Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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: oesophageal squamous cell carcinoma, PD-L1 expression ≥ 1%, first-line, combination with ipilimumab)

of 20 October 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient nivolumab (Opdivo) was listed for the first time on 15 July 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 1 April 2022, Opdivo received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 29 April 2022, i.e. at the latest within four weeks after the notification of the pharmaceutical company of the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure

(VerfO) of the G-BA on the active ingredient nivolumab with the new therapeutic indication (nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 August 2022, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of nivolumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of nivolumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of Nivolumab (Opdivo) in accordance with the product information

Opdivo in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

Therapeutic indication of the resolution (resolution of 20.10.2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with advanced, recurrent or metastatic, curatively untreatable oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%; first-line therapy

Appropriate comparator therapy for nivolumab in combination with ipilimumab:

- Cisplatin in combination with 5-fluorouracil

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the (G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

zu 1. In addition to nivolumab in combination with ipilimumab, medicinal products with the active ingredients 5-fluorouracil, cisplatin, docetaxel, mitomycin, nivolumab in combination with fluoropyrimidine and platinum-based combination chemotherapy and pembrolizumab in combination with fluoropyrimidine and platinum-based chemotherapy are approved in the present therapeutic indication.

zu 2. A non-medicinal treatment option is not considered for the therapeutic indication in question. This does not affect the use of radiotherapy as a palliative treatment option.

zu 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Pembrolizumab (resolution of 5 May 2022)

zu 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a, paragraph 7 SGB V.

Among the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

For the therapeutic indication, it is assumed that curative treatment with definitive radiotherapy is not an option for patients with unresectable cancer. The treatment

decision in the first-line treatment of advanced, relapsed or metastatic carcinoma of the oesophagus is essentially determined by the tumour histology (squamous cell carcinoma, adenocarcinoma).

According to the German S3 guideline "Diagnostics and therapy of squamous cell carcinomas and adenocarcinomas of the oesophagus" (last revised: June 2022), patients with metastatic or locally advanced, non-curatively treatable oesophageal squamous cell carcinoma with a CPS ≤ 10 may be treated with a combination therapy consisting of a platinum derivative and a fluoropyrimidine or a taxane. According to the guideline, combination therapy of cisplatin with a fluoropyrimidine (5-fluorouracil or capecitabine) was often used in the underlying clinical studies.

Capecitabine and oxaliplatin are not approved in the indication and are therefore not determined as appropriate comparator therapy.

The S3 guideline points out that a life-prolonging effect of systemic palliative chemotherapy for oesophageal squamous cell carcinoma is not certain. For the determination of the appropriate comparator therapy, it is assumed that the patients are suitable for cisplatin-containing chemotherapy.

For patients with a PD-L1 CPS ≥ 10, pembrolizumab should be used in combination with platinum and fluoropyrimidine-based chemotherapy according to the current S3 guideline recommendation.

Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy is another, still new treatment option for adults with locally advanced or metastatic, non-curatively treatable oesophageal squamous cell carcinoma with PD-L1 expressing tumours (Combined Positive Score (CPS) ≥ 10) in first-line therapy. The benefit assessment of pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy showed an indication of a considerable additional benefit for adults with CPS ≥ 10 compared with cisplatin in combination with 5-fluorouracil (resolution of 5 May 2022).

In the written statements on the present benefit assessment, the clinical experts again stated that the treatment standard in systemic first-line therapy of unresectable, advanced, relapsed or metastatic oesophageal squamous cell carcinoma is the combination of a fluoropyrimidine (5-fluorouracil or capecitabine) and a platinum analogue (cisplatin or oxaliplatin). According to the clinical assessment expert, no standard therapy is (currently) derived on the basis of PD-L1 expression.

In the overall assessment, the G-BA determined cisplatin in combination with 5-fluorouracil as an appropriate comparator therapy for the first-line therapy of adults with unresectable, advanced, relapsed or metastatic oesophageal squamous cell carcinoma.

