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 – Palbociclib

of 18 May 2017

At its session on 18 May 2017 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 18 May 2017 (Federal Gazette, BAnz AT 6 June 2017 B5), as follows:

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

Palbociclib

Resolution of: 18 May 2017
Entry into force on: 18 May 2017
Federal Gazette, BAnz AT DD MM YYYY Bx

Approved therapeutic indication (according to the marketing authorisation of 9 November 2016):

Ibrance is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer:

- in combination with an aromatase inhibitor;
- in combination with fulvestrant 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 = luteinizing hormone-releasing hormone).

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

a1) Post-menopausal patients in first-line treatment:

Appropriate comparator therapy:

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

Extent and probability of the additional benefit compared with letrozole:

An additional benefit is not proven

a2) Pre-/peri-menopausal patients in first-line treatment:

Appropriate comparator therapy:

Tamoxifen in combination with an elimination of ovarian function.

Extent and probability of the additional benefit compared with the appropriate comparator therapy:

An additional benefit is not proven

b1) Post-menopausal patients with progression after previous endocrine therapy:

Appropriate comparator therapy:

- 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 compared with the appropriate comparator therapy:

An additional benefit is not proven

b2) Pre-/peri-menopausal patients with progression after previous endocrine therapy:

Appropriate comparator therapy:

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

Extent and probability of the additional benefit compared with the appropriate comparator therapy:

An additional benefit is not proven

Study results according to endpoints:

a1) Post-menopausal patients in first-line treatment:

PALOMA-2 study: Palbociclib + letrozole vs placebo + letrozole[1]

Endpoint	**Intervention group** Palbociclib + letrozole		**Control group** (Placebo +) letrozole		Intervention vs control
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference
Mortality					
Overall survival					
	444	no data available 95 (21.4)	222	no data available 38 (17.1)	RR: 1.25 [0.89; 1.76] 0.198
Morbidity					
Progression-free survival[2]					
	444	24.8 [22.1; n.a.] 194 (43.7)	222	14.5 [12.9; 17.1] 137 (61.7)	HR: 0.58 [0.46; 0.72] < 0.001 AD: + 10.3 months[a]

[1] Data from the IQWiG dossier assessment (A 16-74), unless otherwise indicated.
[2] Data from the IQWiG addendum to order A16-74

Endpoint	**Intervention group** Palbociclib + letrozole		**Control group** (Placebo +) letrozole		Intervention vs control
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference
Time to first subsequent chemotherapy[2]					
	444	n.a. [30.8; n.a.] 107 (24.1)	222	n.a. [n.a.; n.a.] 71 (32.0)	HR: 0.70 [0.52; 0.94] 0.017
Time to first subsequent intravenous chemotherapy[2]					
	444	n.a. [n.a.; n.a.] 71 (16.0)	222	n.a. [n.a.; n.a.] 51 (23.0)	HR: 0.66 [0.46; 0.95] 0.024

Endpoint	**Intervention group** Palbociclib + letrozole			**Control group** Placebo + letrozole			Intervention vs control
	N	Values at the start of study MV (SD)	Change at the end of treatment MV (SD)	N	Values at the start of study MV (SD)	Change at the end of treatment MV (SD)	MD [95% CI] p value
Morbidity							
Health status (EQ-5D-VAS)							
	437[b]	71.3 (21.2)	−3.4 (21.2)	218	72.3 (19.8)	−0.6 (17.9)	−0.18 [−2.29; 1.93] 0.869

(Continuation)

Endpoint	**Intervention group** Palbociclib + letrozole		**Control group** (Placebo +) letrozole		Intervention vs control
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference
Health-related quality of life – time to deterioration					
FACT-B					

