Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Abemaciclib(reassessment after the deadline: breast carcinoma, HR+, HER2-, combination with fulvestrant)

of 19 May 2022

At its session on 19 May 2022, the Federal Joint Committee (G-BA) resolved to amend the 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 by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. The information on Abemaciclib in the version of the resolution of 3 September 2020 (BAnz AT 03.11.2020 B2) remains part of the Pharmaceuticals Directive with the lifting of the limitation for patient groups a1 and b1 in accordance with the following changes:

1. The information for Abemaciclib regarding the date and entry into force of the resolutions shall is adopted as follows:

"Resolution of: 2 May 2019
Entry into force on: 2 May 2019
BAnz AT 28.06.2019 B5

Resolution of: 5 December 2019
Entry into force on: 5 December 2019
BAnz AT 24.12.2021 B5

Resolution of: 3 September 2020
Entry into force on: 3 September 2020
BAnz AT 03.01.2020 B2

Resolution of: 1 April 2021
Entry into force on: 1 April 2021
BAnz AT 06.05.2021 B5

Resolution of 19 May 2022
Entry into force on: 19 May 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx“

Therapeutic indication (according to the marketing authorisation of 27 September 2018):

Verzenios 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 LHRH agonist.

Therapeutic indication of the resolution (resolution of 19 May 2022):

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

2. The findings under "1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy" for the patient populations "a1)" and "b1)" is adopted 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 therapy

Appropriate comparator therapy:

- anastrozole

  or

- letrozole

  or

- fulvestrant

  or

- tamoxifen, if necessary, if aromatase inhibitors are not suitable

  or

- ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

  or

- abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

  or

- palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

or

- ribociclib in combination with fulvestrant

  or

- palbociclib in combination with fulvestrant

Extent and probability of the additional benefit of Abemaciclib compared to fulvestrant:

An additional benefit is not proven.

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

Appropriate comparator therapy:

Another endocrine therapy with:

- tamoxifen

  or

- anastrozole

  or

- fulvestrant as monotherapy; only for patients with relapse or progression after antiestrogen treatment

  or

- letrozole; only for patients with relapse or progression after antiestrogen treatment

  or

- exemestane; only for patients with progression after anti-oestrogen treatment

  or

- everolimus in combination with exemestane; only for patients without symptomatic visceral metastasis following progression after a non-steroidal aromatase inhibitor.

  or

- ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

  or

- abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

  or

- palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

  or

- ribociclib in combination with fulvestrant

  or

- palbociclib in combination with fulvestrant

Extent and probability of the additional benefit of Abemaciclib compared to fulvestrant:

Indication of a minor additional benefit

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 therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment
Morbidity	n. a.	There are no assessable data in morbidity (except for pain).
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↓↓	Disadvantages in the case of serious AEs, in the case of severe AEs, in the case of therapy discontinuations due to AEs and in detail disadvantages in the case of 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		

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-153) unless otherwise indicated.

MONARCH 2 study: Abemaciclib + fulvestrant **vs** placebo + fulvestrant

MONARCH plus study: Abemaciclib + fulvestrant **vs** placebo + fulvestrant

Total: pooled data of patients from MONARCH 2 and MONARCH plus study

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

Relevant sub-population: postmenopausal patients with initial endocrine therapy

Mortality

Endpoint	**Abemaciclib + fulvestrant**		**Placebo + fulvestrant**		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Overall survival					
MONARCH 2[c] (sub-population a1)	246	44.0 [37.8; 51.7] 123 (50.0)	128	37.3 [33.0; 48.9] 68 (53.1)	0.82 [0.61; 1.10] 0.186
MONARCH plus[c] (sub-population a1)	81	n.a. 20 (24.7)	40	n.a. [19.9; n.c.] 14 (35.0)	0.56 [0.28; 1.11] 0.091
Total[d] (sub-population a1)					0.77 [0.59; 1.01] 0.061