In the course of further development of the generally recognised state of medical knowledge, the significance of the treatment options in the present therapeutic indication may change, which may require a redetermination of the appropriate comparator therapy by the G-BA in the foreseeable future.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of nivolumab in combination with ipilimumab is assessed as follows:

Adults with advanced, recurrent or metastatic, curatively untreatable oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%; first-line therapy

Hint of a considerable additional benefit

Justification:

For the benefit assessment, the pharmaceutical company used the results of the still ongoing, open-label, randomised, parallel phase III marketing authorisation study CA209-648 (CheckMate 648), in which either nivolumab in combination with ipilimumab or nivolumab in combination with cisplatin and 5-fluorouracil is compared with cisplatin in combination with 5-fluorouracil. A total of 970 adults with histologically confirmed, advanced, unresectable, relapsed or metastatic squamous cell or an adenosquamous carcinoma (with predominant squamous differentiation) of the oesophagus were enrolled in the three-arm study, regardless of their tumour cell PD-L1 expression status. Patients in the treatment arms nivolumab in combination with ipilimumab (intervention arm) and cisplatin in combination with 5-fluorouracil (control arm) with a tumour cell PD-L1 expression ≥ 1% are relevant for the present benefit assessment.

In the 1:1:1 randomisation, 325 patients were assigned to treatment with nivolumab in combination with ipilimumab and 324 patients to the chemotherapy control arm. The relevant sub-population with a tumour cell PD-L1 expression ≥ 1% comprises 158 patients in the intervention arm and 157 patients in the control arm.

Patients must not have received systemic treatment in the advanced or metastatic treatment setting and must not be eligible for curative therapeutic approaches. Randomisation was stratified by tumour cell PD-L1 expression, geographic region, sex, ECOG-PS (0 vs 1) and number of organs with metastases (≤ 1 vs ≥ 2).

In the intervention arm, treatment with nivolumab in combination with ipilimumab was given according to a weight-based dosing scheme (nivolumab: 3 mg/kg body weight every 2 weeks and ipilimumab: 1 mg/kg body weight every 6 weeks). The treatment was carried out according to the requirements in the product information. In the control arm, the use of cisplatin in combination with 5-fluorouracil was basically in accordance with the recommendations of the guidelines. Cisplatin was used according to the requirements in the product information. In the control arm, a total 5-fluorouracil dose of 4,000 mg/m² body surface area/ cycle with a fixed cycle length of 4 weeks was specified. In contrast, the product information of 5-fluorouracil for the treatment of oesophageal cancer provides for a total dose of 5,000 mg/m² body surface area/ cycle with a cycle length of 3-4 weeks, whereby a dose reduction is only to be carried out if side effects occur.

The study population was treated until disease progression, unacceptable toxicity, therapy discontinuation, withdrawal of consent, or a maximum treatment duration of 24 months. The maximum treatment duration applies to the active ingredient nivolumab, which could also be passed on after disease progression until loss of clinical benefit, provided the patient tolerated the treatment. A changeover to the treatment of the other study arm was not planned.

The still ongoing study is being conducted at 187 study sites in 27 countries. Primary endpoints in the study are overall survival and progression-free survival (PFS). Secondary endpoints are endpoints in the categories morbidity, health-related quality of life and side effects.

At the time of the benefit assessment, two data cut-offs of the still ongoing CheckMate 648 study were available:

- 1st data cut-off from 18.01.2021 with database lock on 01.03.2021 (pre-specified final analysis of the endpoint of PFS and interim analysis of the endpoint of overall survival)
- 2nd data cut-off from 23.08.2021 with database lock on 04.10.2021 (requested by the European Medicines Agency (EMA))

For the present benefit assessment, the pharmaceutical company used the evaluations of the second data cut-off. IQWiG noted in the dossier assessment that the study report submitted by the pharmaceutical company is dated 08.06.2021 and does not represent the second data cut-off. In this regard, the pharmaceutical company submitted the clarifying information in the written statement procedure that no updated study report was prepared on the basis of this data cut-off requested by the EMA and that the study report on the first data cut-off was submitted as part of the study documentation.

For the present benefit assessment, the results of the 2nd data cut-off were used.

Extent and probability of the additional benefit

Mortality

Overall survival

The overall survival is defined in the CheckMate 648 study as the time from randomisation to death from any cause.

In the assessment-relevant sub-population with tumour cell PD-L1 expression ≥ 1%, 119 patients in the intervention arm (75.3%) and 130 in the control arm (82.8%) died by the data cut-off date of 23.08.2021. The median survival time is 13.70 months in the intervention arm and 9.07 months in the comparator arm, which corresponds to a median prolongation of 4.63 months. The time-to-event analysis shows a statistically significant difference (hazard ratio (HR): 0.63 [95% confidence interval (CI): 0.49; 0.82]; p value < 0.001). The corresponding Kaplan-Meier curves show an intersecting course. In the first 6 months, the intervention arm shows an initially stronger drop in the Kaplan-Meier curve than the control arm. After about 6 months, the Kaplan-Meier curves intersect, with the curve of the intervention arm lying above that of the control arm in the further course of the observation period.