Endpoint	**Intervention group** Palbociclib + letrozole		**Control group** (Placebo +) letrozole		Intervention vs control
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference
FACT-G Total Score[d] (decrease by ≥ 7 points)					
	439[e]	7.6 [5.6; 11.0] 262 (59.7)	218[e]	9.2 [5.6; 12.9] 118 (54.1)	HR: 1.06 [0.85; 1.31] 0.601
FACT-G Total Score (decrease by ≥ 5 points)					
	439[e]	5.5 [3.7; 8.1] 276 (62.9)	218[e]	5.6 [3.7; 9.3] 130 (59.6)	HR: 0.98 [0.80; 1.21] 0.919
Breast Cancer Subscale (decrease by ≥ 2 points)					
	439[e]	5.6 [3.9; 7.5] 279 (63.6)	218[e]	7.5 [5.5; 12.9] 120 (55.0)	HR: 1.18 [0.95; 1.46] 0.121
Trial Outcome Index (decrease by ≥ 5 points)					
	439[e]	7.4 [5.6; 11.0] 265 (60.4)	218[e]	9.2 [3.7; 11.3] 126 (57.8)	HR: 0.98 [0.79; 1.21] 0.917
FACT-G sub-scales (decrease by ≥ 2 points)					
Physical well-being	439[e]	4.1 [3.7; 5.6] 302 (68.8)	218[e]	3.7 [2.0; 5.6] 150 (68.8)	HR: 0.92 [0.76; 1.12] 0.448
Social well-being	439[e]	5.5 [3.7; 6.2] 284 (6.7)	218[e]	3.7 [1.9; 5.5] 139 (63.8)	HR: 0.86 [0.70; 1.06] 0.173
Emotional well-being	439[e]	8.5 [6.5; 11.2] 260 (59.2)	218[e]	11.1 [5.7; 16.7] 120 (55.0)	HR: 1.03 [0.83; 1.28] 0.741
Functional well-being	439[e]	5.6 [3.8; 7.6] 284 (64.7)	218[e]	3.7 [2.6; 7.3] 139 (63.8)	HR: 0.91 [0.74; 1.11] 0.365
Side effects					
Adverse events (presented additionally)					
	444	no data available 439 (98.9)	222	no data available 212 (95.5)	–

(Continuation)

Endpoint	**Intervention group** Palbociclib + letrozole		**Control group** (Placebo +) letrozole		Intervention vs control
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference
Serious adverse events (SAE)					
	444	n.a. [n.a.; n.a.] 87 (19.6)	222	n.a. [n.a.; n.a.] 28 (12.6)	HR: 1.63 [1.06; 2.49] 0.023
Severe AE (CTCAE grade 3 or 4)					
	444	1.0 [1.0; 1.4] 344 (77.5)	222	n.a. [n.a.; n.a.] 56 (25.2)	HR: 5.50 [4.14; 7.31] < 0.001
Severe AE (CTCAE grade 3 or 4), without laboratory values					
	444	n.a. [n.a.; n.a.] 156 (35.1)	222	n.a. [n.a.; n.a.] 56 (25.2)	HR: 1.47 [1.08; 1.99] 0.013
Discontinuation because of AE					
Discontinuation of palbociclib or placebo	444	n.a. [n.a.; n.a.] 41 (9.2)	222	n.a. [n.a.; n.a.] 12 (5.4)	HR: 1.74 [0.92; 3.32] 0.087
Discontinuation of all active ingredient components	444	no data available 27 (6.1)	222	no data available 11 (5.0)	RR: 1.23 [0.62; 2.43] 0.617

Endpoint	**Intervention group** Palbociclib + letrozole		**Control group** Placebo + letrozole	
	N	Patients with event n (%)	N	Patients with event n (%)
Frequent severe AE (CTCAE grade ≥ 3) (in PT ≥ 1% in at least one study arm)				
SOC[f] PT[f]				
Total rate of AE with CTCAE grade ≥ 3	444	346 (77.9)[g]	222	58 (26.1)[h]
Blood and lymphatic system disorders	444	258 (58.1)	222	6 (2.7)
Anaemia	444	25 (5.4)	222	4 (1.8)

Endpoint	**Intervention group** Palbociclib + letrozole		**Control group** Placebo + letrozole	
	N	Patients with event n (%)	N	Patients with event n (%)
Febrile neutropoenia	444	8 (1.8)	222	0 (0)
Leukopoenia	444	66 (14.9)	222	0 (0)
Neutropoenia	444	245 (55.2)	222	2 (0.9)
Thrombocytopoenia	444	6 (1.4)	222	0 (0)
Cardiac disorders	444	11 (2.5)	222	1 (0.5)
Eye disorders	444	6 (1.4)	222	0 (0)
Gastrointestinal disorders	444	27 (6.1)	222	12 (5.4)
Diarrhoea	444	6 (1.4)	222	3 (1.4)
Nausea	444	1 (0.2)	222	4 (1.8)
Vomiting	444	2 (0.5)	222	3 (1.4)
General disorders and administration site conditions	444	37 (8.3)	222	6 (2.7)
Asthenia	444	10 (2.3)	222	0 (0)
Fatigue	444	8 (1.8)	222	1 (0.5)
General deterioration of the physical health status	444	5 (1.1)	222	1 (0.5)
Infections and infestations	444	29 (6.5)	222	10 (4.5)
Pneumonia	444	5 (1.1)	222	2 (0.9)
Renal infection	444	5 (1.1)	222	0 (0)
Injury, poisoning, and procedural complications	444	8 (1.8)	222	1 (0.5)
Investigations	444	109 (24.5)	222	5 (2.3)
Increased alanine aminotransferase	444	10 (2.3)	222	0 (0)
Increased aspartate aminotransferase	444	11 (2.5)	222	2 (0.9)

