Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Nivolumab (New Therapeutic Indication: Renal cell carcinoma, first-line treatment, combination with cabozantinib)

of 21 October 2021

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 studies 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 benefits,
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. Costs of therapy for the statutory health insurance,
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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient nivolumab (Opdivo) was listed for the first time in the Great German Specialties Tax (LAUER-TAXE®) on 15 July 2015.

On 13 April 2021, 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 December 2008, p. 7).

On 30 April 2021, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 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 (first-line therapy of advanced renal cell carcinoma, combination with cabozantinib)

in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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 2 August 2021, 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 to 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 addenda 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 cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma

Therapeutic indication of the resolution (resolution from 21.10.2021):

- see therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)

Appropriate comparator therapy:

- Pembrolizumab in combination with axitinib

b) Adult patients with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3)

1 General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Appropriate comparator therapy:

- Avelumab in combination with axitinib (only for patients with a poor-risk profile)

  or
- Nivolumab in combination with ipilimumab

  or
- Pembrolizumab in combination with axitinib

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 according to 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 Federal Joint Committee has already determined the patient-relevant benefit 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:

on 1. In terms of authorisation status, the active ingredients aldesleukin, avelumab in combination with axitinib, bevacizumab in combination with interferon alfa-2a, cabozantinib, interferon alfa-2a, ipilimumab in combination with nivolumab, nivolumab in combination with ipilimumab, pazopanib, pembrolizumab in combination with axitinib, sunitinib, temsirolimus and tivozanib are available for the treatment of advanced renal cell carcinoma in previously untreated adults.

on 2. For patients in the present therapeutic indication, it is assumed that surgery and/or radiotherapy with curative objectives are not (or no longer) an option at the time of the treatment decision and that the treatment is palliative. Therefore, a non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication. The use of resection and/or radiotherapy as a palliative patient-

individual therapy option for symptom control depending on the localisation and symptomatology of the metastases remains unaffected.

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

- Avelumab in combination with axitinib: Resolution of 14 May 2020
- Pembrolizumab in combination with axitinib: Resolution of 14 May 2020
- Ipilimumab in combination with nivolumab: Resolution of 15 August 2019
- Nivolumab in combination with ipilimumab: Resolution of 15 August 2019
- Cabozantinib: Resolution of 6 December 2018
- Tivozanib: Resolution of 19 April 2018

Annex VI - Prescribability of approved medicinal products in non-approved therapeutic indications; Part B: Active ingredients that are not prescribable in off-label uses:

- Inhaled interleukin-2 (Proleukin®) for the treatment of renal cell carcinoma - resolution of 8 June 2016

on 4. The general state of medical knowledge in the present therapeutic indication was represented by a systematic search for guidelines and reviews of clinical studies. 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 therapeutic 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 health care provision.

For first-line treatment of advanced renal cell carcinoma, current guidelines unanimously recommend immune checkpoint inhibitor-based combination therapies.

For these immune checkpoint inhibitor-based combination therapies, results from benefit assessment procedures are also available.

Accordingly, the G-BA identified an indication of a considerable additional benefit compared with sunitinib for the combination therapy of nivolumab and ipilimumab in adult patients with previously untreated advanced renal cell carcinoma with an intermediate risk profile (IMDC score[2] 1-2) and poor-risk profile (IMDC score ≥ 3) by resolution of 15 August 2019.

For pembrolizumab in combination with axitinib, the resolution dated 14 May 2020 identified a hint for a considerable additional benefit over sunitinib for adult patients with previously untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0-2). For adults with a poor-risk profile (IMDC score ≥ 3), there was an indication of a considerable additional benefit over sunitinib.

According to the resolution of 14 May 2020, there is no additional benefit for avelumab in combination with axitinib over sunitinib for adult patients with previously untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC

[2] International Metastatic Renal-Cell Carcinoma Database Consortium

score 0-2). For adults with a poor-risk profile (IMDC score ≥ 3), a hint for a considerable additional benefit over sunitinib was identified.

In the guidelines and the written statements of the scientific-medical societies, a distinction is made between patients with a favourable, intermediate and poor-risk profile on the basis of risk scores (IMDC score), and therapy recommendations are made separately according to IMDC risk profile.

For patients with a favourable risk profile (IMDC score 0), combination therapy of pembrolizumab and axitinib is recommended. In addition, the combination of avelumab and axitinib (with a weaker recommendation grade) is also recommended.

