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 Abemaciclib (Reassessment after the Deadline: Breast Cancer, HR+, HER2-, Combination with Fulvestrant)

of 3 September 2020

At its session on 3 September 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. With the repeal of the limitation for patient groups a1, b1 and b2, the findings set out in Annex XII for the active ingredient abemaciclib as amended by the resolution of 2 May 2019 shall remain part of the Pharmaceuticals Directive in accordance with the following amendments:

1. The information for abemaciclib on the date and entry into force of the resolutions is adopted as follows:

Resolution of: 2 May 2019
Entry into force on: 2 May 2019
Federal Gazette, BAnz AT 28 June 2019 B5

Resolution of: 5 December 2019
Entry into force on: 5 December 2019
Federal Gazette, BAnz AT 24 December 2019 B5

Resolution of: 3 September 2020
Entry into force on: 3 September 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

2. The following findings are added to the findings under "Approved therapeutic indication (according to the marketing authorisation of 27 September 2018)":

The following sentence is hereby supplemented to the information contained in the point above:

"The resolution of 3 September 2020 relates exclusively to the assessment of the additional benefit of abemaciclib in combination with fulvestrant in the following sub-populations: a1) postmenopausal women as initial endocrine-based therapy, b1) postmenopausal women who have received prior endocrine therapy and b2) pre- or perimenopausal women who have received prior endocrine therapy."

3. The findings under "1. Additional benefit of the medicinal product in relation to fulvestrant" for the patient populations "a1)", "b1)" and "b2)" are formulated as follows

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

Appropriate comparator therapy:

- anastrozole or
- letrozole or
- fulvestrant or
- tamoxifen, if aromatase inhibitors are not appropriate

Extent and probability of the additional benefit of abemaciclib in combination with fulvestrant compared with fulvestrant:

An additional benefit is not proven

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

Appropriate comparator therapy:

A further 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

Extent and probability of the additional benefit of abemaciclib in combination with fulvestrant compared with fulvestrant:

Hint for a minor additional benefit

b2) Pre- or perimenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received 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"

Extent and probability of the additional benefit of abemaciclib in combination with fulvestrant compared with the appropriate comparator therapy:

An additional benefit is not proven

Study results according to endpoints:[1]

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

MONARCH2 study: Abemaciclib + fulvestrant vs placebo + fulvestrant

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

Relevant sub-population: Postmenopausal patients as initial endocrine-based therapy (52.5 % of the study population)

Mortality

Endpoint	**Abemaciclib + fulvestrant**		**Abemaciclib**		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					
	246	43.96 [37.78; 51.65] 123 (50.0)	128	37.25 [33.04; 48.89] 68 (53.1)	0.82 [0.61; 1.10] 0.186

Morbidity

Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		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]					
	246	16.44 [14.17; 19.73] 163 (66.3)	128	11.08 [7.43; 15.91] 109 (85.2)	0.596 [0.467; 0.761] < 0.0001 AD: +5.4 months
Time to first subsequent chemotherapy[e]					
	246	25.81 [19.63; 32.19] 148 (60.2)	128	22.13 [16.60; 26.37] 92 (71.9)	0.730 [0.562; 0.947] < 0.0175 AD: +3.68 months
Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		Intervention vs control

[1] Data from the dossier assessment of the IQWiG (A20-32) unless otherwise indicated.

