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 cancer, HR+, HER2-, combination with aromatase inhibitor))

of 15 June 2023

At its session on 15 June 2023, 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:

The information on Abemaciclib in the version of the resolution of 2 May 2019 (BAnz AT 29.07.2019 B2) remains part of the Pharmaceuticals Directive with the repeal of the limitation for patient group a1 in accordance with the following changes:

1. **The information on Abemaciclib regarding 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
   BAnzAT 29.07.2019 B2

   Resolution of: 15 June 2023
   Entry into force on: 15 June 2023
   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 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 15 June 2023):

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 an aromatase inhibitor as initial 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" are adopted as follows:

"a1) postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (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 unsuitable

  or
- Exemestane (only for patients with progression after anti-oestrogen treatment)

  or
- Ribociclib 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

- Abemaciclib in combination with fulvestrant

  or
- Palbociclib in combination with fulvestrant

Extent and probability of the additional benefit of abemaciclib in combination with anastrozole or letrozole versus anastrozole or letrozole:

Hint for a minor additional benefit

Study results according to endpoints:[1]

a1) postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (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	↑	Advantage in overall survival
Morbidity	↓↓	Disadvantages, especially in the endpoints of fatigue, nausea and vomiting, appetite loss
Health-related quality of life	↔	No relevant differences for the benefit assessment
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) (A22-137) unless otherwise indicated.

MONARCH 3 study: Abemaciclib + anastrozole or letrozole **vs** placebo + anastrozole or letrozole

MONARCH plus study: Abemaciclib + anastrozole or letrozole **vs** placebo + anastrozole or letrozole

Total: pooled data of patients from the MONARCH 3 and MONARCH plus studies

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

Relevant sub-population: postmenopausal patients with initial endocrine therapy

Mortality

Endpoint	**Abemaciclib + anastrozole or letrozole**		**Placebo + anastrozole or letrozole**		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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 3	328	67.1 [59.3; n.c.] 158 (48.2)	165	54.5 [44.8; 62.6] 97 (58.8)	0.75 [0.58; 0.97] 0.030 AD = + 12.6 months
MONARCH plus	207	40.0 [40.0; n.c.] 49 (23.7)	99	n.r. [32.8; n.c.] 26 (26.3)	0.89 [0.55; 1.44] 0.645
Total					0.78 [0.63; 0.98] 0.034

Morbidity

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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)[l]					
MONARCH 3	328	29.0 [23.97; 34.06] 204 (62.2)	165	14.8 [11.24; 19.20] 137 (83.0)	0.52 [0.42; 0.65] < 0.001 AD = + 14.2 months
MONARCH plus	207	28.3 [23.01; 32.45] 101 (48.8)	99	14.7 [11.21; 18.87] 71 (71.7)	0.48 [0.35; 0.65] < 0.001 AD = + 13.6 months
Total					0.507 [0.424; 0.606] < 0.001
Time until the first subsequent chemotherapy[l]					
MONARCH 3	328	n.r. [59.44; n.r.] 122 (37.2)	165	32.5 [28.60; 37.97] 98 (59.4)	0.52 [0.39; 0.67] < 0.001
MONARCH plus	Endpoint not assessed				
Symptomatology (EORTC QLQ-C30 – first-time deterioration)[c]					
Fatigue					
MONARCH 3	327	3.7 [2.3; 4.0] 220 (67.3)	161	7.4 [4.7; 13.4] 83 (51.6)	1.50 [1.16; 1.93] 0.001 AD = - 3.7 months
MONARCH plus	205	1.9 [1.1; 3.7] 138 (67.3)	99	3.7 [1.9; 11.0] 59 (59.6)	1.19 [0.88; 1.61] 0.278

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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					1.36 [1.12; 1.66] 0.002
Nausea and vomiting					
MONARCH 3	327	7.4 [4.6; 9.2] 195 (59.6)	161	19.4 [9.2; 32.9] 74 (46.0)	1.51 [1.16; 1.98] 0.002 AD = - 12.0 months
MONARCH plus	205	22.6 [7.7; n.c.] 94 (45.9)	99	n.r. [11.4; n.c.] 35 (35.4)	1.25 [0.85; 1.85] 0.280
Total					1.42 [1.14; 1.78] 0.002
Pain					
MONARCH 3	327	11.1 [7.6; 15.8] 172 (52.6)	161	12.8 [7.5; 19.8] 78 (48.4)	1.08 [0.83; 1.41] 0.564
MONARCH plus	205	14.9 [6.5; n.c.] 94 (45.9)	99	9.1 [5.6; n.c.] 46 (46.5)	0.94 [0.66; 1.33] 0.693
Total					1.03 [0.83; 1.27] 0.817
Dyspnoea					
MONARCH 3	327	14.8 [11.5; 29.0] 153 (46.8)	161	37.4 [14.3; 54.4] 60 (37.3)	1.25 [0.92; 1.68] 0.150

