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 Niraparib (Reassessment of an Orphan Drug after the € 50 Million Turnover Limit Was Exceeded (Ovarian Carcinoma, Tubal Carcinoma, or Primary Peritoneal Carcinomatosis; Maintenance Treatment after Second-Line Therapy))

of 2 April 2020

On 2 April 2020, the Federal Joint Committee (G-BA) resolved by written statement 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. Annex XII will be amended as follows:

1. The information relating to niraparib as amended by the resolution of 7 June 2018 (Federal Gazette, BAnz AT 12 July 2018 B3) is hereby repealed.

2. Annex XII shall be amended in alphabetical order to include niraparib as follows:

Niraparib

Resolution of: 2 April 2020
Entry into force on: 2 April 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 16 November 2017):

Zejula is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

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

Adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy; maintenance treatment

Appropriate comparator therapy:

- olaparib

or

- monitoring wait-and-see approach

Extent and probability of the additional benefit of niraparib compared with olaparib:

An additional benefit is not proven

Study results according to endpoints[1]:

Adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy; maintenance treatment

Indirect comparison: Niraparib (NOVA study[2]) vs Olaparib (SOLO2 study[3] and Study 19[4]) via the bridge comparator placebo:

Mortality

Endpoint	**Niraparib (intervention) or Olaparib (appropriate comparator therapy)**		**Placebo**		Group difference
	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]
Overall survival					
Niraparib vs. placebo					
NOVA	372	n.a. 60 (16.1)	181	n.a. 35 (19.3)	0.73 [0.48; 1.13] 0.155
Olaparib vs placebo					
Study 19	136	29.8 [no data available] 98 (72.1)	129	27.8 [no data available] 112 (86.8)	0.73 [0.55; 0.95] 0.021
SOLO2	196	n.a. 45 (23.0)	99	n.a. 27 (27.3)	0.80 [0.50; 1.31] 0.427
Total					0.74 [0.59; 0.94] 0.011[b]
Indirect comparison via bridge comparator (according to Bucher)[b]: Niraparib vs olaparib					0.99 [0.61; 1.60] 0.956

[1] Data from the dossier evaluation of the IQWiG (A19-88) and the addendum (A20-16) unless otherwise indicated.
[2] Data cut-off of 30 May 2016
[3] Data cut-off 19/09/2016
[4] Data cut-off 09/05/2016

Morbidity

Endpoint	**Niraparib (intervention) or Olaparib (appropriate comparator therapy)**		**Placebo**		Group difference
	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]
Progression-free survival (PFS)					
No usable data[c]					
Health status					
EQ-5D VAS					
No usable data[d]					

Health-related quality of life

Endpoint	**Niraparib (intervention) or Olaparib (appropriate comparator therapy)**		**Placebo**		Group difference
	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]
FACT-O total score					
No usable data[e]					

Side effects

Endpoint	**Niraparib (intervention) or Olaparib (appropriate comparator therapy)**		**Placebo**		Group difference
	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)					
Niraparib vs. placebo					
NOVA	367	no data available 367 (100.0)	179	no data available 171 (95.5)	-
Olaparib vs placebo					
Study 19	136	0.1 [no data available] 132 (97.1)	128	0.3 [no data available] 119 (93.0)	-
SOLO2	195	0.1 [no data available] 192 (98.5)	99	0.2 [no data available] 94 (94.9)	-
Serious adverse events (SAE)					
Niraparib vs. placebo					
NOVA (gBRCAmut cohort)	136	n.a. [22.8; n.a.] 42 (30.9)	65	n.a. [11.0; n.a.] 7 (10.8)	2.36 [1.04; 5.34] 0.034
NOVA (Cohort: non-gBRCAmut)	231	n.a. [n.a.; n.a.] 68 (29.4)	114	n.a. [n.a.; n.a.] 20 (17.5)	1.69 [1.02; 2.81] 0.040
Total					1.85 [1.21; 2.85] 0.005[b]
Olaparib vs placebo					
Study 19	136	67.9 [no data available] 31 (22.8)	128	42.0 [no data available] 11 (8.6)	1.61 [0.79; 3.46] 0.218
SOLO2	195	n.a. 35 (17.9)	99	n.a. 8 (8.1)	1.64 [0.79; 3.84] 0.234
Total					1.62 [0.94; 2.81] 0.083[b]
Indirect comparison via bridge comparator (according to Bucher)[b]: Niraparib vs olaparib					–[f]

