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 in Accordance with Section 35a SGB V – Ribociclib (New Therapeutic Indication: Breast Cancer in Combination with an Aromatase Inhibitor)

of 4 July 2019

At its session on 4 July 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. The findings set out in Annex XII for the active ingredient ribociclib, as amended by the resolution of 16 March 2018, shall remain part of the Pharmaceuticals Directive in accordance with the following amendments:

1. The following information is inserted after the heading "1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy":

"a1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:"

2. The following information is inserted after the heading "2. Number of patients or demarcation of patient groups eligible for treatment":

"a1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:"

3. Under "4. Treatment costs", the following information is inserted after the heading "Annual treatment costs":

"a1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine

therapy:”

4. After No. 4, the following findings will be added to the findings on the benefit assessment of ribociclib in accordance with the resolution of 16 March 2018:

Ribociclib

Resolution of: 4 July 2019
Entry into force on: 4 July 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 17 December 2018):

Kisqali is indicated for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

Indication:

This resolution relates exclusively to the assessment of the additional benefit of ribociclib in combination with an aromatase inhibitor. For the assessment of the additional benefit of ribociclib with fulvestrant, reference is made to the separate benefit assessment procedure for this combination therapy.

For the assessment of the additional benefit for patient group a1, reference is made to the previous benefit assessment procedure for ribociclib in the resolution of 16 March 2018. This patient group is not the subject of the present benefit assessment procedure.

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

a2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

Appropriate comparator therapy:

- tamoxifen in combination with an elimination of the ovarian function,
- possibly letrozole in combination with an elimination of ovarian function in women previously treated with anti-oestrogens,

The extent and probability of additional benefit of ribociclib in combination with letrozole compared with letrozole:

An additional benefit is not proven

b1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally

advanced or metastatic breast cancer with prior endocrine therapy:

Appropriate comparator therapy:

another endocrine therapy depending on the previous therapy with:

- tamoxifen *or*
- anastrozole *or*
- fulvestrant; only for patients with relapse or progress after anti-oestrogen treatment *or*
- letrozole; only for patients with relapse or progress after anti-oestrogen treatment *or*
- exemestane; only for patients with progress after anti-oestrogen treatment *or*
- everolimus in combination with exemestane; only for patients without symptomatic visceral metastasis after progression after a non-steroidal aromatase inhibitor.

The extent and probability of additional benefit of ribociclib in combination with an aromatase inhibitor compared with appropriate comparator therapy:

An additional benefit is not proven

b2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

Appropriate comparator therapy:

endocrine therapy according to the doctor's instructions, taking into account the respective marketing authorisation.

Tamoxifen, letrozole, exemestane, megestrol acetate, and medroxyprogesterone acetate are approved for the present therapeutic indication.

The extent and probability of additional benefit of ribociclib in combination with an aromatase inhibitor compared with appropriate comparator therapy:

An additional benefit is not proven

Study results according to endpoints:

a2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

MONALEESA-7 Study: ribociclib + tamoxifen or anastrozole/letrozole vs placebo + tamoxifen or anastrozole/letrozole[1,2]

[1] Data from the dossier evaluation of the IQWiG (A19-06) and from the addendum (A19-46), unless otherwise indicated.

Study design: randomised, double-blind, two-armed

Relevant sub-population: Pre-/peri-menopausal patients who have not yet received initial endocrine therapy for metastatic/locally advanced disease and who have relapsed during or within 12 months after the end of (neo-)adjuvant endocrine therapy (approximately 30.5% of the study population).

Mortality

Endpoint	**Ribociclib + letrozole**		**Letrozole**		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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	100	38.2 [38.2; n.c.] 35 (35.0)	105	36.7 [28.5; 40.9] 46 (43.8)	0.78 [0.50; 1.21] 0.268

Morbidity

Endpoint	**Ribociclib + letrozole**		**Letrozole**		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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS)					
	100	17.9 [12.9; 24.2] 66 (66.0)	105	9.2 [5.5; 14.5] 79 (75.2)	0.59 [0.42; 0.83] 0.002 AD: 8.7 months
Time to first subsequent chemotherapy					
	100	26.0 [22.8; 33.8] 56 (56.0)	105	17.2 [11.3; 25.4] 73 (69.5)	0.67 [0.47; 0.95] 0.022 AD: 8.8 months
Disease symptoms – time until permanent deterioration[b]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	100	n.a. 20 (20.0)	105	33.1 [30.4; n.c.] 32 (30.5)	0.51 [0.29; 0.90] 0.018
Nausea and	100	n.a.	105	n.a.	1.40

