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, adjuvant treatment, adolescents ≥ 12 to 18 years, monotherapy)

of 21 December 2023

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 31 May 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 28 June 2023, the pharmaceutical company has submitted in due time a dossier in accordance with Section 4, paragraph 3, number 3 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 "adjuvant treatment of adolescents 12 years of age and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection".

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 2 October 2023 on the G-BA website (www.g-ba.de), 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, and the statements submitted in the written statement and oral hearing procedure. 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 melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

Therapeutic indication of the resolution (resolution of 21.12.2023):

Nivolumab as monotherapy is indicated for the adjuvant treatment of adolescents 12 years of age and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adolescents 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection, adjuvant treatment

Appropriate comparator therapy for nivolumab as monotherapy:

– Pembrolizumab (monotherapy)

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

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA 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 this therapeutic indication, the active ingredient pembrolizumab is approved alongside nivolumab as monotherapy for the adjuvant treatment of children and

adolescents 12 years of age and older with melanoma in tumour stages IIB, IIC or III after complete resection.

No other medicinal products are approved for the adjuvant treatment of adolescents 12 years of age and older with melanoma in tumour stage IV after complete resection.

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

on 3. For adolescents 12 years of age and older in the indication of adjuvant treatment of melanoma after complete resection, the following resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V is available:

- 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".

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

Regarding the treatment options for adjuvant treatment specifically in adolescents 12 years of age and older, the evidence is limited with regard to tumour stage III (with lymph node involvement) after complete resection. There is hardly any evidence on tumour stage IV in completely resected distant metastases. The available guidelines do not contain any explicit recommendations for adjuvant treatment in adolescents 12 years of age and older.

From the participation of the scientific-medical societies on the question of comparator therapy, a joint written statement is available from the Working Group for Dermatological Oncology (ADO) of the DKG (German Cancer Society) and the German Society for Haematology and Medical Oncology (DGHO). Accordingly, there is no separate standard for children and adolescents. The therapy of these few patients is oriented towards the therapy of adults. In this regard, the written statement mentions various systemic treatment options depending on BRAF-V600 mutational status, which are based on the therapy recommendations for adults. Accordingly, the PD-1 antibodies nivolumab and pembrolizumab are recommended for patients with BRAF wild type and both PD-1 antibody nivolumab and pembrolizumab as well as the targeted therapy with dabrafenib in combination with trametinib for patients with BRAF-V600 mutation.

Pembrolizumab is approved for the adjuvant treatment of children and adolescents 12 years of age and older with melanoma in tumour stage III after complete resection.

No additional benefit was identified for pembrolizumab as monotherapy in the benefit assessment for the adjuvant treatment of children and adolescents 12 years of age and older with melanoma in tumour stage III after complete resection, as no data were presented for the benefit assessment (resolution of 19 January 2023).

For the adjuvant treatment of melanoma in tumour stage IV after complete resection, only the medicinal product to be assessed (nivolumab) is approved for adolescents 12 years of age and older. The active ingredients pembrolizumab and dabrafenib + trametinib recommended in the written statement of the scientific-medical societies for the treatment of adolescents 12 years of age and older are also not approved for the adjuvant treatment of stage IV melanoma. Dabrafenib + trametinib is approved for the adjuvant treatment of stage III melanoma in adults, but not in adolescents 12 years of age and older.

In view of the fact that the therapy recommendations for adolescents 12 years of age and older are based on the treatment of adults according to the written statement of the scientific-medical societies, the present determination of the appropriate comparator therapy is based on the corresponding evidence for adults.

Overall, the guidelines strongly recommend treatment with anti-PD-1 antibodies for adjuvant treatment of adults with stage III and IV melanoma. For adults with a BRAF-V600E/K mutation in tumour stage III, there is also a strong recommendation for the combination of active ingredients dabrafenib + trametinib. For a BRAF-V600E/K mutation, both treatment with anti-PD-1 antibodies and with dabrafenib + trametinib are equally recommended first-line therapy options – a preference cannot be derived from the guidelines. This also corresponds to the statement of the scientific-medical societies.

With regard to the available anti-PD-1 antibodies nivolumab and pembrolizumab, each as monotherapy, nivolumab is ruled out as an appropriate comparator therapy with regard to the research question of the present benefit assessment.

With regard to tumour stage IV and a BRAF-V600E/K mutation, no clear or unanimous recommendation for treatment with dabrafenib + trametinib can be derived from the guidelines. For example, the recommendation for dabrafenib + trametinib in the S3 guideline refers specifically only to tumour stage III.