	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]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	245	41.33 [32.48; 52.08] 90 (36.7)	128	22.59 [11.51; 39.19] 53 (41.4)	0.73 [0.51; 1.03] 0.068
Nausea/vomiting	245	n.a. [47.67; n.c.] 50 (20.4)	128	30.71 [22.68; 46.09] 35 (27.3)	0.54 [0.35; 0.84] 0.006
Pain	245	51.85 [42.90; n.c.] 64 (26.1)	128	33.34 [17.79; n.c.] 39 (29.7)	0.69 [0.46; 1.04] 0.075
Dyspnoea	245	47.21 [42.84; 51.35] 65 (26.5)	128	n.a. [40.37; n.c.] 23 (18.0)	1.16 [0.72; 1.88] 0.540
Insomnia	245	51.85 [46,88; n.c.] 47 (19.2)	128	n.a. [30.08; n.c.] 25 (19.5)	0.71 [0.43; 1.16] 0.169
Loss of appetite	245	n.a. [47.05; n.c.] 55 (22.4)	128	48.46 [27.68; n.c.] 26 (20.3)	0.93 [0.58; 1.49] 0.768
Constipation	245	n.a. [47.67; n.c.] 33 (13.5)	128	49.74 [35.97; n.c.] 24 (18.8)	0.53 [0.31; 0.90] 0.017
Diarrhoea	245	49.91 [44.48; n.c.] 65 (26.5)	128	n.a. [48.46; n.c.] 15 (11.7)	2.13 [1.21; 3.75] 0.007
Symptom scales of the EORTC QLQ-BR23					
Side effects of systemic treatment	245	42.77 [39.42; n.c.] 76 (31.0)	128	38.96 [23.01; n.c.] 30 (23.4)	1.17 [0.76; 1.79] 0.488
Breast symptoms	245	n.a. [53.03; n.c.] 28 (11.4)	128	n.a. [32.22; n.c.] 20 (15.6)	0.50 [0.28; 0.90] 0.020
Arm symptoms	245	51.52 [41.03; n.c.] 65 (26.5)	128	25.12 [13.18; 40.37] 51 (39.8)	0.48 [0.33; 0.70] < 0.001 AD: +26.4 months
Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		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]
Burden of hair loss	No usable data[h]				
Health status[e]					
EQ-5D VAS (time until deterioration by ≥ 7 points)[k]					
	245	48.36 [45.70; n.a.] 66 (26.9)	128	24.23 [16.67; 48.89] 48 (37.5)	0.58 [0.40; 0.85] 0.004 AD = 24.1 months
EQ-5D VAS (time until deterioration by ≥ 10 points)[k]					
	245	48.36 [45.70; n.a.] 63 (25.7)	128	26.76 [19.76; n.a.] 46 (35.9)	0.58 [0.40; 0.85] 0.005 AD = 21.6 months
EQ-5D VAS (mean change over the course of the study)					
Analyses of differences in mean values are not available.					

Health-related quality of life

Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		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]					
General health status and functional scales of the EORTC QLQ-C30					
Global health status	245	45.99 [40,31; n.c.] 71 (29.0)	128	32.48 [22,68; n.c.] 36 (28.1)	0.84 [0.56; 1.26] 0.390
Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		Intervention vs control
	N	Median time to event in months [95% CI][b]	N	Median time to event in months [95% CI][b]	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]

		Patients with event n (%)		*Patients with event n (%)*	
Physical functioning	245	47.67 [39.81; n.c.] 66 (26.9)	128	44.78 [26.76; n.c.] 34 (26.6)	0.85 [0.56; 1.29] 0.452
Role functioning	245	47.67 [38.93; 55.59] 71 (29.0)	128	40.37 [22.16; 49.74] 42 (32.8)	0.72 [0.49; 1.07] 0.100
Emotional functioning	245	55.13 [51.85; 55.59] 48 (19.6)	128	51.91 [51,91; n.c.] 23 (18.0)	0.88 [0.53; 1.45] 0.605
Cognitive functioning	245	50.43 [43.30; n.c.] 65 (26.5)	128	44.78 [25.05; 54.81] 37 (28.9)	0.76 [0.50; 1.14] 0.177
Social functioning	245	51.85 [44.48; n.c.] 63 (25.7)	128	33.24 [20.32; 40.60] 42 (32.8)	0.58 [0.39; 0.87] 0.007 AD: +18.6 months
Functional scales of the EORTC QLQ-BR23					
Body image	245	n.a. [43.50; n.c.] 58 (23.7)	128	44.78 [37.58; n.c.] 28 (21.9)	0.87 [0.55; 1.37] 0.542
Sexual functioning	245	n.a. 33 (13.5)	128	n.a. 15 (11.7)	1.07 [0.58; 1.98] 0.827
Sexual enjoyment	No usable data[h]				
Future perspective	245	n.a. [51.85; n.c.] 38 (15.5)	128	54.81 [40.60; 54.81] 17 (13.3)	1.0 [0.56; 1.78] 0.987