Morbidity

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Progression-free survival (PFS)[k]					
MONARCH 2[c]	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
MONARCH plus[c]	81	11.4 [9.53; 16.96] 57 (70.4)	40	5.7 [3.65; 11.21] 31 (77.5)	0.63 [0.41; 0.98] 0.0382
Total[d]					0.604 [0.488; 0.748] < 0.0001
Time until the first subsequent chemotherapy treatment[k]					
MONARCH 2[c]	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
MONARCH plus[c]	Endpoint not assessed				
Pain (composite endpoint), time to 1st deterioration (BPI-SF)[e]					
MONARCH 2[c]	245	11.1 [6.0; 14.8] 124 (50.6)	128	9.3 [5.8; 18.4] 64 (50.0)	0.95 [0.70; 1.28] 0.722
MONARCH plus[c]	Endpoint not assessed				
Strongest pain in the last 24 hours (deterioration by ≥ 2 points on the symptom scale of the mBPI-SF)					
MONARCH 2[c]	245	16.6 [8.1; 34.9] 104 (42.4)	128	16.7 [8.7; 24.7] 54 (42.2)	0.94 [0.67; 1.31] 0.695
MONARCH plus[c]	81	n.a. [13.6; n.c.] 26 (32.1)	40	n.a. [10.3; n.c.] 10 (25.0)	1.22 [0.59; 2.53] 0.600

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Total[d]					0.98 [0.73; 1.33] 0.899
Increase in use of analgesics by ≥ 1 level (BPI-SF)					
MONARCH 2[c]	245	n.a. 46 (18.8)	128	n.a. 22 (17.2)	0.94 [0.56; 1.56] 0.804
MONARCH plus[c]	Endpoint not assessed				
Symptomatology (EORTC QLQ-C30 and EORTC QLQ-BR23)					
No usable data available					
Health status (EQ 5D-VAS)					
No usable data available					

Health-related quality of life

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
No usable data available					

Side effects

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Total adverse events (presented additionally)					
MONARCH 2[c]	245	0.1 [0.1; 0.1] 242 (98.8)	128	0.6 [0.5; 1.0] 117 (91.4)	-
MONARCH plus[c]	81	0.1 [0.1; 0.2] 81 (100)	40	1.0 [0.4; 2.1] 34 (85.0)	-
Serious adverse events (SAE)					
MONARCH 2[c]	245	n.a. [36.8; n.c.] 72 (29.4)	128	52.0 [42.5; n.c.] 18 (14.1)	1.96 [1.17; 3.30] 0.009
MONARCH plus[c]	81	n.a. [26.7; n.c.] 18 (22.2)	40	n.a. 3 (7.5)	2.60 [0.76; 8.84] 0.113
Total[d]					2.05 [1.27; 3.30] 0.003
Severe adverse events (CTCAE grade ≥ 3)					
MONARCH 2[c]	245	3.7 [2.7; 5.6] 166 (67.8)	128	42.5 [20.8; n.c.] 38 (29.7)	3.39 [2.37; 4.85] < 0.001
MONARCH plus[c]	81	8.4 [3.7; 13.1] 52 (64.2)	40	n.a. [10.7; n.c.] 8 (20.0)	3.99 [1.90; 8.41] < 0.001
Total[d]					3.50 [2.53; 4.83] < 0.001
Therapy discontinuation due to adverse events[f]					
MONARCH 2[c]	245	n.a. 52 (21.2)	128	n.a. 7 (5.5)	3.50 [1.59; 7.72] < 0.001

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
MONARCH plus[c]	81	n.a. [26.8; n.c.] 10 (12.3)	40	n.a. 1 (2.5)	3.60 [0.46; 28.20] 0.192
Total[d]					3.51 [1.68; 7.35] < 0.001
Specific adverse events					
Neutropenia[g] (severe AEs)					
MONARCH 2[c]	245	n.a. 63 (25.7)	128	n.a. 2 (1.6)	18.27 [4.47; 74.70] < 0.001
MONARCH plus[c]	81	n.a. [14.7; n.c.] 28 (34.6)	40	n.a. 2 (5.0)	7.14 [1.70; 29.99] 0.002
Total[d]					11.52 [4.22; 31.49] < 0.001
Diarrhoea (PT, severe AEs)					
MONARCH 2[c]	245	n.a. 35 (14.3)	128	n.a. 1 (0.8)	18.30 [2.51; 133.70] < 0.001
MONARCH plus[c]	81	n.a. 1 (1.2[h])	40	n.a. 0 (0)	n. c.[i] 0.482
Total[d]					n.a.
Anaemia (PT, severe AEs)					
MONARCH 2[c]	245	n.a. 19 (7.8)	128	n.a. 2 (1.6)	4.15 [0.96; 17.89] 0.038
MONARCH plus[c]	81	n.a. [26.7; n.c.] 14 (17.3)	40	n.a. 1 (2.5)	5.73 [0.75; 43.71] 0.057
Total[d]					4.63 [1.41; 15.17] 0.011

