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 Ribociclib (Reassessment after the Deadline (Breast Cancer, HR+, HER2-, Combination with an Aromatase Inhibitor))

of 20 August 2020

At its session on 20 August 2020, 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 will be amended as follows:

1. The information on ribociclib as amended by the resolution of 16 March 2018 (Federal Gazette, BAnz AT 12 April 2018 B1) as last amended on 21 February 2019 (Federal Gazette, BAnz AT 15 March 2019 B1) is hereby repealed.

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

Ribociclib

Resolution of: 20 August 2020
Entry into force on: 20 August 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

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 peri-menopausal women, the endocrine therapy should be combined with an LHRH agonist (LHRH = luteinising hormone-releasing hormone).

Indication:

This assessment 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. The subject of this benefit assessment procedure is the patient group "post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine 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* possibly tamoxifen if aromatase inhibitors are not suitable.

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

Hint for a minor additional benefit

Study results according to endpoints:[1]

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-2 study: Ribociclib + letrozole vs placebo + letrozole[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

Mortality

Endpoint	**Ribociclib + letrozole**		**Letrozole**		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Overall survival					
	334	n.a. [52.2; n.c.] 136 (40.7)	334	51.4 [47.2; 58.4] 167 (50.0)	0.78 [0.62; 0.98] 0.034

Morbidity

Endpoint	**Ribociclib + letrozole**		**Letrozole**		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Progression-free survival (PFS)[e]					
	334	27.6 [23.9; 33.1] 188 (56.3)	334	16.0 [13.6; 18.2] 247 (74.0)	0.57 [0.47; 0.69] < 0.001 AD: +11.6 months
Time to first subsequent chemotherapy[e]					
	334	42.5 [37.09; 50.04] 178 (53.3)	334	33.0 [28.39; 39.62] 212 (63.5)	0.73 [0.60; 0.90] 0.002 AD: +9.5 months

[1] Data from the dossier assessment of the IQWiG (A20-21) and the addendum (A20-57) unless otherwise indicated.

[2] Data cut-off of 8 May 2019

Endpoint	Ribociclib + letrozole		Letrozole		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Symptomatology – time until permanent deterioration[f,g]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	334	n.a. [48.76; n.c.] 92 (27.5)	334	55.1 [39,52; n.c.] 91 (27.2)	0.82 [0.61; 1.09] 0.171
Nausea/vomiting	334	n.a. 15 (4.5)	334	n.a. 15 (4.5)	0.84 [0.41; 1.73] 0.634
Pain	334	n.a. 57 (17.1)	334	n.a. 64 (19.2)	0.72 [0.50; 1.03] 0.068
Dyspnoea	334	n.a. 24 (7.2)	334	n.a. 12 (3.6)	1.73 [0.86; 3.48] 0.120
Insomnia	334	n.a. 28 (8.4)	334	n.a. 21 (6.3)	1.04 [0.58; 1.84] 0.902
Loss of appetite	334	n.a. 17 (5.1)	334	n.a. 22 (6.6)	0.66 [0.35; 1.26] 0.204
Constipation	334	n.a. 13 (3.9)	334	n.a. 11 (3.3)	0.98 [0.43; 2.20] 0.955
Diarrhoea	334	n.a. 5 (1.5)	334	n.a. 5 (1.5)	0.92 [0.26; 3.16] 0.889
Symptom scales EORTC QLQ-BR23					
SE of the systemic treatments	334	32.0 [19.35; 41.66] 155 (46.4)	334	31.3 [19.42; 40.21] 129 (38.6)	1.14 [0.90; 1.44] 0.292
Breast symptoms	334	n.a. 35 (10.5)	334	n.a. [55.20; n.c.] 27 (8.1)	1.07 [0.64; 1.77] 0.804
Arm symptoms	334	58.0 [n.c.] 34 (10.2)	334	n.a. [52.47; n.c.] 38 (11.4)	0.70 [0.44; 1.12] 0.139
Endpoint	**Ribociclib + letrozole**		**Letrozole**		Intervention vs control