For patients with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3), pembrolizumab in combination with axitinib and nivolumab in combination with ipilimumab are preferred. In addition, the combination of avelumab and axitinib is also recommended, with a weaker level of recommendation.

Patients with favourable, intermediate, and poor-risk profiles have different prognoses and responses to therapy, which translates into considerable differences in overall survival.

Against this background and taking into account the existing therapy recommendations separated according to risk profile (favourable; intermediate/poor) as well as the authorisation status of the medicinal products under consideration, the G-BA considers it appropriate to consider the patient populations with the favourable risk profile and intermediate/poor-risk profile separately, despite partially overlapping therapy recommendations.

Therefore, in the overall assessment of the available evidence, pembrolizumab in combination with axitinib represents the appropriate comparator therapy for a) patients with previously untreated, advanced renal cell carcinoma with a favourable risk profile (IMDC score 0).

For b) patients with previously untreated advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3), multiple treatment options with comparable evidence are available with pembrolizumab in combination with axitinib, nivolumab in combination with ipilimumab and avelumab in combination with axitinib (only for patients with poor-risk profile) and are determined to be equally appropriate comparators.

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 cabozantinib is assessed as follows:

a) Adult patients with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)

An additional benefit is not proven.

b) Adult patients with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3)

An additional benefit is not proven.

Justification:

Data basis

In the absence of direct comparative studies of nivolumab in combination with cabozantinib versus the appropriate comparator therapy for patient groups a) and b), the pharmaceutical company presents in the dossier a total of three adjusted indirect comparisons according to the method of Bucher et al. for the proof of an additional benefit.. In each case, they draw on the CheckMate 9ER study on the intervention side (nivolumab in combination with cabozantinib vs sunitinib) and, on the comparator side, the KEYNOTE-426 (pembrolizumab in combination with axitinib vs sunitinib), CheckMate 214 (nivolumab in combination with ipilimumab vs sunitinib) and JAVELIN Renal 101 (avelumab in combination with axitinib vs sunitinib) studies. Sunitinib acts as a bridge comparator in all three indirect comparisons. The pharmaceutical company considers the following populations in detail within the scope of the indirect comparisons carried out by him:

- Nivolumab in combination with cabozantinib versus pembrolizumab in combination with axitinib: Patients with any risk profile,
- Nivolumab in combination with cabozantinib versus nivolumab in combination with ipilimumab: Patients with intermediate or poor-risk profile,
- Nivolumab in combination with cabozantinib versus avelumab in combination with axitinib: Patients with a poor-risk profile.

In each case, the pharmaceutical company presents the results obtained from these three indirect comparisons for the respective population they are considering. The pharmaceutical company does not allocate the results to the separate patient populations a) and b).

Evaluation:

a) Adult patients with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)

The adjusted indirect comparison of nivolumab in combination with cabozantinib (CheckMate 9ER) versus pembrolizumab in combination with axitinib (KEYNOTE-426) submitted by the pharmaceutical company includes patients with any risk profile. The pharmaceutical company does not submit a separate consideration of patient population a) from the adjusted indirect comparison of nivolumab in combination with cabozantinib versus pembrolizumab in combination with axitinib. However, this would have been possible in principle, since according to the pharmaceutical company's information in the dossier from the KEYNOTE-426 study, separate results are available for the patient group with a favourable risk profile.

Overall, therefore, there are no suitable data to assess the additional benefit of nivolumab in combination with cabozantinib for patient population a).

b) Adult patients with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3)

As previously described, the pharmaceutical company presents a total of three adjusted indirect comparisons of nivolumab in combination with cabozantinib versus the three different options of the appropriate comparator therapy. In doing so, the pharmaceutical company considers patients with any risk profile, patients with an intermediate or poor-risk profile and patients with a poor-risk profile. However, the pharmaceutical company does not assign these results to separate patient populations a) and b).

Thus, there is no separate analysis for patient population b) considering all three adjusted indirect comparisons. However, this would have been possible in principle. Since the pharmaceutical company did not select any individual therapy option from the possible options of the appropriate comparator therapy for patient population b), it is necessary to make a statement on the additional benefit primarily against the totality of the therapy options of the appropriate comparator therapy.

Overall, therefore, there are no suitable data to assess the additional benefit of nivolumab in combination with cabozantinib for patient population b).

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the medicinal product Opdivo with the active ingredient nivolumab.

The therapeutic indication assessed here is as follows: "Opdivo in combination with cabozantinib is indicated for the first-line treatment of adult patients

with advanced renal cell carcinoma. "

In the therapeutic indication to be considered, two patient populations were differentiated:

a) Adult patients with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)

and

b) Adult patients with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3).

