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 (change to the therapeutic indication: oesophageal or gastro-oesophageal junction carcinoma, PD-L1 expression ≥ 10 (CPS), first-line, combination with platinum and fluoropyrimidine-containing chemotherapy)
Pembrolizumab (new therapeutic indication: gastric or gastro-oesophageal junction adenocarcinoma, PD-L1 expression ≥ 1, HER2-, first-line, combination with fluoropyrimidine and platinum-containing chemotherapy)

of 20 June 2024

At its session on 20 June 2024, the Federal Joint Committee (G-BA) resolved to amend Annex XII of 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. The information on the active ingredient Pembrolizumab (new therapeutic indication: oesophageal or gastro-oesophageal junction carcinoma, PD-L1 expression ≥ 10 (CPS), first-line, combination with fluoropyrimidine and platinum-containing chemotherapy) in the version of the resolution of 5 May 2022 (BAnz AT 27.05.2022 B2) shall be amended as follows:

1. The following information is added after the information under the heading "New therapeutic indication (according to the marketing authorisation of 24 June 2021)":

"**Therapeutic indication (according to the marketing authorisation of 23 November 2023)**

KEYTRUDA, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥ 10."

2. Under number 1 "Additional benefit of the medicinal product in relation to the appropriate comparator therapy", under the heading "Study results by endpoint", under number 2 "Number of patients or demarcation of the patient groups eligible for

treatment" and under number 4 "Treatment costs", a footnote "2" is added in each case after the words "or of the gastro-oesophageal junction".

3. The explanatory text of the footnote is worded as follows:

"The therapeutic indication for pembrolizumab was amended on 23 November 2023, among other things, to the effect that the information in section 4.1. on the indication "Oesophageal carcinoma" with reference to "HER2-negative adenocarcinoma of the gastro-oesophageal junction" was deleted and moved to the new therapeutic indication with the heading "Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma". The findings on sub-population b1) "Adults with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy" were updated by resolution of 20 June 2024 for patients with locally advanced unresectable or metastatic HER2-negative adenocarcinoma of the gastro-oesophageal junction in adults whose tumours express PD-L1 (CPS ≥ 1)."

II. The following information is added after No. 5 to the information on the benefit assessment of Pembrolizumab in the version of the resolution of 20 June 2024 for the therapeutic indication: "Gastric or gastro-oesophageal junction adenocarcinoma, PD-L1 expression ≥ 1, HER2+, first-line, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy":

Pembrolizumab

Resolution of: 20 June 2024
Entry into force on: 20 June 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 23 November 2023):

KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

Therapeutic indication of the resolution (resolution of 20 June 2024):

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 unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

Appropriate comparator therapy for pembrolizumab in combination with fluoropyrimidine and platinum-containing chemotherapy:

- cisplatin + capecitabine

  or

- oxaliplatin + capecitabine

  or

- cisplatin + S-1 (tegafur/ gimeracil/ oteracil)

  or

- cisplatin + 5-fluorouracil (only for patients with adenocarcinoma of the oesophagus)

  or

- cisplatin + 5-fluorouracil + folinic acid (only for patients with adenocarcinoma of the oesophagus)

  or

- epirubicin + cisplatin + capecitabine

  or

- epirubicin + cisplatin + 5-fluorouracil

  or

- epirubicin + oxaliplatin + capecitabine

  or

- docetaxel + cisplatin + 5-fluorouracil

  or

- Nivolumab in combination with fluoropyrimidine and platinum-containing combination chemotherapy (only for tumours with PD-L1 expression (Combined Positive Score [CPS] ≥ 5))

  or

- 5-fluorouracil + oxaliplatin + epirubicin (only for patients with adenocarcinoma of the oesophagus)

Extent and probability of the additional benefit of pembrolizumab in combination with fluoropyrimidine and platinum-containing chemotherapy compared with cisplatin + 5-fluorouracil or cisplatin + capecitabine or oxaliplatin + capecitabine

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.
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		

Meta-analysis from the KEYNOTE-859 and KEYNOTE-062 studies

KEYNOTE-859 study

Pembrolizumab + fluoropyrimidine and platinum-containing chemotherapy* vs fluoropyrimidine and platinum-containing chemotherapy*

(* cisplatin + 5-fluorouracil or oxaliplatin + capecitabine)

KEYNOTE-062 study

Pembrolizumab + fluoropyrimidine and platinum-containing chemotherapy* vs fluoropyrimidine and platinum-containing chemotherapy*

(* cisplatin + 5-fluorouracil or cisplatin + capecitabine)

Relevant or approximate sub-population used:

Patients treated according to the appropriate comparator therapy, in particular treatment with cisplatin + 5-fluorouracil only in patients with adenocarcinoma of the oesophagus.