As a non-medicinal treatment, adjuvant radiotherapy can, in principle, be considered in stage III. This serves to improve regional tumour control. Adjuvant radiotherapy is used on a patient-individual basis depending on the risk of recurrence and taking into account possible therapy-related side effects. There are no data demonstrating a positive impact of adjuvant radiotherapy on overall survival. A regular application cannot be derived, which is why adjuvant radiotherapy cannot be considered as an appropriate comparator therapy.

In summary, pembrolizumab is approved for the adjuvant treatment of children and adolescents 12 years of age and older with melanoma in tumour stage III after complete resection. Dabrafenib + trametinib is approved for the adjuvant treatment of stage III melanoma in adults, but not in adolescents 12 years of age and older. With regard to an exceptional determination of dabrafenib + trametinib as an appropriate comparator therapy in the off-label use for adolescents 12 years of age and older, a prerequisite according to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) would be that an off-label use of dabrafenib + trametinib would generally be preferable to the medicinal products previously

approved in the therapeutic indication (pembrolizumab) according to the generally recognised state of medical knowledge. This cannot be established, even taking into account the evidence on adults.

Pembrolizumab is approved for the adjuvant treatment of adolescents 12 years of age and older with melanoma in tumour stage IIB, IIC or III. Treatment with pembrolizumab in relation to tumour stage IV therefore represents an off-label use as there are no other approved therapy options in tumour stage IV apart from the medicinal product to be assessed. The G-BA considers it appropriate to determine pembrolizumab, including this off-label use for the adjuvant treatment of adolescents 12 years of age and older with stage IV melanoma, as an appropriate comparator therapy, Section 6, paragraph 2, sentence 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). This takes into account the rarity of the disease in the age group of adolescents 12 years of age and older and the severity of the disease. Furthermore, reference is made to the therapy recommendations and the available evidence for treatment with an anti-PD-1 antibody in adults together with the written statement of the scientific-medical societies on the question of comparator therapy, according to which there is no separate standard for children and adolescents and the treatment of these few patients is based on the treatment of adults.

The determination of the off-label use of medicinal products as an appropriate comparator therapy by resolution on the benefit assessment according to Section 35a paragraph 3 SGB V does not affect the procedure according to Section 35c SGB V.

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:

Originally, the appropriate comparator therapy was determined as follows:

a) Adolescents 12 years of age and older with melanoma with lymph node involvement (tumour stage III) after complete resection; adjuvant treatment

Appropriate comparator therapy for nivolumab (monotherapy):

- Pembrolizumab

b) Adolescents 12 years of age and older with melanoma with metastasis (tumour stage IV) after complete resection; adjuvant treatment

Appropriate comparator therapy for nivolumab (monotherapy):

- Monitoring wait-and-see approach

This appropriate comparator therapy was determined for the present benefit assessment procedure on nivolumab under the effects of the ruling of the Federal Social Court (FSC) of 22 February 2023. According to the FSC's comments on this ruling (file ref.: B 3 KR 14/21 R), medicinal products that do not have a marketing authorisation for the present indication and whose prescribability in off-label use has also not been recognised by the G-BA in the Pharmaceuticals Directive are generally not considered as appropriate comparator therapy in the narrower sense of Section 2, paragraph 1, sentence 3, Section 12 SGB V.

Within the scope of this provision, it was to be noted that medicinal therapies not approved for the adjuvant treatment of adolescents 12 years of age and older with melanoma are mentioned by the scientific-medical societies and/or the AkdÄ (Drugs Commission of the German Medical Association) according to Section 35a, paragraph 7, sentence 4 SGB V.

With the entry into force of the ALBVVG (Act to Combat Supply Shortages and Improve the Supply of Medicines) on 27 July 2023, the G-BA can exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy in accordance with Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

In view of the fact that for the present benefit assessment of nivolumab, off-label use of medicinal products can be considered as an appropriate comparator therapy, also taking into account the statements of scientific-medical societies in the present procedure, a review of the appropriate comparator therapy under the regulations after the entry into force of the ALBVVG was necessary. In the course of this, the appropriate comparator therapy was changed for the present resolution.

The change in the appropriate comparator therapy has no impact on the benefit assessment of nivolumab (monotherapy) for the adjuvant treatment of adolescents 12 years of age and older with melanoma with lymph node involvement or metastasis after complete resection.

2.1.3 Extent and probability of the additional benefit

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

<u>Adolescents 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection, adjuvant treatment</u>

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of nivolumab for the adjuvant treatment of adolescents aged 12 to 17 years with melanoma with lymph node involvement or metastasis after complete resection, the pharmaceutical company did not present any direct comparator data versus the appropriate comparator therapy. Furthermore, no clinical study relevant to the present therapeutic indication could be identified and therefore no indirect comparison with the appropriate comparator therapy could be done.

For the assessment of the additional benefit, the pharmaceutical company refers in the benefit assessment dossier to two individual case reports of the label-enabling, randomised, double-blind phase III CA209-915 study, but does not present these for data protection reasons.

If no suitable data are available for the benefit assessment in adolescents, a so-called evidence transfer, a transfer of data from the adult population to adolescents 12 years of age and older,

should be examined. In the dossier, the pharmaceutical company classifies a transfer of evidence as infeasible, as there are no clinical studies with adolescents in the therapeutic indication and therefore no results on patient-relevant endpoints that would allow the transferability of therapeutic effects from adults to adolescents.

Thus, for the adjuvant treatment of adolescents 12 years of age and older with melanoma with lymph node involvement or metastasis after complete resection, no data were presented for the assessment of the additional benefit of nivolumab compared with the appropriate comparator therapy.

Overall, no additional benefit can be derived for adolescents 12 years of age and older compared with the appropriate comparator therapy.

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 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"

In this case, nivolumab is only assessed for the adjuvant treatment of melanoma in adolescents 12 years of age and older with lymph node involvement or metastasis after complete resection.

The G-BA defined adjuvant treatment with the immune checkpoint inhibitor pembrolizumab as an appropriate comparator therapy.

No data were submitted by the pharmaceutical company that would allow an assessment of the additional benefit. A transfer of evidence from the adult population to adolescents 12 years of age and older was also classified as infeasible by the pharmaceutical company. An additional benefit 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).

To estimate the potential number of patients, the pharmaceutical company refers to the benefit assessment of pembrolizumab in the same therapeutic indication. On this basis, the pharmaceutical company indicates a number of one to four patients in the SHI target population. Overall, it can be assumed that the number of patients is underestimated because the projected sample size for 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: 8 December 2023):

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 December 2023.

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.

<u>Adolescents 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection, adjuvant treatment</u>

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Nivolumab	1 x per 14-day cycle	26.1	1	26
	or			
	1 x per 28-day cycle	13.0	1	13
Appropriate comparator therapy				
Therapy according to doctor's instructions				
Pembrolizumab	1 x per 21-day cycle	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.

The dosage of pembrolizumab 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 67.0 kg for 17-year-olds is therefore assumed according to the official representative statistics "Microcensus 2017"[2].

[2] 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
Medicinal product to be assessed					
Nivolumab	Adolescents < 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
	Adolescents ≥ 50 kg BW				
	240 mg	240 mg	2 x 120 mg	26	52 x 120 mg
	or				
	Adolescents < 50 kg BW				
	6 mg/kg BW = 282.6 mg	282.6 mg	3 x 100 mg	13	39 x 100 mg
	Adolescents ≥ 50 kg BW				
	480 mg	480 mg	4 x 120 mg	13	52 x 120 mg
Appropriate comparator therapy					
Therapy according to doctor's instructions					
Pembrolizumab	2 mg/kg = 94.2 mg	94.2 mg	1 x 100 mg	17	17 x 100 mg
	2 mg/kg = 134 mg	134 mg	2 x 100 mg	17	34 x 100 mg

Costs:

Costs of the medicinal products:

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.

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	€ 48.60	€ 472.80
Nivolumab 100 mg	1 CIS	€ 1,291.52	€ 2.00	€ 121.51	€ 1,168.01
Nivolumab 120 mg	1 CIS	€ 1,546.96	€ 2.00	€ 145.81	€ 1,399.15
Appropriate comparator therapy					
Pembrolizumab	1 CIS	€ 2974.82	€ 2.00	€ 285.60	€ 2,687.22

LAUER-TAXE® last revised: 1 December 2023

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:

Adolescents 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection, adjuvant treatment

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.

References:

Product information for nivolumab (Opdivo); Opdivo 10 mg/ml concentrate for the preparation of an infusion solution; last revised: August 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 11 October 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 06 June 2023.

On 28 June 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 5, sentence 2 VerfO.

By letter dated 30 June 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 28 September 2023, and the written statement procedure was initiated with publication on the G-BA website on 2 October 2023. The deadline for submitting statements was 23 October 2023.

The oral hearing was held on 6 November 2023.

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 December 2023, and the proposed resolution was approved.

At its session on 21 December 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 October 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	6 June 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	1 November 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	6 November 2023	Conduct of the oral hearing
Working group Section 35a	15 November 2023 6 December 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	12 December 2023	Concluding discussion of the draft resolution
Plenum	21 December 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 21 December 2023

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

Prof. Hecken