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 Alpelisib in Combination with Fulvestrant (Breast Cancer with PIK3CA Mutation, HR+, HER2-, Combination with Fulvestrant)

of 18 February 2021

At its session on 18 February 2021 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 amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient alpelisib in combination with fulvestrant as follows:

Alpelisib in combination with fulvestrant

Resolution of: 18 February 2021
Entry into force on: 18 February 2021
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 27 July 2020):

Piqray is indicated in combination with fulvestrant for the treatment of post-menopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy.

Therapeutic indication of the resolution (resolution of 18 February 2021):

See therapeutic indication according to marketing authorisation

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

a1) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are not present:

Appropriate comparator therapy:

- Ribociclib in combination with a non-steroidal aromatase inhibitor

or

- Ribociclib in combination with fulvestrant

or

- Anastrozole

or

- Letrozole

or

- Fulvestrant

or

- Tamoxifen, if aromatase inhibitors are not appropriate

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

Indication of a minor benefit.

a2) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are present:

Appropriate comparator therapy:

- Ribociclib in combination with a non-steroidal aromatase inhibitor

or

- Ribociclib in combination with fulvestrant

or

- Anastrozole

or

- Letrozole

or

- Fulvestrant

or

- Tamoxifen, if aromatase inhibitors are not appropriate

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

An additional benefit is not proven.

a3) Men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation:

Appropriate comparator therapy:

Therapy according to the doctor's instructions

Extent and probability of the additional benefit of alpelisib 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, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage

Appropriate comparator therapy:

- Abemaciclib in combination with fulvestrant

or

- Ribociclib in combination with fulvestrant

or

- Tamoxifen

or

- Anastrozole

or

- Fulvestrant as monotherapy; 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 alpelisib in combination with fulvestrant compared with fulvestrant:

Indication of a minor benefit.

b2) Men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage:

Appropriate comparator therapy:

Therapy according to the doctor's instructions

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

An additional benefit is not proven.

Study results according to endpoints:[1]

a1) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are not present

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No statistically significant difference
Morbidity	↓↓	Disadvantages in the symptomatology (nausea/vomiting, loss of appetite, diarrhoea).
Health-related quality of life	↓	Disadvantage in the social functioning scale
Side effects	↓↓	Disadvantages in SAEs, severe AEs CTCAE grade ≥ 3 and therapy discontinuations because of 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		

a2) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are present

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Statistically significant advantage
Morbidity	↓↓	Disadvantages in the symptomatology (nausea/vomiting, loss of appetite, diarrhoea).
Health-related quality of life	↓	Disadvantage in the social functioning scale

[1] Data from the dossier assessment of the IQWiG (A20-81) and the addendum (A21-05) unless otherwise indicated.

Side effects	↓↓	Disadvantages in SAEs, severe AEs CTCAE grade ≥ 3 and therapy discontinuations because of 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

SOLAR-1 study: Alpelisib plus fulvestrant vs placebo plus fulvestrant

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

Data cut-off: 3rd data cut-off of 23 April 2020

Relevant sub-population: Post-menopausal women with previous endocrine therapy that took place in the (neo-)adjuvant therapy situation.

Mortality

Endpoint	**Alpelisib + fulvestrant**		**Placebo + 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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Overall survival/mortality					
	88	41.9 [34.1; n.c.] *41 (46.6)*	89	34.5 [24.3; 46.7] *49 (55.1)*	0.78 [0.51; 1.19]; 0.253
Subgroups by type of disease:					
Lung and/or liver metastases present	44	40.6 [30.23; n.a.] *21 (47.7)*	47	22.2 [17.68; 29.27] *35 (74.5)*	0.52 [0.30; 0.91]; 0.020 AD: +18.4 months
Lung and/or liver metastases not present	44	41.9 [31.87; n.a.] *20 (45.5)*	42	n.a. [41.30; n.a.] *14 (33.3)*	1.49 [0.74; 3.01]; 0.256
				Interaction	0.036

Morbidity

Endpoint	**Alpelisib + fulvestrant**		**Placebo + fulvestrant**		Intervention vs control
	N	Median time to event in months [95% CI]	N	Median time to event in months [95% CI]	HR [95% CI] p value

