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
Pembrolizumab: (reassessment after the deadline: breast cancer, triple-negative, high risk of recurrence, neoadjuvant and adjuvant therapy, monotherapy or combination with chemotherapy)

of 20 March 2025

At its session on 20 March 2025, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. The information on Pembrolizumab in the version of the resolution of 15 December 2022 (BAnz AT 27.01.2023 B2), last modified on 28 March 2023, is repealed.

2. In Annex XII, the following information shall be added after Number 5 to the information on the benefit assessment of Pembrolizumab in the version of the resolution of 17 October 2024 on the therapeutic indication "in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment for resectable non-small cell lung carcinoma at high risk of recurrence ":

Pembrolizumab

Resolution of: 20 March 2025
Entry into force on: 20 March 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 19 May 2022):

KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence.

Therapeutic indication of the resolution (resolution of 20 March 2025):

See new therapeutic indication according to marketing authorisation.

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

Adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence; neoadjuvant and adjuvant therapy

Appropriate comparator therapy:

An individualised taxane and anthracycline-based neoadjuvant chemotherapy with selection of:

- Cyclophosphamide
- Docetaxel
- Doxorubicin
- Epirubicin
- Paclitaxel
- Carboplatin

followed by monitoring wait-and-see approach after surgery

a) Extent and probability of additional benefit of pembrolizumab in combination with paclitaxel and carboplatin followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant) versus paclitaxel and carboplatin followed by doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and monitoring wait-and-see approach (adjuvant):

Indication of a minor additional benefit

b) Extent and probability of the additional benefit of pembrolizumab in combination with chemotherapy other than paclitaxel and carboplatin followed by pembrolizumab in combination with chemotherapy other than doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant) versus the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence; neoadjuvant and adjuvant therapy

a) Pembrolizumab in combination with paclitaxel and carboplatin followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival.
Morbidity	↑↑	Advantage in the avoidance of failure of the curative therapeutic approach (event rate and event-free survival).
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↓↓	Disadvantages in the endpoints of SAE and discontinuation due to AEs. In detail, disadvantages in 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 ∅: No data available. n.a.: not assessable		

KEYNOTE 522 study:

- ongoing, double-blind, randomised, controlled phase III study
- Pembrolizumab + paclitaxel and carboplatin followed by pembrolizumab + doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant) *vs*

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A24-104) unless otherwise indicated.

paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide (neoadjuvant) and placebo (adjuvant)

– 4th data cut-off from 23 March 2021 and 7th data cut-off from 22 March 2024

Mortality

Endpoint	**Pembrolizumab + chemotherapy/ pembrolizumab**		**Chemotherapy/ monitoring wait-and-see approach**		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 (%)*	Hazard ratio (HR) [95% CI] p value[a]
Overall survival[b]					
	784	n.r. *115 (14.7)*	390	n.r. *85 (21.8)*	HR: 0.66 [0.50; 0.87] 0.003[c]

Morbidity

Endpoint	**Pembrolizumab + chemotherapy/ pembrolizumab**		**Chemotherapy/ monitoring wait-and-see approach**		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk (RR) [95% CI] p value[a]
Failure of the curative therapeutic approach[b]					
Event rate	784	*159 (20.3)*	390	*114 (29.2)*	0.69 [0.56; 0.85]; < 0.001
Death	784	*19 (2.4)*	390	*13 (3.3)*	-
Distant metastases	784	*4 (0.5)*	390	*1 (0.3)*	-
Distant recurrence	784	*77 (9.8)*	390	*56 (14.4)*	-
Local progression, which precludes a definitive surgery	784	*1 (0.1)*	390	*0 (0)*	-
Local progression, which precludes a surgery	784	*3 (0.4)*	390	*4 (1.0)*	-

Endpoint	**Pembrolizumab + chemotherapy/ pembrolizumab**		**Chemotherapy/ monitoring wait-and-see approach**		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk (RR) [95% CI] p value[a]
Local recurrence	784	*33 (4.2)*	390	*20 (5.1)*	-
Positive resection margin at the last surgery	784	*6 (0.8)*	390	*10 (2.6)*	-
Second primary tumour	784	*16 (2.0)*	390	*10 (2.6)*	-
	N	Median time to event [95% CI]	N	Median time to event [95% CI]	Hazard ratio (HR) [95% CI] p value[a]
Event-free survival	784	n.r.	390	n.r.	HR: 0.65 [0.51; 0.83] < 0.001[c]
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk (RR) [95% CI] p value[a]
Pathological complete remission (ypT0/Tis ypN0)[d] (presented additionally)					
	784	*494 (63.0)*	390	*217 (55.6)*	1.13 [1.02; 1.26] 0.016
Breast-conserving surgery					
	784	*354 (45.2)*	390	*178 (45.6)*	0.99 [0.87; 1.13] 0.889[e]
Symptomatology (EORTC QLQ-C30)					
	No suitable data				
Symptomatology (EORTC QLQ-BR23)					
	No suitable data				
Health status (EQ-5D VAS)					
	No suitable data				

