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: melanoma (stage IIB or IIC), adjuvant treatment, ≥ 12 years, monotherapy)

of 21 March 2024

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 21 August 2023, nivolumab 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, sentence 7).

On 18 September 2023, 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 "monotherapy of adults and adolescents 12 years of age and older for the adjuvant treatment of stage IIB or IIC melanoma who have undergone complete resection" 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 dossier assessment. The benefit assessment was published on 2 January 2024 on the G-BA website (www.g-ba.de), therefore 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 as monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

Therapeutic indication of the resolution (resolution of 21.03.2024):

Nivolumab as monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with stage IIB or IIC melanoma who have undergone complete resection.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults and adolescents 12 years of age and older for the adjuvant treatment of stage IIB or IIC melanoma who have undergone complete resection

Appropriate comparator therapy for nivolumab as monotherapy:

Pembrolizumab

[1] General Methods, version 7.0 from 19.09.2023. 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 and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. In addition to nivolumab, the following active ingredients are approved for the adjuvant treatment of stage IIB or IIC melanoma: pembrolizumab, interferon alfa-2a. Interferon alfa-2a is currently not sold in Germany.

on 2. Adjuvant radiotherapy can be considered in principle in the present therapeutic indication.

On 3. Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the indication adjuvant treatment of stage IIB or IIC melanoma:

- Pembrolizumab: Resolution of 19 January 2023

on 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 indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a 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.

According to the S3 guideline, adjuvant interferon therapy should be offered in tumour stage IIB/C. The S3 guideline also points out that patients at high risk of stage II metastasis can only be followed up. The statements of the clinical experts in the benefit assessment procedure for pembrolizumab (resolution of 19 January 2023) showed that the use of interferon alfa in the adjuvant therapy of stage IIB/C melanoma is associated with only limited efficacy. Against the background of weighing up the benefits and side effects of such treatment, interferon alfa has only been used to a limited extent in the German healthcare context, according to clinical experts. In the present benefit assessment procedure, both the DGHO (German Society for Haematology and Medical Oncology) and the ADO (Working Group of Dermatologic Oncology) point out that, although the currently valid S3 guideline still recommends the offer of adjuvant interferon therapy, this option has practically disappeared from clinical care, also because no corresponding medicinal products are available on the German market.

Against this background, interferon alfa-2a cannot be considered as an appropriate comparator therapy.

The PD-1 inhibitor pembrolizumab is an approved treatment option in care for the present treatment setting. In the benefit assessment, by resolution of 19 January 2023, an indication of a non-quantifiable additional benefit was identified for the adjuvant treatment of stage IIB or IIC melanoma after complete resection compared with monitoring wait-and-see approach. According to the current guidelines of ASCO[2] and SIGN[3], treatment with pembrolizumab is recommended in the adjuvant treatment setting of stage IIB or IIC melanoma. In the oral hearing, the ADO stated that

2 Seth et al.: Systemic Therapy for Melanoma: ASCO Guideline Update, 2023
3 Scottish Intercollegiate Guidelines Network (SIGN), 2017, Cutaneous melanoma; Revised 2023

pembrolizumab has become the current therapy standard in clinical practice since its marketing authorisation.

As there is no evidence regarding non-medicinal treatment with adjuvant radiotherapy for stage IIB/C, adjuvant radiotherapy is not considered as an appropriate comparator therapy.

With regard to the treatment decision for children and adolescents aged 12 years and older with stage IIB or IIC melanoma, the clinical experts' statements on pembrolizumab (resolution of 19 January 2023) already indicated that the number of adolescents affected is low and that there is no specific treatment standard for adolescents at this stage of the disease. The therapy of these patients is oriented towards the therapy of adults recommended in the guidelines. In this regard, the available guidelines also do not contain any separate recommendations for adjuvant treatment of adolescents aged 12 years and older.

In the overall analysis, pembrolizumab is determined as the appropriate comparator therapy.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

Change of the appropriate comparator therapy

For the adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB or IIC melanoma, the appropriate comparator therapy was originally formulated as follows:

"monitoring wait-and-see approach".

In the oral hearing in the present benefit assessment procedure on the question of the therapy currently used in clinical practice, it emerged from the ADO's assessment that pembrolizumab has become the current therapy standard in clinical practice since marketing authorisation. This is also reflected in the recommendations of the current guidelines. Due to the further development of the state of medical knowledge, pembrolizumab is defined as the appropriate comparator therapy for the present resolution.

This change in the appropriate comparator therapy means that the results of the CA209-76K study submitted by the pharmaceutical company in the dossier cannot be used for the present assessment.

The present resolution is subject to a time limit that enables the pharmaceutical company to submit suitable evaluations that correspond to the appropriate comparator therapy determined by the present resolution.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of nivolumab is assessed as follows:

Adults and adolescents 12 years of age and older for the adjuvant treatment of stage IIB or IIC melanoma who have undergone complete resection

An additional benefit is not proven.

Justification:

The present benefit assessment concerns the assessment of nivolumab as monotherapy for the adjuvant treatment of adolescents aged 12 years and older and adults with stage IIB or IIC melanoma who have undergone complete resection as a result of an extension of the therapeutic indication.

