Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee 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: Oesophageal squamous cell carcinoma, pretreated patients)

of 1 July 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 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:

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Treatment costs for statutory health insurance funds,

6th 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 online 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 20 November 2020, Opdivo received marketing authorisation for a new therapeutic indication classified as a major type 2 variation as defined according to Annex 2 No. 2a to Regulation (EC) number 1234/2008 of the Commission from 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 16 December 2020, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No.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 (oesophageal squamous cell carcinoma, pretreated patients) 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 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 as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Therapeutic indication of the resolution (resolution of 1 July 2021):

see approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy, for whom chemotherapy is an appropriate treatment option:

Appropriate comparator therapy:

- Chemotherapy according to the doctor's instructions

b) adult patients with unresectable advanced, recurrent or

metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and

platinum-based chemotherapy, for whom chemotherapy is not an appropriate treatment option:

Appropriate comparator therapy:

- Best supportive care

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section

[1] General Methods, version 6.0 of 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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:

on 1. The chemotherapeutic agents 5-fluorouracil, cisplatin and mitomycin are approved for the present therapeutic indication.

on 2. Radiotherapy is generally considered as a non-medicinal treatment in the present therapeutic indication. Patients for whom radiotherapy with curative objectives is indicated are exceptional cases within the patient group defined by the therapeutic indication and are not considered in the context of the present question. The target population is assumed to be those patients for whom radiotherapy with curative goals is unsuitable. A non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication. This does not affect the use of radiotherapy as a palliative treatment option.

on 3. The following resolutions or guidelines of the G-BA are available for the planned therapeutic indication:

- Resolution on quality assurance measures for proton therapy in patients with oesophageal carcinoma (last revision: 14 December 2018)

on 4. The generally recognised state of medical knowledge on which the resolution of the G-BA is based, was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

With regard to the evidence on treatments with medical products, there is no higher quality evidence based on systematic reviews for the treatment situation of second-line therapy of locally advanced or metastatic oesophageal carcinoma with squamous histology.

According to the present authoritative S3 guideline of the German Cancer Society (DKG), German Cancer Aid and the Association of the Scientific Medical Societies (AWMF) as well as the guideline of the National Institute for Health and Care Excellence (NICE), palliative chemotherapies can also be used for the treatment of patients with oesophageal carcinoma in second-line therapy. In the German S3 guideline, the recommendation for systemic second-line therapy with cytotoxic medicinal products for squamous cell carcinoma is weak. The guideline states that there are no reliable

data on the efficacy of second-line chemotherapy for oesophageal squamous cell carcinoma, but small phase II studies with substances such as taxanes, platinum derivatives or irinotecan, but also those with older substances such as mitomycin C exist. Symptom control would be a theoretical goal in the context of individualised treatment, as neither prolongation of overall survival nor preservation of quality of life have been demonstrated.

Within the framework of the written statement procedure, the professional societies explained that in the reality of care, chemotherapy with taxanes represents the recommended and current standard of therapy for a selected patient population. The decision for or against systemic therapy with antineoplastic agents (chemotherapy) is based in particular on individual factors, which include the disease characteristics and dominant symptoms as well as the general condition of the patient.

For the present determination of the appropriate comparator therapy, it is therefore taken into account that a patient population is eligible for treatment with chemotherapy that can be distinguished from patients treated with chemotherapy-free best supportive care.

Accordingly, chemotherapy was determined to be the appropriate comparator therapy for patients for whom chemotherapy is an appropriate treatment option according to the doctor's instructions. The active ingredients paclitaxel and docetaxel are not approved in the present therapeutic indication, but are recommended in guidelines. There is a discrepancy between medicinal therapies approved in the indication and those recommended by guidelines or used in care. Within the framework of a study, treatment with the active ingredients paclitaxel or docetaxel is considered adequate with regard to the implementation of chemotherapy according to the doctor's instructions.

For patients for whom chemotherapy is not an appropriate treatment option, best supportive care was determined as the appropriate comparator therapy. Best supportive care for this patient population is thus defined as those therapies other than chemotherapy ("chemotherapy-free best supportive care") that provide the best possible supportive care, patient-individual optimised, to alleviate symptoms and improve quality of life.

Change of the appropriate comparator therapy:

Originally, the appropriate comparator therapy was determined as follows:

Adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) after prior fluoropyrimidine- and platinum-based combination chemotherapy:

- Best supportive care

In the course of the written statement procedure, the clinical experts explained that the decision for chemotherapy is based in particular on individual factors, which include the disease characteristics and dominant symptoms as well as the patient's general condition and wish for therapy. According to the assessment experts, chemotherapy with taxanes is the standard of care for this demarcarcable patient population.