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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	205	13.9 [7.6; n.c.] 96 (46.8)	99	27.8 [12.9; n.c.] 35 (35.4)	1.31 [0.89; 1.93] 0.178
Total					1.27 [1.00; 1.61] 0.048
Insomnia					
MONARCH 3	327	9.5 [7.6; 13.3] 170 (52.0)	161	14.9 [9.2; 37.8] 69 (42.9)	1.22 [0.92; 1.61] 0.162
MONARCH plus	205	7.6 [5.8; 23.4] 106 (51.7)	99	11.1 [7.4; n.c.] 43 (43.4)	1.25 [0.87; 1.78] 0.233
Total					1.23 [0.99; 1.53] 0.068
Appetite loss					
MONARCH 3	327	5.7 [3.8; 9.4] 187 (57.2)	161	30.1 [11.1; 39.4] 64 (39.8)	1.69 [1.27; 2.25] < 0.001 AD = - 24.4 months
MONARCH plus	205	5.6 [1.9; 14.9] 113 (55.1)	99	19.7 [10.5; n.c.] 39 (39.4)	1.61 [1.12; 2.31] 0.015 AD = - 14.1 months
Total					1.66 [1.33; 2.08] < 0.001

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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]
Constipation					
MONARCH 3	327	15.1 [11.5; 25.1] 151 (46.2)	161	13.9 [9.5; 62.7] 69 (42.9)	0.97 [0.73; 1.30] 0.888
MONARCH plus	205	n.r. [30.9; n.c.] 70 (34.1)	99	n.r. [13.8; n.c.] 31 (31.3)	0.96 [0.63; 1.46] 0.839
Total					0.97 [0.77; 1.23] 0.792
Diarrhoea					
MONARCH 3	327	2.0 [1.9; 2.1] 240 (73.4)	161	22.1 [13.2; 33.2] 63 (39.1)	3.34 [2.52; 4.42] < 0.001 AD = - 20.1 months
MONARCH plus	205	1.0 [0.95; 1.05] 161 (78.5)	99	n.r. 20 (20.2)	7.67 [4.80; 12.27] <0.001
Total					4.16 [3.27; 5.29] < 0.001[d]
Symptomatology (EORTC QLQ-BR23 – first-time deterioration)[c]					
Side effects of systemic therapy					
MONARCH 3	327	4.0 [3.7; 5.5] 213 (65.1)	161	13.2 [7.4; n.c.] 67 (41.6)	1.95 [1.48; 2.56] < 0.001 AD = - 9.2 months
MONARCH plus	Not assessed				

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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]
Arm symptoms					
MONARCH 3	327	9.2 [7.2; 11.3] 191 (58.4)	161	9.3 [5.8; 12.9] 84 (52.2)	1.08 [0.84; 1.40] 0.529
MONARCH plus	Not assessed				
Chest symptoms					
MONARCH 3	327	61.9 [39.1; n.c.] 102 (31.2)	161	47.1 [28.5; n.c.] 44 (27.3)	1.03 [0.72; 1.46] 0.883
MONARCH plus	Not assessed				
Burden due to hair loss					
MONARCH 3	No suitable data[e]				
MONARCH plus	Not assessed				
Strongest pain in the last 24 hours (mBPI-SF – first-time deterioration)[f]					
MONARCH 3	Not assessed				
MONARCH plus	205	n.r. [30.5; n.c.] 58 (28.3)	99	n.r. [18.9; n.c.] 32 (32.3)	0.77 [0.50; 1.19] 0.249

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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 – first-time deterioration)[g]					
MONARCH 3	327	22.2 [13.0; 33.6] 142 (43.4)	161	30.4 [14.9; n.c.] 56 (34.8)	1.17 [0.86; 1.59] 0.325
MONARCH plus	Not assessed				