For the proof of an additional benefit of nivolumab, the pharmaceutical company presented the results of the phase III CA209-76K study.

CA209-76K is an ongoing, double-blind, randomised controlled trial comparing nivolumab and placebo in the adjuvant treatment of melanoma. The study should enrol adolescents aged 12 years and older and adults who had undergone complete resection of a cutaneous melanoma in tumour stages IIB or IIC (according to version 8 of the American Joint Committee on Cancer [AJCC] classification). In addition, patients were not allowed to have received any further treatment for melanoma, they were not allowed to have any evidence of residual disease at the start of study and a negative sentinel lymph node biopsy had to be available. Furthermore, the patients should be in good general health (for adults corresponding to a performance status according to the Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1). Exclusion criteria were a pre-existing autoimmune disease and a history of metastatic melanoma. Contrary to the plan, no subject below 18 years of age was enrolled in the study.

The 790 patients enrolled were randomised 2:1 to treatment with nivolumab (N = 526) or placebo (N = 264).

The CA209-76K study is divided into 2 parts, of which part 1 covers the initial adjuvant treatment and the subsequent observation period. In the event of a relapse, patients in both study arms have the option, under certain conditions, to cross over to the unblinded part 2 of the study and be treated with nivolumab. The evaluations of patient-relevant endpoints presented with the dossier refer to part 1 of the study.

In part 1 of the CA209-76K study, treatment with nivolumab in the intervention arm was largely carried out in accordance with the requirements in the product information. There were minor deviations from the recommendations for readmission after AEs had subsided. The duration of adjuvant treatment of melanoma was limited to 1 year in the study according to the product information or ended with the occurrence of unacceptable toxicity or relapse.

CA209-76K is conducted in 129 study sites in Australia, Europe and North America. The study was launched in October 2019 and is currently ongoing.

The primary endpoint of the study is recurrence-free survival (RFS). Patient-relevant secondary endpoints are overall survival, symptomatology, health status, health-related quality of life, and adverse events (AE).

Assessment:

The data from the CA209-76K study are unsuitable for the assessment of the additional benefit, as the appropriate comparator therapy pembrolizumab specified by the G-BA for the present resolution has not been implemented.

Conclusion:

There are no suitable data available for an assessment of the additional benefit of nivolumab. Thus, an additional benefit of nivolumab as monotherapy in adults and adolescents aged 12

years and older for the adjuvant treatment of melanoma in tumour stages IIB or IIC after complete resection compared with the appropriate comparator therapy is not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the present benefit assessment of nivolumab finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a paragraph 1 SGB V.

Due to the present change in the appropriate comparator therapy, the G-BA considers it appropriate to limit the resolution on the additional benefit of nivolumab. The limitation enables the pharmaceutical company to submit suitable evaluations, which correspond to the appropriate comparator therapy determined by the present resolution, in a new dossier in a timely manner. For this purpose, a limitation of the period of validity of the resolution to 6 months is considered to be appropriate.

In accordance with Section 3 paragraph 1, number 5 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of the medicinal product with the active ingredient nivolumab recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of nivolumab (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit is considered as being not proven. The possibility that a benefit assessment for the medicinal product with the active ingredient nivolumab can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, Nos. 2 to 6 or No. 8 VerfO) remains unaffected hereof.

A new assessment according to Section 3, paragraph 1, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 1, paragraph 2, No. 7 Rules of the Procedure (VerfO) will not take place if the pharmaceutical company does not wish to make use of the option to submit suitable evaluations corresponding to the appropriate comparator therapy specified in this resolution and irrevocably applies in writing to the G-BA for the resolution to be cancelled within 3 months of this resolution coming into force. In the event of a timely application for cancellation of the time limit, the G-BA shall cancel the limitation on the validity of this resolution with the consequence that the findings of this resolution shall then continue to apply beyond the end of the time limit.

2.1.5 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:

"Nivolumab as monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with stage IIB or IIC melanoma who have undergone complete resection".

The G-BA determined the active ingredient pembrolizumab as the appropriate comparator therapy.

With the present resolution, a change was made to the appropriate comparator therapy. This was changed from the previous "monitoring wait-and-see approach" to "pembrolizumab". This takes into account the statements of clinical experts and the recommendations in current guidelines, according to which pembrolizumab has become the current therapy standard for this therapeutic indication since marketing authorisation. Due to the change in the appropriate comparator therapy, the evidence on the additional benefit submitted by the pharmaceutical company cannot be used or does not allow a statement on the comparison with pembrolizumab. The present resolution is limited in time until 1 October 2024, which enables the pharmaceutical company to submit suitable evaluations in a new dossier for comparison with the appropriate comparator therapy specified in the present resolution.

As a result, no suitable data are available for an assessment of the additional benefit of nivolumab. Thus, an additional benefit of nivolumab as monotherapy in adults and adolescents aged 12 years and older for the adjuvant treatment of melanoma in tumour stages IIB or IIC after complete resection compared with the appropriate comparator therapy is 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).