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Eye disorders (SOC, AEs)					
MONARCH 2[c]	245	n.a. 48 (19.6)	128	n.a. 9 (7.0)	2.65 [1.30; 5.40] 0.005
MONARCH plus[c]	81	n.d. 7 (8.6[h])	40	n.d. 1 (2.5[h])	2.97 [0.37; 24.17] 0.309[j]
Total[d]					2.68 [1.36; 5.26] 0.004
Gastrointestinal disorders (SOC, AEs)					
MONARCH 2[c]	245	0.2 [0.1; 0.2] 232 (94.7)	128	3.7 [2.3; 8.0] 81 (63.3)	3.87 [2.97; 5.04] < 0.001
MONARCH plus[c]	81	0.2 [0.1; 0.3] 70 (86.4)	40	n.a. [4.8; n.c.] 14 (35.0)	5.29 [2.95; 9.50] < 0.001
Total[d]					4.08 [3.21; 5.19] < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)					
MONARCH 2[c]	245	8.5 [6.3; 19.0] 117 (47.8)	128	n.a. [33.3; n.c.] 29 (22.7)	2.38 [1.58; 3.57] < 0.001
MONARCH plus[c]	81	n.a. 18 (22.2)	40	n.a. 3 (7.5)	2.59 [0.76; 8.82] 0.114
Total[d]					2.40 [1.63; 3.53] < 0.001
Renal and urinary disorders (SOC, SAEs)					
MONARCH 2[c]	245	n.a. 36 (14.7)	128	n.a. 5 (3.9)	3.35 [1.31; 8.58] 0.007

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
MONARCH plus[c]	81	n.d. 7 (8.6)	40	n.d. 1 (2.5)	2.61 [0.32; 21.24] 0.371[j]
Total[d]					3.22 [1.37; 7.58] 0.008

a. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b. HR [95% CI]: Cox proportional hazards model with treatment group as factor; p-value: unstratified log-rank test
c. Data cut-off: MONARCH 2 study: 20.06.2019; MONARCH plus study: 18 May 2020
d. calculated from meta-analysis
e. Time until the 1st deterioration defined as an increase of 2 points on the symptom scale of the mBPI-SF "Strongest pain in the last 24 hours" (scale range: 0 to 11) from start of the study or increase in use of analgesics by ≥ 1 step (according to the WHO 3-step cancer pain management system) first occurrence in each case. In the analysis, death is not evaluated and censored as an event.
f. Discontinuation of at least one of the two medicinal products
g. PT collection of the pharmaceutical company: operationalised via the PTs neutropenia, febrile neutropenia and decreased neutrophil count
h. own calculation
i. As no events occurred in one study arm, the HR cannot be estimated.
j. p-value presumably Wald test
k. from the dossier of the pharmaceutical company

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; HR = Hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; RCT = randomised controlled trial; SOC = system organ class; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; WHO = World Health Organization; vs = versus

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	n.a.	There are no assessable data in morbidity (except for pain).
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↓↓	Disadvantages in the case of severe AE, in the case of therapy discontinuations due to AE and in detail disadvantages in the case of 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		