[2] data cut-off 30 November 2018

Endpoint	Ribociclib + letrozole		Letrozole		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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
vomiting		7 (7.0)		4 (3.8)	[0.40; 4.88] 0.595
Pain	100	n.a. 16 (16.0)	105	33.1 [19.6; n.c.] 28 (26.7)	0.43 [0.23; 0.81] 0.007
Dyspnoea	100	n.a. 5 (5.0)	105	n.a. 3 (2.9)	1.60 [0.38; 6.70] 0.519
Insomnia	100	n.a. 11 (11.0)	105	n.a. 5 (4.8)	1.62 [0.56; 4.71] 0.372
Loss of appetite	100	n.a. 9 (9.0)	105	n.a. 6 (5.7)	1.28 [0.45; 3.63] 0.639
Constipation	100	n.a. 8 (8.0)	105	n.a. 3 (2.9)	1.92 [0.50; 7.32] 0.334
Diarrhoea	100	n.a. 1 (1.0)	105	n.a. 1 (1.0)	0.95 [0.06; 15.30] 0.972
Symptom scales of the EORTC QLQ-BR23					
Side effects of systemic treatment	100	22.0 [14.8; 33.1] 47 (47.0)	105	16.6 [9.2; 27.6] 47 (44.8)	0.82 [0.54; 1.23]; 0.338
Breast symptoms	100	n.a. 14 (14.0)	105	33.2 [33.2; n.c.] 17 (16.2)	0.57 [0.28; 1.18]; 0.126
Arm symptoms	100	n.a. 17 (17.0)	105	n.a. 17 (16.2)	0.79 [0.40; 1.58]; 0.518
Burden of hair loss	No usable data[c]				
Health status					
EQ-5D VAS (time until permanent deterioration by ≥ 7 points)[d]					
	100	27.6 [15.0; 33.1]; 43 (43.0)	105	33.1 [21.0; n.c.] 32 (30.5)	1.11 [0.69; 1.77] 0.652
EQ-5D VAS (time until permanent deterioration by ≥ 10 points)[d]					

Endpoint	Ribociclib + letrozole		Letrozole		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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
	100	30.4 [15.0; n.c.] 41(41.0)	105	33.1 [21.0; n.c.] 31 (29.5)	1.14 [0.71; 1.83] 0.584

Health-related quality of life

Endpoint	Ribociclib + letrozole		Letrozole		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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Health-related quality of life – time until permanent deterioration[e]					
General health status and functional scales of the EORTC QLQ-C30					
General health status	100	33.1 [22.1; 35.9] 38 (38.0)	105	19.5 [14.7; 33.1] 38 (36.2)	0.74 [0.46; 1.19] 0.203
Bodily function	100	n.a. [33.2; n.c.] 22 (22.0)	105	n.a. [30.4; n.c.] 23 (21.9)	0.81 [0.45; 1.46] 0.470
Role function	100	35.9 [27.6; n.c.] 29 (29.0)	105	27.9 [23.1; n.c.] 33 (31.4)	0.67 [0.40; 1.12] 0.131
Emotional function	100	n.a. [24.9; n.c.] 32 (32.0)	105	27.7 [16.5; 33.1] 38 (36.2)	0.65 [0.40; 1.05] 0.081
Cognitive function	100	n.a. [19.4; n.c.] 34 (34.0)	105	23.1 [11.3; 33.1] 40 (38.1)	0.61 [0.38; 0.97] 0.040
Social function	100	35.9 [24.0; n.c.] 32 (32.0)	105	30.4 [22.3; n.c.] 30 (28.6)	0.76 [0.46; 1.27] 0.295
Functional scales of the EORTC QLQ-BR23					
Body image	100	30.4 [19.4; 38.7] 40 (40.0)	105	27.5 [14.8; 35.9] 38 (36.2)	0.84 [0.53; 1.34] 0.467
Sexual activity	100	n.a. [30.4; n.c.]	105	n.a. 20 (19.0)	0.92

Endpoint	Ribociclib + letrozole		Letrozole		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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Health-related quality of life – time until permanent deterioration[e]					
		20 (20.0)			[0.49; 1.71] 0.793
Sex drive	No usable data[c]				
Future perspective	100	n.a. [33.1; n.c.] 16 (16.0)	105	24.8 [19.5; n.c.] 29 (27.6)	0.42 [0.23; 0.80] 0.006