Health-related quality of life

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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]
EORTC QLQ-C30 – first-time deterioration[h]					
Global health status					
MONARCH 3	327	7.6 [6.5; 11.0] 194 (59.3)	161	14.9 [7.9; 31.7] 74 (46.0)	1.32 [1.01; 1.73] 0.038 AD = - 7.3 months
MONARCH plus	205	8.5 [3.8; 16.7] 117 (57.1)	99	9.9 [5.8; 17.3] 51 (51.5)	1.04 [0.75; 1.45] 0.804

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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					1.20 [0.98; 1.48] 0.082
Physical functioning					
MONARCH 3	327	11.4 [9.3; 20.9] 170 (52.0)	161	19.4 [12.0; 43.3] 71 (44.1)	1.23 [0.93; 1.62] 0.140
MONARCH plus	205	10.3 [5.6; 23.8] 108 (52.7)	99	11.6 [5.6; n.c.] 45 (45.5)	1.12 [0.79; 1.58] 0.533
Total					1.18 [0.95; 1.47] 0.127
Role functioning					
MONARCH 3	327	5.6 [4.0; 8.4] 202 (61.8)	161	11.1 [7.4; 16.0] 82 (50.9)	1.26 [0.98; 1.64] 0.072
MONARCH plus	205	11.5 [3.9; 23.6] 105 (51.2)	99	11.8 [5.5; n.c.] 44 (44.4)	1.13 [0.80; 1.61] 0.493
Total					1.22 [0.99; 1.50] 0.065

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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]
Emotional functioning					
MONARCH 3	327	24.8 [14.4; 42.6] 137 (41.9)	161	16.9 [11.1; n.c.] 64 (39.8)	0.97 [0.72; 1.30] 0.840
MONARCH plus	205	28.0 [14.1; n.c.] 86 (42.0)	99	20.3 [6.6; n.c.] 43 (43.4)	0.80 [0.56; 1.16] 0.260
Total					0.90 [0.71; 1.13] 0.370
Cognitive functioning					
MONARCH 3	327	7.4 [5.6; 10.7] 204 (62.4)	161	5.6 [3.7; 9.2] 92 (57.1)	0.93 [0.72; 1.19] 0.612
MONARCH plus	205	3.7 [3.0; 6.5] 125 (61.0)	99	6.4 [3.3; 17.5] 51 (51.5)	1.19 [0.86; 1.65] 0.298
Total					1.02 [0.83; 1.24] 0.885
Social functioning					
MONARCH 3	327	10.4 [5.8; 13.8] 184 (56.3)	161	12.7 [8.3; 27.6] 76 (47.2)	1.18 [0.90; 1.55] 0.220
MONARCH plus	205	5.7 [3.7; 10.3] 116 (56.6)	99	11.8 [4.0; n.c.] 46 (46.5)	1.24 [0.88; 1.74] 0.222

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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					1.20 [0.97; 1.49] 0.086
EORTC QLQ-BR23 – first-time deterioration					
Body image					
MONARCH 3	327	9.2 [7.4; 13.0] 158 (48.3)	161	60.8 [16.3; n.c.] 57 (35.4)	1.48 [1.09; 2.01] 0.010 AD = - 51.6 months
MONARCH plus	Not assessed				
Sexual functioning					
MONARCH 3	327	n.r. 74 (22.6)	161	n.r. 22 (13.7)	1.52 [0.94; 2.45] 0.081
MONARCH plus	Not assessed				
Sexual pleasure					
MONARCH 3	No suitable data				
MONARCH plus	Not assessed				
Future prospects					
MONARCH 3	327	n.r. [47.9; n.c.] 108 (33.0)	161	n.r. [31.1; n.c.] 52 (32.3)	0.92 [0.66; 1.28] 0.672
MONARCH plus	Not assessed				

Side effects

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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 3	327	0.2 [0.1; 0.2] 323 (98.8)	161	0.9 [0.5; 1.0] 152 (94.4)	
MONARCH plus	205	0.2 [0.1; 0.2] 204 (99.5)	99	0.8 [0.4; 1.1] 89 (89.9)	
Serious adverse events (SAE)					
MONARCH 3	327	50.3 [38.4; 65.9] 122 (37.3)	161	n.r. 29 (18.0)	1.95 [1.30; 2.93] 0.001
MONARCH plus (sub-population a1)	205	n.r. 56 (27.3)	99	n.r. 11 (11.1)	2.17 [1.13; 4.14] 0.016
Total					2.01 [1.42; 2.83] < 0.001
Severe adverse events (CTCAE grade ≥ 3)					
MONARCH 3	327	7.9 [4.8; 11.1] 224 (68.5)	161	n.r. [32.5; n.c.] 46 (28.6)	3.13 [2.28; 4.30] < 0.001
MONARCH plus	205	7.4 [4.8; 11.1] 141 (68.8)	99	n.r. [22.7; n.c.] 29 (29.3)	2.96 [1.99; 4.42] < 0.001
Total					3.07 [2.39; 3.93] < 0.001