Health-related quality of life

EORTC QLQ-C30
No suitable data

EORTC QLQ-BR23	
	No suitable data

Side effects[f]

Endpoint	**Pembrolizumab + chemotherapy/ pembrolizumab**		**Chemotherapy/ monitoring wait-and-see approach**		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk (RR) [95% CI] p value[a]
Total adverse events (presented additionally)					
	783	*777 (99.2)*	389	*389 (100)*	-
Serious adverse events (SAE)					
	783	*341 (43.6)*	389	*111 (28.5)*	1.53 [1.28; 1.82]; < 0.001
Severe adverse events (CTCAE grade ≥ 3)					
	783	*645 (82.4)*	389	*306 (78.7)*	1.05 [0.99; 1.11] 0.128
Therapy discontinuation due to adverse events[g]					
	783	*234 (29.9)*	389	*60 (15.4)*	1.94 [1.50; 2.50] < 0.001
Specific adverse events					
Immune-mediated AEs (presented additionally)	783	*341 (43.6)*	389	*85 (21.9)*	-
Immune-mediated SAEs	783	*83 (10.6)*	389	*5 (1.3)*	8.25 [3.37; 20.17]; < 0.001
Immune-mediated severe AEs[h]	783	*117 (14.9)*	389	*8 (2.1)*	7.27 [3.59; 14.72]; < 0.001
Other specific adverse events					
Blood and lymphatic system disorders (SOC, SAE)	783	*154 (19.7)*	389	*58 (14.9)*	1.32 [1.00; 1.74] 0.047
Injury, poisoning and procedural complications (SOC, SAE)	783	*23 (2.9)*	389	*4 (1.0)*	2.86 [0.99; 8.20] 0.041

Endpoint	Pembrolizumab + chemotherapy/ pembrolizumab		Chemotherapy/ monitoring wait-and-see approach		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk (RR) [95% CI] p value[a]
Endocrine disorders (SOC, severe AE[h])	783	*25 (3.2)*	389	*0 (0)*	25.37 [1.55; 415.62]; < 0.001
Gastrointestinal disorders (SOC, severe AE[h])	783	*92 (11.7)*	389	*28 (7.2)*	1.63 [1.09; 2.45] 0.016
General disorders and administration site conditions (SOC, severe AE[h])	783	*90 (11.5)*	389	*24 (6.2)*	1.86 [1.21; 2.87] 0.004
Hepatobiliary disorders (SOC, severe AE[h])	783	*24 (3.1)*	389	*2 (0.5)*	5.96 [1.42; 25.10] 0.005
Skin and subcutaneous tissue disorders (SOC, severe AE[h])	783	*49 (6.3)*	389	*3 (0.8)*	8.11 [2.55; 25.87] < 0.001

[a] IQWiG calculation of effect and CI (asymptotic). p value: IQWiG calculation (unconditional exact test, CSZ method according to Martín Andrés and Silva Mato,1994).
[b] Data cut-off from 22 March 2024
[c] HR, CI and p value: Cox proportional hazards model stratified by nodal status (positive vs negative), tumour size (T1/T2 vs T3/T4) and choice of carboplatin (every 3 weeks vs once weekly).
[d] Data cut-off from 23 March 2021; absence of invasive tumour cells in the breast and lymph nodes. Results taken from the dossier of the pharmaceutical company.
[e] Cochran-Mantel-Haenszel method, stratified by nodal status (positive vs negative), tumour size (T1/T2 vs T3/T4) and choice of carboplatin (Q3W vs once weekly)
[f] Data cut-off from 23 March 2021; the follow-up for AEs had already been completed at this data cut-off.
[g] Discontinuation of at least one component
[h] Operationalised as CTCAE grade ≥ 3

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; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; QLQ-BR23 = Quality of life Questionnaire and Breast Cancer Specific Module 23; QLQ-C30 = Quality of life Questionnaire - Core 30; RR = relative risk; SOC = system organ class; SAE = serious adverse event; AE = adverse event; vs = versus

b) Pembrolizumab in combination with chemotherapy other than paclitaxel and carboplatin followed by pembrolizumab in combination with chemotherapy other than doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)

No data are available to allow an 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
∅: No data available.
n.a.: not assessable

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

Adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence; neoadjuvant and adjuvant therapy

Approx. 2,440 - 2,610 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 Keytruda (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 11 March 2025):

https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with breast cancer, as well as specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with pembrolizumab as well as on infusion-related reactions.

