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 Fulvestrant)

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. In Annex XII, the following shall be added after No. 4 to the findings on the benefit assessment of ribociclib (new therapeutic indication: breast cancer in combination with an aromatase inhibitor) as amended by the resolution of 4 July 2019:

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

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:

Appropriate comparator therapy:

Anastrozole *or* letrozole *or* fulvestrant *or* possible tamoxifen if aromatase inhibitors are not suitable.

The extent and probability of additional benefit of ribociclib in combination with fulvestrant compared with the appropriate comparator therapy:

An additional benefit is not proven

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 fulvestrant compared with the appropriate comparator therapy:

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 fulvestrant compared with the 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 fulvestrant compared with the appropriate comparator therapy:

An additional benefit is not proven

Study results according to endpoints:

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:

MONALEESA-3 Study: ribociclib + fulvestrant vs placebo + fulvestrant [1,2]

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

Relevant sub-population: Post-menopausal patients who have not yet received initial endocrine therapy for metastatic/locally advanced disease (approx. 79.2% of study population)

Mortality

Endpoint	Ribociclib + fulvestrant		Fulvestrant		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					
	375	n.a. 45 (12.0)	200	n.a. 37 (18.5)	0.66 [0.43; 1.02] 0.061

Morbidity

Endpoint	Ribociclib + fulvestrant		Fulvestrant		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)					
	375	20.6 [18.0; n.c.] 160 (42.7)	200	12.9 [11.0; n.c.] 124 (62.0)	0.61 [0.48; 0.77] < 0.001 AD: 7.7 months
Time to first subsequent chemotherapy					
	375	n.a. 112 (29.9[b])	200	26.6 [21.6; 26.6]	0.71 [0.54; 0.95]

[1] Data from the dossier evaluation of the IQWiG (A19-06) and from the addendum (A19-45), unless otherwise indicated.

[2] data cut-off 3 November 2017

Endpoint	Ribociclib + fulvestrant		Fulvestrant		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]
				82 (41.0[b])	0.020
Disease symptoms – time until permanent deterioration[c]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	375	22.4 [22.1; n.c.] 106 (28.3)	200	19.5 [17.7; n.c.] 56 (28.0)	0.96 [0.70; 1.34] 0.829
Nausea and vomiting	375	n.a. 12 (3.2)	200	n.a. 4 (2.0)	1.35 [0.43; 4.23] 0.605
Pain	375	n.a. [24.9; n.c.] 67 (17.9)	200	n.a. 29 (14.5)	1.16 [0.75; 1.80] 0.513
Dyspnoea	375	n.a. 19 (5.1)	200	n.a. 12 (6.0)	0.73 [0.35; 1.52] 0.398
Insomnia	375	n.a. 28 (7.5)	200	n.a. [24.9; n.c.] 12 (6.0)	1.16 [0.59; 2.28] 0.676
Loss of appetite	375	n.a. 23 (6.1)	200	n.a. 5 (2.5)	2.41 [0.91; 6.33] 0.066
Constipation	375	n.a. 18 (4.8)	200	n.a. 6 (3.0)	1.59 [0.63; 4.01] 0.323
Diarrhoea	375	n.a. 7 (1.9)	200	n.a. 0 (0)	–[d] 0.065
Health status					
EQ-5D VAS (time until permanent deterioration by ≥ 7 points)[e]					
	375	22.2 [22.1; 25.8] 113 (30.1)	200	19.7 [19.4; n.c.] 58 (29.0)	0.98 [0.71; 1.35] 0.901
EQ-5D VAS (time until permanent deterioration by ≥ 10 points)[e]					
	375	22.2 [22.1; 25.8] 105 (28.0)	200	19.7 [19.4; n.c.] 56 (28.0)	0.93 [0.67; 1.29] 0.666
Pain (BPI-SF)					

Endpoint	Ribociclib + fulvestrant		Fulvestrant		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]
No usable data					

Health-related quality of life

Endpoint	Ribociclib + fulvestrant		Fulvestrant		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[c]					
General health status and functional scales of the EORTC QLQ-C30					
General health status	375	22.4 [22.1; n.c.] 107 (28.5)	200	19.4 [16.6; n.c.] 62 (31.0)	0.87 [0.63; 1.19] 0.371
Bodily function	375	22.1 [20.4; n.c.] 100 (26.7)	200	n.a. [19.4; n.c.] 47 (23.5)	1.07 [0.75; 1.51] 0.724
Role function	375	n.a. [19.4; n.c.] 106 (28.3)	200	n.a. [22.3; n.c.] 42 (21.0)	1.33 [0.93; 1.91] 0.116
Emotional function	375	22.3 [22.1; n.c.] 95 (25.3)	200	22.4 [19.4; n.c.] 49 (24.5)	0.96 [0.68; 1.36] 0.838
Cognitive function	375	22.1 [19.4; n.c.] 111 (29.6)	200	22.4 [19.4; n.c.] 51 (25.5)	1.15 [0.83; 1.61] 0.411
Social function	375	n.a. [22.4; n.c.] 89 (23.7)	200	22.9 [21.3; n.c.] 36 (18.0)	1.30 [0.88; 1.93] 0.182

