Resolution

Gemeinsamer Bundesausschuss

of the Resolution 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 after the deadline (Ovarian, fallopian tube or primary peritoneal cancer))

of 15 July 2021

At its session on 15 July 2021, 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 on DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. I. Annex XII is amended as follows:

1. The information on niraparib in the version of the resolution of 2 April 2020 (BAnz AT 04.06.2019 B3) last modified on 20 August 2020 (BAnz AT 07.10.2020 B1) is repealed.

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

Niraparib

Resolution of: 15 July 2021
Entry into force on: 15 July 2021
BAnz AT TT. MM YYYY Bx

New 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.

Therapeutic indication of the resolution (resolution of 15 July 2021):

see therapeutic indication according to marketing authorisation.

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

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

Appropriate comparator therapy:

- Olaparib

or

- monitoring wait-and-see approach

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

An additional benefit is not proven

Study results according to endpoints:[1]

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↓	Disadvantages in the endpoint severe AEs (CTCAE grade ≥ 3)

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

Indirect comparison via the bridge comparator placebo: Niraparib vs olaparib

NOVA study: Niraparib vs placebo (data cut-offs from 01.10.2020 and 30.05.2016)

Study 19: Olaparib vs placebo (data cut-off from 09.05.2016)

SOLO2 study: Olaparib vs placebo (data cut-off from 19.09.2016 and 03.02.2020)

Mortality

Endpoint category Endpoint Comparison Study (Data cut-off)	Niraparib or olaparib		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)[p]
Overall survival					

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-17) unless otherwise indicated.

Niraparib vs placebo					
NOVA (01.10.2020)	372	35.6 [32.2; 40.6] 245 (65.9)	181	37.1 [29.9; 41.8] 120 (66.3)	1.01 [0.81; 1.27]; 0.903[a]
NOVA (30.05.2016)[b]	372	n.r. 60 (16.1)	181	n.a. 35 (19.3)	0.73 [0.48; 1.13]; 0.155[a]
Olaparib vs placebo					
Study 19 (09.05.2016)	136	29.8 [n. d.] 98 (72.1)	129	27.8 [n. d.] 112 (86.8)	0.73 [0.55; 0.95]; 0.021[c]
SOLO2 (03.02.2020)	196	51.7 [41.5; 59.1] 116 (59.2)	99	38.8 [31.4; 48.6] 65 (65.7)	0.74 [0.54; 1.0] 0.054[d]
Total[e]					0.73 [0.60; 0.90]; 0.003
Indirect comparison via bridge comparators[f]:					
Niraparib vs olaparib (with NOVA 01.10.2020)					–[g]
Niraparib vs olaparib (with NOVA 30.05.2016)					1.00 [0.62; 1.61]; > 0.999

Morbidity

Progression-free survival (PFS)	
	no usable data available[q]
Symptomatology	
Health status (EQ-5D VAS)	no usable data available[h]
FOSI	no usable data available[i]

Health-related quality of life

FACT-O total score	no usable data available[i]

Side effects

Endpoint category **Endpoint** **Comparison** **Study** **(Data cut-off)**	**Niraparib or olaparib**		**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

Adverse events (AE) in total					
Niraparib vs placebo					
NOVA (01.10.2020)	367	0.1 [19.1; n. c.] 367 (100.0)	179	0.3[0.2; 0.3] 172 (96.1)	-
Olaparib vs placebo					
Study 19 (09.05.2016)	136	0.1 [n. d.] 132 (97.1)	128	0.3 [n. d.] 119 (93.0)	-
SOLO2 (19.09.2016)	195	0.1 [n. d.] 192 (98.5)	99	0.2 [n. d.] 94 (94.9)	-
Serious adverse events (SAEs)					
Niraparib vs placebo					
NOVA (01.10.2020)	367	43.2 [29.6; 70.9] 126 (34.3)[k]	179	n. a. 27 (15.1)[k]	2.14 [1.41; 3.25]; < 0.001[l]
Olaparib vs placebo					
Study 19 (09.05.2016)	136	67.9 [n. d.] 31 (22.8)	128	42.0 [n. d.] 11 (8.6)	1.61 [0.79; 3.46]; 0.218[c]
SOLO2 (19.09.2016)	195	n. a. 35 (17.9)	99	n. a. 8 (8.1)	1.64 [0.79; 3.84]; 0.234[d]
Total[m]					1.62 [0.94; 2.81]; 0.083
Indirect comparison via bridge comparators[f]:					
Niraparib vs olaparib					–[g]
Severe adverse events (CTCAE grade 3 or 4)					
Niraparib vs placebo					
NOVA (01.10.2020)	367	0.1 [19.1; n. c.] 367 (100.0)	179	0.3[0.2; 0.3] 172 (96.1)	5.24 [3.79; 7.27]; < 0.001[l]
Olaparib vs placebo					
Study 19 (09.05.2016)	136	0.1 [n. d.] 132 (97.1)	128	0.3 [n. d.] 119 (93.0)	1.88 [1.20; 3.01]; 0.013[c]
SOLO2 (19.09.2016)	195	0.1 [n. d.] 192 (98.5)	99	0.2 [n. d.] 94 (94.9)	1.92 [1.17; 3.33]; 0.012[d]
Total[m]					1.90 [1.34; 2.68]; < 0.001

