Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Abemaciclib (Breast Cancer; in Combination with Fulvestrant)

of 2 May 2019

At its session on 2 May 2019, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on 21 February 2019 (Federal Gazette, BAnz AT 14 May 2019 B2), as follows:

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

Abemaciclib

Resolution of: 2 May 2019
Entry into force on: 2 May 2019
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 peri-menopausal women, the endocrine therapy should be combined with an LHRH agonist (LHRH = luteinising hormone-releasing hormone).

Indication:

This resolution relates exclusively to the assessment of the additional benefit abemaciclib in combination with fulvestrant. For the assessment of the additional benefit of abemaciclib with an aromatase inhibitor, reference is made to the separate benefit assessment procedure for this combination therapy.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

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

Appropriate comparator therapy:

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

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

a2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

Appropriate comparator therapy:

tamoxifen in combination with an elimination of the ovarian function.

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

b1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally

advanced or metastatic breast cancer with prior endocrine therapy:

Appropriate comparator therapy:

Another endocrine therapy depending on the previous therapy with:

- tamoxifen *or*
- anastrozole *or*
- fulvestrant; only for patients with relapse or progress after anti-oestrogen treatment *or*
- letrozole; only for patients with relapse or progress after anti-oestrogen treatment *or*
- exemestane; only for patients with progress after anti-oestrogen treatment *or*
- everolimus in combination with exemestane; only for patients without symptomatic visceral metastasis after progression after a non-steroidal aromatase inhibitor

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

b2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

Appropriate comparator therapy:

Endocrine therapy according to the doctor's instructions, taking into account the respective marketing authorisation.

Tamoxifen, letrozole, exemestane, megestrol acetate, and medroxyprogesterone acetate are approved for the present therapeutic indication.

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:

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

MONARCH-2 Study: Abemaciclib + fulvestrant vs placebo + fulvestrant [1,2]

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

Relevant sub-population: Post-menopausal patients who have not yet received initial endocrine therapy for metastatic/locally advanced disease (approx. 50.5% of study population)

[1] Data from the dossier evaluation of the IQWiG (A18-73) and from the addendum (A19-25), unless otherwise indicated.

[2] Data cut-off 14 February 2017

Mortality

Endpoint	Abemaciclib + fulvestrant		Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	224	n.a. 44 (19.6 [b])	114	n.a. [24.13; n.c.] 27 (23.7 [b])	0.76 [0.47; 1.23] 0.279

Morbidity

No usable data available for the relevant sub-population.

Progression-free survival (PFS)

No usable data available for the relevant sub-population.

Health-related quality of life

No usable data available for the relevant sub-population.

Side effects

Endpoint	Abemaciclib + fulvestrant		Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Adverse events (AE) (presented additionally)					
	224	0.13 [0.10; 0.13] 222 (99.1[b])	114	0.79 [0.49; 1.02] 99 (86.8[b])	-
Serious adverse events (SAE)					
	224	n.a. 58 (25.9[b])	114	n.a. 10 (8.8[b])	3.11 [1.59; 6.09] < 0.001
Severe adverse events (CTCAE grade 3 or 4)					
	224	3.55 [2.60; 5.56] 142 (63.4[b])	114	n.a. [19.36; n.c.] 27 (23.7[b])	3.83 [2.54; 5.79] < 0.001
Therapy discontinuation because of adverse events [c]					

	224	n.a. 40 (17.9[b])	114	n.a. 5 (4.4[b])	4.04 [1.59; 10.23] 0.002
Specific adverse events					
Neutropoenia (CTCAE grade ≥ 3)	no data available				

References:
[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Calculation of the IQWiG
[c] Discontinuation of one or both medications

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; vs = versus

a2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

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

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

MONARCH-2 Study: Abemaciclib + fulvestrant vs placebo + fulvestrant [3,4]

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

Relevant sub-population: Post-menopausal patients who have received prior endocrine therapy for metastatic/locally advanced disease (approx. 31.8% of study population)

Mortality

Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	147	n.a.	66	26.76	1.09

[3] Data from the dossier evaluation of the IQWiG (A18-73) and from the addendum (A19-25), unless otherwise indicated.
[4] Data cut-off 14 February 2017

		[25.25; n.c.] 31 (21.2[b])		[24.20; n.c.] 13 (19.7[b])	[0.57; 2.09] 0.751

Morbidity

No usable data available for the relevant sub-population.

Progression-free survival (PFS)

No usable data available for the relevant sub-population.

Health-related quality of life

No usable data available for the relevant sub-population.