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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]
Therapy discontinuation due to adverse events[i]					
MONARCH 3	327	n.r. [63.0; n.c.] 98 (30.0)	161	n.r. 7 (4.3)	6.06 [2.81; 13.06] < 0.001
MONARCH plus	205	n.r. 40 (19.5)	99	n.r. 4 (4.0)	3.42 [1.22; 9.58] 0.013
Total					4.94 [2.67; 9.14] < 0.001
Specific adverse events					
Neutropenia (PT, severe AEs[j]**)**					
MONARCH 3	327	n.r. [60.6; n.c.] 89 (27.2)	161	n.r. 2 (1.2)	22.86 [5.63; 92.84] < 0.001
MONARCH plus	205	n.r. 64 (31.2)	99	n.r. 8 (8.1)	4.01 [1.92; 8.37] < 0.001
Total					5.84 [3.05; 11.21] < 0.001
Diarrhoea (PT, severe AEs)					
MONARCH 3	327	n.r. 32 (9.8)	161	n.r. 2 (1.2)	7.85 [1.88; 32.78] < 0.001
MONARCH plus	205	n.r. 9 (4.4)	99	n.r. 1 (1.0)	3.73 [0.47; 29.46] 0.181
Total					6.17 [1.90; 19.99] 0.002

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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]
Blood and lymphatic system disorders (SOC, severe AEs)					
MONARCH 3	327	46.3 [32.4; n.r.] 119 (36.4)	161	n.r. 5 (3.1)	12.97 [5.30; 31.74] < 0.001
MONARCH plus	205	n.r. 27 (13.2)	99	n.r. 3 (3.0)	3.73 [1.13; 12.32] 0.020
Total					8.29 [4.05; 16.96] < 0.001
Infections and infestations (SOC, severe AEs)					
MONARCH 3	327	n.r. 33 (10.1)	161	n.r. 7 (4.3)	1.91 [0.84; 4.33] 0.114
MONARCH plus	205	n.r. 12 (5.9)	99	n.r. 1 (1.0)	4.42 [0.57; 34.07] 0.119
Total					2.15 [1.00; 4.59] 0.049
Metabolism and nutrition disorders (SOC, severe AEs)					
MONARCH 3	327	n.r. 42 (12.8)	161	n.r. 5 (3.1)	3.78 [1.49; 9.57] 0.003
MONARCH plus	205	n.r. 28 (13.7)	99	n.r. 1 (1.0)	11.93 [1.62; 87.70] 0.002
Total					4.64 [2.0; 10.77] < 0.001

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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]
Investigations[k] (SOC, severe AEs)					
MONARCH 3	327	n.r. 47 (14.4)	161	n.r. 8 (5.0)	2.66 [1.25; 5.64] 0.008
MONARCH plus	205	21.5 [13.7; 27.0] 102 (49.8)	99	n.r. 16 (16.2)	3.40 [2.01; 5.76] < 0.001
Total					3.13 [2.04; 4.83] < 0.001
Gastrointestinal disorders (SOC, AEs)					
MONARCH 3	327	0.2 [0.2; 0.3] 297 (90.8)	161	4.2 [3.0; 8.9] 104 (64.6)	3.12 [2.48; 3.94] < 0.001 AD = - 4 months
MONARCH plus	205	0.2 [0.2; 0.3] 176 (85.9)	99	16.2 [5.6; n.c.] 48 (48.5)	3.48 [2.52; 4.81] < 0.001 AD = -16 months
Total					3.24 [2.68; 3.91] < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)					
MONARCH 3	327	6.8 [5.7; 8.8] 182 (55.7)	161	43.3 [23.0; n.c.] 54 (33.5)	2.04 [1.50; 2.76] < 0.001 AD = -36.5 months
MONARCH plus	205	n.r. [29.1; n.c.] 71 (34.6)	99	n.r. 18 (18.2)	1.84 [1.09; 3.08] 0.019

