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: Nivolumab (new therapeutic indication: MSI-H or dMMR colorectal cancer, after prior fluoropyrimidine-based combination chemotherapy, combination with ipilimumab)

of 20 January 2022

At its session on 20 January 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 Nivolumab in accordance with the resolution of 16 December 2021:

Nivolumab

Resolution of: 20 January 2022
Entry into force on: 20 January 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 24 June 2021):

OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.

Therapeutic indication of the resolution (resolution of 20 January 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 metastatic, mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer after prior fluoropyrimidine-based combination therapy

Appropriate comparator therapy for Nivolumab in combination with Ipilimumab:

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 + folinic acid + irinotecan (FOLFIRI) ± bevacizumab or aflibercept or ramucirumab
- 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± cetuximab or panitumumab (only for patients with wild-type RAS)
- 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ± bevacizumab
- Capecitabine + oxaliplatin (CAPOX) ± bevacizumab
- 5-fluorouracil + folinic acid ± bevacizumab
- Capecitabine ± 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 + cetuximab (only for patients with wild-type RAS)
- Encorafenib + cetuximab (only for patients with BRAF-V600E mutation)

Extent and probability of the additional benefit of Nivolumab in combination with Ipilimumab compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

No adequate 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.a.	There are no assessable data.
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 ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

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

Adults with metastatic, mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer after prior fluoropyrimidine-based combination therapy

approx. 350 – 475 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 Opdivo (active ingredient: nivolumab) at the following publicly accessible link (last access: 6 January 2022):

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

Treatment with nivolumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of adults with metastatic colorectal cancer, specialists in internal medicine and gastroenterology, and other doctors from specialist groups participating in the Oncology Agreement.

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-99) unless otherwise indicated.

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

In accordance with the Medicines Agency requirements regarding additional risk minimisation measures, the pharmaceutical company must provide healthcare professionals and patients with a patient card. The patient card contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with nivolumab as well as on infusion-related reactions. The prescribing doctors must discuss the risks of therapy with nivolumab with the patients.

4. Treatment costs

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

Annual treatment costs:

Adults with metastatic, mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer after prior fluoropyrimidine-based combination therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Nivolumab in combination with Ipilimumab	
Initial treatment	
Nivolumab	€ 12,204.16
Ipilimumab	€ 29,047.92
Total	€ 41,252.08
Follow-up treatment	
Nivolumab	€ 61,325.90
Initial treatment + total follow-up treatment	€ 102,577.98
Appropriate comparator therapy:	
FOLFOX (5-Fluorouracil + Folinic acid + Oxaliplatin) ± Bevacizumab	
FOLFOX 4	
Oxaliplatin	€ 4,549.32
Folinic acid	€ 4,317.84
5-Fluorouracil	€ 498.88
FOLFOX 4 total	€ 9,366.04
Bevacizumab	€ 38,265.47 - € 76,530.94
FOLFOX 4 + Bevacizumab total	€ 47,631.51 - € 85,896.98
FOLFOX 6	
Oxaliplatin	€ 4,549.32
Folinic acid	€ 3,318.46

Designation of the therapy	Annual treatment costs/ patient
5-fluorouracil	€ 498.88
FOLFOX 6 total	€ 8,366.66
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	€ 1,051.41
FOLFIRI total	€ 25,209.73
Bevacizumab	€ 38,265.47
FOLFIRI + Bevacizumab total	€ 63,475.20
Aflibercept	€ 40,094.82
FOLFIRI + Aflibercept total	€ 65,304.55
Ramucirumab	€ 74,428.85
FOLFIRI + Ramucirumab total	€ 99,638.58
Cetuximab	€ 74,618.12
FOLFIRI + Cetuximab total	€ 99,827.85
Additionally required SHI services	incalculable
Panitumumab	€ 79,785.09
FOLFIRI + Panitumumab total	€ 104,994.82
5-Fluorouracil + Folinic acid ± Bevacizumab	
5-Fluorouracil	€ 9,287.74
Folinic acid	€ 1,051.41
5-Fluorouracil + Folinic acid total	€ 10,339.15
Bevacizumab	€ 38,265.47
5-Fluorouracil + Folinic acid + Bevacizumab total	€ 48,604.62
Capecitabine ± Bevacizumab	
Capecitabine	€ 2,785.32
Bevacizumab	€ 38,520.64
Capecitabine + Bevacizumab total	€ 41,305.96
CAPOX (Capecitabine + Oxaliplatin) ± Bevacizumab	
CAPOX	
Oxaliplatin	€ 6,024.32
Capecitabine	€ 1,052.34
CAPOX total	€ 7,076.66
Bevacizumab	€ 38,520.64

Designation of the therapy	Annual treatment costs/ patient
CAPOX + Bevacizumab total	€ 45,597.30
Irinotecan ± Cetuximab	
Irinotecan	€ 22,025.96
Cetuximab	€ 74,618.12
Irinotecan + Cetuximab total	€ 96,644.08
Additionally required SHI service (cetuximab)	incalculable
Trifluridine/ Tipiracil	
Trifluridine/Tipiracil	€ 43,989.96
Cetuximab	
Cetuximab	€ 74,618.12
Panitumumab	
Panitumumab	€ 79,785.09
Encorafenib + Cetuximab	
Encorafenib	€ 54,171.04
Cetuximab	€ 74,618.12
Encorafenib + Cetuximab total	€ 128,789.16
Additionally required SHI services	incalculable

Costs after deduction of statutory rebates (LAUER-TAXE®as last revised: 1 January 2022)

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:					
Nivolumab (Follow-up treatment with nivolumab in the 14-day cycle)	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	24.1	€ 1,711.10
Ipilimumab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	4	€ 284
Appropriate comparator therapy:					
FOLFOX 4					
Oxaliplatin	Surcharge for production of a parenteral preparation	€ 81	1	12	€ 972

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	containing cytostatic agents				
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	2	24	€ 936
5-Fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	24	€ 1,944
FOLFOX 6					
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	12	€ 972
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	1	12	€ 468
5-Fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	12	€ 972
FOLFIRI					
Irinotecan	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	1	26.1	€ 1,017.90
5-Fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
CAPOX					
Oxaliplatin	Surcharge for production of a parenteral preparation	€ 81	1	8	€ 648

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	containing cytostatic agents				
5-Fluorouracil (de Gramont)					
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	2	52.2	€ 2,035.80
5-Fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	52.2	€ 4,228.20
Combination and monotherapies					
Bevacizumab (14-day cycle)	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
Bevacizumab (21-day cycle)	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	17.4	€ 1,235.40
Ramucirumab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
Aflibercept	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
Irinotecan	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Cetuximab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	52.1	€ 3,699.10
Panitumumab	Surcharge for the preparation of parenteral solutions	€ 71	1	26.1	€ 1,853.10

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	containing monoclonal antibodies				

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 20 January 2022.

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

Berlin, 20 January 2022

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

Prof. Hecken