Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Rucaparib (maintenance treatment)

of 15 August 2019

At its session on 15 August 2019, 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. Annex XII shall be amended in alphabetical order to include the active ingredient rucaparib as follows:

Rucaparib

Resolution of: 15 August 2019
Entry into force on: 15 August 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 23 May 2018):

Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade 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

Maintenance treatment of adult patients with platinum-sensitive relapsed high-grade 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 rucaparib compared with a monitoring wait-and-see approach:

An additional benefit is not proven.

Study results according to endpoints:[1]

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

ARIEL3 study: Rucaparib **vs** placebo

Mortality

Endpoint	**Rucaparib**		**Placebo**[a]		Rucaparib vs placebo
	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[b] Absolute difference (AD)[c]
Overall survival					
	375	29.6 [28.6; n.c.] *81 (21.6)*	189	n.a. [27.2; n.c.] *42 (22.2)*	0.88 [0.60; 1.28] 0.504

[1] Data from the dossier evaluation of the IQWiG (A19-23) unless otherwise indicated.

Morbidity

Endpoint	Rucaparib		Placebo[a]		Rucaparib vs placebo
	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[b] Absolute difference (AD)[c]
Progression-free survival					
invPFS1 (PFS1 collected by the investigator)	375	10.8 [8.3; 11.4] *234 (62.4)*	189	5.4 [5.3; 5.5] *167 (88.4)*	0.365 [0.295; 0.451] < 0.0001 AD: + 5.4 months
Health status					
EQ-5D VAS (MID 7 points)	375	2.3 [1.9; 2.8] *224 (59.7)*	189	3.7 [2.8; 4.6] *105 (55.6)*	1.26 [0.99; 1.60] 0.056

	Rucaparib			Placebo[a]			Rucaparib vs placebo
	N[d]	Values at start of study MV (SD)	Change to treatment cycle 3[e] MV (SE)[f]	N[d]	Values at start of study MV (SD)	Change to treatment cycle 3[e] MV (SE)[f]	MD [95% CI] p value[f]
Health status							
EQ-5D VAS (MD at treatment cycle 3 vs start of study)[g]	270	79.3 (13.94)	−4.8 (1.05)	148	77.8 (15.41)	1.0 (1.78)	−4.4 [−7.0; −1.8] 0.001 Hedges' g: −0.34 [−0.54; −0.14][h]

	Rucaparib			Placebo[a]			Rucaparib vs placebo
	N[d]	Values at start of study MV (SD)	Change to treatment cycle 3[e] MV (SE)[f]	N[d]	Values at start of study MV (SD)	Change to treatment cycle 3[e] MV (SE)[f]	MD [95% CI] p value[f]
Symptomatology							
DRS-P sub-scale of FOSI-18 (MD at treatment cycle 3 vs start of study)[g]	273	29.3 (4.37)	−2.8 (0.33)	149	29.2 (4.89)	−0.5 (0.39)	−2.3 [−3.1; −1.5] < 0.001 Hedges' g: −0.57 [−0.78; −0.37][h]

Health-related quality of life

Not collected

Side effects

Endpoint	Rucaparib		Placebo[a]		Rucaparib vs placebo
	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[b] Absolute difference (AD)[c]
Adverse events (AEs) presented additionally					
	372	0.1 [0.07; 0.10] *372 (100)*	189	0.3 [0.16; 0.46] *182 (96.3)*	-
Serious adverse events (SAEs)					
	372	n.a. *83 (22.3)*	189	n.a. *20 (10.6)*	1.45 [0.88; 2.40] 0.143
Severe adverse events (CTCAE grade ≥ 3)					
	372	5.1 [3.71; 7.79] *222 (59.7)*	189	42.0 [21.98; n.c.] *30 (15.9)*	4.33 [2.93; 6.40] < 0.001 - 36.9 months
Withdrawal because of AEs					
	372	n.a. [38.1; n.c.] *61 (16.4)*	189	n.a. *4 (2.1)*	5.55 [2.00; 15.40] 0.001 AD: n.c.
Specific adverse events					
Musculoskeletal, connective tissue and bone disorders (AE, SOC)	372	13.8 [8.8; 19.2] *172 (46.2)*	189	7.3 [5.9; 10.9] *86 (45.5)*	0.74 [0.57; 0.96] 0.026 AD: +6.5 months
General disorders and administration site conditions (AE SOC)	372	0.9 [0.7; 1.1] *296 (79.6)*	189	3.8 [2.4; 5.7] *108 (57.1)*	1.70 [1.36; 2.12] < 0.001 AD: −2.9 months
Gastrointestinal disorders (AE, SOC)	372	0.1 [0.1; 0.2] *344 (92.5)*	189	1.8 [1.1; 2.8] *146 (77.2)*	2.22 [1.81; 2.72] < 0.001 AD: −1.7 months

Photosensitivity reaction (AE, PT)	372	n.a. *68 (18.3)*	189	n.a. *1 (0.5)*	26.32 [3.64; 190.22] 0.001 AD: n.c.
Taste disorder (AE, PT)	372	n.a. *148 (39.8)*	189	n.a. *13 (6.9)*	6.69 [3.79; 11.81] < 0.001 AD: n.c.
Blood and lymphatic system disorders SOC (CTCAE grade ≥ 3)	372	n.a. [n.c.; n.c.] *95 (25.5)*	189	n.a. [21.9; n.c.] *3 (1.6)*	14.87 [4.70; 47.04] < 0.001 AD: n.c.
Myelodysplastic syndrome (AE, PT)	372	n.a. *2 (0.5)*	189	n.a. *0 (0)*	n.c.
Acute myeloid leukaemia (AE, PT)	372	n.a. *1 (0.3)*	189	n.a. *0 (0)*	n.c.

[a] Adequate approximation to the appropriate comparator therapy monitoring wait-and-see approach but with limitations

[b] HR, CI, p value: Cox proportional hazards model stratified according to HRD classification, best response to last platinum-based regime before start of maintenance treatment, and interval between termination of penultimate platinum-based regime and disease progression.

[c] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation

[d] 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.

[e] One treatment cycle lasted 28 days.

[f] ANCOVA adjusted for HRD classification, best response to last platinum-based regime before start of maintenance treatment, and interval between termination of penultimate platinum-based regime and disease progression.

[g] A positive change from start of study to end of study means an improvement; a positive effect estimate means an advantage for the intervention.

[h] Calculation of the IQWiG based on MD and CI of ANCOVA

Abbreviations used:
ANCOVA= analysis of covariance; AD = absolute difference; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; DRS-P: disease-related symptoms sub-scale – physical; EQ-5D = European Quality of Life Questionnaire 5 Dimensions; FOSI: functional assessment of cancer therapy ovarian symptom index; HR = hazard ratio; MD = mean difference; MV = mean; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; SD = standard deviation; SE = standard error; VAS = visual analogue scale; SOC = system organ class; vs = versus

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

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

approx. 1900–2400 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 Rubraca® (active ingredient: rucaparib) at the following publicly accessible link (last access: 5 July 2019):

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

Only specialists in internal medicine, haematology and oncology with experience treating patients with ovarian cancer, and specialist in gynaecology and other doctors from other specialisms participating in the oncology agreement may initiate and monitor treatment with rucaparib.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is expected. The EMA will evaluate new information on this medicinal product at least annually and update the product information if necessary.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Rucaparib	€ 106,668.82
Appropriate comparator therapy:	
Olaparib	€ 82,740.68
Monitoring wait-and-see approach	not quantifiable

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

2. The period of validity of the resolution is limited to 1 April 2023.

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

Berlin, 15 August 2019

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

Prof Hecken