In its dossier, the pharmaceutical company refers to the patient numbers of patient group a) for the resolution on pembrolizumab (resolution of 19 January 2023) in the same therapeutic indication. In the dossier assessment of pembrolizumab (resolution of 19 January 2023), the data were assessed as being in a largely plausible range despite uncertainties. It should be noted that the number of adolescents in the SHI target population may be slightly higher because the predicted number of adolescents aged 12 to 17 years with melanoma is too low.

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: 12 March 2024):

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 melanoma, as well as specialists in skin and sexually transmitted diseases, and specialists in paediatrics and adolescent medicine with specialisation in paediatric haematology and oncology, and other specialists participating in the Oncology Agreement.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient identification card).

The training material contains, in particular, information and warnings about immune-mediated side effects as well as infusion-related reactions.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 March 2024).

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 varies from patient to patient 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.

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

Adults and adolescents 12 years of age and older for the adjuvant treatment of stage IIB or IIC melanoma who have undergone complete resection

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				
Adults and adolescents aged 12 years and above				
Nivolumab	1 x per 14-day cycle	26.1	1	26
	or			
	1 x per 28-day cycle	13.0	1	13
Appropriate comparator therapy				
Pembrolizumab				
Adults				
Pembrolizumab	1 x every 21 days	17.4	1	17
	or			
	1 x every 42 days	8.7	1	8
Children and adolescents aged from 12 to < 18 years				
Pembrolizumab	1 x every 21 days	17.4	1	17

Consumption:

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.

According to the product information for nivolumab, the dosage in adults and adolescents aged 12 years and older with a body weight ≥ 50 kg with melanoma is either 240 mg every 14 days or 480 mg every 28 days. The dosage for adolescents aged 12 years and older with a body weight < 50 kg is 3 mg per kg of body weight every 14 days or 6 mg per kg of body weight every 28 days.

According to the product information for pembrolizumab, the dosage in adults is either 200 mg every 21 days or 400 mg every 42 days. The dosage in adolescents 12 years and older with melanoma is 2 mg per kg body weight, up to a maximum of 200 mg every 21 days.

For the calculation of the consumption of medicinal products to be dosed according to weight, the G-BA generally uses non-indication-specific average weights as a basis. For body weight, a range between 47.1 kg for 12-year-olds and 67.2 kg for 17-year-olds is therefore assumed according to the official representative statistics "Microcensus 2017" (for 12-year-olds) and "Microcensus 2021" (for 17-year-olds)[4].

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Nivolumab	Adults and adolescents aged 12 years and above with ≥ 50 kg BW				
	240 mg	240 mg	2 x 120 mg	26	52 x 120 mg
	or				
	480 mg	480 mg	4 x 120 mg	13	52 x 120 mg
	Adolescents aged 12 years and above with < 50 kg BW				
	3 mg/kg BW = 141.3 mg	141.3 mg	1 x 40 mg + 1 x 120 mg	26	26 x 40 mg + 26 x 120 mg
	or				
	6 mg/kg BW = 282.6 mg	282.6 mg	3 x 100 mg	13	39 x 100 mg
Appropriate comparator therapy					

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Pembrolizumab					
Adults					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17	34 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8	32 x 100 mg
Children and adolescents aged from 12 to < 18 years					
Pembrolizumab	2 mg/ kg = 94.2 mg - 2 mg / kg = 134.4 mg	94.2 mg - 134.4 mg	1 x 100 mg - 2 x 100 mg	17	17 x 100 mg - 34 x 100 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. 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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Adults and adolescents 12 years of age and older for the adjuvant treatment of stage IIB or IIC melanoma who have undergone complete resection

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 40 mg	1 CIS	€ 523.40	€ 2.00	€ 28.35	€ 493.05
Nivolumab 100 mg	1 CIS	€ 1,291.52	€ 2.00	€ 70.88	€ 1,218.64
Nivolumab 120 mg	1 CIS	€ 1,546.96	€ 2.00	€ 85.05	€ 1,459.91

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
Appropriate comparator therapy					
Pembrolizumab					
Pembrolizumab 100 mg	1 CIS	€ 2,974.82	€ 2.00	€ 166.60	€ 2,806.22
CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 March 2024

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.

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 need 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 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 € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible

concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of

medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults and adolescents 12 years of age and older for the adjuvant treatment of stage IIB or IIC melanoma who have undergone complete resection

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

Product information for nivolumab (Opdivo); Opdivo 10 mg/ml concentrate for the preparation of an infusion solution; last revised: October 2023

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 24 January 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 18 September 2023 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 29 September 2023 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 22 December 2023, and the written statement procedure was initiated with publication on the G-BA website on 2 January 2024. The deadline for submitting statements was 23 January 2024.

The oral hearing was held on 5 February 2024.

By letter dated 6 February 2024, 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 29 February 2024.

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 March 2024, and the proposed resolution was approved.

At its session on 21 March 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 January 2023	Determination of the appropriate comparator therapy
Working group Section 35a	31 January 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	5 February 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	14 February 2024 6 March 2024	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	12 March 2024	Concluding discussion of the draft resolution
Plenum	21 March 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 21 March 2024

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

Prof. Hecken