Endpoint	Niraparib (intervention) or Olaparib (appropriate comparator therapy)		Placebo		Group difference
	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]
Severe adverse events (CTCAE grade ≥3)					
Niraparib vs. placebo					
NOVA (gBRCAmut cohort)	136	1.2 [0.8; 2.0] 108 (79.4)	65	n.a. [11.0; n.a.] 14 (21.5)	5.82 [3.32; 10.22] < 0.001
NOVA (Cohort: non-gBRCAmut)	231	1.6 [1.0; 2.7] 164 (71.0)	114	n.a. [20.1; n.a.] 27 (23.7)	4.61 [3.06; 6.96] < 0.001
Total					5.00 [3.59; 6.97] < 0.001[b]
Olaparib vs placebo					
Study 19	136	22.9 [no data available] 59 (43.4)	128	n.a. 28 (21.9)	1.88 [1.20; 3.01] 0.013
SOLO2	195	n.a. 72 (36.9)	99	n.a. 18 (18.2)	1.92 [1.17; 3.33] 0.012
Total					1.90 [1.34; 2.68] < 0.001[b]
Indirect comparison via bridge comparator (according to Bucher)[b]: Niraparib vs olaparib					2.63 [1.63; 4.25] < 0.001
Discontinuation because of AE					
Niraparib vs. placebo					
NOVA (gBRCAmut cohort)	136	n.a. [23.6; n.a.] 18 (13.2)	65	n.a. [n.a.; n.a.] 1 (1.5)	6.00 [0.79; 45.54] 0.049
NOVA (Cohort: non-gBRCAmut)	231	n.a. [n.a.; n.a.] 36 (15.6)	114	n.a. [n.a.; n.a.] 3 (2.6)	5.99 [1.84; 19.55] < 0.001
Total					5.99 [2.16; 16.64] < 0.001[b]
Olaparib vs placebo					

Endpoint	Niraparib (intervention) or Olaparib (appropriate comparator therapy)		Placebo		Group difference
	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]
Study 19	136	n.a. 8 (5.9)	128	n.a. 2 (1.6)	1.96 [0.44; 13.68] 0.528
SOLO2	195	n.a. 21 (10.8)	99	n.a. 2 (2.0)	3.71 [1.07; 23.40] 0.063
Total					2.79 [0.89; 8.80] 0.080[b]
Indirect comparison via bridge comparator (according to Bucher)[b]: Niraparib vs olaparib					–[f]
Specific adverse events					
No usable data					

References:
[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Calculation of the IQWiG
[c] No usable data are available for PFS because no results were reported for the total population of the NOVA study
[d] no usable data available because the studies used different follow-up strategies for this endpoint
[e] no usable data available because this endpoint was not surveyed in the NOVA study
[f] The results cannot be interpreted because of an insufficient certainty of results for this data constellation

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; FACT-O = Functional Analysis of Cancer Therapy – Ovarian; EQ-5D VAS = European Quality of Life Questionnaire 5 Dimensions Visual Analogue Scale; 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; SAE = serious adverse event; AE = adverse event; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No difference relevant for the benefit assessment
Morbidity	n.a.	No data suitable for the benefit assessment
Health-related quality of life	n.a.	No data suitable for the benefit assessment
Side effects	↓	Disadvantage in the endpoint severe AE (CTCAE grade ≥ 3)

Explanations:
↑: positive statistically significant and relevant effect with low/unclear reliability of data
↓: negative statistically significant and relevant effect with low/unclear reliability of data
↑↑: positive statistically significant and relevant effect with high reliability of data
↓↓: negative statistically significant and relevant 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

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

Adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy; maintenance treatment

approx. 1,900 to 2,400 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 Zejula® (active ingredient: niraparib) at the following publicly accessible link (last access: 28 January 2020):
https://www.ema.europa.eu/documents/product-information/zejula-epar-product-information_de.pdf

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

4. Treatment costs

Annual treatment costs:

Adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy; maintenance treatment

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Niraparib	€ 100,953.53
Appropriate comparator therapy:	
Olaparib	€ 82,741.46
Monitoring wait-and-see approach	not quantifiable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2020

Costs for additionally required SHI services: not applicable

II. Entry into force

1. **The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 2 April 2020.**
2. **The period of validity of the resolution is limited to 1 October 2020.**

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

Berlin, 2 April 2020

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

Prof. Hecken