Endpoint	**Intervention group** Palbociclib + letrozole		**Control group** Placebo + letrozole	
	N	Patients with event n (%)	N	Patients with event n (%)
Reduced neutrophil number	444	67 (15.1)	222	1 (0.5)
Reduced leukocyte number	444	46 (10.4)	222	0 (0)
Metabolism and nutrition disorders	444	15 (3.5)	222	6 (2.7)
Musculoskeletal and connective tissue disorders	444	13 (2.9)	222	6 (2.7)
Back pain	444	6 (1.4)	222	0 (0)
Pain in one extremity	444	1 (0.2)	222	3 (1.4)
Nervous system disorders	444	12 (2.7)	222	9 (41)
Headache	444	1 (0.2)	222	4 (1.8)
Syncope	444	5 (1.1)	222	3 (1.4)
Renal and urinary disorders	444	11 (2.5)	222	0 (0)
Respiratory, thoracic and mediastinal disorders	444	16 (3.6)	222	8 (3.6)
Dyspnoea	444	5 (1.1)	222	3 (1.4)
Pulmonary embolism	444	6 (1.4)	222	5 (2.3)
Skin and subcutaneous tissue disorders	444	6 (1.4)	222	2 (0.9)
Vascular disorders	444	16 (3.6)	222	13 (5.9)
Hypertension	444	15 (3.4)	222	13 (5.9)

a: Own calculation
b: Number of patients included in the evaluation to calculate the effect estimator. Number of patients for whom a measurement was available at the end of treatment: Palbociclib + letrozole N = 179 and letrozole N = 131. The values at the start of the study are based on other patient numbers.
c: Effect, 95% CI, and p value: Mixed model with repeated measurements (MMRM) with an intercept term, the factors treatment, time, an interaction term treatment*time, and baseline as covariates.
d: The FACT-B total score is calculated as the sum of the general questionnaire FACT-G and the breast cancer specific sub-scale BCS.
e: Patients who have answered at least 80% of the questions

Endpoint	Intervention group Palbociclib + letrozole		Control group Placebo + letrozole	
	N	Patients with event n (%)	N	Patients with event n (%)
f: MedDRA Version: 18.1; SOC and PT designations taken from MedDRA without adaptation g: Of these, 276 (62.2%) were grade 3, 60 (13.5%) grade 4. and 10 (2.3%) grade 5; discrepancies within the study report (indicated elsewhere for the overall rate of AE with CTCAE grade 3 or 4; 344 patients) h: Of these, 49 (22.1%) were grade 3, 5 (2.3%) grade 4. and 4 (1.8%) grade 5; discrepancies within the study report (indicated elsewhere for the overall rate of AE with CTCAE grade 3 or 4; 56 patients). Abbreviations: AD: Absolute difference; BCS: Breast Cancer Subscale; CTCAE: Common Terminology Criteria for Adverse Events; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-G: Functional Assessment of Cancer Therapy – General; HR: hazard ratio; i.v.: intravenous; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients evaluated; n: number of patients with (at least one) event; n.a.: not achieved; PFS: progression-free survival; PT: preferred term RCT: randomised controlled trial; RR: relative risk; SOC: system organ class; SAE: serious adverse event; TOI: Trial Outcome Index; AE: adverse event; vs: versus				

a2) Pre-/peri-menopausal patients in first-line treatment:

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

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 patients in first-line treatment:

approx. 7,180–34,790 patients

a2) Pre-/peri-menopausal patients in first-line treatment:

approx. 1,190–5,760 patients

b1) Post-menopausal patients with progression after previous endocrine therapy:

approx. 5,310–25,740 patients

b2) Pre-/peri-menopausal patients with progression after previous 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 Ibrance® (active ingredient: palbociclib) at the following publicly accessible link (last access: 12 April 2017):

http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/003853/WC500217196.pdf

Treatment with palbociclib 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 patients in first-line treatment:

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed:	
Palbociclib plus aromatase inhibitor[3]	
Palbociclib	€ 66,527.76
Aromatase inhibitor	€ 289.05 – 418.07
Total	€ 66,816.81 – 66,945.83
Palbociclib plus fulvestrant	
Palbociclib	€ 66,527.76
Fulvestrant	€ 10,501.01
Total	€ 77,028.77
Appropriate comparator therapy:	
Anastrozole	€ 303.39
Letrozole	€ 289.05
Tamoxifen	€ 71.10

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 May 2017

Costs for additionally required SHI services: not applicable

[3] Anastrozole, letrozole or exemestane

a2) Pre-/peri-menopausal patients in first-line treatment:

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed:	
Palbociclib plus aromatase inhibitor[4]	
Palbociclib	€ 66,527.76
Aromatase inhibitor	€ 289.05 – 418.07
Total	€ 66,816.81 – 66,945.83
Palbociclib plus fulvestrant	
Palbociclib	€ 66,527.76
Fulvestrant	€ 10,501.01
Total	€ 77,028.77
LHRH analogues[5]	€ 1,759.02 – 2,235.96
Appropriate comparator therapy:	
Tamoxifen plus LHRH analogues[5]	
Tamoxifen	€ 71.10
LHRH analogues	€ 1,759.02 – 2,235.96
Total	€ 1,830.12 – 2,307.06

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 May 2017

Costs for additionally required SHI services: not applicable

b1) Post-menopausal patients with progression after previous endocrine therapy:

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed:	
Palbociclib plus aromatase inhibitor[4]	
Palbociclib	€ 66,527.76
Aromatase inhibitor	€ 289.05 – 418.07
Total	€ 66,816.81 – 66,945.83
Palbociclib plus fulvestrant	
Palbociclib	€ 66,527.76
Fulvestrant	€ 10,501.01
Total	€ 77,028.77

[4] Anastrozole, letrozole or exemestane
[5] Leuprorelin or goserelin

Designation of the therapy	Annual treatment costs per patient
Appropriate comparator therapy:	
Tamoxifen	€ 71.10
Anastrozole	€ 303.39
Fulvestrant	€ 10,501.01
Letrozole	€ 289.05
Exemestane	€ 418.07
Everolimus plus exemestane	
Everolimus	€ 53,738.75
Exemestane	€ 418.07
Total	€ 54,156.82

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 May 2017

Costs for additionally required SHI services: not applicable

b2) Pre-/peri-menopausal patients with progression after previous endocrine therapy:

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed:	
Palbociclib plus aromatase inhibitor[6]	
Palbociclib	€ 66,527.76
Aromatase inhibitor	€ 289.05 – 418.07
Total	€ 66,816.81 – 66,945.83
Palbociclib plus fulvestrant	
Palbociclib	€ 66,527.76
Fulvestrant	€ 10,501.01
Total	€ 77,028.77
LHRH analogues[7]	€ 1,759.02 – 2,235.96
Appropriate comparator therapy: An endocrine therapy according to the doctor's instructions	
Tamoxifen	€ 71.10
Medroxyprogesterone acetate	€ 1,081.79 – 2,163.58
Megestrol acetate	€ 5,409.30
Exemestane	€ 418.07
Letrozole	€ 289.05

[6] Anastrozole, letrozole or exemestane
[7] Leuprorelin or goserelin

Designation of the therapy	Annual treatment costs per patient
Leuprorelin	€ 1,759.02
Goserelin	€ 2,235.96

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 May 2017

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 18 May 2017.**
2. **The period of validity of this resolution shall be limited in accordance with the following provisions:**

   a) Regarding patient group

   a1) Post-menopausal patients in first-line treatment

   the conclusions arrived at under Section Nos. 1, 2, 3 and 4 are limited until 1 March 2019.

   b) The statements made on the patient groups

   b1) Post-menopausal patients with progression after previous endocrine therapy, and

   b2) Pre-/peri-menopausal patients with progression after previous endocrine therapy

   the conclusions arrived at under Section Nos. 1, 2, 3 and 4 are limited until 1 October 2018.

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

Berlin, 18 May 2017

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

Prof. Hecken