Overall, in the endpoint category of mortality, there is thus a prolongation of overall survival for nivolumab in combination with ipilimumab compared to cisplatin in combination with 5-fluorouracil, which is assessed as a significant improvement in terms of the extent.

Morbidity

Progression-free survival (PFS)

PFS is operationalised in the CheckMate 648 study as the time from randomisation to the first documentation of disease progression or death from any cause, whichever occurs first. The occurrence of disease progression was assessed using RECIST criteria (version 1.1).

Overall, for PFS there was no statistically significant difference between treatment groups.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component “mortality” was already surveyed in the present study via the endpoint “overall survival” as an independent endpoint. The morbidity component assessment was not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST version 1.1 criteria).

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint of PFS. The overall statement on the additional benefit remains unaffected.

Health status (assessed by EQ-5D VAS)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the benefit assessment, the pharmaceutical company submitted responder analyses for this endpoint for what it called the "time to permanent deterioration". This was defined by the pharmaceutical company as a clinically relevant deterioration by ≥ 15 points from baseline without subsequent improvement to a value that no longer represents a clinically relevant deterioration. The responder analyses here refer exclusively to evaluations up to the 2nd follow-up visit (114 ± 14 days after the last dose of study medication), resulting in a shortened duration of observation for this endpoint compared to the duration of observation for overall survival. Accordingly, the median observation times for overall survival of the relevant sub-population were approx. 13 months (intervention arm) and approx. 8.6 months (control arm). In contrast, the estimated median observation period for morbidity endpoints is approximately 7.3 months in both study arms. Overall, the observation period for the endpoint thus only covers part of the total possible observation period compared to overall survival, which means that it is not considered appropriate to define the evaluations as "permanent deterioration". The responder analyses submitted by the pharmaceutical company for what it calls the "time to permanent deterioration" are therefore not taken into account for the assessment.

As part of the written statement procedure, responder analyses were submitted by the pharmaceutical company on the time to first deterioration by ≥ 15 points compared to the baseline, which are used as a basis for the assessment.

For the endpoint of health status, there was no statistically significant difference between the treatment arms.

Quality of life

Health-related quality of life (surveyed using FACT-E)

Health-related quality of life is assessed in the CheckMate 648 study using the FACT-E (Functional Assessment of Cancer Therapy-Esophageal) questionnaire. This comprises the FACT-G (FACT-General) and the oesophageal cancer-specific subscale ECS (FACT-Esophageal Cancer Subscale). The planned follow-up duration for the FACT-E was 114 ± 14 days after the last dose of study medication (2nd follow-up visit). However, in the survival follow-up, only the abridged version of the FACT-G7 (FACT-General 7 Item Version) questionnaire and the ECS, but no longer the full FACT-E, were collected. The instruments FACT-G7 and ECS are not suitable for mapping the complex construct of health-related quality of life. Therefore, only the responder analyses for the FACT-E total score are considered for the present benefit assessment.

In the dossier for the benefit assessment, the pharmaceutical company submitted responder analyses for this endpoint for what it called the "time to permanent deterioration". This was defined by the pharmaceutical company as a clinically relevant deterioration by ≥ 27 points from baseline without subsequent improvement to a value that no longer represents a clinically relevant deterioration.

In accordance with the explanations for the endpoint of health status, the responder analyses on the "time to permanent deterioration" submitted by the pharmaceutical company for the health-related quality of life are not taken into account for the assessment.

As part of the written statement procedure, responder analyses were submitted by the pharmaceutical company on the time to first deterioration by ≥ 27 points compared to the baseline. These are used as the basis for the benefit assessment.

For the endpoint of health-related quality of life, there was no statistically significant difference between treatment arms.

Side effects

Adverse events (AEs) in total

Almost all participants in the CheckMate 648 study experienced adverse events. The results for the endpoint "total adverse events" are only presented additionally.

Serious AEs (SAEs)

For the endpoint of SAE, there is a statistically significant difference to the disadvantage of nivolumab in combination with ipilimumab.

Severe AEs (CTCAE grade ≥ 3), therapy discontinuations due to AEs

For the endpoints of severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs (discontinuation of at least 1 active ingredient component), there is no statistically significant difference between the treatment arms.