Side effects

Endpoint	Ribociclib + letrozole		Letrozole		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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Adverse events (AE) (presented additionally)					
	100	no data available	105	no data available	-
Serious adverse events (SAE)					
	100	36.4 [36.4; n.c.] 21 (21.0)	105	n.a. [27.33; n.c.] 19 (18.1)	0.89 [0.47; 1.67] 0.709
Severe adverse events (CTCAE grade 3 or 4)					
	100	1.0 [0.95; 1.97] 80 (80.0)	105	23.0 [14.39; n.c.] 40 (38.1)	3.23 [2.20; 4.75] < 0.001 AD: 22 months
Therapy discontinuation because of adverse events [f]					
	100	n.a. 6 (6.0)	105	n.a. 4 (3.8)	1.16 [0.32; 4.18] 0.822
Specific adverse events					
Blood and lymphatic system disorders (CTCAE grade ≥ 3)	100	8.3 [1.0; n.c.] 56 (56.0)	105	n.a. 8 (7.6)	9.88 [4.69; 20.84] < 0.001

Contained therein: neutropenia (CTCAE grade ≥ 3)	100	11.1 [1.8; n.c.] 52 (52.0)	105	n.a. 5 (4.8)	13.50 [5.38; 33.91] < 0.001

References:

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

[b] A permanent deterioration was defined as an increase of at least 10 points in comparison to baseline without subsequent improvement to a score below this level.

[c] Unclear proportion of patients with missing values at the start of study and during the course of the study; up to the 1st survey day (cycle 3), decreasing proportion of patients in the evaluation

[d] A permanent deterioration was defined as an increase of at least 7 or 10 points in comparison to baseline without subsequent improvement to a score above this level.

[e] A permanent deterioration was defined as an increase of at least 10 points in comparison to baseline without subsequent improvement to a score above this level.

[f] Defined as AEs that led to the withdrawal of ribociclib or placebo therapy; the study did not allow termination of the letrozole treatment alone.

Abbreviations used:

AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer 23; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L = European Quality of Life-5 Dimensions-5-Level; 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; VAS = visual analogue scale; vs = versus

b1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

There is no data that would allow for the assessment of the additional benefit.

b2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

There is no data that would allow for the assessment of the additional benefit.

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

Total population according to therapeutic indication:

14,560 to 70,550 patients

a2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

approx. 1,190–5,760 patients

b1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

approx. 5,310–25,740 patients

b2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

approx. 880–4,260 patients

3. Requirements for a quality-assured application

The requirements of 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 Kisqali® (active ingredient: ribociclib) at the following publicly accessible link (last access: 23 May 2019):

https://www.ema.europa.eu/documents/product-information/kisqali-epar-product-information_de.pdf

Treatment with ribociclib 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.

4. Treatment costs

Annual treatment costs:

The annual treatment costs shown refer to the first year of treatment.

a2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed:	

Designation of the therapy	Annual treatment costs per patient
Ribociclib aromatase inhibitor[3]	
Ribociclib	€29,711.07
Aromatase inhibitor	€230.16–424.28
Total	€29,941.23–30,135.34
LHRH analogues[4]	€1,790.38–2,235.96
Appropriate comparator therapy:	
Tamoxifen plus LHRH analogues	
Tamoxifen	€71.10
LHRH analogues	€1,790.38–2,235.96
Total	€1,861.48–2,307.06
Letrozole plus LHRH analogues	
Letrozole	€230.16
LHRH analogues	€1,790.38–2,235.96
Total	€2,020.54–2,466.12

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

Costs for additionally required SHI services: not applicable

b1) <u>Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:</u>

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed:	
Ribociclib aromatase inhibitor	
Ribociclib	€29,711.07
Aromatase inhibitor	€230.16–424.28
Total	€29,941.23–30,135.34
Appropriate comparator therapy:	
Tamoxifen	€71.10
Anastrozole	€258.68
Fulvestrant	€9,696.87
Letrozole	€230.16
Exemestane	€424.28
Everolimus plus exemestane	

[3] Anastrozole, letrozole, or exemestane
[4] leuprorelin or goserelin

Designation of the therapy	Annual treatment costs per patient
Everolimus	€20,594.19
Exemestane	€424.28
Total	€21,018.47

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

Costs for additionally required SHI services: not applicable

b2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed:	
Ribociclib aromatase inhibitor	
Ribociclib	€29,711.07
Aromatase inhibitor	€230.16–424.28
Total	€29,941.23–30,135.34
LHRH analogues	€1,790.38–2,235.96
Appropriate comparator therapy: An endocrine therapy according to the doctor's instructions	
Tamoxifen	€71.10
Medroxyprogesterone acetate	€1,187.56–2,375.13
Megestrol acetate	€5,409.30
Exemestane	€424.28
Letrozole	€230.16
Leuprorelin	€1,790.38
Goserelin	€2,235.96

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

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 4 July 2019.

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

Berlin, 4 July 2019

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

Prof Hecken