Patient population a)

Pembrolizumab in combination with axitinib was determined to be the appropriate comparator therapy.

The adjusted indirect comparison of nivolumab in combination with cabozantinib (CheckMate 9ER study) versus pembrolizumab in combination with axitinib (KEYNOTE-426 study)

submitted by the pharmaceutical company via the bridge comparator sunitinib includes patients with any risk profile. The pharmaceutical company does not submit a separate consideration of patient population a) from the adjusted indirect comparison of nivolumab in combination with cabozantinib versus pembrolizumab in combination with axitinib. Therefore, no suitable data are available to assess the additional benefit of nivolumab in combination with cabozantinib for patient population a).

An additional benefit of nivolumab in combination with cabozantinib versus the appropriate comparator therapy is therefore not proven.

Patient population b)

The appropriate comparator therapy was determined to be:

- Avelumab in combination with axitinib (only for patients with a poor-risk profile)

  or
- Nivolumab in combination with ipilimumab

  or
- Pembrolizumab in combination with axitinib

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In the absence of direct comparative studies of nivolumab in combination with cabozantinib versus the appropriate comparator therapy, the pharmaceutical company presents a total of three adjusted indirect comparisons according to the method of Bucher et al. In doing so, he considers the following populations: Patients with any risk profile, patients with intermediate or poor-risk profile, and patients with the poor-risk profile. The pharmaceutical company does not allocate the results to the separate patient populations a) and b).

Thus, there is no separate analysis for patient population b) considering all three adjusted indirect comparisons. However, this would have been possible in principle. Since the pharmaceutical company did not select any individual therapy option from the possible options of the appropriate comparator therapy for patient population b), it is necessary to make a statement on the additional benefit primarily against the totality of the therapy options of the appropriate comparator therapy.

Overall, therefore, there are no suitable data to assess the additional benefit of nivolumab in combination with cabozantinib for patient population b).

An additional benefit of nivolumab in combination with cabozantinib versus the appropriate comparator therapy is therefore not proven.

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 G-BA based its decision on the patient numbers from the parallel resolutions on cabozantinib in combination with nivolumab in the identical therapeutic indication. Compared to the patient numbers derived by the pharmaceutical company in the dossier, these figures represent a broader range. This broader range is considered more appropriate in view of the

uncertainties involved in determining the stage distribution in both cases and, in addition, because of the uncertainty regarding the older data source in the present derivation.

In addition, this allows for a consistent consideration of patient numbers with the parallel resolution on cabozantinib in combination with nivolumab.

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: 15 September 2021):

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, as well as specialists in internal medicine and nephrology and other specialists participating in the Oncology Agreement experienced in the treatment of patients with advanced renal cell carcinoma.

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 doctor must discuss the risks of therapy with nivolumab with the patient. The patient card should be made available to the patient.

In the CheckMate 9ER study, only patients with renal cell carcinoma with clear cell histology were examined. No data are available for patients with non-clear cell renal cell carcinoma.

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 2021).

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 the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed: Nivolumab in combination with cabozantinib				
Nivolumab	1 x per 14 day cycle	26.1	1	26.1
	or			
	1 x per 28 day cycle	13.0	1	13.0
Cabozantinib	1 x daily	365	1	365
Appropriate comparator therapy				
a) Adult patients with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)				
Pembrolizumab in combination with axitinib				
Pembrolizumab	1 x per 21 day cycle	17.4	1	17.4
	or			
	1 x per 42 day cycle	8.7	1	8.7
Axitinib	2 x daily	365	1	365
b) Adult patients with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3)				
Avelumab in combination with axitinib (only for patients with a poor-risk profile)				
Avelumab	1 x per 14 day cycle	26.1	1	26.1
Axitinib	2 x daily	365	1	365
Nivolumab in combination with ipilimumab				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Initial treatment				
Nivolumab	1 x per 21 day cycle	4.0	1	4.0
Ipilimumab	1 x per 21 day cycle	4.0	1	4.0
Follow-up treatment				
Nivolumab	1 x per 14 day cycle (3 weeks after last dose of initial treatment)	20.1	1	20.1
	or			
	1 x per 28 day cycle (6 weeks after last dose of initial treatment)	9.3	1	9.3
Pembrolizumab in combination with axitinib				
Pembrolizumab	1 x per 21 day cycle	17.4	1	17.4
	or			
	1 x per 42 day cycle	8.7	1	8.7
Axitinib	2 x daily	365	1	365

Consumption:

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg) [3].