Side effects

Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		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)					
	245	0.13 [0.10; 0.13] 242 (98.8)	128	0.58 [049; 0.95] 117 (91.4)	-

Serious adverse events (SAEs)					
	245	n.a. [36.82; n.c.] 72 (29.4)	128	51.98 [42.51; n.c.] 18 (14.1)	1.96 [1.17; 3.30] 0.009
Severe adverse events (CTCAE grade ≥ 3)					
	245	3.72 [2.73; 5.56] 166 (67.8)	128	42.51 [20.84; n.c.] 38 (29.7)	3.39 [2.37; 4.85] < 0.001 AD: - 38.8 months
Therapy discontinuation due to adverse events[i]					
	245	n.a. 52 (21.2)	128	n.a. 7 (5.5)	3.50 [1.59; 7.72] < 0.001
Specific adverse events					
Neutropoenia (PT, CTCAE grade ≥ 3)[j]	245	no data available 62 (25.3)	128	no data available 2 (1.6)	no data available
Diarrhoea (PT, CTCAE grade ≥ 3)[j]	245	no data available 35 (14.3)	128	no data available 1 (0.8)	no data available

[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, unstratified Cox proportional hazards model
[d] p value: unstratified log-rank test
[e] Information from the dossier of the pharmaceutical company
[f] A permanent deterioration was defined as an increase of at least 10 points compared to the baseline without subsequent improvement to a score below this level. Deaths were not counted as a result.
[g] A permanent deterioration was defined as a decrease of at least 10 points compared to the baseline without subsequent improvement to a score above this level. Deaths were not counted as a result.
[h] For the EORTC QLQ-BR23 scales evaluating the extent to which patients were burdened by hair loss and whether they experienced sexual pleasure during the period of treatment, the presented data is not usable as the percentage of patients included in the evaluation was very low.
[i] Discontinuation of at least one of the two medications
[j] Since the PC has not submitted any time-to-event analyses, by way of exception, the patient populations experiencing the specific listed side effects in the study groups are presented.
[k] A decrease of the score by 7 points or 10 points compared with baseline was considered a deterioration
[l] Time to deterioration defined as an increase of 2 points (on the symptom scale “strongest pain in the last 24 hours”) from baseline or increase in pain medication use by more than 1 level; death is not considered as an event and is censored.

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 Cancer-30; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer 23; EQ-5D: European Quality of Life Questionnaire-5 Dimensions; HR = hazard ratio; CI = confidence interval; mBPI_SF: modified Brief Pain Index – Short Form; 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; RCT = randomised controlled trial; 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	↔	No differences relevant for the benefit assessment
Morbidity	↑	Benefits in health status and symptomatology
Health-related quality of life	↔	No differences relevant for the benefit assessment
Side effects	↓↓	Detriments in the endpoints serious adverse events (SAEs), severe AEs (CTCAE grade ≥ 3), and therapy discontinuation due to AEs as well as in detail for specific AEs

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

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

MONARCH2 study: Abemaciclib + fulvestrant vs placebo + fulvestrant

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

Relevant sub-population: Postmenopausal patients who have received prior endocrine therapy (29.5 % of the study population)

Mortality

Endpoint	Abemaciclib + fulvestrant		Fulvestrant		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					
	144	48.82 [35.18; n.c.] 66 (45.8)	66	34.78 [28.83; 41.29] 44 (66.7)	0.67 [0.46; 0.98] 0.037 AD = 14 months