Indirect comparison via bridge comparators[f]:					
Niraparib vs olaparib					2.76 [1.71; 4.44]; < 0.001[o]
Therapy discontinuation due to adverse events					
Niraparib vs placebo					
NOVA (01.10.2020)	367	n. a. [58,4: n. c.] 67 (18.3)	179	n. a. 4 (2.2)	6.61 [2.40; 18.20]; 0.001[l]
Olaparib vs placebo					
Study 19 (09.05.2016)	136	n. a. 8 (5.9)	128	n. a. 2 (1.6)	1.96 [0.44; 13.68]; 0.528[c]
SOLO2 (19.09.2016)	195	n. a. 21 (10.8)	99	n. a. 2 (2.0)	3.71; [1.07; 23.40]; 0.063[d]
Total[m]					2.79 [0.89; 8.80]; 0.080
Indirect comparison via bridge comparators[f]:					
Niraparib vs olaparib					–[g]

a. HR and associated CI: Cox proportional hazards model stratified by time to disease progression after penultimate platinum-based therapy before the time of enrolment, use of bevacizumab on the penultimate or last platinum-based therapy, and best response during last platinum-based therapy; p value from log-rank test
b. Additional consideration of the primary data cut-off (30.05.2016) due to insufficient certainty of results for the endpoint overall survival in the final data cut-off (01.10.2020;) for conducting an indirect comparison
c. Cox-Proportional-Hazards-Model with profile likelihood method to estimate 95% CI; p value: Log-rank test; both analyses by the company adjusted for Jewish ancestry (yes / no), time to progression after penultimate platinum-containing chemotherapy (> 6-12 months vs > 12 months) and objective response to last platinum-containing chemotherapy before study inclusion (complete vs partial)
d. Cox-Proportional-Hazards-Model with profile likelihood method to estimate 95% CI; p-value: Log-rank test; both analyses adjusted for objective response to last platinum-containing chemotherapy before time of enrolment (complete vs partial) and time to progression after penultimate platinum-containing chemotherapy (> 6-12 months vs > 12 months)
e. Own calculation from meta-analysis with fixed effect
f. Indirect comparison according to Bucher [52]
g. Due to insufficient certainty of results in the NOVA study, no indirect comparison is calculated
h. No indirect comparison possible because of different follow-up strategies for this endpoint in the NOVA and SOLO2 studies i. No indirect comparison is possible because only data from one potentially highly biased study (Study 19) are available on the olaparib edge.
j. No indirect comparison is possible, because the subscales of the FACT-O were not collected completely in the NOVA study, but only the 8 items for the calculation of the symptom score FOSI were available.
k. Non-fatal SAEs; in the study, there were an additional 3 (0.8%) fatal SAEs in the niraparib arm and none in the placebo arm.
l. Unstratified Cox-Proportional-Hazards-Model ; p-value from log-rank test
m. Meta-analysis with fixed effect (results were taken from the dossier assessment A19-88)
n. Operationalised as CTCAE 3
o. Own calculation; due to the size of the observed effect in the indirect comparison, it can be assumed that this is not completely called into question by potential biases alone
a Absolute difference (AD) is given only in the case of a statistically significant difference; own calculation
q. For the indirect comparison used (without the Nora study), no PFS calculations are available.

Abbreviations used:
AD = Absolute Difference; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire - 5 Dimensions; FACT-O: Functional Analysis of Cancer Therapy – Ovarian; FOSI: FACT-Ovarian Symptom Index; n. d.: no data; 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; RCT: randomised controlled trial; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs = versus

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

approx. 700 to 1,000 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: 15 June 2021):
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 obstetrics and others,

and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with ovarian cancer.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Niraparib	€ 81,456.79
Appropriate comparator therapy:	
Olaparib	€ 69,059.30
Monitoring wait-and-see approach	incalculable

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 June 2021)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 15 July 2021.

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

Berlin, 15 July 2021

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

Prof. Hecken