1 Data from IQWiG's dossier assessment (A24-02)

Mortality

Endpoint	**Pembrolizumab + chemotherapy** [a]		**Chemotherapy** [a]		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 [95% CI] p value
Overall survival					
KEYNOTE 062 [b]	159 [c]	n.d. 125 (78.6)	155 [c]	n.d. 132 (85.2)	0.77 [0.6; 0.98] 0.037 [d]
KEYNOTE 859 [e]	618 [c]	13.0 [11.6; 14.2] 464 (75.1)	617 [c]	11.4 [10.5; 12.0] 526 (85.3)	0.74 [0.65; 0.84] < 0.001 [f]
Total					0.75 [0.67; 0.84] < 0.001

Morbidity

Endpoint	**Pembrolizumab + chemotherapy** [a]		**Placebo + chemotherapy** [a]		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	N	Median survival time in months [95% CI] *Patients with event n (%)*
KEYNOTE 062	No suitable data for a quantitative or qualitative summary				
KEYNOTE 859					
Total					

Health-related quality of life

Endpoint	**Pembrolizumab + chemotherapy** [a]		**Placebo + chemotherapy** [a]		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	N	Median survival time in months [95% CI] *Patients with event n (%)*
KEYNOTE 062	No suitable data for a quantitative or qualitative summary				

KEYNOTE 859	
Total	

Side effects

Endpoint	**Pembrolizumab + chemotherapy [a]**		**Placebo + chemotherapy [a]**		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	N	Median survival time in months [95% CI] *Patients with event n (%)*
KEYNOTE 062	No suitable data for a quantitative or qualitative summary				
KEYNOTE 859					
Total					

a Cisplatin + 5-FU or cisplatin + capecitabine was used as chemotherapy in the KEYNOTE 062 study and cisplatin + 5-FU or oxaliplatin + capecitabine in the KEYNOTE 859 study.

b Pre-specified 3rd data cut-off: 26.03.2019

c Patients in the approximate sub-population used

d Effect and CI: Cox proportional hazards model, unstratified; p value: own calculation based on 95% CI

e Pre-specified 1st data cut-off: 03.10.2022

f Effect and CI: Cox proportional hazards model; stratified by region (Europe/ Israel/ North America/ Australia vs Asia vs rest of the world) and chemotherapy (FP vs CAPOX)

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; 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.r. = not reached; vs = versus

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

Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

Approx. 285 – 2,613 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: 6 May 2024):

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 as well as specialists in internal medicine and gastroenterology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with gastric or gastro-oesophageal junction carcinomas.

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 unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab in combination with cisplatin and 5-fluorouracil (5-FU)	
Pembrolizumab	€ 97,656.46
Cisplatin	€ 11,370.90
5-FU	€ 1,794.81
Total	€ 110,822.17
Additionally required SHI services	€ 1,642.91 - € 2,108.09
Pembrolizumab in combination with oxaliplatin and capecitabine	
Pembrolizumab	€ 97,656.46
Oxaliplatin	€ 8,301.02
Capecitabine	€ 2,169.32
Total	€ 108,126.79
Appropriate comparator therapy:	

Designation of the therapy	Annual treatment costs/ patient
Cisplatin in combination with capecitabine	
Cisplatin	€ 2,274.18
Capecitabine	€ 2,085.66
Total	€ 4,359.84
Additionally required SHI services	€ 328.58 - € 421.62
Oxaliplatin in combination with capecitabine	
Oxaliplatin	€ 8,301.02
Capecitabine	€ 2,085.66
Total	€ 10,386.68
Cisplatin in combination with S-1 (tegafur/ gimeracil/ oteracil)	
Cisplatin	€ 692.82
S-1 (tegafur/ gimeracil/ oteracil)	€ 6,993.74
Total	€ 7,686.56
Additionally required SHI services	€ 156.26 - € 209.73
Cisplatin in combination with 5-fluorouracil (5-FU) (only for patients with adenocarcinoma of the oesophagus)	
Cisplatin	€ 2,274.18
5-FU	€ 1,794.81
Total	€ 4,068.99
Additionally required SHI services	€ 328.58 - € 421.62
Cisplatin in combination with 5-fluorouracil (5-FU) and folinic acid (only for patients with adenocarcinoma of the oesophagus)	
Cisplatin	€ 2,274.18
5-FU	€ 1,794.81
Folinic acid	€ 4,862.43
Total	€ 8,931.42
Additionally required SHI services	€ 328.58 - € 421.62
Epirubicin in combination with cisplatin and capecitabine	
Epirubicin	€ 4,960.74
Cisplatin	€ 1,773.93
Capecitabine	€ 2,281.13
Total	€ 9,015.80
Additionally required SHI services	€ 328.58 - € 421.62
Epirubicin in combination with cisplatin and 5-fluorouracil (5-FU)	
Epirubicin	€ 4,960.74
Cisplatin	€ 1,773.93

