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 (new therapeutic indication: breast cancer, triple-negative, high risk of recurrence, neoadjuvant and adjuvant therapy, monotherapy or combination with chemotherapy)

of 15 December 2022

At its session on 15 December 2022, 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. **In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Pembrolizumab in accordance with the resolution of 7 July 2019:**

Courtesy translation – only the German version is legally binding.

Pembrolizumab

Resolution of: 15 December 2022
Entry into force on: 15 December 2022
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 15 December 2022):

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:

Chemotherapy according to doctor's instructions for neoadjuvant treatment 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):

Hint for a minor additional benefit

b) Extent and probability of 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 chemotherapy according to doctor's instructions for neoadjuvant treatment followed by monitoring wait-and-see approach after surgery:

An additional benefit is not proven.

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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	↔	No relevant difference for the benefit assessment.
Morbidity	↑	Advantage in avoiding recurrences (recurrence rate and event-free survival)
Health-related quality of life	n.c.	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 ∅: There are no usable data for the benefit assessment. n.c.: not calculable		

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*** paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide (neoadjuvant) and placebo (adjuvant)
- 4th Data cut-off of 23 March 2021

[1] Data from the dossier assessment of the IQWiG (A22-63) and from the addendum (A22-119), unless otherwise indicated.

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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					
	784	n.a. [n.c.; n.c.] *80 (10.2)*	390	n.a. [n.c.; n.c.] *55 (14.1)*	0.72 [0.51; 1.02]; 0.065[b]

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]
Recurrences[c]					
Recurrence rate	784	*123 (15.7)*	390	*93 (23.8)*	0.66 [0.52; 0.84]; < 0.001
Death	784	*15 (1.9)*	390	*6 (1.5)*	–
Remote metastases	784	*4 (0.5)*	390	*1 (0.3)*	–
Remote recurrence	784	*60 (7.7)*	390	*51 (13.1)*	–
Local progression preventing definitive surgery	784	*1 (0.1)*	390	*0 (0)*	–

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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 progression preventing surgery	784	*3 (0.4)*	390	*4 (1.0)*	–
Local recurrence	784	*28 (3.6)*	390	*17 (4.4)*	–
Positive resection margin in the last surgery	784	*6 (0.8)*	390	*10 (2.6)*	–
Second primary tumour	784	*6 (0.8)*	390	*4 (1.0)*	–
	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.a. [n.c.; n.c.]	390	n.a. [n.c.; n.c.]	0.63 [0.48; 0.82]; < 0.001[b]
	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 usable data available.				
Symptomatology (EORTC QLQ-BR23)					
	No usable data available.				
Health status (EQ-5D VAS)					

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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]
	No usable data available.				

Health-related quality of life

EORTC QLQ-C30	
	No usable data available.
EORTC QLQ-BR23	
	No usable data available.

Side effects

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	*234 (29.9)*	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					
	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	*341 (43.6)*	–
Immune-mediated SAEs	783	*83 (10.6)*	389	*83 (10.6)*	8.25 [3.37; 20.17]; < 0.001

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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]
Immune-mediated severe AEs[f]	783	*117 (14.9)*	389	*117 (14.9)*	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
Endocrine disorders (SOC, severe AE[f])	783	*25 (3.2)*	389	*0 (0)*	25.37 [1.55; 415.62]; < 0.001
Gastrointestinal disorders (SOC, severe AE[f])	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[f])	783	*90 (11.5)*	389	*24 (6.2)*	1.86 [1.21; 2.87]; 0.004
Hepatobiliary disorders (SOC, severe AE[f])	783	*24 (3.1)*	389	*2 (0.5)*	5.96 [1.42; 25.10]; 0.005
Skin and subcutaneous tissue disorders (SOC, severe AE[f])	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] 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).
[c] Percentage of patients, individual components are shown in the rows below (in each case only with the qualifying events that come into play in the formation of the combined endpoint; calculation of effect estimators therefore not meaningful)
[d] 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)

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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]
[f] operationalised as CTCAE grade ≥ 3 Abbreviations used: 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; RCT = randomised controlled trial; 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 ∅: There are no usable data for the benefit assessment. n.c.: not calculable		

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. 2440 - 2520 patients

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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: 1 July 2022):

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	€ 45,825.92
Paclitaxel	€ 5,138.40
Carboplatin	€ 1,268.20 - € 1,315.32
Doxorubicin	€ 1,252.00
Cyclophosphamide	€ 169.30
Total	€ 53,653.82 - € 53,700.94

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Designation of the therapy	Annual treatment costs/ patient
Additionally required SHI services	€ 176.77
Paclitaxel and carboplatin followed by epirubicin and cyclophosphamide	
Pembrolizumab	€ 45,825.92
Paclitaxel	€ 5,138.40
Carboplatin	€ 1,268.20 - € 1,315.32
Epirubicin	€ 1,873.84
Cyclophosphamide	€ 169.30
Total	€ 54,275.66 - € 54,322.78
Additionally required SHI services	€ 176.77
Adjuvant treatment	
Pembrolizumab monotherapy	
1st treatment year	
Pembrolizumab	€ 51,554.16 - € 57,282.40
Subsequent years	
Pembrolizumab	€ 99,671.38
Appropriate comparator therapy:	
Neoadjuvant therapy	
Therapy according to doctor's instructions[2]	No data available
Adjuvant treatment	
Monitoring wait-and-see approach	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 November 2022)

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 - 17.4	€ 900 - € 1,740
Carboplatin	Surcharge for production of a	€ 100	1 - 3	4.0 - 12.0	€ 400 - € 1,200

[2] For the present benefit assessment, a sequential or combined chemotherapy regimen containing a taxane and an anthracycline is a suitable comparator in the context of a therapy according to doctor's instructions in the neoadjuvant phase. However, taxanes are not approved in the present therapeutic indication and therefore, the costs are not represented.

Courtesy translation – only the German version is legally binding.

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	parenteral preparation containing cytostatic agents				
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4.0	€ 400
Doxorubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4.0	€ 400
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) 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)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Neoadjuvant therapy	
Pembrolizumab in combination with a chemotherapy other than the one mentioned in the marketing authorisation study	
Pembrolizumab	€ 45,825.92
Other chemotherapy	Not determinable

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Designation of the therapy	Annual treatment costs/ patient
Adjuvant treatment	
Pembrolizumab monotherapy	
1st treatment year	
Pembrolizumab	€ 51,554.16 - € 57,282.40
Subsequent years	
Pembrolizumab	€ 99,671.38
Appropriate comparator therapy:	
Neoadjuvant therapy	
Therapy according to doctor's instructions[3]	No data available
Adjuvant treatment	
Monitoring wait-and-see approach	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 November 2022)

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 - 17.4	€ 900 - € 1,740
Other chemotherapy	Not determinable				

5. 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 Pembrolizumab

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with pembrolizumab for the neoadjuvant and, subsequently

[3] For the present benefit assessment, a sequential or combined chemotherapy regimen containing a taxane and an anthracycline is a suitable comparator in the context of a therapy according to doctor's instructions in the neoadjuvant phase. However, taxanes are not approved in the present therapeutic indication and therefore, the costs are not represented.

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after surgery, for the adjuvant treatment of adults with locally advanced, or early triple-negative breast cancer at high risk of recurrence on the basis of the marketing authorisation granted under Medicinal Products Act:

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

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

II. Entry into force

1. **The resolution will enter into force on the day of its publication on the website of the G-BA on 15 December 2022.**

2. **The period of validity of the resolution is limited to 1 October 2024.**

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

Berlin, 15 December 2022

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

Prof. Hecken

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