Specific AEs

For the specific adverse events, there are both advantages and disadvantages for nivolumab in combination with ipilimumab compared to cisplatin in combination with 5-fluorouracil.

There are statistically significant differences to the advantage of nivolumab in combination with ipilimumab with respect to gastrointestinal disorders (SOC, AE), mucositis (PT, AE), alopecia (PT, AE), hiccups (PT, AE), renal and urinary disorders (SOC, AE), vomiting (PT, SAE), anaemia (PT, severe AE, CTCAE grade ≥ 3), neutropenia (PT, severe AE, CTCAE grade ≥ 3) and nervous system disorders (SOC, severe AE, CTCAE grade ≥ 3).

Statistically significant differences to the disadvantage of nivolumab in combination with ipilimumab are present with regard to immune-mediated SAEs and immune-mediated severe AEs (CTCAE grade ≥ 3).

The overall assessment of the results on side effects shows a disadvantage for nivolumab in combination with ipilimumab compared to cisplatin in combination with 5-fluorouracil in terms of serious AEs. In detail, there are advantages and disadvantages for specific adverse events.

Overall assessment

For the benefit assessment of nivolumab in combination with ipilimumab for the first-line treatment of adults with unresectable, advanced, relapsed or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%, results of the CheckMate 648 study are available for the endpoint categories of mortality, morbidity, quality of life and side effects.

In the still ongoing study, nivolumab in combination with ipilimumab is compared with the appropriate comparator therapy cisplatin in combination with 5-fluorouracil.

For overall survival, there is a statistically significant advantage of nivolumab in combination with ipilimumab. The prolongation of survival time is assessed as a significant improvement in its extent.

For the endpoints of health status (assessed using EQ-5D-VAS) and health-related quality of life (assessed using FACT-E), there are no statistically significant differences between the treatment arms.

In terms of side effects, nivolumab in combination with ipilimumab shows a disadvantage compared to cisplatin in combination with 5-fluorouracil in terms of serious adverse events. In detail, there are advantages and disadvantages for specific adverse events.

In the overall analysis of the available results on the patient-relevant endpoints, the G-BA comes to the conclusion that the clear advantage in overall survival outweighs the disadvantage in serious adverse events. There is a significant improvement in the therapy-relevant benefit that has not been achieved so far.

As a result, the G-BA identified a considerable additional benefit of nivolumab in combination with ipilimumab compared to the appropriate comparator therapy cisplatin in combination with 5-fluorouracil for the first-line treatment of adults with unresectable, advanced, relapsed or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of an open-label, randomised, multicentre controlled study. The risk of bias at the study level is rated as low.

Relevant uncertainties remain for the endpoint of overall survival, as the Kaplan-Meier curves for overall survival intersect after about 6 months. Only then does the advantage of nivolumab in combination with ipilimumab become apparent. Based on the available data, it therefore remains unclear whether the hazard ratio presented adequately reflects the effect in the entire observation period.

The risk of bias for the patient-reported endpoints on health status and health-related quality of life is rated as high due to the lack of blinding.

Furthermore, due to the open-label study design, the results for the endpoint of therapy discontinuation due to adverse events are considered to have a high risk of bias.

In the overall assessment, the available data basis is fraught with uncertainties. These limitations lead to the reliability of data of the additional benefit being classified overall as "hint".

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient nivolumab. The therapeutic indication assessed here is as follows:

"Opdivo in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%“.

The G-BA determined cisplatin in combination with 5-fluorouracil as appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company submitted the results of the CheckMate 648 study, in which nivolumab in combination with ipilimumab is compared to cisplatin in combination with 5-fluorouracil. The comparator therapy in the study corresponds to the appropriate comparator therapy.

For the endpoint of overall survival, nivolumab in combination with ipilimumab shows an advantage compared to cisplatin in combination with 5-fluorouracil, which is assessed as a significant improvement.

For the endpoint categories of morbidity and health-related quality of life, there is no difference between the treatment arms that is relevant for the assessment.

In terms of side effects, nivolumab in combination with ipilimumab shows a disadvantage in terms of serious adverse events. In detail, there are advantages and disadvantages for the specific adverse events.

Relevant uncertainties arise from the course of the Kaplan-Meier curves for overall survival. These intersect after about 6 months. Only then does the advantage of nivolumab in combination with ipilimumab become apparent.

In the overall analysis, the G-BA comes to the conclusion that the clear advantage in overall survival outweighs the disadvantage in serious adverse events.