		Patients with event n (%)		*Patients with event n (%)*	Absolute difference (AD)[a]
Progression-free survival[b]					
	88	11.0 [7.26; 15.93] *61 (69.3)*	89	6.8 [3.55; 9.26] *76 (85.4)*	0.51 [0.32; 0.82]; 0.005 AD: +4.2 months
Symptomatology (EORTC QLQ-C30, symptom scales)					
Fatigue	88	15.4 [3.9; 33.1] *41 (46.6)*	89	16.6 [11.0; n.a.] *29 (32.6)*	1.33 [0.82; 2.15]; 0.264
Nausea and vomiting	88	9.2 [4.2; n.a.] *38 (43.2)*	89	n.a. [19.6; n.a.] *17 (19.1)*	2.44 [1.37; 4.35]; 0.002 AD = n.c.
Pain	88	14.7 [7.5; 27.6] *37 (42.0)*	89	7.5 [3.7; 14.7] *38 (42.7)*	0.80 [0.50; 1.26]; 0.332
Dyspnoea	88	16.6 [7.4; n.a.] *35 (39.8)*	89	19.4 [5.7; n.a.] *29 (32.6)*	1.04 [0.63; 1.70]; 0.879
Insomnia	88	22.1 [11.0; 34.4] *36 (40.9)*	89	22.1 [7.5; n.a.] *29 (32.6)*	0.96 [0.58; 1.58]; 0.883
Loss of appetite	88	4.2 [3.7; 9.3] *48 (54.5)*	89	22.1 [9.2; n.a.] *28 (31.5)*	2.01 [1.25; 3.22]; 0.003 AD: −19.7 months
Constipation	88	n.a. [22.1; n.a.] *21 (23.9)*	89	n.a. [5.6; n.a.] *26 (29.2)*	0.62 [0.35; 1.11]; 0.102
Diarrhoea	88	7.4 [3.7; 11.1] *43 (48.9)*	89	n.a. [n.a.; n.a.] *14 (15.7)*	3.96 [2.13; 7.35]; < 0.001 AD = n.c.
Pain (BPI-SF)					
Strongest pain	88	13.1 [7.4; 30.4] *39 (44.3)*	89	11.2 [5.6; 25.3] *35 (39.3)*	0.91 [0.57; 1.45]; 0.700
Pain intensity	No usable data				
Impairment due to pain	No usable data				
Health status (EQ-5D VAS)					
Health status (EQ-5D-5L VAS)	88	22.1 [5.6; n.a.] *36 (40.9)*	89	22.3 [9.2; n.a.] *28 (31.5)*	1.24 [0.75: 2.04]; 0.418

Health-related quality of life

Endpoint	**Alpelisib + fulvestrant**		**Placebo + fulvestrant**		Intervention vs control
	N	Median time to event in months [95% CI]	N	Median time to event in months [95% CI]	HR [95% CI] p value Absolute difference (AD)[a]

		Patients with event n (%)		*Patients with event n (%)*	
EORTC QLQ-C30 (global health status functional scales)					
Global health status	88	9.2 [3.9; 22.2] *44 (50.0)*	89	7.5 [5.6; 24.9] *34 (38.2)*	1.07 [0.68; 1.68]; 0.786
Physical functioning	88	n.a. [33.1; n.a.] *19 (21.6)*	89	n.a. [19.3; n.a.] *21 (23.6)*	0.78 [0.42; 1.45]; 0.434
Role functioning	88	11.0 [5.6; 20.4] *40 (45.5)*	89	13.1 [5.6; 24.8] *38 (42.7)*	1.00 [0.63; 1.56]; 0.972
Emotional functioning	88	11.1 [5.6; 33.1] *36 (40.9)*	89	26.9 [9.3; n.a.] *26 (29.2)*	1.30 [0.78; 2.18]; 0.315
Cognitive functioning	88	5.6 [3.8; 27.6] *45 (51.1)*	89	12.9 [3.7; 19.6] *36 (40.4)*	1.10 [0.70; 1.71]; 0.672
Social functioning	88	5.6 [3.7; 19.3] *47 (53.4)*	89	16.5 [7.4; n.a.] *27 (30.3)*	1.89 [1.17; 3.05]; 0.009 AD: −9.9 months