Side effects

Endpoint	Abemaciclib + fulvestrant		Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Adverse events (AE) (presented additionally)					
	146	0.10 [0.07; 0.13] 143 (97.9[b])	66	0.54 [0.26; 0.95] 59 (89.4[b])	-
Serious adverse events (SAE)					
	146	n.a. 33 (22.6[b])	66	n.a. 12 (18.2[b])	1.07 [0.55; 2.08] 0.924
Severe adverse events (CTCAE grade 3 or 4)					
	146	4.77 [2.76; 9.47] 89 (61.0[b])	66	n.a. [9.93; n.c.] 19 (28.8[b])	2.70 [1.64; 4.43] < 0.001
Therapy discontinuation because of adverse events [c]					
	146	n.a. 26 (17.8 [b])	66	n.a. 2 (3.0[b])	5.42 [1.29; 22.85] 0.008
Specific adverse events					
Neutropoenia (CTCAE grade ≥ 3)	no data available				

References:

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

[b] Calculation of the IQWiG

[c] Discontinuation of one or both medications

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; vs = versus

b2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

MONARCH-2 Study: Abemaciclib + fulvestrant vs placebo + fulvestrant [5,6]

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

Relevant sub-population: Pre-/peri-menopausal patients who have received prior endocrine therapy for metastatic/locally advanced disease (approx. 6.9% of study population)

Mortality

Endpoint	**Abemaciclib + fulvestrant**		**Fulvestrant**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	26	no data available 3 (11.5[b])	20	no data available 4 (20.0[b])	no data available[c]

Morbidity

No usable data available for the relevant sub-population.

Progression-free survival (PFS)

No usable data available for the relevant sub-population.

Health-related quality of life

No usable data available for the relevant sub-population.

[5] Data from the dossier evaluation of the IQWiG (A18-73) and from the addendum (A19-25), unless otherwise indicated.

[6] Data cut-off 14 February 2017

Side effects

Endpoint	Abemaciclib + fulvestrant		Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Adverse events (AE) (presented additionally)					
	26	0.13 [0.10; 0.23] 25 (96.2[b])	20	0.44 [0.16; 1.58] 19 (95.0[b])	-
Serious adverse events (SAE)					
	26	no data available 5 (19.2[b])	20	no data available 1 (5.0[b])	no data available[c]
Severe adverse events (CTCAE grade 3 or 4)					
	26	3.72 [0.95; 6.77] 18 (69.2[b])	20	n.a. [9.24; n.c.] 3 (15.0[b])	6.55 [1.93; 22.30] < 0.001
Therapy discontinuation because of adverse events[d]					
	26	no data available 2 (7.7[b])	20	no data available 0	n.c. no data available[c]
Specific adverse events					
Neutropoenia (CTCAE grade ≥ 3)	no data available				

References:
[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Calculation of the IQWiG
[c] If there were fewer than 10 events, no evaluation was carried out by the pharmaceutical company
[d] Discontinuation of one or both medications

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; vs = versus

2. Number of patients or demarcation of patient groups eligible for treatment

Total population according to therapeutic indication:

14,560 to 70,550 patients

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

therapy:

approx. 7,180–34,790 patients

a2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

approx. 1,190–5,760 patients

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

approx. 5,310–25,740 patients

b2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

approx. 880–4,260 patients

3. Requirements for a quality-assured application

The requirements 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: 13 March 2019):

https://www.ema.europa.eu/en/documents/product-information/verzenios-epar-product-information_de.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.

4. Treatment costs

Annual treatment costs:

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

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

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed:	
Abemaciclib plus fulvestrant	
Abemaciclib	€ 41,008.92
Fulvestrant	€ 9,696.87
Total	€ 50,705.80
Appropriate comparator therapy:	
Tamoxifen	€ 71.10
Fulvestrant	€ 9,696.87
Anastrozole	€ 258.68
Letrozole	€ 230.16

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

Costs for additionally required SHI services: not applicable

a2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed:	
Abemaciclib plus fulvestrant	
Abemaciclib	€ 41,008.92
Fulvestrant	€ 9,696.87
Total	€ 50,705.80
LHRH analogue[7]	€ 1,790.38–2,235.96
Appropriate comparator therapy:	
Tamoxifen plus LHRH analogues	
Tamoxifen	€ 71.10
LHRH analogue	€ 1,790.38–2,235.96
Total	€ 1,861.48–2,307.06

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

Costs for additionally required SHI services: not applicable

[7] leuprorelin or goserelin

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

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed:	
Abemaciclib plus fulvestrant	
Abemaciclib	€ 41,008.92
Fulvestrant	€ 9,696.87
Total	€ 50,705.80
Appropriate comparator therapy:	
Tamoxifen	€ 71.10
Anastrozole	€ 258.68
Fulvestrant	€ 9,696.87
Letrozole	€ 230.16
Exemestane	€ 424.28
Everolimus plus exemestane	
Everolimus	€ 23,467.68
Exemestane	€ 424.28
Total	€ 23,891.95

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

Costs for additionally required SHI services: not applicable

b2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed:	
Abemaciclib plus fulvestrant	
Abemaciclib	€ 41,008.92
Fulvestrant	€ 9,696.87
Total	€ 50,705.80
LHRH analogue	€ 1,790.38–2,235.96
Appropriate comparator therapy: An endocrine therapy according to the doctor's instructions	
Tamoxifen	€ 71.10
Medroxyprogesterone acetate	€ 1,187.56–2,375.13

Designation of the therapy	Annual treatment costs per patient
Megestrol acetate	€ 5,409.30
Exemestane	€ 424.28
Letrozole	€ 230.16
Leuprorelin	€ 1,790.38
Goserelin	€ 2,235.96

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

Costs for additionally required SHI services: not applicable

II. Entry into force

1. **The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 2 May 2019.**

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

   The findings for patient groups

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

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

   b2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy

   The findings in numbers 1, 2, 3, and 4 are limited until 31 December 2020.

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

Berlin, 2 May 2019

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

Prof Hecken