Morbidity

Endpoint	Ribociclib + fulvestrant		Fulvestrant		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]					
	144	16.14 [12.0; 19.69] 103 (71.5)	66	6.84 [4.14; 9.47] 59 (89.4)	0.476 [0.344; 0.659] < 0.0001 AD: + 9.3 months
Time to first subsequent chemotherapy[e]					
	144	21.07 [17.72; 25.71] 89 (61.8)	66	10.52 [7.63; 19.17] 58 (87.9)	0.497 [0.356; 0.694] < 0.0001 AD: + 10.6 months
Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		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	143	22.8 [14.60; 29.95] 71 (49.7)	66	7.59 [4.67; 28.47] 37 (56.1)	0.68 [0.45; 1.01] 0.054
Nausea/vomiting	143	44.94 [41.46; n.c.] 32 (22.4)	66	28.47 [9.63; n.c.] 21 (31.8)	0.49 [0.28; 0.86] 0.011 AD = 16.5 months
Pain	143	44.19 [29.95; n.c.] 41 (28.7)	66	22.95 [12.69; 37.48] 26 (39.4)	0.49 [0.29; 0.80] 0.004 AD = 21.2 months
Dyspnoea	143	44.94 [33.37; 49.02] 44 (30.8)	66	n.a. [23.97; n.c.] 16 (24.2)	0.93 [0.52; 1.67] 0.809
Insomnia	143	41.95 [34.32; n.c.] 36 (25.2)	66	34.95 [15.72; n.c.] 18 (27.3)	0.58 [0.33; 1.03] 0.062

Loss of appetite	143	39.65 [28.47; n.c.] 43 (30.1)	66	34.95 [9.27; n.c.] 22 (33.3)	0.60 [0.35; 1.01] 0.051
Constipation	143	n.a. [38.96; n.c.] 29 (20.3)	66	n.a. [15.68; n.c.] 15 (22.7)	0.54 [0.29; 1.03] 0.057
Diarrhoea	143	45.40 [38.96; 54.41] 42 (29.4)	66	n.a. [23.05; n.c.] 12 (18.2)	1.27 [0.66; 2.44] 0.479
Symptom scales of the EORTC QLQ-BR23					
Side effects of systemic treatment	143	40.70 [25.32; 49.02] 52 (36.4)	66	28.47 [13.87; n.c.] 16 (24.2)	1.07 [0.61; 1.89] 0.820
Breast symptoms	143	n.a. 13 (9.1)	66	n.a. [23.97; n.c.] 5 (7.6)	0.71 [0.25; 2.06] 0.531
Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		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]
Arm symptoms	143	36.85 [28.93; 50.63] 43 (30.1)	66	37.48 [16.57; n.c.] 16 (24.2)	0.85 [0.48; 1.53] 0.592
Suffering due to hair loss	No usable data[h]				
Health status					
EQ-5D VAS (time until deterioration by ≥ 7 points)[k]					
	143	27.65 [16.60; 38.73] 62 (43.4)	66	16.6 [12.69; 34.95] 23 (34.8)	0.89 [0.55; 1.45] 0.632
EQ-5D VAS (time until deterioration by ≥ 10 points)[k]					
	143	30.44 [16.60; 38.73] 61 (42.7)	66	19.36 [12.69; 34.95] 23 (34.8)	0.88 [0.54; 1.43] 0.596
EQ-5D VAS (mean change over the course of the study)					
Analyses of differences in mean values are not available.					