4. Treatment costs

Annual treatment costs:

Adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence; neoadjuvant and adjuvant therapy

a) Pembrolizumab in combination with paclitaxel and carboplatin followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Neoadjuvant therapy:	
Pembrolizumab in combination with	
paclitaxel and carboplatin followed by doxorubicin and cyclophosphamide	
Pembrolizumab	€ 41,406.88
Paclitaxel	€ 4,888.56
Carboplatin	€ 1,268.44 - € 1,316.04
Doxorubicin	€ 1,281.12
Cyclophosphamide	€ 115.01
Total:	€ 50,276.05
Paclitaxel and carboplatin followed by epirubicin and cyclophosphamide	
Pembrolizumab	€ 41,406.88
Paclitaxel	€ 4,888.56
Carboplatin	€ 1,268.44 - € 1,316.04
Epirubicin	€ 1,874.28
Cyclophosphamide	€ 115.01
Total:	€ 50,869.21
Adjuvant therapy:	
Pembrolizumab monotherapy	
Pembrolizumab	€ 46,582.74 - € 51,758.60
Appropriate comparator therapy:	
An individualised taxane and anthracycline-based neoadjuvant chemotherapy with selection of: Cyclophosphamide, docetaxel, doxorubicin, epirubicin, paclitaxel, carboplatin	

Designation of the therapy	Annual treatment costs/ patient
followed by monitoring wait-and-see approach after surgery.	
Neoadjuvant therapy:	
paclitaxel and carboplatin followed by doxorubicin and cyclophosphamide	
Paclitaxel	€ 4,888.56
Carboplatin	€ 1,268.44 - € 1,316.04
Doxorubicin	€ 1,281.12
Cyclophosphamide	€ 115.01
Total:	€ 8,869.17
Paclitaxel and carboplatin followed by epirubicin and cyclophosphamide	
Paclitaxel	€ 4,888.56
Carboplatin	€ 1,268.44 - € 1,316.04
Epirubicin	€ 1,874.28
Cyclophosphamide	€ 115.01
Total:	€ 9,462.33
Docetaxel in combination with doxorubicin and cyclophosphamide	
Doxorubicin	€ 5,102.28
Cyclophosphamide	€ 401.25
Docetaxel	€ 12,311.28
Total:	€ 17,814.81
Adjuvant therapy:	
Monitoring wait-and-see approach	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 March 2025)

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	9.0 - 17.0	€ 900 - € 1,700

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1 - 3	4.0 - 12.0	€ 400 - € 1,200
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4.0 – 18.0	€ 400 - € 1,800
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	18.0	€ 1,800
Doxorubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4.0 – 18.0	€ 400 - € 1,800
Epirubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4.0	€ 400
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	12.0	€ 1,200

b) <u>Pembrolizumab in combination with chemotherapy other than paclitaxel and carboplatin followed by pembrolizumab in combination with chemotherapy other than doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)</u>

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Neoadjuvant therapy:	
Pembrolizumab in combination with	
Chemotherapy other than the one mentioned in the approval study	
Pembrolizumab	€ 41,406.88
Other chemotherapy	Not determinable
Adjuvant therapy:	
Pembrolizumab monotherapy	
Pembrolizumab	€ 46,582.74 - € 51,758.60
Appropriate comparator therapy:	
An individualised taxane and anthracycline-based neoadjuvant chemotherapy with selection of: Cyclophosphamide, docetaxel, doxorubicin, epirubicin, paclitaxel, carboplatin followed by monitoring wait-and-see approach after surgery.	
Neoadjuvant therapy:	
paclitaxel and carboplatin followed by doxorubicin and cyclophosphamide	
Paclitaxel	€ 4,888.56
Carboplatin	€ 1,268.44 - € 1,316.04
Doxorubicin	€ 1,281.12
Cyclophosphamide	€ 115.01
Total:	€ 8,869.17
Paclitaxel and carboplatin followed by epirubicin and cyclophosphamide	
Paclitaxel	€ 4,888.56
Carboplatin	€ 1,268.44 - € 1,316.04
Epirubicin	€ 1,874.28
Cyclophosphamide	€ 115.01
Total:	€ 9,462.33
Docetaxel in combination with doxorubicin and cyclophosphamide	
Doxorubicin	€ 5,102.28
Cyclophosphamide	€ 401.25
Docetaxel	€ 12,311.28
Total:	€ 17,814.81
Adjuvant therapy:	
Monitoring wait-and-see approach	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 March 2025)

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	9.0 - 17.0	€ 900 - € 1,700
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1 - 3	4.0 - 12.0	€ 400 - € 1,200
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4.0 – 18.0	€ 400 - € 1,800
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	18.0	€ 1,800
Doxorubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4.0 – 18.0	€ 400 - € 1,800
Epirubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4.0	€ 400
Paclitaxel	Surcharge for production of a parenteral	€ 100	3	12.0	€ 1,200

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	preparation containing cytostatic agents				

5. Designation of 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 assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence; neoadjuvant and adjuvant therapy

a) Pembrolizumab in combination with paclitaxel and carboplatin followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)

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

b) Pembrolizumab in combination with chemotherapy other than paclitaxel and carboplatin followed by pembrolizumab in combination with chemotherapy other than doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)

- No medicinal product with new active ingredients 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 20 March 2025.

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

Berlin, 20 March 2025

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

Prof. Hecken