MONARCH 2 study: Abemaciclib + fulvestrant **vs** placebo + fulvestrant

MONARCH plus study: Abemaciclib + fulvestrant **vs** placebo + fulvestrant

Total: pooled data of patients from MONARCH 2 and MONARCH plus study

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

Relevant sub-population: postmenopausal patients with previous endocrine therapy

Mortality

Endpoint	**Abemaciclib + fulvestrant**		**Placebo + fulvestrant**		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Overall survival					
MONARCH 2[c]	144	48.8 [35.2; n.c.] 66 (45.8)	66	34.8 [28.8; 41.3] 44 (66.7)	0.67 [0.46; 0.98] 0.037
MONARCH plus[c]	23	n.a. [21.5; n.c.] 6 (26.1)	13	n.a. [5.7; n.c.] 5 (38.5)	0.45 [0.14; 1.49] 0.179
Total[d]					0.64 [0.45; 0.93] 0.017
Subgroups according to type of disease					
MONARCH 2[c]					
non-visceral metastases	66	n.d. 33 (50.0[h])	27	n.d. 15 (55.6[h])	1.09 [0.59; 2.01] 0.777
visceral metastases	78	n.d. 33 (42.3[h])	39	n.d. 29 (74.4[h])	0.46 [0.28; 0.76] 0.003
MONARCH plus[c]					
non-visceral metastases	6	n.d. 1 (16.7[h])	3	n.d. 0 (0)	n. c.[i] 0.999
visceral metastases	17	n.d. 5 (29.4[h])	10	n.d. 5 (50.0[h])	0.34 [0.10; 1.21] 0.097

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Total[d]					Interaction: 0.022[j]
non-visceral metastases					n.a.
visceral metastases					0.44 [0.28; 0.71] 0.001

Morbidity

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Progression-free survival (PFS)[k]					
MONARCH 2[c]	144	16.14 [12.00; 19.69] 103 (71.5)	66	6.84 [4.14; 9.47] 59 (89.4)	0.476 [0.344; 0.659] < 0.0001
MONARCH plus[c]	23	15.8 [7.43; n.a.] 40 (60.9)	13	5.6 [1.68; 7.69] 10 (76.9)	0.34 [0.14; 0.79] 0.0087
Total[d]					0.455 [0.336; 0.617] < 0.0001

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Time until the first subsequent chemotherapy treatment[k]					
MONARCH 2[c]	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
MONARCH plus[c]	Endpoint not assessed				
Pain (composite endpoint), time to 1st deterioration (BPI-SF)[e]					
MONARCH 2[c]	143	13.9 [9.3; 22.2] 70 (49.0)	66	6.0 [2.6; 20.3] 32 (48.5)	0.74 [0.49; 1.14] 0.171
MONARCH plus[c]	Endpoint not assessed				
Strongest pain in the last 24 hours (deterioration by ≥ 2 points on the symptom scale of the mBPI-SF)					
MONARCH 2[c]	143	18.5 [11.1; 38.7] 61 (42.7)	66	16.8 [3.8; 35.0] 29 (43.9)	0.70 [0.45; 1.10] 0.121
MONARCH plus[c]	23	n.a. [3.2; n.c.] 8 (34.8)	13	n.a. [1.0; n.c.] 3 (23.1)	1.45 [0.38; 5.50] 0.573
Total[d]					0.76 [0.49; 1.16] 0.196
Increase in use of analgesics by ≥ 1 level (BPI-SF)					
MONARCH 2[c]	143	n.a. 23 (16.1)	66	n.a. 7 (10.6)	1.10 [0.47; 2.60] 0.827
MONARCH plus[c]	Endpoint not assessed				
Symptomatology (EORTC QLQ-C30 and EORTC QLQ-BR23)					
No usable data available					

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Health status (EQ 5D-VAS)					
No usable data available					

Health-related quality of life

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
No usable data available					

Side effects

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Total adverse events (presented additionally)					
MONARCH 2[c]	143	0.1 [<0.1; 0.1] 140 (97.9)	66	0.5 [0.3; 1.0] 59 (89.4)	-
MONARCH plus[c]	23	0.2 [0.1; 0.4] 23 (100)	13	0.9 [0.5; n.c.] 9 (69.2)	-
Serious adverse events (SAE)					
MONARCH 2[c]	143	47.1 [34.0; n.c.] 40 (28.0)	66	29.9 [15.1; n.c.] 14 (21.1)	0.96 [0.52; 1.78] 0.896
MONARCH plus[c]	23	n.a. [22.9; n.c.] 6 (26.1)	13	n.a. 1 (7.7)	2.21 [0.26; 18.84] 0.459
Total[d]					1.02 [0.56; 1.86] 0.941
Severe adverse events (CTCAE grade ≥ 3)					
MONARCH 2[c]	143	4.6 [1.9; 9.0] 99 (69.2)	66	28.0 [9.9; n.c.] 21 (31.8)	2.61 [1.63; 4.19] < 0.001
MONARCH plus[c]	23	5.6 [1.8; 13.3] 16 (69.6)	13	n.a. [2.7; n.c.] 1 (7.7)	9.57 [1.27; 72.27] < 0.007
Total[d]					2.79 [1.76; 4.43] < 0.001
Therapy discontinuation due to adverse events[f]					
MONARCH 2[c]	143	n.a. [38.1; n.c.] 34 (23.8)	66	n.a. 2 (3.0)	6.49 [1.55; 27.12] 0.003

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
MONARCH plus[c]	23	n.a. [18.5; n.c.] 2 (8.7)	13	n.a. 1 (7.7)	0.56 [0.05; 6.73] 0.643
Total[d]					3.53 [1.02; 12.19] 0.046
Specific adverse events					
Neutropenia[g] (severe AEs)					
MONARCH 2[c]	143	n.a. [26.6; n.c.] 43 (30.1)	66	n.a. 1 (1.5)	20.30 [2.79; 147.50] < 0.001
MONARCH plus[c]	23	n.a. [3.6; n.c.] 7 (30.4)	13	n.a. 0 (0)	n.a. 0.055
Total[d]					n.a.
Diarrhoea (PT, severe AEs)					
MONARCH 2[c]	143	n.a. 25 (17.5)	66	n.a. 0 (0)	n. c.[i] < 0.001
MONARCH plus[c]	23	n.a. 1 (4.3)	13	n.a. 0 (0)	n. c.[i] 0.452
Total[d]					n.a.
Gastrointestinal disorders (SOC, AEs)					
MONARCH 2[c]	143	0.1 [0.1; 0.2] 134 (93.7)	66	3.6 [1.6; 5.6] 43 (65.2)	4.00 [2.78; 5.76] < 0.001
MONARCH plus[c]	23	0.3 [0.1; 0.7] 18 (78.3)	13	12.7 [1.9; n.c.] 4 (30.8)	4.68 [1.57; 13.99] 0.003
Total[d]					4.07 [2.88; 5.74] < 0.001

Endpoint	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs Placebo + fulvestrant
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Skin and subcutaneous tissue disorders (SOC, AEs)					
MONARCH 2[c]	143	9.7 [6.1; 18.3] 72 (50.3)	66	n.a. [11.7; n.c.] 15 (22.7)	2.38 [1.36; 4.17] 0.002
MONARCH plus[c]	23	n.a. [10.8; n.c.] 5 (21.7)	13	n.a. 1 (7.7)	2.49 [0.29; 21.65] 0.394
Total[d]					2.39 [1.39; 4.11] 0.002

a. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b. HR [95% CI]: Cox proportional hazards model with treatment group as factor; p-value: unstratified log-rank test
c. Data cut-off: MONARCH 2 study: 20.06.2019; MONARCH plus study: 18 May 2020
d. calculated from meta-analysis
e. Time until the 1st deterioration defined as an increase of 2 points on the symptom scale of the mBPI-SF "Strongest pain in the last 24 hours" (scale range: 0 to 11) from start of the study or increase in use of analgesics by ≥ 1 step (according to the WHO 3-step cancer pain management system) first occurrence in each case. In the analysis, death is not evaluated and censored as an event.
f. Discontinuation of at least one of the two medicinal products
g. PT collection of the pharmaceutical company: operationalised via the PTs neutropenia, febrile neutropenia and decreased neutrophil count
h. own calculation
i. As no events occurred in one study arm, the HR cannot be estimated.
k. from the dossier of the pharmaceutical company

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; HR = hazard ratio; n.d. = no data available; CI = confidence interval; mBPI-SF = modified Brief Pain Inventory-Short Form; N = number of patients evaluated; n = number of patients with event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; RCT = randomised controlled trial; SOC = system organ class; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; WHO = World Health Organization; vs = versus

„

3. The findings under "2. Number of patients or demarcation of patient groups eligible for treatment" regarding the patient populations "a1)" and "b1)" are adopted 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 therapy

approx. 7,400 to 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 to 24,900 patients

4. The findings under "3. Requirements for quality-assured application" are adopted 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: 18 February 2022):

https://www.ema.europa.eu/en/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, obstetrics and gynaecology, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with locally advanced or metastatic breast cancer.