[3] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient / year	Average annual consumption by potency
Medicinal product to be assessed: Nivolumab in combination with cabozantinib					
Nivolumab	240 mg	240 mg	2 x 100 mg + 1 x 40 mg	26.1	52.2 x 100 mg + 26.1 x 40 mg
	or				
	480 mg	480 mg	4 x 100 mg + 2 x 40 mg	13.0	52.0 x 100 mg 26.0 x 40 mg
Cabozantinib	40 mg	40 mg	1 x 40 mg	365	365 x 40 mg
Appropriate comparator therapy					
a) Adult patients with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)					
Pembrolizumab in combination with axitinib					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
Axitinib	5 mg	10 mg	2 x 5 mg	365	730 x 5 mg
b) Adult patients with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3)					
Avelumab in combination with axitinib (only for patients with a poor-risk profile)					
Avelumab	800 mg	800 mg	4 x 200 mg	26.1	104.4 x 200 mg
Axitinib	5 mg	10 mg	2 x 5 mg	365	730 x 5 mg
Nivolumab in combination with ipilimumab					
Initial treatment					
Nivolumab	3 mg/kg KG	231 mg	2 x 100 mg 1 x 40 mg	4	8 x 100 mg + 4 x 40 mg
Ipilimumab	1 mg/kg KG	77 mg	2 x 50 mg	4	8 x 50 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient / year	Average annual consumption by potency
Follow-up treatment					
Nivolumab	240 mg	240 mg	2 x 100 mg 1 x 40 mg	20.1	40.2 x 100 mg + 20.1 x 40 mg
	or				
	480 mg	480 mg	4 x 100 mg 2 x 40 mg	9.3	37.2 x 100 mg + 18.6 x 40 mg
Pembrolizumab in combination with axitinib					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
Axitinib	5 mg	10 mg	2x 5 mg	365	730 x 5 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

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 100 mg	1 CIS	€ 1,344.24	€ 1.77	€ 73.81	€ 1,268.66
Nivolumab 40 mg	1 CIS	€ 544.32	€ 1.77	€ 29.53	€ 513.02
Cabozantinib 40 mg	30 HC	€ 5,709.38	€ 1.77	€ 322.79	€ 5,384.82
Appropriate comparator therapy					

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
Avelumab 200 mg	1 CIS	€ 834.55	€ 1.77	€ 45.59	€ 787.19
Axitinib 5 mg	56 FCT	€ 3,597.14	€ 1.77	€ 0.00	€ 3,595.37
Ipilimumab 50 mg	1 CIS	€ 3,849.07	€ 1.77	€ 216.54	€ 3,630.76
Nivolumab 100 mg	1 CIS	€ 1,344.24	€ 1.77	€ 73.81	€ 1,268.66
Nivolumab 40 mg	1 CIS	€ 544.32	€ 1.77	€ 29.53	€ 513.02
Pembrolizumab 100 mg	1 CIS	€ 3,037.06	€ 1.77	€ 170.17	€ 2,865.12
Abbreviations: FCT = film-coated tablets, CIS = concentrate for the preparation of an infusion solution.					

LAUER-TAXE® last revised: 1st October 2021

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 standard expenditure in the course of the treatment are not shown.

According to the avelumab product information, patients are required to be premedicated with an antihistamine and paracetamol prior to the first 4 infusions of avelumab. The product information does not provide any specific information why the necessary costs cannot be quantified.

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 instead 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 sales 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 22 September 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 30 April 2021, 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 03 May 2021, in conjunction with the resolution of the G-BA of 1st 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 29 July 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 2 August 2021. The deadline for submitting written statements was 23 August 2021.

The oral hearing was held on 6 September 2021.

On 1st October 2021, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1, dated 1st October 2021, replaces version 1.0 of the dossier assessment dated 29 July 2021. The evaluation result was not affected by the changes in version 1.1 compared to version 1.0.

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 12 October 2021, and the proposed resolution was approved.

At its session on 21 October 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation

Subcommittee Medicinal product	22 September 2020	Determination of the appropriate comparator therapy
Working group Section 35a	1 September 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	6 September 2021	Conduct of the oral hearing
Working group Section 35a	15 September 2021 22 September 2021 6 October 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	12 October 2021	Concluding discussion of the draft resolution
Plenum	21 October 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 21 October 2021

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

Prof. Hecken