Side effects

Endpoint	Ribociclib + fulvestrant		Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI]	N	Median time to event in months [95% CI]	Hazard Ratio [95% CI] p value Absolute

		Patients with event n (%)		*Patients with event n (%)*	difference (AD)[a]
Adverse events (AE) (presented additionally)					
		0.3 [0.2; 0.3] 370 (98.9)		0.4 [0.3; 0.5] 192 (96.0)	-
Serious adverse events (SAE)					
	374	n.a. 103 (27.5)	200	n.a. 34 (17.0)	1.61 [1.09; 2.38] 0.015
Severe adverse events (CTCAE grade 3 or 4)					
	374	1.9 [1.1; 1.9] 292 (78.1)	200	n.a. [20.2; n.c.] 60 (30.0)	4.49 [3.39; 5.95] < 0.001
Therapy discontinuation because of adverse events [g]					
	374	n.a. [26.0; n.c.] 57 (15.2)	200	n.a. 13 (6.5)	2.33 [1.27; 4.26] 0.005
Specific adverse events					
Blood and lymphatic system disorders (CTCAE grade ≥ 3)	374	15.7 [9.3; n.c.] 171 (45.7)	200	n.a. 3 (1.5)	40.72 [13.00; 127.56] < 0.001
Contained therein: neutropenia (CTCAE grade ≥ 3)	374	19.3 [11.2; n.c.] 164 (43.9)	200	n.a. 0 (0)	–[d] < 0.001

References:

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

[b] Calculation of the IQWiG

[c] 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.

[d] Effect estimation cannot be interpreted meaningfully

[e] 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.

[f] 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.

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

Abbreviations used:

AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; 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

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:

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

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

MONALEESA-3 Study: ribociclib + fulvestrant vs placebo + fulvestrant [3,4]

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

Relevant sub-population: Post menopausal patients who have received prior endocrine therapy for metastatic/locally advanced disease (approx. 18.9% of study population)

Mortality

Endpoint	Ribociclib + fulvestrant		Fulvestrant		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					
	99	n.a. 24 (24.2)	38	n.a. [19.8; n.c.] 12 (31.6)	0.60 [0.30; 1.23] 0.166

Morbidity

Endpoint	Ribociclib + fulvestrant	Fulvestrant	Intervention vs control

[3] Data from the dossier evaluation of the IQWiG (A19-06) and from the addendum (A19-45), unless otherwise indicated.

[4] data cut-off 3 November 2017

	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)					
	99	18.8 [12.5; n.c.] 47 (47.5)	38	11.4 [3.6; 16.3] 26 (68.4)	0.52 [0.32; 0.86] 0.009 AD: 7.4 months
Time to first subsequent chemotherapy					
	99	n.a. [16.2; n.c.] 42 (42.4[b])	38	16.6 [7.7; n.c.] 18 (47.4[b])	0.76 [0.43; 1.33] 0.330
Disease symptoms – time until permanent deterioration[c]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	99	n.a. [14.8; n.c.] 27 (27.3)	38	n.a. [7.4; n.c.] 8 (21.1)	0.95 [0.43; 2.13] 0.898
Nausea and vomiting	99	n.a. 1 (1.0)	38	n.a. 2 (5.3)	0.20 [0.02; 2.26] 0.148
Pain	99	23.1 [22.0; n.c.] 20 (20.2)	38	16.7 [11.1; n.c.] 9 (23.7)	0.62 [0.28; 1.39] 0.243
Dyspnoea	99	n.a. 3 (3.0)	38	22.1 [14.8; n.c.] 3 (7.9)	0.35 [0.07; 1.76] 0.181
Insomnia	99	n.a. 8 (8.1)	38	n.a. 5 (13.2)	0.54 [0.17; 1.69] 0.283
Loss of appetite	99	n.a. 2 (2.0)	38	n.a. 0 (0)	–[d] 0.388
Constipation	99	n.a. 3 (3.0)	38	n.a. 2 (5.3)	0.50 [0.08; 3.06] 0.445
Diarrhoea	99	n.a. 0 (0)	38	n.a. 0 (0)	–
Health status					
EQ-5D VAS (time until permanent deterioration by ≥ 7 points)[e]					
	99	19.0 [14.8; n.c.] 32 (32.3)	38	16.7 [9.3; n.c.] 11 (28.9)	0.92 [0.46; 1.86] 0.825
EQ-5D VAS (time until permanent deterioration by ≥ 10 points)[e]					

Endpoint	Ribociclib + fulvestrant		Fulvestrant		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]
	99	n.a. [14.8; n.c.] 30 (30.3)	38	16.7 [9.3; n.c.] 11 (28.9)	0.83 [0.41; 1.69] 0.614
Pain (BPI-SF)					
No usable data					

Health-related quality of life

Endpoint	Ribociclib + fulvestrant		Fulvestrant		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[c]					
General health status and functional scales of the EORTC QLQ-C30					
General health status	99	n.a. [16.6; n.c.] 24 (24.2)	38	16.7 [11.8; n.c.] 12 (31.6)	0.58 [0.28; 1.20] 0.142
Bodily function	99	24.9 [16.6; n.c.] 26 (26.3)	38	14.8 [9.3; n.c.] 1 3 (34.2)	0.52 [0.26; 1.04] 0.058
Role function	99	23.1 [16.5; n.c.] 26 (26.3)	38	16.7 [14.9; n.c.] 10 (26.3)	0.75 [0.35; 1.60] 0.466
Emotional function	99	23.1 [17.4; n.c.] 24 (24.2)	38	19.5 [9.2; 22.6] 12 (31.6)	0.61 [0.30; 1.24] 0.166
Cognitive function	99	22.0 [14.8; 23.1] 32 (32.3)	38	n.a. [14.8; n.c.] 6 (15.8)	1.42 [0.58; 3.51] 0.449
Social function	99	24.9 [19.7; n.c.] 24 (24.2)	38	14.9 [11.2; n.c.] 12 (31.6)	0.51 [0.25; 1.06] 0.070

Side effects

Endpoint	Ribociclib + fulvestrant	Fulvestrant	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)					
	99	0.3 [0.1; 0.4] 99 (100)	38	0.5 [0.1; 1.0] 36 (94.7)	-
Serious adverse events (SAE)					
	99	n.a. [15.5; n.c.] 32 (32.3)	38	n.a. 6 (15.8)	1.94 [0.80; 4.69] 0.137
Severe adverse events (CTCAE grade 3 or 4)					
	99	1.8 [1.0; 3.8] 79 (79.8)	38	n.a. [9.6; n.c.] 11 (28.9)	3.69 [1.95; 7.01] < 0.001
Therapy discontinuation because of adverse events [g]					
	99	n.a. 24 (24.2)	38	n.a. 2 (5.3)	4.58 [1.08; 19.48] 0.024
Specific adverse events					
Blood and lymphatic system disorders (CTCAE grade ≥ 3)	99	15.7 [7.4; n.c.] 44 (44.4)	38	n.a. 2 (5.3)	10.31 [2.49; 42.69] < 0.001
Contained therein: neutropenia (CTCAE grade ≥ 3)	99	n.a. [15.7; n.c.] 36 (36.4)	38	n.a. 0 (0)	–[d] < 0.001

References:

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

[b] Calculation of the IQWiG

[c] 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.

[d] Effect estimation cannot be interpreted meaningfully

[e] 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.

[f] 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.

[g] Defined as AEs that led to the withdrawal of ribociclib or placebo therapy;

the study did not allow termination of the fulvestrant treatment alone.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; 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

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

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:

approx. 7,180–34,790 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.

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:

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed:	
Ribociclib plus fulvestrant	
Ribociclib	€29,711.07
Fulvestrant	€10,442.79
Total	€40,153.85
Appropriate comparator therapy:	
Tamoxifen	€71.10
Fulvestrant	€9,696.87
Anastrozole	€258.68
Letrozole	€230.16

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

Costs for additionally required SHI services: not applicable

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:	
Ribociclib plus fulvestrant	
Ribociclib	€29,711.07
Fulvestrant	€10,442.79
Total	€40,153.85
LHRH analogues[5]	€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	

[5] leuprorelin or goserelin

Designation of the therapy	Annual treatment costs per patient
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) Post-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 plus fulvestrant	
Ribociclib	€29,711.07
Fulvestrant	€10,442.79
Total	€40,153.85
Appropriate comparator therapy:	
Tamoxifen	€71.10
Anastrozole	€258.68
Fulvestrant	€9,696.87
Letrozole	€230.16
Exemestane	€424.28
Everolimus plus exemestane	
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 plus fulvestrant	
Ribociclib	€29,711.07

Designation of the therapy	Annual treatment costs per patient
Fulvestrant	€10,442.79
Total	€40,153.85
LHRH analogues[6]	€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. 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 4 July 2019.**

2. **The period of validity of this resolution shall be limited in accordance with the following provisions:**

   The findings for patient groups

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

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

   in numbers 1, 2, 3, and 4 are limited until 1 March 2020.

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

Berlin, 4 July 2019

[6] leuprorelin or goserelin

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

Prof Hecken