5. Under "4. Treatment costs ", the findings on the annual treatment costs under "a1)" and "b1)" are adopted 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 therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Abemaciclib in combination with fulvestrant	
Abemaciclib	€ 23,637.40
+ fulvestrant	€ 3,708.90
Total	€ 27,346.30
Appropriate comparator therapy:	
Non-steroidal aromatase inhibitors	
Anastrozole	€ 190.09
letrozole	€ 176.44
Antiestrogens	
Fulvestrant	€ 3,708.90
Tamoxifen	€ 72.20
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)	
Ribociclib	€ 29,658.81
Anastrozole	€ 190.09
Letrozole	€ 176.44
Ribociclib + anastrozole	€ 29,848.90
Ribociclib + letrozole	€ 29,835.25
Abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)	
Abemaciclib	€ 23,637.40
Anastrozole	€ 190.09
Letrozole	€ 176.44
Abemaciclib + anastrozole	€ 23,827.49
Abemaciclib + letrozole	€ 23,813.84
Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)	
Palbociclib	€ 30,196.27
Anastrozole	€ 190.09
Letrozole	€ 176.44

Designation of the therapy	Annual treatment costs/ patient
Palbociclib + anastrozole	€ 30,386.36
Palbociclib + letrozole	€ 30,372.71
Ribociclib in combination with fulvestrant	
Ribociclib	€ 29,658.81
+ fulvestrant	€ 3,994.20
Total	€ 33,653.01
Palbociclib in combination with fulvestrant	
Palbociclib	€ 4,113.06
+ fulvestrant	€ 3,994.20
Total	€ 34,190.47

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 May 2022)

Costs for additionally required SHI services: not applicable

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Abemaciclib in combination with fulvestrant	
Abemaciclib	€ 23,637.40
+ fulvestrant	€ 3,708.90
Total	€ 27,346.30
Appropriate comparator therapy:	
Antiestrogens	
Fulvestrant	€ 3,708.90
Tamoxifen	€ 72.20
Non-steroidal aromatase inhibitors	
Anastrozole	€ 190.09
Letrozole	€ 176.44
Steroidal aromatase inhibitors	
Exemestane	€ 425.37
Everolimus in combination with exemestane **Fehler! Textmarke nicht definiert.**	
Everolimus	€ 8,907.10
+ exemestane	€ 425.37

Designation of the therapy	Annual treatment costs/ patient
Total	€ 9,332.47
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)	
Ribociclib	€ 29,658.81
Anastrozole	€ 190.09
Letrozole	€ 176.44
Ribociclib + anastrozole	€ 29,848.90
Ribociclib + letrozole	€ 29,835.25
Abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)	
Abemaciclib	€ 23,637.40
Anastrozole	€ 190.09
Letrozole	€ 176.44
Abemaciclib + anastrozole	€ 23,827.49
Abemaciclib + letrozole	€ 23,813.84
palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)	
Palbociclib	€ 30,196.27
Anastrozole	€ 190.09
Letrozole	€ 176.44
Palbociclib + anastrozole	€ 30,386.36
Palbociclib + letrozole	€ 30,372.71
Ribociclib in combination with fulvestrant	
Ribociclib	€ 29,658.81
+ fulvestrant	€ 3,994.20
Total	€ 33,653.01
Palbociclib in combination with fulvestrant	
Palbociclib	€ 4,113.06
+ fulvestrant	€ 3,994.20
Total	€ 34,190.47

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 May 2022)

Costs for additionally required SHI services: not applicable".

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 19 May 2022.

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

Berlin, 19 May 2022

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

Prof. Hecken