Side effects

Endpoint	**Alpelisib + fulvestrant**		**Placebo + 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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	88	0.3 [0.2; 0.3] *88 (100)*	89	0.5 [0.4; 0.9] *82 (92.1)*	-
Serious adverse events (SAE)					
	88	38.6 [17.0; n.c.] *32 (36.4)*	89	n.a. [29.6; n.c.] *18 (20.2)*	1.85 [1.04; 3.30]; 0.035 AD = n.c.
Severe adverse events (CTCAE grade 3 or 4)					
	88	1.0 [0.6; 1.4] *71 (80.7)*	89	n.a. [6.7; n.c.] *33 (37.1)*	3.48 [2.30; 5.29]; < 0.001 AD = n.c.
Therapy discontinuations because of adverse events[c]					
	88	n.a. [22.7; n.c.] *25 (28.4)*	89	n.a. [30,7; n.c.] *6 (6.7)*	4.62 [1.89; 11.26]; < 0.001 AD = n.c.
Specific adverse events					
Hyperglycaemia (SMQ, severe AEs)	88	n.a. [n.a.; n.a.] *36 (40.9)*	89	n.a. [n.a.; n.a.] *1 (1.1)*	45.00 [6.17; 328.46]; < 0.001

					AD = n.c.
Skin rash (CMQ, severe AEs)	88	n.a. [n.a.; n.a.] *21 (23.9)*	89	n.a. [n.a.; n.a.] *0 (0)*	n.a.; < 0.001 AD = n.c.
Taste disorder (PT, AEs)	88	n.a. [n.a.; n.a.] *15 (17.0)*	89	n.a. [n.a.; n.a.] *3 (3.4)*	5.14 [1.49; 17.78]; 0.004 AD = n.c.
Alopecia (PT, AEs)	88	n.a. [n.a.; n.a.] *20 (22.7)*	89	n.a. [n.a.; n.a.] *4 (4.6)*	4.65 [1.58; 13.63]; 0.002 AD = n.c.
Gastrointestinal disorders (SOC, AEs)	88	0.4 [0.3; 0.7] *76 (86.4)*	89	13.2 [5.7; 32.2] *40 (44.9)*	3.17 [2.14; 4.71]; < 0.001 AD: −12.8 months
Mucosa inflammation (PT, AEs)	88	n.a. [n.a.; n.a.] *14 (15.9)*	89	n.a. [n.a.; n.a.] *2 (2.2)*	7.61 [1.73; 33.53]; 0.002 AD = n.c.
Peripheral oedema (PT, AE)	88	n.a. [n.a.; n.a.] *12 (13.6)*	89	n.a. [n.a.; n.a.] *1 (1.1)*	10.96 [1.42; 84.80]; 0.004 AD = n.c.
Diarrhoea (PT, severe AEs)	88	n.a. [n.a.; n.a.] *8 (9.1)*	89	n.a. [n.a.; n.a.] *0 (0)*	n.a.; 0.007 AD = n.c.
Gamma-glutamyl transferase increased (PT, severe AEs)	88	n.a. [n.a.; n.a.] *1 (1.1)*	89	n.a. [n.a.; n.a.] *6 (6.7)*	0.16 [0.02; 1.30]; 0.048 AD = n.c.
Hypertension (PT, severe AEs)	88	n.a. [0.9; n.a.] *7 (8.0)*	89	n.a. [n.a.; n.a.] *1 (1.1)*	7.14 [0.88; 58.22]; 0.032 AD = n.c.
Weight decreased (PT, severe AEs)	88	n.a. [n.a.; n.a.] *5 (5.7)*	89	n.a. [n.a.; n.a.] *0 (0)*	n.a.; 0.032 AD = n.c.
Metabolism and nutrition disorders (SOC, severe AEs)	88	22.3 [4.2; n.a.] *42 (47.7)*	89	n.a. [n.a.; n.a.] *7 (7.9)*	7.61 [3.41; 16.98]; < 0.001 AD = n.c.

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Data from the written statement of the pharmaceutical company.
[c] Termination of therapy with alpelisib or placebo and/or fulvestrant.

Abbreviations used:
AD: absolute difference; BPI-SF: Brief Pain Inventory-Short Form; CDK: cyclin-dependent kinase; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L: European Quality of Life-5 Dimensions-5-Level; HR = Hazard Ratio; CI = confidence interval; n: Number of patients with (at least 1) event; N: number of patients evaluated; n.c. = not calculable; n.a.: not achieved; RCT: randomised controlled trial; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus

a3) Men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.
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) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	no statistically significant difference
Morbidity	↓↓	Advantage for the dyspnoea functional scale Disadvantages in the symptomatology (nausea/vomiting, diarrhoea, loss of appetite)
Health-related quality of life	↓	Disadvantages in the social functioning scale
Side effects	↓↓	Disadvantages in SAEs, severe AEs CTCAE grade ≥ 3 and therapy discontinuations because of 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