	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Symptom scales EORTC QLQ-BR23					
Burden of hair loss	No usable data[h]				
Health status					
EQ-5D VAS (time until deterioration by ≥ 7 points)[k]					
	334	51.1 [48.23; 57.99] 96 (28.7)	334	55.2 [40.21; 55.49] 82 (24.6)	0.91 [0.67; 1.23] 0.553
EQ-5D VAS (time until deterioration by ≥ 10 points)[k]					
	334	52.5 [49.81; n.a.] 92 (27.5)	334	55.2 [40.21; 55.49] 79 (23.7)	0.91 [0.67; 1.23] 0.518
EQ-5D VAS (mean change during the course of the study)[l]					
		Values at start of study MV (SD)	**Mean change during the course of the study [95% CI]**		**Values at start of study MV (SD)**	**Mean change during the course of the study [95% CI]**	**MD [95% CI] p value**
	306	no data available	no data available	304	no data available	no data available	−1.38 [−3.43; 0.67] 0.187

Health-related quality of life

Endpoint	Ribociclib + letrozole		Letrozole		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Health-related quality of life – time until permanent deterioration[g, i]					
General health status and functional scales of the EORTC QLQ-C30					
Global health status	334	47.9 [39.33; 52.47] 112 (33.5)	334	46.9 [33.12; 55.49] 106 (31.7)	0.89 [0.68; 1.16] 0.400
Physical function	334	52.7 [44.09; n.c.]	334	55.1 [41.43; n.c.] 81 (24.3)	1.00 [0.75; 1.35] 0.986
Role function	334	52.5 [46.92; n.c.] 102 (30.5)	334	40.1 [30.46; n.c.] 98 (29.3)	0.84 [0.63; 1.11] 0.218
Emotional function	334	52.7 [49.71; n.c.] 92 (27.5)	334	48.4 [39.13; n.c.] 95 (28.4)	0.76 [0.57; 1.02] 0.069
Cognitive function	334	50.6 [38.67; 52.50] 116 (34.7)	334	41.5 [33.02; 49.71] 113 (33.8)	0.85 [0.66; 1.11] 0.227
Social function	334	n.a. [50.04; n.c.] 88 (26.3)	334	56.1 [39.56; n.c.] 78 (23.4)	0.93 [0.68; 1.26] 0.641
Functional scales of the EORTC QLQ-BR23					
Body image	334	58.2 [50.73; 58.22] 99 (29.6)	334	n.a. [49.68; n.c.] 74 (22.2)	1.23 [0.91; 1.67] 0.179
Sexual function	334	n.a. 43 (12.9)	334	n.a. [55.20; n.c.] 54 (16.2)	0.68 [0.46; 1.02] 0.059
Sexual enjoyment	No usable data[h]				
Future perspective	334	n.a. 55 (16.5)	334	n.a. [41.43; n.c.] 69 (20.7)	0.63 [0.44; 0.90] 0.011

Side effects

Endpoint	Ribociclib + letrozole		Letrozole		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Adverse events in total (presented additionally)					
	334	0.20 [0.13; 0.26] 331 (99.1)	330	0.38 [0.26; 0.46] 322 (97.6)	
Serious adverse events (SAE)					
	334	n.a. [48.69; n.c.] 100 (29.9)	330	n.a. [52.47; n.c.] 61 (18.5)	1.52 [1.11; 2.10] 0.009
Severe adverse events (CTCAE grade 3 or 4)					
	334	0.95 [n.c.] 295 (88.3)	330	27.63 [19.35; 37.55] 139 (42.1)	3.99 [3.25; 4.90] < 0.001 AD: −27.7 months
Therapy discontinuation because of adverse events[j]					
	334	n.a. 66 (19.8)	330	n.a. 15 (4.5)	4.08 [2.33; 7.16] < 0.001
Specific adverse events					
Eye disorders	334	n.a. [40.84; n.c.] 105 (31.4)	330	42.64 [17.25; n.c.] 130 (39.4)	2.15 [1.73; 2.67] < 0.001
Skin and subcutaneous tissue disorders	334	4.67 [3.71; 6.47] 217 (65.0)	330	42.64 [17.25; n.c.] 130 (39.4)	2.15 [1.73; 2.67] < 0.001 AD: −38 months
Specific AE – severe AE (CTCAE grade 3 or 4)					
Blood and lymphatic system disorders	334	3.14 [6.37; 20.73] 187 (56.0)	330	n.a. 11 (3.3)	23.58 [12.83; 43.34] < 0.001
Contained therein: Neutropoenia	334	15.67 [7.82; 26.02] 173 (51.8)	330	n.a. 3 (0.9)	77.22 [24.65; 241.83]; < 0.001
Gastrointestinal disorders	334	n.a. 49 (14.7)	330	n.a. 14 (4.2)	3.35 [1.85; 6.07] < 0.001
Endpoint	**Ribociclib + letrozole**		**Letrozole**		Intervention vs