Designation of the therapy	Annual treatment costs/ patient
5-FU	€ 4,358.10
Total	€ 11,092.77
Additionally required SHI services	€ 328.58 - € 421.62
Epirubicin in combination with oxaliplatin and capecitabine	
Epirubicin	€ 4,960.74
Oxaliplatin	€ 8,301.02
Capecitabine	€ 2,281.13
Total	€ 15,542.89
Epirubicin in combination with oxaliplatin and 5-fluorouracil (5-FU)	
Epirubicin	€ 4,960.74
Oxaliplatin	€ 8,301.02
5-FU	€ 4,358.10
Total	€ 17,619.86
Docetaxel in combination with cisplatin and 5-fluorouracil (5-FU) *(only for patients with adenocarcinoma of the oesophagus)*	
Docetaxel	€ 8,523.22
Cisplatin	€ 2,274.18
5-FU	€ 1,794.81
Total	€ 12,592.21
Additionally required SHI services	€ 328.58 - € 421.62
Nivolumab in combination with 5-fluorouracil (5-FU) + folinic acid + oxaliplatin (FOLFOX-4) *(only for tumours with PD-L1 expression (CPS ≥ 5))*	
Nivolumab	€ 76,207.30
5-FU	€ 1,820.74
Folinic acid	€ 7,898.38
Oxaliplatin	€ 9,827.96
Total	€ 95,754.38
Nivolumab in combination with 5-fluorouracil (5-FU) + folinic acid + oxaliplatin (mod. FOLFOX-6) *(only for tumours with PD-L1 expression (CPS ≥ 5))*	
Nivolumab	€ 76,207.30
5-FU	€ 1,160.67
Folinic acid	€ 4,862.43
Oxaliplatin	€ 9,827.96
Total	€ 94,489.57
Nivolumab in combination with capecitabine and oxaliplatin *(only for tumours with PD-L1 expression (CPS ≥ 5))*	
Nivolumab	€ 76,207.30

Designation of the therapy	Annual treatment costs/ patient
Capecitabine	€ 2,283.63
Oxaliplatin	€ 8,301.02
Total	€ 86,791.95

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 June 2024)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient year	Costs/ patient year
Medicinal product to be assessed					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4	€ 1,740
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	5	87.0	€ 8,700
5-FU	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	5	87.0	€ 8,700
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Appropriate comparator therapy					
Cisplatin in combination with capecitabine					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Oxaliplatin in combination with capecitabine					
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740

Cisplatin in combination with S-1 (tegafur/ gimeracil/ oteracil)					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	6	€ 600
Cisplatin in combination with 5-fluorouracil (5-FU) (only for patients with adenocarcinoma of the oesophagus)					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
5-FU	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	5	87.0	€ 8,700
Cisplatin in combination with 5-fluorouracil (5-FU) and folinic acid (only for patients with adenocarcinoma of the oesophagus)					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
5-FU	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	5	87.0	€ 8,700
Folinic acid	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Epirubicin in combination with cisplatin and capecitabine					
Epirubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Epirubicin in combination with cisplatin and 5-fluorouracil (5-FU)					
Epirubicin	Surcharge for production of a	€ 100	1	17.4	€ 1,740

	parenteral preparation containing cytostatic agents				
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
5-FU	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	365.0	€ 36,500
Epirubicin in combination with oxaliplatin and capecitabine					
Epirubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Epirubicin in combination with oxaliplatin and 5-fluorouracil (5-FU)					
Epirubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
5-FU	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	365.0	€ 36,500
Docetaxel in combination with cisplatin and 5-fluorouracil (5-FU) (only for patients with adenocarcinoma of the oesophagus)					
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740

5-FU	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	5	87.0	€ 8,700
Nivolumab in combination with 5-fluorouracil (5-FU) + folinic acid + oxaliplatin (FOLFOX-4) (only for tumours with PD-L1 expression (CPS ≥ 5))					
Nivolumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	26.1	€ 2,610
5-FU Bolus	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	52.2	€ 5,220
5-FU 22 h infusion	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	52.2	€ 5,220
Folinic acid	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	52.2	€ 5,220
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	26.1	€ 2,610
Nivolumab in combination with 5-fluorouracil (5-FU) + folinic acid + oxaliplatin (FOLFOX-6) (only for tumours with PD-L1 expression (CPS ≥ 5))					
Nivolumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	26.1	€ 2,610
5-FU Bolus	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	26.1	€ 2,610
5-FU 22 h infusion	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	26.1	€ 2,610
Folinic acid	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	26.1	€ 2,610

Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	26.1	€ 2,610
Nivolumab in combination with capecitabine and oxaliplatin (only for tumours with PD-L1 expression (CPS ≥ 5))					
Nivolumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4	€ 1,740
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740

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 unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

– No medicinal product with new active ingredients that can be used in a combination therapy and 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.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 20 June 2024.

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

Berlin, 20 June 2024

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

Prof. Hecken