 0.11]; 0.084 –
Role functioning	772	80.12 (24.22)	2.45 (0.58)	774	81.31 (23.89)	3.21 (0.58)	-0.76 [-2.38; 0.85]; 0.355 –
Cognitive functioning	769	81.64 (20.99)	-1.82 (0.54)	772	82.82 (20.22)	-1.73 (0.54)	-0.09 [-1.60; 1.42]; 0.908 –
Emotional functioning	769	76.99 (22.33)	-0.05 (0.54)	771	77.77 (20.80)	-0.04 (0.54)	-0.02 [-1.51; 1.48]; 0.984 –
Social functioning	769	78.63 (25.07)	5.34 (0.57)	773	79.28 (24.03)	5.94 (0.57)	-0.60 [-2.19; 0.99]; 0.457 –

Side effects

Endpoint	Olaparib		Placebo		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value[a] Absolute difference (AD)[b]
Total adverse events (presented additionally)					
	911	*836 (91.8)*	904	*758 (83.8)*	–

Endpoint	Olaparib		Placebo		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value[a] Absolute difference (AD)[b]
Serious adverse events (SAE)[j]					
	911	75 (8.2)	904	58 (6.4)	1.28 [0.92; 1.79] 0.147
Severe adverse events (CTCAE grade ≥ 3)					
	911	*170 (18.7)*	904	*82 (9.1)*	2.06 [1.61; 2.63]; < 0.001
Therapy discontinuation due to adverse events					
	911	*98 (10.8)*	904	*42 (4.6)*	2.32 [1.63; 3.28]; < 0.001
Specific adverse events					
MDS and AML (SMQ + PT list, AEs)[k, n]	911	*2 (0.2)*	904	*2 (0.2)*	0.99 [0.14; 7.03] > 0.999
Pneumonitis (SMQ, AEs)[k, n]	911	*9 (1.0)*	904	*12 (1.3)*	0.74 [0.32; 1.76] 0.533
Fatigue (PT, AEs)	911	*366 (40.2)*	904	*246 (27.2)*	1.48 [1.29; 1.69]; < 0.001
Gastrointestinal disorders (SOC, AEs)	911	*654 (71.8)*	904	*430 (47.6)*	1.51 [1.39; 1.63]; < 0.001
Dysgeusia (PT, AEs)	911	*107 (11.7)*	904	*38 (4.2)*	2.79 [1.95; 4.00]; < 0.001
Loss of appetite (PT, AEs)	911	*119 (13.1)*	904	*53 (5.9)*	2.23 [1.63; 3.04]; < 0.001
Anaemia (PT, SAEs)	911	*15 (1.6)*	904	*1 (0.1)*	14.88 [1.97; 112.45]; < 0.001
Investigations (SOC, severe AEs[l, m])	911	*50 (5.5)*	904	*10 (1.1)*	4.96 [2.53; 9.72]; < 0.001

[a] IQWiG calculation of RR, 95% CI (asymptotic) and p value (unconditional exact test, CSZ method according to Martín Andrés et al.[2]
[b] Data on absolute difference (AD) only in the case of statistically significant difference; own calculation
[c] Cox proportional hazards model (HR, 95% CI) and log-rank test (p value) stratified by hormone receptor status, type of prior chemotherapy and prior platinum-based chemotherapy for breast cancer
[d] The individual components of the combined endpoint are shown in the lines below.
[e] Number of patients with one value at the start of the study and at least one value at a later visit.
[f] MMRM of change at the start of the study with treatment, visit, interaction from treatment and visit, value at start of the study and interaction from value at start of the study and visit as covariates.
[g] Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 100).
[h] Higher (increasing) values mean better symptomatology; positive effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 52).
[i] Higher (increasing) values mean better health-related quality of life; positive effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 100).
[j] Without consideration of SOC benign, malignant and unspecified neoplasms (including cysts and polyps)
[k] Pre-determined in the study as AESI
[l] Operationalised as CTCAE grade ≥ 3
[m] The following PTs with a statistically significant effect are included in the SOC study: Leukopenia, neutropenia and lymphopenia.
[n] Observation period until death or end of study

Abbreviations used:
AD = Absolute Difference; AML = acute myeloid leukaemia; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = EORTC: European Organisation for Research and Treatment of Cancer; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy - Fatigue; HR = hazard ratio; CI = confidence interval; MD = mean difference; MDS = myelodysplastic syndrome; MMRM = mixed model for repeated measures; MV = mean value; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PT = preferred term; QLQ-C3 = Quality of life Questionnaire - Core 30; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation; SE = standard error; SMD = standardised mean difference; SMQ = standard MedDRA query; SOC = system organ class; SAE = serious adverse event; AE = adverse event; AESI = adverse events of special interest; vs = versus

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

Adults with germline BRCA-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy; adjuvant therapy

approx. 540 – 690 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: 31 January 2023):

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

[2] 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. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

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

4. Treatment costs

Annual treatment costs:

Adults with germline BRCA-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Olaparib monotherapy	
Olaparib	€ 59,905.20
Olaparib in combination with endocrine therapy	
Olaparib	€ 59,905.20
Endocrine therapy	€ 71.36 - € 2,215.66
Total	€ 59,976.56 - € 62,120.86
Appropriate comparator therapy:	
Monitoring wait-and-see approach	Incalculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2023)

Costs for additionally required SHI services: not applicable

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 for the adjuvant treatment of germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy:

Adults with germline BRCA-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy; adjuvant 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.

II. **The resolution will enter into force on the day of its publication on the website of the G-BA on 16 February 2023.**

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

Berlin, 16 February 2023

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

Prof. Hecken