					control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Infections and infestations	334	n.a. 29 (8.7)	330	n.a. 12 (3.6)	2.13 [1.08; 4.18] 0.024
Examinations	334	53.95 [27.53; n.c.] 136 (40.7)	330	n.a. 28 (8.5)	5.54 [3.69; 8.33] < 0.001

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Median time to event and associated 95% CI were estimated using the Kaplan-Meier method.
[c] Effect and CI: Cox proportional hazard model, stratified by the presence of liver and/or lung metastases in accordance with IRT
[d] p value: Log-rank test, stratified by the presence of liver and/or lung metastases in accordance with IRT
[e] Results from the dossier of the pharmaceutical company
[f] An increase of the respective score by at least 10 points was considered clinically relevant deterioration, even if this applied to all subsequent values or if the deterioration occurred at the last time the patient was surveyed.
[g] Deaths were not counted as deterioration.
[h] Because of the absence of hair loss or sexual activity at the start of study, an unknown proportion (but up to 80% of patients) are censored at Month 0. The procedure of the pharmaceutical company does not ensure that the exposure of patients who only develop hair loss or become sexually active in the course of treatment is recorded.
[i] A decrease of the respective score by at least 10 points was regarded as a clinically relevant deterioration if this also applied to all subsequent scores or if the deterioration occurred at the last time the patient was assessed.
[j] Discontinuation of treatment with ribociclib or placebo or the combination of ribociclib and letrozole or placebo and letrozole; a discontinuation of letrozole treatment alone was not allowed in the study
[k] A decrease of the score by 7 points or 10 points compared with baseline was considered a deterioration.
[l] A positive effect estimate indicates an advantage for ribociclib.

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; GIT = gastrointestinal tract; HR = hazard ratio; IRT = Interactive Response Technology; CI = confidence interval; MD = mean difference; MV = value; N = number of patients assessed; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; SE = side effects; PT = preferred term; RCT = randomised controlled trial; SD = standard deviation; SOC = system organ class; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↔	No differences relevant for the benefit assessment
Health-related quality of life	↔	Advantage in the functional scale future perspective
Side effects	↓↓	Detriments in the endpoints serious adverse events (SAE), severe AE (CTCAE grade 3–4), and therapy discontinuation because of AE as well as in detail for specific AE
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		

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:

- approx. 7,400–34,790 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 Kisqali® (active ingredient: ribociclib) at the following publicly accessible link (last access: 2 June 2020):

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/patient
Medicinal product to be assessed:	
Ribociclib	€ 28,917.11
plus aromatase inhibitor:	
Anastrozole	€ 183.96
Letrozole	€ 164.58
Exemestane	€ 412.78
Total:	€ 20,081.69 – 29,329.89
Appropriate comparator therapy:	
Anastrozole	€ 183.96
Letrozole	€ 164.58
Fulvestrant	€ 8,980.21
Tamoxifen	€ 69.28

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 August 2020

Costs for additionally required SHI services: not applicable

II. 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 20 August 2020.

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

Berlin, 20 August 2020

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

Prof. Hecken