Health-related quality of life

Endpoint	Abemaciclib + fulvestrant		Fulvestrant		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]					
General health status and functional scales of the EORTC QLQ-C30					
Global health status	143	30.81 [19.27; 38.96] 57 (39.9)	66	14.56 [5.98; 28.47] 28 (42.4)	0.63 [0.40; 1.00] 0.049 AD: 16.3 months
Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		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]
Physical functioning	143	44.91 [27.68; n.c.] 37 (25.9)	66	28.47 [9.27; n.c.] 22 (33.3)	0.54 [0.31; 0.92] 0.021 AD = 16.4 months
Role functioning	143	35.97 [27.29; 44.94] 56 (39.2)	66	19.89 [7.99; 33.11] 26 (39.4)	0.72 [0.45; 1.16] 0.180
Emotional functioning	143	44.22 [29.95; n.c.] 37 (25.9)	66	23.05 [13.18; 37.48] 22 (33.3)	0.47 [0.27; 0.81] 0.005 AD = 21.2 months
Cognitive functioning	143	33.93 [19.76; 41.46] 52 (36.3)	66	16.57 [9.63; 28.47] 25 (37.9)	0.66 [0.40; 1.06] 0.085
Social functioning	143	31.23 [22.75; 46.55] 53 (37.1)	66	23.05 [12.69; n.c.] 23 (34.8)	0.79 [0.48; 1.29] 0.338
Functional scales of the EORTC QLQ-BR23					
Body image	143	n.a. [24.89; n.c.] 40 (28.0)	66	34.55 [17.06; n.c.] 13 (19.7)	1.10 [0.59; 2.07] 0.763
Sexual functioning	143	n.a. 17 (11.9)	66	42.41 [42.41; n.c.] 8 (12.1)	0.62 [0.26; 1.46] 0.270

Sexual enjoyment	No usable data[h]				
Future perspective	143	41.72 [32.38; n.a.] 37 (25.9)	66	n.a. [37.48; n.c.] 7 (10.6)	1.53 [0.67; 3.46] 0.309

Side effects

Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		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)					
	143	0.10 [0.07; 0.13] 140 (97.9)	66	0.54 [0.26; 0.95] 59 (89.4)	-
Serious adverse events (SAEs)					
	143	47.11 [34.03; n.c.] 40 (28.0)	66	29.92 [15.06; n.c.] 14 (21.2)	0.96 [0.52; 1.78] 0.896
Severe adverse events (CTCAE grade ≥ 3)					
	143	4.64 [1.91; 9.01] 99 (69.2)	66	27.98 [9.93; n.c.] 21 (31.8)	2.61 [1.63; 4.19] < 0.001 AD: - 23.3 months
Therapy discontinuation due to adverse events[i]					
	143	n.a. [38.07; n.c.] 34 (23.8)	66	n.a. 2 (3.0)	6.49 [1.55; 27.12] 0.003
Specific adverse events					
Neutropoenia (PT, CTCAE grade ≥ 3)[j]	143	no data available 42 (29.4)	66	no data available 1 (1.5)	no data available
Diarrhoea (PT, CTCAE grade ≥ 3)[j]	143	no data available 25 (17.5)	66	no data available 0 (0)	no data available

[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, unstratified Cox proportional hazard model
[d] p value: unstratified log-rank test
[e] Information from the dossier of the pharmaceutical company
[f] A permanent deterioration was defined as an increase of at least 10 points compared to the baseline without subsequent improvement to a score below this level. Deaths were not counted as a result.

[g] A permanent deterioration was defined as a decrease of at least 10 points compared to the baseline without subsequent improvement to a score above this level. Deaths were not counted as a result.
[h] For the EORTC QLQ-BR23 scales evaluating the extent to which patients experienced hair loss and whether they experienced sexual pleasure during the period of treatment, the presented data is not usable as the percentage of patients included in the evaluation was very low.
[i] Discontinuation of at least one of the two medications
[j] The results are not utilisable for the assessment of additional benefit, as the PC has not submitted time-to-event analyses. The rates are, however, presented as a supplement.
[k] A decrease of the score by 7 points or 10 points compared with baseline was considered a deterioration

