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: colorectal cancer with MSI-H or with dMMR, after fluoropyrimidine-based combination therapy)

of 19 January 2023

At its session on 19 January 2023, 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 Pembrolizumab in accordance with the resolution of 19 January 2023 on the therapeutic indication "monotherapy for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions":

Pembrolizumab

Resolution of: 19 January 2023
Entry into force on: 19 January 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 25 April 2022):

Keytruda as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings:

- treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy.

Therapeutic indication of the resolution (resolution of 19 January 2023):

See therapeutic indication according to marketing authorisation.

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

Adults with unresectable or metastatic colorectal cancer with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR); after previous fluoropyrimidine-based combination therapy

Appropriate comparator therapy:

A patient-individual therapy, depending on the type and number of previous therapies, RAS and BRAF mutational status, location of the primary tumour, general condition and risk of toxicity induced by anti-VEGF and anti-VEGFR agents, selecting:

- 5-fluorouracil in combination with folinic acid and irinotecan (FOLFIRI) with or without bevacizumab or aflibercept or ramucirumab
- 5-fluorouracil in combination with folinic acid and irinotecan (FOLFIRI) with or without cetuximab or panitumumab (only for patients with wild-type RAS)
- 5-fluorouracil in combination with folinic acid and oxaliplatin (FOLFOX) with or without bevacizumab
- Capecitabine in combination with oxaliplatin (CAPOX) with or without bevacizumab
- 5-fluorouracil in combination with folinic acid with or without bevacizumab
- Capecitabine with or without bevacizumab
- Irinotecan as monotherapy
- Panitumumab as monotherapy (only for patients with wild-type RAS)
- Cetuximab as monotherapy (only for patients with wild-type RAS)
- Trifluridine/ tipiracil
- Irinotecan in combination with cetuximab (only for patients with wild-type RAS)
- Encorafenib in combination with cetuximab (only for patients with BRAF-V600E mutation)

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

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with unresectable or metastatic colorectal cancer with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR); after previous fluoropyrimidine-based combination therapy

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	n.c.	There are no assessable data.
Morbidity	n.c.	There are no assessable data.
Health-related quality of life	∅	No data available.
Side effects	n.c.	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 ∅: 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

approx. 350 – 1,470 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: 3 January 2023):

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

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 experienced in the treatment of adults with unresectable metastatic colorectal cancer, specialists in internal medicine and gastroenterology, and other doctors from specialist groups participating in the Oncology Agreement.

Before initiation of therapy with pembrolizumab, the presence of microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) should be confirmed by a validated test in a tumour sample.

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

The annual treatment costs shown refer to the first year of treatment.

Annual treatment costs:

Adults with unresectable or metastatic colorectal cancer with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR); after previous fluoropyrimidine-based combination therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab monotherapy	
Pembrolizumab	€ 93,522.22
Appropriate comparator therapy:	
FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) ± bevacizumab	
FOLFOX 4	
Oxaliplatin	€ 4,549.32
Folinic acid	€ 3,524.48
5-fluorouracil	€ 956.64
FOLFOX 4 total	€ 9,030.44
Bevacizumab	€ 36,673.11 - € 73,346.22
FOLFOX 4 + bevacizumab total	€ 45,703.55 - € 82,376.66
FOLFOX 6	
Oxaliplatin	€ 4,549.32

Designation of the therapy	Annual treatment costs/ patient
Folinic acid	€ 3,318.46
5-fluorouracil	€ 538.44
FOLFOX 6 total	€ 8,406.22
FOLFIRI (5-fluorouracil + folinic acid + irinotecan) ± bevacizumab or aflibercept or ramucirumab or cetuximab or panitumumab	
FOLFIRI	
Irinotecan	€ 16,956.91
Folinic acid	€ 7,201.41
5-fluorouracil	€ 1,171.11
FOLFIRI total	€ 25,329.43
Bevacizumab	€ 36,673.11
FOLFIRI + bevacizumab total	€ 62,002.54
Aflibercept	€ 38,528.82
FOLFIRI + aflibercept total	€ 63,858.25
Ramucirumab	€ 71,322.95
FOLFIRI + ramucirumab total	€ 96,652.38
Cetuximab	€ 73,689.30
FOLFIRI + cetuximab total	€ 99,018.74
Additionally required SHI services	incalculable
Panitumumab	€ 78,746.05
FOLFIRI + panitumumab total	€ 104,075.48
5-fluorouracil + folinic acid ± bevacizumab	
Folinic acid	€ 7,617.34
5-fluorouracil	€ 2,080.69
5-fluorouracil + folinic acid total	€ 9,698.03
Bevacizumab	€ 36,673.11
5-fluorouracil + folinic acid + bevacizumab total	€ 46,371.14
Capecitabine ± bevacizumab	
Capecitabine	€ 2,785.32
Bevacizumab	€ 36,928.02
Capecitabine + bevacizumab total	€ 39,713.34
CAPOX (capecitabine + oxaliplatin) ± bevacizumab	
CAPOX	
Oxaliplatin	€ 4,279.52
Capecitabine	€ 1,052.34
CAPOX total	€ 5,331.86

Designation of the therapy	Annual treatment costs/ patient
Bevacizumab	€ 36,928.02
CAPOX + bevacizumab total	€ 42,259.88
Irinotecan ± cetuximab	
Irinotecan	€ 22,025.96
Cetuximab	€ 73,689.30
Irinotecan + cetuximab total	€ 95,715.26
Additionally required SHI service (cetuximab)	incalculable
Trifluridine/ tipiracil	
Trifluridine/ tipiracil	€ 42,234.96
Cetuximab	
Cetuximab	€ 73,689.30
Panitumumab	
Panitumumab	€ 78,746.05
Encorafenib + cetuximab	
Encorafenib	€ 51,981.04
Cetuximab	€ 73,689.30
Encorafenib + cetuximab total	€ 125,670.34
Additionally required SHI services	incalculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 January 2023

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 parenteral solutions containing monoclonal antibodies	€ 100	1	8.7 – 17.4	€ 870 - € 1,740
Appropriate comparator therapy:					
FOLFOX 4					
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	12	€ 1,200.00

Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 100	2	24	€ 2,400.00
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	24	€ 2,400.00
FOLFOX 6					
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	12	€ 1,200.00
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 100	1	12	€ 1,200.00
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	12	€ 1,200.00
FOLFIRI					
Irinotecan	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	26.1	€ 2,610.00
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 100	1	26.1	€ 2,610.00
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	26.1	€ 2,610.00
CAPOX					
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740.00
5-fluorouracil (de Gramont)					
Folinic acid	Surcharge for production of a	€ 100	2	52.2	€ 5,220.00

	parenteral calcium folinate solution				
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	52.2	€ 5,220.00
Combination and monotherapies					
Bevacizumab (14-day cycle)	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 100	1	26.1	€ 2,610.00
Bevacizumab (21-day cycle)	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 100	1	17.4	€ 1,740.00
Ramucirumab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 100	1	26.1	€ 2,610.00
Aflibercept	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	26.1	€ 2,610.00
Irinotecan	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740.00
Cetuximab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 100	1	52.1	€ 5,220.00
Panitumumab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 100	1	26.1	€ 2,610.00

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 treatment of adults with unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy on the basis of the marketing authorisation granted under Medicinal Products Act:

Adults with unresectable or metastatic colorectal cancer with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR); after previous fluoropyrimidine-based combination therapy

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

I. The resolution will enter into force on the day of its publication on the website of the G-BA on 19 January 2023.

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

Berlin, 19 January 2023

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

Prof. Hecken