In the original version of the appropriate comparative therapy, treatment with chemotherapy (taxanes) was considered as a treatment option in the context of best supportive care. In view of the statements of the clinical experts, the G-BA now considers it appropriate for the present assessment to differentiate the patient population according to the therapeutic indication into patients for whom chemotherapy is a suitable therapy option and patients for whom chemotherapy is not a suitable therapy option.

This change to the appropriate comparator therapy has no effects on the present assessment of the additional benefit, nor does it require the benefit assessment to be carried out again.

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 is assessed as follows:

a) Adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy, for whom chemotherapy is an appropriate treatment option:

   Hint for a minor additional benefit.

b) Adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy, for whom chemotherapy is not an appropriate treatment option:

   An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company submits the results of the open-label randomised controlled ATTRACTION-3 study comparing nivolumab versus a monotherapy with docetaxel or paclitaxel.

Adults with oesophageal carcinoma who were refractory or intolerant to fluoropyrimidine- and platinum-based combination chemotherapy and ineligible for radical resection were enrolled in the study. The 419 patients included were assigned randomised to the two study arms in a 1:1 ratio. The patients must have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1. Prior to randomisation, medical investigators determined for each patient whether monochemotherapy with docetaxel or with paclitaxel would be administered if the patient was assigned to the control arm of the study. In addition to the medicinal therapy options nivolumab or docetaxel or paclitaxel, no further interventions such as surgical measures or radiotherapy/chemotherapy were allowed per protocol.

The primary endpoint of the study was overall survival; patient-relevant secondary endpoints were health status and adverse events.

The data cut-off from 12.11.2018 is used for the present benefit assessment, which is the planned final analysis for the overall survival endpoint after 331 deaths.

Implementation of the appropriate comparator therapy:

In the comparator arm of the ATTRACTION-3 study, patients were treated with monochemotherapy with docetaxel or paclitaxel. According to guidelines and scientific-medical societies, systemic therapy for symptom control may be considered as part of palliative treatment for patients in good general condition. Treatment options beyond antineoplastic therapy, which are used according to guidelines for symptomatic treatment of advanced oesophageal carcinoma as part of best supportive care, were not allowed in the study or were not intended to be part of the intervention and could only be given after completion of study treatment. In their statements, the scientific-medical societies explained that the patients in the study were nevertheless not deprived of any medically indicated measures that could be classified as best supportive care, insofar as these were not yet required at the time of enrolment. In cases where appropriate measures were required in the further course of the disease, tumour progression would have to be assumed as a consequence of which the study treatment would be terminated in accordance with the protocol, and the patients could then be treated accordingly.

Extent and probability of the additional benefit

a) Adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy, for whom chemotherapy is an appropriate treatment option:

Mortality

The overall survival is defined in the ATTRACTION-3 study as the time from randomisation to death from any cause.

For the endpoint Overall survival, there is a statistically significant difference between the treatment groups in favour of nivolumab, the extent of which is considered to be a relevant improvement against the background of the remaining life expectancy of the patients in the present therapy situation.

Morbidity

Progression-free survival

Radiographic progression-free survival (PFS) represented was operationalised in the ATTRACTION-3 study as the time from randomisation to radiologically detected progression or death regardless of the underlying cause of death. The occurrence of disease progression was assessed by imaging techniques and based on the RECIST criteria (version 1.1). The evaluation was conducted by a central, blinded, independent committee (BICR).

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

The endpoint component Mortality is already surveyed via the endpoint Overall survival as an independent endpoint. The morbidity component "Disease progression" was assessed solely by means of imaging procedures (radiologically determined disease progression according to the RECIST criteria). Thus, morbidity is not primarily assessed on the basis of disease symptoms, but solely on the basis of asymptomatic findings that are not directly relevant to the patient.

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

Health status (EQ-5D VAS)

In the ATTRACTION-3 study, health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

In the dossier, the pharmaceutical company presented responder analysis, operationalised as time to permanent deterioration. Time to first deterioration was defined as a reduction of at least 7 or 10 points.

Within the written statement procedure, the pharmaceutical company submitted responder analyses using a response threshold of 15%.

The responder analyses are not used for the evaluation because the response rate to week 24 was less than 50%, and the results are therefore not usable for the present benefit assessment.

In conclusion, neither an advantage nor a disadvantage can be determined overall for the endpoint category Morbidity. Data on disease symptomatology are not available. According to the statements of the medical societies, the disease symptomatology of the patients are pronounced in the reality of care. Thus, it remains unclear what the effect of treatment with nivolumab is in this regard.

Quality of life

Health-related quality of life was not assessed in the ATTRACTION-3 study.

Side effects

Adverse events

The results for the endpoint Total adverse events are only presented supplementary. There are no statistically significant differences between the treatment groups.

Serious AEs

For the endpoint Serious adverse events no statistically significant difference was detected between the treatment groups.