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 Cancer-30; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer 23; EQ-5D: European Quality of Life Questionnaire-5 Dimensions; HR = hazard ratio; CI = confidence interval; mBPI_SF: modified Brief Pain Index – Short Form; 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; RCT = randomised controlled trial; 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	↑	Benefits in symptomatology (nausea/vomiting and pain)
Health-related quality of life	↑	Benefits as measured by global health, physical and emotional functioning scales
Side effects	↓↓	Detriments in the endpoints, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs as well as in detail for specific AEs

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

b2) Pre- or perimenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy

MONARCH2 study: Abemaciclib + fulvestrant vs placebo + fulvestrant

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

Relevant sub-population: Pre- or perimenopausal patients who have received prior endocrine-based therapy (6.5 % of the study population)

Mortality

Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		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					
	26	n.a. [38.96; n.c.] 8 (30.8)	20	45.83 [27,16; n.c.] 9 (45.0)	0.55 [0.21; 1.45] 0.217

Morbidity

Endpoint	**Ribociclib + fulvestrant**		**Fulvestrant**		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]					
	26	28.21 [14.83; 50.60] 17 (65.4)	20	9.67 [4.31; 15.62] 16 (80)	0.372 [0.181; 0.766] 0.0055 AD: + 18.5 months
Time to first subsequent chemotherapy[e]					
	26	50.24 [18.28; n.a.] 11 (42.3)	20	17.46 [9.93; 31.13] 17 (85.0)	0.271 [0.122; 0.601] 0.0006 AD: + 32.8 months
Symptomatology – time until permanent deterioration[f,g]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	26	n.a. [18.94; n.c.]	20	17.16 [7.43; n.c.]	0.45 [0.17; 1.24]

		9 (34.6)		8 (40.0)	0.115
Nausea/vomiting	26	53.23 [19.92; 53.23] 8 (30.8)	20	n.a. [10.59; n.c.] 2 (10.0)	1.63 [0.33; 8.19] 0.546
Endpoint	**Ribociclib + fulvestrant**		**Fulvestrant**		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]
Pain	26	47.70 [38.96; n.c.] 9 (34.6)	20	35.93 [10.59; n.c.] 5 (25.0)	0.71 [0.22; 2.32] 0.565
Dyspnoea	26	n.a. [19.92; n.c.] 8 (30.8)	20	n.a. [9.27; n.c.] 4 (20.0)	0.93 [0.27; 3.19] 0.899
Insomnia	26	51.35 [47.70; n.c.] 7 (26.9)	20	19.69 [3.75; n.c.] 8 (40.0)	0.34 [0.11; 1.05] 0.050
Loss of appetite	26	51.75 [38.96; 53.23] 8 (30.8)	20	32.12 [11.51; n.c.] 5 (25.0)	0.46 [0.14; 1.58] 0.210
Constipation	26	n.a. 3 (11.5)	20	39.85 [9.21; 39.85] 5 (25.0)	0.21 [0.05; 0.93] 0.026
Diarrhoea	26	39.12 [5.56; 47.70] 14 (53.8)	20	n.a. [11.51; n.c.] 2 (10.0)	3.36 [0.73; 15.49] 0.100
Symptom scales of the EORTC QLQ-BR23					
Side effects of systemic treatment	26	n.a. [42.21; n.c.] 6 (23.1)	20	30.51 [9.34; n.c.] 7 (35.0)	0.31 [0.09; 1.03] 0.045
Breast symptoms	26	n.a. [47.24; n.c.] 4 (15.1)	20	n.a. [10.59; n.c.] 2 (10.0)	0.77 [0.12; 4.86] 0.779
Arm symptoms	26	52.08 [31.04; 52.08] 7 (26.9)	20	n.a. [9.53; n.c.] 5 (25.0)	0.42 [0.11; 1.56] 0.185
Suffering due to hair loss	No usable data[h]				
Health status					
EQ-5D VAS (time until deterioration by ≥ 7 points)[k]					
	26	44.25	20	n.a.	0.94

		[30.51; n.a.] 9 (34.6)		[10.59; n.a.] 4 (20.0)	[0.28; 3.23] 0.923
Endpoint	**Ribociclib + fulvestrant**		**Fulvestrant**		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]
EQ-5D VAS (time until deterioration by ≥ 10 points)[k]					
	26	44.25 [30.51; n.a.] 9 (34.6)	20	n.a. [10.59; n.a.] 4 (20.0)	0.94 [0.28; 3.23] 0.923
EQ-5D VAS (mean change over the course of the study)					
Analyses of differences in mean values are not available.					