Endpoint	Abemaciclib + anastrozole or letrozole		placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole vs placebo + anastrozole or letrozole
	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					1.98 [1.53; 2.58] < 0.001
Eye disorders (SOC, AEs)					
MONARCH 3	327	n.r. [65.4; n.c.] 71 (21.7)	161	n.r. 9 (5.6)	3.77 [1.88; 7.55] < 0.001
MONARCH plus	205	n.r. 27 (13.2)	99	n.r. 4 (4.0)	3.01 [1.05; 8.61] 0.031
Total					3.52 [1.97; 6.28] < 0.001

a. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b. Overall survival: Cox model with stratification variables previous endocrine therapy, type of diseases and with treatment as covariate; p value: stratified log-rank test (stratified analysis was prespecified for overall survival); all other endpoints: unstratified Cox model; p value: log-rank test; meta-analysis: Model with fixed effect
c. An increase in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
d. IQWiG calculation: Meta-analysis with fixed effect
e. Unclear percentage of patients with missing values at the start and during the course of the study
f. Measured via the symptom scale "strongest pain in the last 24 hours"; an increase of ≥ 2 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 10).
g. A decrease in score by ≥ 15 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
h. A decrease in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
i. Discontinuation of at least 1 therapy component
j. According to information provided by the pharmaceutical company in Module 4 A, joint consideration of the events - neutropenia (PT) and febrile neutropenia (PT)
k. Among them, significantly in the MONARCH 3 study: Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased; in the MONARCH plus study: Neutropenia, leukopenia, alanine aminotransferase increased, aspartate aminotransferase increased, thrombocytopenia, lymphopenia
l. From the dossier of the pharmaceutical company

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; CI = confidence interval; mBPI-SF = modified Brief Pain Inventory-Short Form; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PT = preferred term QLQ-BR23 = Quality of Life

Questionaire-Breast Cancer 23; QLQ-C30 = Quality of Life Questionnaire-Core 30; RCT = randomised controlled trial; SOC = system organ class; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus

"

3. The findings under "2. Number of patients or demarcation of patient groups eligible for treatment" regarding the patient population "a1" is adopted as follows:

"

a1) postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy

approx. 7,400 to 34,790 patients

"

4. The findings under "3. Requirements for a 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: 21 March 2023):

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 patient group "a1" are adopted as follows:

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

a1) postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (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 aromatase inhibitor	
Abemaciclib	€ 22,624.26
Anastrozole	€ 178.88
Letrozole	€ 169.30
Exemestane	€ 424.53
Total:	

Designation of the therapy	Annual treatment costs/ patient
Abemaciclib + anastrozole	€ 22,803.14
Abemaciclib + letrozole	€ 22,793.56
Abemaciclib + exemestane	€ 23,048.80
Appropriate comparator therapy:	
Non-steroidal aromatase inhibitors	
Anastrozole	€ 178.88
Letrozole	€ 169.30
Anti-oestrogens	
Fulvestrant	€ 4,176.64
Tamoxifen	€ 71.36
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)	
Ribociclib	€ 28,457.82
Anastrozole	€ 178.88
Letrozole	€ 169.30
Total:	
Ribociclib + anastrozole	€ 28,636.70
Ribociclib + letrozole	€ 28,627.12
Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)	
Palbociclib	€ 28,916.81
Anastrozole	€ 178.88
Letrozole	€ 169.30
Total:	
Palbociclib + anastrozole	€ 29,095.69
Palbociclib + letrozole	€ 29,086.11
Ribociclib in combination with fulvestrant	
Ribociclib	€ 28,457.82
Fulvestrant	€ 4,497.92
Total:	
Ribociclib + fulvestrant	€ 32,955.74
Abemaciclib in combination with fulvestrant	
Abemaciclib	€ 22,624.26
Fulvestrant	€ 4,176.64
Total:	
Abemaciclib + fulvestrant	€ 26,800.90
Palbociclib in combination with fulvestrant	
Palbociclib	€ 28,918.37

Designation of the therapy	Annual treatment costs/ patient
Fulvestrant	€ 4,497.92
Total:	
Palbociclib + fulvestrant	€ 33,416.29

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 May 2023)

Costs for additionally required SHI services: not applicable".

6. Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the active ingredient Abemaciclib

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients which, on the basis of the marketing authorisation under Medicinal Products Act, can be used in a combination therapy with abemaciclib for the treatment of (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine therapy:

a1) postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

- No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 15 June 2023.

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

Berlin, 15 June 2023

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

Prof. Hecken