SOLAR-1 study: Alpelisib plus fulvestrant vs placebo plus fulvestrant

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

Data cut-off: 3rd data cut-off of 23 April 2020

Relevant sub-population: Post-menopausal women with previous endocrine therapy that was given at a locally advanced or metastatic stage

Mortality

Endpoint	**Alpelisib + fulvestrant**		**Placebo + 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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Overall survival/mortality					
	79	37.2 [25.6; 43.8] *44 (55.7)*	82	31.2 [25.9; 43.2] *44 (53.7)*	0.93 [0.61; 1.43]; 0.752

Morbidity

Endpoint	**Alpelisib + fulvestrant**		**Placebo + 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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Progression-free survival[b]					
	79	10.9 [5.59; 14.55] *61 (77.2)*	82	3.7 [3.58; 7.36] *72 (87.8)*	0.63 [0.45; 0.89]; 0.010 AD: +7.2 months
Symptomatology (EORTC QLQ-C30, symptom scales)					
Fatigue	79	7.4 [5.6; 16.6] *35 (44.3)*	82	n.a. [11.1; n.a.] *21 (25.6)*	1.71 [0.98; 2.96]; 0.054 AD = n.c.
Nausea and vomiting	79	7.4 [4.7; 11.2] *40 (50.6)*	82	12.9 [9.2; n.a.] *23 (28.0)*	1.89 [1.12; 3.18]; 0.016 AD: −5.5 months

Pain	79	9.2 [5.5; 12.9] *37 (46.8)*	82	6.5 [3.7; 14.7] *35 (42.7)*	0.79 [0.49; 1.28]; 0.330
Dyspnoea	79	22.6 [12.9; n.a.] *19 (24.1)*	82	9.2 [3.8; 13.0] *33 (40.2)*	0.39 [0.22; 0.70]; 0.001 AD: +13.4 months
Insomnia	79	6.5 [3.7; 11.1] *38 (48.1)*	82	n.a. [5.6; n.a.] *25 (30.5)*	1.39 [0.83; 2.33]; 0.203
Loss of appetite	79	4.0 [1.9; 19.4] *39 (49.4)*	82	13.9 [7.4; 22.1] *28 (34.1)*	1.67 [1.02; 2.73]; 0.045 AD: −9.9 months
Constipation	79	28.6 [11.0; n.a.] *21 (26.6)*	82	9.3 [7.4; 19.9] *29 (35.4)*	0.61 [0.34; 1.08]; 0.092
Diarrhoea	79	5.6 [3.7; 9.2] *40 (50.6)*	82	n.a. [14.8; n.a.] *16 (19.5)*	2.86 [1.59; 5.12]; < 0.001 AD = n.c.
Pain (BPI-SF)					
Strongest pain	79	12.9 [7.4; 28.6] *29 (36.7)*	82	9.2 [3.9; 14.8] *32 (39.0)*	0.63 [0.37; 1.07]; 0.089
Pain intensity	No usable data				
Impairment due to pain	No usable data				
Health status (EQ-5D VAS)					
Health status (EQ-5D-5L VAS)	79	14.3 [5.7; n.a.] *28 (35.4)*	82	22.1 [9.4; n.a.] *22 (26.8)*	1.06 [0.60; 1.89]; 0.839

Health-related quality of life

Endpoint	**Alpelisib + fulvestrant**		**Placebo + 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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
EORTC QLQ-C30 (global health status functional scales)					
Global health status	79	5.6 [3.7; 11.1] *40 (50.6)*	82	9.2 [4.2; n.a.] *27 (32.9)*	1.43 [0.87; 2.34]; 0.145
Physical functioning	79	n.a. [28.6; n.a.] *19 (24.1)*	82	n.a. [11.1; n.a.] *17 (20.7)*	1.01 [0.51; 1.98]; 0.990
Role functioning	79	5.6 [2.0; 9.3] *37 (46.8)*	82	5.6 [3.7; 11.4] *38 (46.3)*	1.07 [0.68; 1.69]; 0.827