Health-related quality of life

Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		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]					
General health status and functional scales of the EORTC QLQ-C30					
Global health status	26	n.a. [35.54; n.c.] 5 (19.2)	20	22.65 [9.21; n.c.] 6 (30.0)	0.33 [0.09; 1.22] 0.083
Physical functioning	26	n.a. 4 (15.4)	20	33.17 [10.59; n.c.] 5 (25.0)	0.37 [0.10; 1.45] 0.140
Role functioning	26	47.70 [37.58; n.c.] 9 (34.6)	20	38.70 [10.59; 42.87] 8 (40.0)	0.37 [0.12; 1.12] 0.067
Emotional functioning	26	n.a. [44.25; n.c.] 3 (11.5)	20	n.a. [10.59; n.c.] 3 (15.0)	0.29 [0.05; 1.63] 0.142
Cognitive functioning	26	47.70 [18.94; n.c.] 9 (34.6)	20	19.36 [5.82; n.c.] 8 (40.0)	0.43 [0.16; 1.21] 0.101

Endpoint	Ribociclib + fulvestrant		Fulvestrant		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]
Social functioning	26	n.a. [51.42; n.c.] 5 (19.2)	20	24.89 [9.34; n.c.] 5 (25.0)	0.34 [0.09; 1.29] 0.098
Functional scales of the EORTC QLQ-BR23					
Body image	26	n.a. [23.54; n.c.] 6 (23.1)	20	n.a. 3 (15.0)	0.98 [0.24; 4.04] 0.979
Sexual functioning	26	n.a. [11.93; n.c.] 7 (26.9)	20	45.63 [12.89; 45.63] 4 (20.0)	0.93 [0.27; 3.23] 0.907
Sexual enjoyment	No usable data[h]				
Future perspective	26	n.a. 3 (11.5)	20	36.89 [13.15; n.c.] 3 (6.7)	0.32 [0.05; 2.06] 0.208

Side effects

Endpoint	Abemaciclib + fulvestrant		Fulvestrant		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)					
	26	0.13 [0.07; 0.23] 25 (96.2)	20	0.44 [0.16; 1.58] 19 (95.0)	-
Serious adverse events (SAEs)					
	26	n.a. [37.45; n.c.] 7 (26.9)	20	n.a. 1 (5.0)	4.33 [0.52; 36.10] 0.140
Endpoint	**Ribociclib + fulvestrant**		**Fulvestrant**		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]
Severe adverse events (CTCAE grade ≥ 3)					
	26	3.02 [0.95; 6.77] 19 (73.1)	20	27.35 [9.24; n.c.] 4 (20.0)	5.75 [1.94; 17.06] < 0.001 AD: ~ 24.3 months
Therapy discontinuation due to adverse events[i]					
	26	n.a. [48.72; n.c.] 3 (11.5)	20	n.a. 0 (0)	-[l] 0.213
Specific adverse events					
Neutropoenia (PT, CTCAE grade ≥ 3)[j]	26	no data available 14 (53.8)	20	no data available 0 (0)	no data available
Diarrhoea (PT, CTCAE grade ≥ 3)[j]	26	no data available 2 (7.7)	20	no data available 0 (0)	no data available

[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, unstratified Cox proportional hazard model
[d] p value: unstratified log-rank test
[e] Information from the dossier of the pharmaceutical company
[f] A permanent deterioration was defined as an increase of at least 10 points compared to the baseline without subsequent improvement to a score below this level. Deaths were not counted as a result.
[g] A permanent deterioration was defined as a decrease of at least 10 points compared to the baseline without subsequent improvement to a score above this level. Deaths were not counted as a result.
[h] For the EORTC QLQ-BR23 scales evaluating the extent to which patients experienced hair loss and whether they experienced sexual pleasure during the period of treatment, the presented data is not usable as the percentage of patients included in the evaluation was very low.
[i] Discontinuation of at least one of the two medications
[j] The results cannot be used in the assessment of additional benefit, as the PC has not submitted time-to-event analyses. The rates are, however, presented as a supplement.
[k] A decrease of the score by 7 points or 10 points compared with baseline was considered a deterioration
[l] HR cannot be reasonably estimated (no event in control arm)

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 Cancer-30; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer 23; EQ-5D: European Quality of Life Questionnaire-5 Dimensions; HR = hazard ratio; CI = confidence interval; mBPI_SF: modified Brief Pain Index – Short Form; 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; RCT = randomised controlled trial; 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	↔	No differences relevant for the benefit assessment
Morbidity	↔	No differences relevant for the benefit assessment
Health-related quality of life	↔	No differences relevant for the benefit assessment
Side effects	↓↓	Detriments in the endpoint severe AEs (CTCAE grade ≥ 3) as well as in detail for specific AEs

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

4. The findings under "2. Number of patients or demarcation of patient groups eligible for treatment" for patient population "a1)", "b1)" and "b2)" are formulated as follows:

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

- approx. 7,400–34,790 patients

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

- approx. 5,470–24,900 patients

b2) Pre- or perimenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy:

- approx. 906–4,118 patients"

5. The findings under "3. Requirements for a quality-assured application" are formulated as follows:

"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 Verzenios® (active ingredient: abemaciclib) at the following publicly accessible link (last access: 2 June 2020):

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

Treatment with abemaciclib 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.

6. Under "4. Treatment costs", the findings on the annual treatment costs for patient populations "a1)", "b1)" and "b2)" are formulated as follows:

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

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Abemaciclib	€ 28,996.56
plus fulvestrant	
Fulvestrant	€ 8,338.76
Total:	€ 37,335.32
Appropriate comparator therapy:	
Anastrozole	€ 183.96
Letrozole	€ 164.58
Fulvestrant	€ 8,338.76
Tamoxifen	€ 69.28

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2020

Costs for additionally required SHI services: not applicable

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Abemaciclib	€ 28,996.56
plus fulvestrant	
Fulvestrant	€ 8,338.76
Total:	€ 37,335.32
Appropriate comparator therapy:	
Tamoxifen	€ 69.28
Anastrozole	€ 183.96
Fulvestrant	€ 8,338.76
Letrozole	€ 164.58
Exemestane	€ 412.78
Everolimus + exemestane	
Everolimus	€ 17,144.37
Exemestane	€ 412.78
Total:	€ 17,557.15

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2020

Costs for additionally required SHI services: not applicable

b2) Pre- or perimenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer previously treated with endocrine therapy

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Abemaciclib	€ 28,996.56
plus fulvestrant	
Fulvestrant	€ 8,338.76
Total:	€ 37,335.32
LHRH analogue	€ 1,793.02–2,176.42
Appropriate comparator therapy:	
Tamoxifen	€ 69.28
Letrozole	€ 164.58
Exemestane	€ 412.78
Megestrol	€ 5,511.38
Medroxyprogesterone	€ 1,188.77–2,377.54
LHRH analogue	€ 1,793.02–2,176.42

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2020

Costs for additionally required SHI services: not applicable“

II. Entry into force

1. 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 3 September 2020.

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

The findings for patient groups

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

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

in numbers 1, 2, 3, and 4 are valid until 1 June 2021.

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

Berlin, 3 September 2020

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

Prof. Hecken