Severe AE (CTCAE grade ≥ 3)

There was a statistically significant difference between treatment groups in the time to severe adverse events with CTCAE grade ≥ 3 with advantage of nivolumab.

Discontinuation due to AE

For the endpoint Discontinuation due to AEs no statistically significant difference was detected between the treatment groups.

Specific AE

In detail, the specific AEs for stomatitis (AEs), general disorders and administration site conditions (AEs), decreased appetite (AEs), alopecia (AEs), skeletal muscle, connective tissue and bone disorders (AEs), nervous system disorders (AEs), febrile neutropenia (SAEs), hyponatremia (serious AEs), examinations (serious AEs), and blood and lymphatic system disorders (serious AEs) each showed a statistically significant difference to the benefit of nivolumab.

In the overall consideration of the endpoints regarding side effects, a relevant advantage for the treatment with nivolumab is observed.

Overall assessment

For the benefit assessment of nivolumab for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy, for whom chemotherapy is an appropriate treatment option, results of the ATTRACTION-3 study are available for the endpoint categories Mortality, Morbidity and Side effects.

For the endpoint Overall survival, there is a statistically significant advantage of nivolumab over docetaxel or paclitaxel, the extent of which is considered to be a relevant improvement given the remaining life expectancy of patients in the present therapy situation.

There are no usable data for the benefit assessment concerning the endpoint category Morbidity. Thus, no conclusions can be drawn as to how treatment with nivolumab affects disease symptomatology, which is pronounced in the present patient population in the reality of care.

Health-related quality of life was not assessed in the ATTRACTION-3 study. Data on health-related quality of life are of great importance, especially in the advanced stage of the disease and treatment with a palliative objective of the therapy.

In the endpoint category Side effects, there is an overall relevant advantage for nivolumab with regard to an improvement in severe AEs, as well as in detail for the specific AEs.

The overall results show an improvement in overall survival and side effects. Data on health-related quality of life are not available; moreover, no statements can be made on the effects on the disease symptomatology. Overall, the extent of improvement in therapeutic benefit is rated as a relevant improvement, but no more than a minor improvement. Thus, a minor additional benefit is found for nivolumab compared to treatment with docetaxel or paclitaxel.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the open-label, randomised, controlled phase III ATTRACTION-3 study.

The risk of bias is rated as low for the endpoint Overall survival.

The risk of bias in the results for the endpoints Serious non-severe specific AEs and for the endpoint Discontinuation due to AEs was rated as high.

In addition, there is uncertainty in the overall statement on the additional benefit in that no statements can be made on health-related quality of life and disease symptomatology, as these are considered to be of great importance in the advanced stage of disease and treatment with a palliative objective of the therapy.

Overall, these limitations lead to the reliability of the additional benefit being classified as "hint".

b) adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy, for whom chemotherapy is not an appropriate treatment option:

The ATTRACTION-3 study provides only a comparison of monotherapy with docetaxel or paclitaxel. Data on other treatment options indicated in the context of best supportive care are not provided by this study. In the dossier for the benefit assessment, the pharmaceutical company formed two subpopulations that differ in whether further antineoplastic therapy is indicated or not. For the subpopulation of patients for whom further antineoplastic therapy is indicated, he uses the results of the ATTRACTION-3 study. He does not identify studies for the sub-population of patients for whom further antineoplastic therapy is not indicated.

Thus, no data are available to assess the additional benefit.

2.1.4 Summary of the assessment

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

"OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy."

In the assessment, two patient groups were distinguished:

Adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy,

a) for whom chemotherapy is an appropriate treatment option,

b) for whom chemotherapy is not an appropriate treatment option.

Patient population a)

For the benefit assessment, the pharmaceutical company submits the results of the ATTRACTION-3 study, a randomised controlled trial with unblinded study treatment, in which nivolumab is compared with antineoplastic therapy with docetaxel or paclitaxel.

For the endpoint Overall survival, there is a statistically significant advantage of nivolumab, the extent of which is considered a relevant improvement against the background of the remaining life expectancy in the present therapy situation.

There are no usable data for the benefit assessment concerning the endpoint category Morbidity. Thus, no conclusions can be drawn regarding the impact of nivolumab treatment on disease symptomatology, which is pronounced in the present patient population in the reality of care.

Health-related quality of life was not assessed. Data on this is particularly important in the advanced stage of the disease and treatment with a palliative goal of therapy.

With regard to side effects, there is an overall relevant advantage for nivolumab with regard to an improvement in severe AEs, as well as in detail for the specific AEs. Due to the open-label study design, a high risk of bias in the reliability of data must be taken into account.

As a result, the G-BA found a hint of minor additional benefit for nivolumab compared with the appropriate comparator therapy.

Patient population b)

No data are available from the ATTRACTION-3 study on which to base an assessment of the patient population. Therefore, an additional benefit is not proven for nivolumab.