As a result, a hint for a considerable additional benefit is identified for nivolumab in combination with ipilimumab compared with the appropriate comparator therapy.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The patient numbers derived by the pharmaceutical company in the dossier tend to be an underestimate.

This is especially due to the pharmaceutical company's restriction of the target population on the basis of retrospective data to those patients who actually receive systemic first-line therapy. However, all patients who are eligible for first-line therapy and thus, for nivolumab in combination with ipilimumab are relevant for the present therapeutic indication.

2.3 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: 29 September 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, who are experienced in the treatment of patients with oesophageal cancer, as well as specialists in internal medicine and gastroenterology and other specialists participating in the Oncology Agreement.

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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 October 2022).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements were applied (average height: 1,72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Nivolumab in combination with ipilimumab				
Nivolumab	1 x per 14-day cycle	26.1	1	26.1
	or			
	1 x per 21-day cycle	17.4	1	17.4
Ipilimumab	1 x per 42-day cycle	8.7	1	8.7

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Appropriate comparator therapy				
Cisplatin + 5-fluorouracil				
Cisplatin	1 x per 21-day or 1 x per 28-day cycle	13 - 17.4	1	13 - 17.4
5-fluorouracil	1 x on day 1-5 of a 21-day or a 28-day cycle	13 - 17.4	5	65 - 87

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Nivolumab in combination with ipilimumab					
Nivolumab	3 mg/kg BW = 231 mg	231 mg	2 x 120 mg	26.1	52.2 x 120 mg
	or				
	360 mg	360 mg	3 x 120 mg	17.4	52.2 x 120 mg
Ipilimumab	1 mg/kg BW = 77 mg	77 mg	2 x 50 mg	8.7	17.4 x 50 mg
Appropriate comparator therapy					
Cisplatin + 5-fluorouracil					
Cisplatin[2]	80 mg/m^2	152 mg	1 x 100 mg	13 - 17.4	13 - 17.4 x

[2] According to the product information, 50 - 120 mg cisplatin/ m^2 body surface in 3 - 4-week cycles; a dosage of 80 mg/ m^2 body surface area is shown here as an example.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	= 152 mg		+ 1 x 50 mg + 1 x 10 mg		100 mg + 13 - 17.4 x 50 mg + 13 - 17.4 x 10 mg
5-fluorouracil	1000 mg/m^2 = 1,900 mg	1,900 mg	2 x 1,000 mg	65 - 87	130 - 174 x 1,000 mg

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Nivolumab 120 mg	12 ml CIS	€ 1,546.93	€ 1.77	€ 85.05	€ 1,460.11
Ipilimumab 50 mg	10 ml CIS	€ 3,489.20	€ 1.77	€ 195.98	€ 3,291.45
Appropriate comparator therapy					
Cisplatin 10 mg	10 ml CIS	€ 17.49	€ 1.77	€ 0.30	€ 15.42
Cisplatin 50 mg	50 ml CIS	€ 47.67	€ 1.77	€ 1.73	€ 44.17
Cisplatin 100 mg	100 ml CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
5-fluorouracil 1,000 mg[3]	20 ml IIS	€ 16.64	€ 1.77	€ 0.42	€ 14.45
CIS = concentrate for the preparation of an infusion solution, IIS = injection/ infusion solution					

LAUER-TAXE® last revised: 1 October 2022

[3] Fixed reimbursement rate

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Cost/ patient/ year
Cisplatin							
Antiemetic treatment							
In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information does not provide any specific information why the necessary costs cannot be quantified.							
Hydration/ diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	13 - 17.4	€ 118.43 – € - 158.51
Sodium chloride 0.9% infusion solution, 3 l - 4.4 l/day	10 x 1000 ml INF	€ 34.68	€ 1.73	€ 1.08	€ 31.87	13 - 17.4	€ 124.29 - € 258.16
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71

per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 23 February 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 April 2022, the pharmaceutical company submitted a dossier for the benefit assessment of nivolumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 3 May 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient nivolumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 July 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 August 2022. The deadline for submitting written statements was 22 August 2022.

The oral hearing was held on 5 September 2022.

By letter dated 6 September 2022, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 28 September 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 11 October 2022, and the proposed resolution was approved.

At its session on 20 October 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 February 2021	Determination of the appropriate comparator therapy
Working group Section 35a	30 August 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	5 September 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	13 September 2022 4 October 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	11 October 2022	Concluding discussion of the draft resolution
Plenum	20 October 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 October 2022

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

Prof. Hecken