Emotional functioning	79	12.8 [5.5; n.a.] *29 (36.7)*	82	11.1 [7.5; 17.1] *27 (32.9)*	1.01 [0.60; 1.71]; 0.965
Cognitive functioning	79	7.4 [5.6; 14.8] *33 (41.8)*	82	11.1 [3.7; n.a.] *30 (36.6)*	1.21 [0.73; 2.00]; 0.450
Social functioning	79	4.7 [3.7; 12.9] *38 (48.1)*	82	14.8 [7.4; 22.1] *26 (31.7)*	1.77 [1.07; 2.92]; 0.027 AD: - 10.1 months

Side effects

Endpoint	**Alpelisib + fulvestrant**		**Placebo + 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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	79	0.2 [0.1; 0.3] *78 (98.7)*	81	0.4 [0.3; 0.5] *72 (88.9)*	-
Serious adverse events (SAE)					
	79	25.5 [8.2; 40.0] *34 (43.0)*	81	21.6 [20.1; n.c.] *15 (18.5)*	2.22 [1.19; 4.11]; 0.010 AD: +3.9 months
Severe adverse events (CTCAE grade 3 or 4)					
	79	0.7 [0.5; 1.4] *67 (84.8)*	81	n.a. [11.7; n.c.] *25 (30.9)*	5.23 [3.24; 8.43]; < 0.001 AD = n.c.
Therapy discontinuations because of adverse events[c]					
	79	40.7 [21.2; n.c.] *21 (26.6)*	81	n.a. [25,0; n.c.] *4 (4.9)*	5.37 [1.83; 15.74]; < 0.001 AD = n.c.
Specific adverse events					
Hyperglycaemia (SMQ, severe AEs)	79	n.a. [n.a.; n.a.] *28 (35.4)*	81	n.a. [n.a.; n.a.] *0 (0)*	n.a.; < 0.001 AD = n.c.
Skin rash (CMQ, severe AEs)	79	n.a. [n.a.; n.a.] *19 (24.1)*	81	n.a. [n.a.; n.a.] *0 (0)*	n.a.; < 0.001 AD = n.c.
Alopecia (PT, AEs)	79	n.a. [n.a.; n.a.] *16 (20.3)*	81	n.a. [n.a.; n.a.] *1 (1.2)*	17.39 [2.30; 131.33]; < 0.001 AD = n.c.

Pruritus (PT, AEs)	79	n.a. [18.9; n.a.] *18 (22.8)*	81	n.a. [n.a.; n.a.] *3 (3.7)*	6.09 [1.78; 20.85]; 0.001 AD = n.c.
Gastrointestinal disorders (SOC, AEs)	79	0.3 [0.2; 0.4] *69 (87.3)*	81	5.4 [2.3; 17.8] *44 (54.3)*	3.30 [2.20; 4.97]; < 0.001 AD: −5.1 months
Mucosa inflammation (PT, AEs)	79	n.a. [31.0; n.a.] *14 (17.7)*	81	n.a. [n.a.; n.a.] *2 (2.5)*	7.61 [1.73; 33.55]; 0.002 AD = n.c.
Weight decreased (PT, severe AEs)	79	n.a. [n.a.; n.a.] *23 (29.1)*	81	n.a. [n.a.; n.a.] *0 (0)*	n.a.; < 0.001 AD = n.c.
Stomatitis (PT, SAEs)	79	n.a. [n.a.; n.a.] *4 (5.1)*	81	n.a. [n.a.; n.a.] *0 (0)*	n.a.; 0.048 AD = n.c.
Musculoskeletal and connective tissue disorders (SOC, SAEs)	79	n.a. [39.5; n.a.] *6 (7.6)*	81	n.a. [n.a.; n.a.] *0 (0)*	n.a.; 0.033 AD = n.c.
Diarrhoea (PT, severe AEs)	79	n.a. [n.a.; n.a.] *5 (6.3)*	81	n.a. [n.a.; n.a.] *0 (0)*	n.a.; 0.029 AD = n.c.
General disorders and administration site conditions (SOC, severe AEs)	79	n.a. [n.a.; n.a.] *6 (6.3)*	81	n.a. [n.a.; n.a.] *0 (0)*	n.a.; 0.014 AD = n.c.
Examinations (SOC, severe AEs)	79	n.a. [n.a.; n.a.] *26 (32.9)*	81	n.a. [n.a.; n.a.] *11 (13.6)*	2.50 [1.23; 5.08]; 0.009 AD = n.c.
Hypokalemia (PT, severe AEs)	79	n.a. [n.a.; n.a.] *5 (6.3)*	81	n.a. [n.a.; n.a.] *0 (0)*	n.a.; 0.032 AD = n.c.

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Data from the written statement of the pharmaceutical company.
[c] Termination of therapy with alpelisib or placebo and/or fulvestrant.

Abbreviations used:
AD: absolute difference; BPI-SF: Brief Pain Inventory-Short Form; CDK: cyclin-dependent kinase; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L: European Quality of Life-5 Dimensions-5-Level; HR = Hazard Ratio; CI = confidence interval; n: Number of patients with (at least 1) event; N: number of patients evaluated; n.c. = not calculable; n.a.: not achieved; RCT: randomised controlled trial; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus

b2) Men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after

disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

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

a1) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are not present

and

a2) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are present

approx. 1 835–16,675 patients

a3) Men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation

approx. 10–250 patients

b1) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage

approx. 475–4,395 patients

b2) Men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage

approx. 2–65 patients

2. 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 Piqray (active ingredient: alpelisib in combination with fulvestrant) at the following publicly accessible link (last access: 11 November 2020):

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

Treatment with alpelisib in combination with fulvestrant 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.

In accordance with the specifications of the EMA regarding additional measures for risk minimisation, the pharmaceutical company must provide training material. The training material for health professionals prescribing Piqray includes, in particular, instructions on the management of severe hyperglycaemia, including ketoacidosis, potentially occurring with alpelisib.

3. Treatment costs

Annual treatment costs:

a1) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are not present

and

a2) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a

PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are present

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Alpelisib	€ 78,481.52
Fulvestrant	€ 8,419.41
Total:	€ 86,900.93
Appropriate comparator therapy:	
Ribociclib in combination with a non-steroidal aromatase inhibitor	
Ribociclib	€ 29,711.33
Non-steroidal aromatase inhibitor	€ 169.27 – 189.22
Total:	€ 29,880.60 – 29,900.55
Ribociclib in combination with fulvestrant	
Ribociclib	€ 29,711.33
Fulvestrant	€ 8,419.41
Total:	€ 38,130.74
Anastrozole	€ 189.22
Letrozole	€ 169.27
Fulvestrant	€ 7,818.03
Tamoxifen	€ 71.32

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2021

Costs for additionally required SHI services: not applicable

a3) Men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Alpelisib	€ 78,481.52
Fulvestrant	€ 8,419.41
Total:	€ 86,900.93
Appropriate comparator therapy:	
Therapy according to the doctor's instructions	

Designation of the therapy	Annual treatment costs/patient
- Tamoxifen[a]	€ 71.32
[a] Costs are shown only for the active ingredient tamoxifen. In addition to tamoxifen, aromatase inhibitors in combination with a GnRH analogue and fulvestrant are also suitable comparators for the present benefit assessment in the context of therapy according to the doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, which is why no costs are presented for these medicinal products.	

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2021

Costs for additionally required SHI services: not applicable

b1) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Alpelisib	€ 78,481.52
Fulvestrant	€ 8,419.41
Total:	€ 86,900.93
Appropriate comparator therapy:	
Abemaciclib in combination with fulvestrant	
Abemaciclib	€ 29,792.95
Fulvestrant	€ 7,818.03
Total:	€ 37,610.98
Ribociclib in combination with fulvestrant	
Ribociclib	€ 29,711.33
Fulvestrant	€ 8,419.41
Total:	€ 38,130.74
Tamoxifen	€ 71.32
Anastrozole	€ 189.22
Fulvestrant	€ 7,818.03
Letrozole	€ 169.27
Exemestane	€ 424.50
Everolimus in combination with exemestane	
Everolimus	€ 16,600.44

Designation of the therapy	Annual treatment costs/patient
Exemestane	€ 424.50
Total:	€ 17,024.94

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2021

Costs for additionally required SHI services: not applicable

b2) Men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Alpelisib	€ 78,481.52
Fulvestrant	€ 8,419.41
Total:	€ 86,900.93
Appropriate comparator therapy:	
Therapy according to the doctor's instructions - Tamoxifen[a]	€ 71.32
[a] Costs are shown only for the active ingredient tamoxifen. In addition to tamoxifen, aromatase inhibitors in combination with a GnRH analogue and fulvestrant are also suitable comparators for the present benefit assessment in the context of therapy according to the doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, which is why no costs are presented for these medicinal products.	

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2021

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 18 February 2021.

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

Berlin, 18 February 2021

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

Prof. Hecken