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 derivation of the patient numbers carried out by the pharmaceutical company in the dossier is mathematically comprehensible, but there are under-or overestimations in individual steps.

The calculation of the target population is limited to newly diagnosed patients and patients with disease progression in the treatment year.

In addition, the proportions of some calculation steps are based on sources whose representativeness or transferability to the German health care context is unclear.

The proportion of patients with systemic treatment in first-line therapy is also subject to uncertainty, as the proportion of patients diagnosed in the metastatic stage over a period of several years who received systemic treatment was used as the lower limit. Similarly, the proportion of patients with a second-line therapy option is subject to uncertainty, as the proportion of patients who received second-line therapy in clinical trials was not taken into account. The proportion of patients with disease progression in the form of recurrences or distant metastases is underestimated because patients who received an R0 resection were not included. An overestimation of this value could be due to the fact that the pharmaceutical company did not restrict the target population to patients on fluoropyrimidine- and platinum-based combination therapy.

In order to calculate the proportion of patients for whom chemotherapy is or is not a suitable therapy option, a proportion value of 30-40% of the patients is defined for whom treatment with chemotherapy may be suitable in the present therapy situation. This proportion was submitted by the scientific-medical societies in the context of the written statement procedure and, according to the assessment experts, represents an accurate estimated proportion in the reality of health care in Germany. This proportion is used for the present resolution as it is assumed that this proportion better reflects the health care reality in Germany than the value used by the pharmaceutical company.

In summary, the data on the number of patients are subject to uncertainties. In particular, taking into account a more differentiated view of patients from previous years, there is an overall underestimation, although the extent of the underestimation cannot be quantified.

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: 14 April 2021):

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

Treatment with nivolumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in gastroenterology, and specialists participating in the Oncology Agreement who are experienced in the treatment of adult patients with oesophageal squamous cell carcinoma.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide a patient card.

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: 15 June 2021).

Treatment duration:

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.

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				
Patient population a)				
Nivolumab	once every 14 days	26.1	1	26.1
Patient population b)				
Nivolumab	once every 14 days	26.1	1	26.1

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ year
Best supportive care	varies patient-individual			
Appropriate comparator therapy for patient population a)				
Chemotherapy according to the doctor's instructions	For the present benefit assessment, paclitaxel and docetaxel are appropriate comparators in the context of therapy according to the doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore no costs are presented for these medicinal products.			
Appropriate comparator therapy for patient population b)				
Best supportive care	varies patient-individual			

Consumption:

Designation of the therapy	Dosage/ application	Dosage/patient/days of treatment	Usage by potency/day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Patient population a)					
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
Patient population b)					
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
Best supportive care	varies patient-individual				
Appropriate comparator therapy for patient population a)					
Chemotherapy according to the doctor's instructions	For the present benefit assessment, paclitaxel and docetaxel are appropriate comparators in the context of therapy according to the doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore no costs are presented for these medicinal products.				

Designation of the therapy	Dosage/ application	Dosage/patient/days of treatment	Usage by potency/day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy for patient population b)					
Best supportive care	varies patient-individual				

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 Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Cost of medicinal product:

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 IFC	€ 1,344.24	€ 1.77	€ 73.81	€ 1,268.66
Nivolumab 40 mg	1 IFC	€ 544.32	€ 1.77	€ 29.53	€ 513.02
Best supportive care	varies patient-individual				
Appropriate comparator therapy					
Best supportive care	varies patient-individual				
Chemotherapy according to the doctor's instructions	For the present benefit assessment, paclitaxel and docetaxel are appropriate comparators in the context of therapy according to the doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore no costs are presented for these medicinal products.				
Abbreviations: IFC =Infusion solution concentrate					

Last revised LAUER-TAXE®: 15 June 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.

Because there are no 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, no costs for additionally required SHI services had to be taken into account.

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 1.10.2009 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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), all surcharges for the production of parenteral preparations containing cytostatic drugs a maximum 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 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 11 February 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. Working group Section 35a determined the appropriate comparator therapy at its session on 3 November 2020.

On 16 December 2020, 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, sentence 2 VerfO.

By letter dated 17 December 2020 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 30 March 2021, and the written statement procedure was initiated with publication on the G-BA website on 1 April 2021. The deadline for submitting written statements was 22 April 2021.

The oral hearing was held on 10 May 2021.

By letter of 11 May 2021, 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 11 June 2021.

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 were discussed at the session of the subcommittee on 22 June 2021, and the draft resolution was approved.

At its session on 1 July 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 February 2020	Implementation of the appropriate comparator therapy
Working group Section 35a	3 November 2020	New determination of the appropriate comparator therapy
Working group Section 35a	5 January 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 May 2021 11 May 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 May 2021 15 June 2021	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	22 June 2021	Concluding discussion of the draft resolution

Plenum	1 July 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 July 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken