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, adolescents ≥ 12 to 18 years, monotherapy or combination with ipilimumab)

of 21 December 2023

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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 Date 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 "advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older".

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 or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older.

Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression.

Therapeutic indication of the resolution (resolution of 21.12.2023):

a) Nivolumab as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older.

b) Nivolumab in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

a) Adolescents 12 years of age and older with advanced (unresectable or metastatic) melanoma

Appropriate comparator therapy for nivolumab as monotherapy:

– Pembrolizumab (monotherapy)

b) Adolescents 12 years of age and older with advanced (unresectable or metastatic) melanoma

Appropriate comparator therapy for nivolumab in combination with ipilimumab:

– Pembrolizumab (monotherapy)

or

– Nivolumab (monotherapy)

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 as monotherapy or nivolumab in combination with ipilimumab, ipilimumab is approved as a monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age (unresectable or metastatic) melanoma in adolescents 12 years of age and older. Pembrolizumab as monotherapy is approved for the treatment of advanced (unresectable or metastatic) melanoma in children and adolescents aged 12 years and older.

In terms of authorisation status, medicinal products with the active ingredients ipilimumab, nivolumab, pembrolizumab, talimogene laherparepvec, dacarbazine and lomustine are available for adults for the treatment of advanced melanoma. For patients whose melanoma has a BRAF V600 mutation, the combination therapies of encorafenib and binimetinib, cobimetinib and vemurafenib, dabrafenib and trametinib as well as the monotherapies dabrafenib, trametinib and vemurafenib are also approved.

on 2. The target population is assumed to be those patients for whom resection and/or radiotherapy with curative goals is unsuitable. In the present therapeutic indication, a non-medicinal treatment is therefore not considered.

on 3. For adolescents 12 years of age and older in the indication of advanced melanoma, the following resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- Pembrolizumab: Resolution of 19 January 2023
- Ipilimumab: Resolution of 2 August 2018

For adults with the indication advanced melanoma, the following resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- Vemurafenib: Resolution of 6 March 2014
- Pembrolizumab: Resolution of 4 February 2016
- Dabrafenib: Resolutions of 17 March 2016 and 16 June 2016 (3 April 2014)
- Trametinib: Resolution of 17 March 2016

- Ipilimumab: Resolutions of 7 April 2016 (2 August 2012), 7 April 2016 (5 June 2014), 2 August 2018 and 20 December 2018
- Cobimetinib: Resolution of 2 June 2016
- Nivolumab: Resolutions of 15 December 2016 (7 January 2016), 15 December 2016, 7 December 2017 and 20 December 2018
- Talimogene laherparepvec: Resolution of 15 December 2016
- Encorafenib: Resolution of 22 March 2019
- Binimetinib: Resolution of 22 March 2019

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").

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.

There is little evidence on treatment options specifically for the treatment of adolescents 12 years of age and older. The existing guidelines for the treatment of advanced (unresectable or metastatic) melanoma do not make any recommendations in this regard.

The PD-1 antibodies nivolumab and pembrolizumab as monotherapy, the CTLA-4 antibody ipilimumab as monotherapy and the combination of nivolumab and ipilimumab are approved for adolescents 12 years of age and older.

From the participation of the scientific-medical societies on the question of comparator therapy, a 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). In the joint written statement, various systemic treatment options are mentioned for advanced melanoma in adults and adolescents 12 years of age and older, depending on the BRAF V600 mutational status. In advanced melanoma without evidence of a BRAF V600 mutation, treatment with PD-1 inhibitors is recommended, either as monotherapy or in combination with a CTLA4 inhibitor. In the presence of a BRAF V600 mutation, there is the option of oral BRAF/MEK combination therapy in addition to the immune checkpoint inhibitors mentioned.

In addition, in a further joint written statement on the question of comparator therapy for the present indication, the above-mentioned scientific-medical societies stated that

there is currently no separate standard for children and adolescents. The therapy is based on the therapy for adults.[2]

In view of the fact that the therapy recommendations for adolescents 12 years of age and older are based on adults, the treatment options for adults are also considered for the present determination of the appropriate comparator therapy.

With regard to the therapy of adults with advanced melanoma, the present guidelines strongly recommend therapy with a PD-1 antibody. In contrast, monotherapy with ipilimumab has lost its value in non-pretreated adults due to its inferiority to PD-1 antibodies and is no longer recommended.

The therapy recommendations for adults in the guidelines also include the combination therapy of nivolumab and ipilimumab. However, the benefit assessment on nivolumab in combination with ipilimumab found a lower benefit compared to nivolumab (as monotherapy) for non-pretreated adults with BRAF V600 wild-type tumour (resolution of 20 December 2018).

For adults with a BRAF-V600 mutation, specific treatment with BRAF or MEK inhibitors is also available, whereby the combination of BRAF and MEK inhibitor represents the current standard due to its superiority over a BRAF inhibitor as monotherapy. In this regard, the combinations dabrafenib and trametinib, cobimetinib and vemurafenib as well as encorafenib and binimetinib are approved for the treatment of adults.

According to the recommendations of the guidelines, PD-1 antibodies and BRAF/MEK inhibitors are equally recommended first-line therapy options for adults with BRAF-V600 mutations. The S3 guideline points out that there are no data on the best sequential therapy of BRAF/MEK inhibitors and checkpoint inhibitors.

Of the above-mentioned treatment options for adults, BRAF and MEK inhibitors are not approved for the treatment of adolescents 12 years of age and older. With regard to the exceptional designation of BRAF/MEK inhibitors as an appropriate comparator therapy in 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 the BRAF/MEK inhibitors would generally be preferable to the medicinal products currently approved in the therapeutic indication (pembrolizumab, nivolumab, ipilimumab, nivolumab in combination with ipilimumab) according to the generally recognised state of medical knowledge. This cannot be established, even taking into account the evidence on adults.

With regard to the medicinal products approved for adolescents 12 years of age and older, no additional benefit was identified for pembrolizumab as monotherapy and for ipilimumab as monotherapy in the G-BA's benefit assessment for adolescents 12 years of age and older compared to the appropriate comparator therapy, as no data suitable for the benefit assessment were presented in each case (resolution of 19 January 2023

[2] Federal Joint Committee (G-BA). Benefit assessment procedure for the active ingredient pembrolizumab (new therapeutic indication: Melanoma, ≥ 12 to < 18 years); information on the appropriate comparator therapy [online]. 2021 [accessed: 01.12.2023]. URL: https://www.g-ba.de/downloads/92-975-5974/2022-08-01_Information-zVT_Pembrolizumab_D-847.pdf

and resolution of 2 August 2018). Nivolumab as monotherapy and nivolumab in combination with ipilimumab were only recently approved in May 2023 and are the medicinal products to be assessed in this benefit assessment.

Taking into account the evidence on the above-mentioned treatment options in the treatment of 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 G-BA considers it appropriate a) to consider nivolumab as monotherapy in addition to pembrolizumab as monotherapy as an appropriate comparator therapy already at this early stage, b) not to include ipilimumab as monotherapy and nivolumab in combination with ipilimumab in the appropriate comparator therapy despite existing marketing authorisation for adolescents 12 years of age and older.

Thus, a therapy with pembrolizumab (monotherapy) is determined as appropriate comparator therapy for the medicinal product nivolumab (monotherapy) to be assessed.

For the medicinal product to be assessed, nivolumab in combination with ipilimumab, a therapy with pembrolizumab (monotherapy) or nivolumab (monotherapy) is determined as appropriate comparator therapy. The appropriate comparator therapy determined here includes several therapy options. These therapeutic alternatives are equally appropriate for the 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:

Originally, the appropriate comparator therapy was determined as follows:

Adolescents 12 years of age and older with advanced (unresectable or metastatic) melanoma

Appropriate comparator therapy for nivolumab (monotherapy) in combination with ipilimumab:

- Pembrolizumab

This appropriate comparator therapy was determined 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 treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older 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 in the present benefit assessment, off-label use of medicinal products is considered, also taking into account the statements of scientific-medical societies on the question of comparator therapy 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 for therapeutic indication a) nivolumab (monotherapy) or therapeutic indication b) nivolumab in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older.

2.1.3 Extent and probability of the additional benefit

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

a) Adolescents 12 years of age and older with advanced (unresectable or metastatic) melanoma

Extent and probability of the additional benefit of nivolumab (monotherapy) compared to the appropriate comparator therapy:

An additional benefit is not proven.

b) Adolescents 12 years of age and older with advanced (unresectable or metastatic) melanoma

Extent and probability of the additional benefit of nivolumab in combination with ipilimumab compared to the appropriate comparator therapy:

An additional benefit is not proven.

Justification:

For adolescents 12 years of age and older with advanced (unresectable or metastatic) melanoma, the pharmaceutical company could not identify a randomised controlled trial for the direct comparison of nivolumab 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 additional benefit, the pharmaceutical company refers in the benefit assessment dossier to an individual case report of the label-enabling, single-arm, open-label, multi-cohort phase I/II CA209-070 study, but does not present it 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, no data were presented for the assessment of the additional benefit of nivolumab (monotherapy) or of nivolumab in combination with ipilimumab compared with the appropriate comparator therapy for the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older.

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 or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older."

In this case, nivolumab is only assessed for the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older.

The therapeutic indication was differentiated with regard to monotherapy and combination therapy:

a) Nivolumab as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older.

b) Nivolumab in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older.

Therapeutic indication a)

a) Adolescents 12 years of age and older with advanced (unresectable or metastatic) melanoma

The G-BA determined the immune checkpoint inhibitor pembrolizumab as the appropriate comparator therapy for nivolumab (monotherapy).

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.

Therapeutic indication b)

b) Adolescents 12 years of age and older with advanced (unresectable or metastatic) melanoma

The G-BA determined the checkpoint inhibitors nivolumab (monotherapy) or pembrolizumab (monotherapy) as the appropriate comparator therapy for nivolumab in combination with ipilimumab.

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 in the benefit assessment of pembrolizumab 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.

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 monotherapy				
Nivolumab	1 x per 14-day cycle	26.1	1	26.1
	or			
	1 x per 28-day cycle	13.0	1	13.0
Nivolumab in combination with ipilimumab				
Initial treatment (combination phase nivolumab + ipilimumab)				
Nivolumab	1 x per 21-day cycle	4	1	4
Ipilimumab	1 x per 21-day cycle	4	1	4
Follow-up treatment (monotherapy phase with nivolumab)				
Nivolumab	1 x per 14-day cycle	20.1	1	20.1
	or			
	1 x per 28-day cycle	9.3	1	9.3
Appropriate comparator therapy				
Pembrolizumab				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4

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"[3].

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Nivolumab as monotherapy					
Nivolumab	Adolescents < 50 kg BW:				
	3 mg/kg BW = 141.3 mg	141.3 mg	1 x 40 mg + 1 x 120 mg	26.1	26.1 x 40 mg + 26.1 x 120 mg
	Adolescents ≥ 50 kg BW				
	240 mg	240 mg	2 x 120 mg	26.1	52.2 x 120 mg
	or				
	Adolescents < 50 kg BW:				
	6 mg/kg BW = 282.6 mg	282.6 mg	3 x 100 mg	13.0	39.0 x 100 mg
	Adolescents ≥ 50 kg BW				
	480 mg	480 mg	4 x 120 mg	13.0	52.0 x 120 mg
Nivolumab in combination with ipilimumab					
Initial treatment					

[3] 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	Annual average consumption by potency
Nivolumab	1 mg/kg BW = 47.1 mg – 1 mg/kg BW = 67 mg	47.1 mg – 67 mg	2 x 40 mg	4	8 x 40 mg
Ipilimumab	3 mg/kg BW = 141.3 mg – 3 mg/kg BW = 201 mg	141.3 mg – 201 mg	3 x 50 mg – 1 x 200 mg + 1 x 50 mg	4	12 x 50 mg – 4 x 200 mg + 4 x 50 mg
Follow-up treatment					
Nivolumab	Adolescents < 50 kg BW:				
	3 mg/kg BW = 141.3 mg	141.3 mg	1 x 40 mg + 1 x 120 mg	20.1	20.1 x 40 mg + 20.1 x 120 mg
	Adolescents ≥ 50 kg BW				
	240 mg	240 mg	2 x 120 mg	20.1	40.2 x 120 mg
	or				
	Adolescents < 50 kg BW:				
	6 mg/kg BW = 282.6 mg	282.6 mg	3 x 100 mg	9.3	27.9 x 100 mg
	Adolescents ≥ 50 kg BW				
	480 mg	480 mg	4 x 120 mg	9.3	37.2 x 120 mg
Appropriate comparator therapy					
Pembrolizumab	2 mg/kg BW = 94.2 mg –	94.2 mg	1 x 100 mg	17.4	17.4 x 100 mg - 34.8 x 100 mg
	2 mg/kg BW = 134 mg	134 mg	2 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:

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
Ipilimumab 50 mg	1 CIS	€ 3,489.23	€ 2.00	€ 335.96	€ 3,151.27
Ipilimumab 200 mg	1 CIS	€ 13,783.97	€ 2.00	€ 1,343.85	€ 12,438.12
Appropriate comparator therapy					
Pembrolizumab 100 mg	1 CIS	€ 2,974.82	€ 2.00	€ 285.60	€ 2,687.22
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

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 of age and older with advanced (unresectable or metastatic) melanoma

a) Nivolumab as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older.

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.

b) Nivolumab in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older.

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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 6 June 2023, 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 6 June 2023.

On 31 May 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 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 27 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