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: urothelial carcinoma, first-line, combination with cisplatin and gemcitabine)

of 19 December 2024

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of all 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 23 May 2024, 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 19 June 2024, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5,

Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient nivolumab with the new therapeutic indication

"OPDIVO in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma."

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The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 October 2024 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 in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

Therapeutic indication of the resolution (resolution of 19 December 2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with unresectable or metastatic urothelial carcinoma; first-line treatment

Appropriate comparator therapy for nivolumab in combination with cisplatin and gemcitabine:

Cisplatin in combination with gemcitabine followed by avelumab as maintenance treatment (maintenance treatment with avelumab only for patients who are progression-free)

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 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, medicinal products with the active ingredients avelumab, cisplatin, doxorubicin, gemcitabine, methotrexate and pembrolizumab in combination with enfortumab vedotin are approved for this therapeutic indication.

On 2. Non-medicinal treatment options are not considered as an appropriate comparator therapy in the present therapeutic indication.

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

- Avelumab: resolution of 19 August 2021

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic 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 therapeutic indication according to Section 35a, paragraph 7 SGB V.

A joint written statement of the German Society for Urology (DGU) and the German Society for Haematology and Medical Oncology (DGHO) is available.

Among the approved active ingredients listed under 1), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

For patients suitable for cisplatin, the guidelines unanimously recommend the combination of cisplatin and gemcitabine as standard therapy. Compared to the alternatively discussed combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC or high-dose MVAC with additional concomitant administration of granulocyte-stimulating factors), the combination of cisplatin and gemcitabine is considered to have a more favourable toxicity profile according to the available evidence. Following cisplatin-based therapy, avelumab as a monotherapy is available as a therapy option for first-line maintenance treatment in adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free after platinum-based chemotherapy. According to the guidelines, patients who achieve at least stable disease with cisplatin-based therapy should be given first-line maintenance treatment with avelumab. In their resolution of 19 August 2021, the G-BA identified in the benefit assessment a hint for a considerable additional benefit of avelumab compared to best supportive care. Cisplatin in combination with gemcitabine, followed by avelumab as maintenance treatment for patients who are progression-free, is thus determined to be the appropriate comparator therapy in this therapeutic indication.

In their written statement, the scientific-medical societies confirm that the current standard for patients suitable for cisplatin is the combination of cisplatin and gemcitabine, followed by avelumab in patients who are progression-free.

Enfortumab vedotin in combination with pembrolizumab is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved for this therapeutic indication (marketing authorisation on 26 August 2024) and is

currently undergoing a benefit assessment procedure. Based on the generally accepted state of medical knowledge, enfortumab vedotin in combination with pembrolizumab is not determined to be an appropriate comparator therapy for the present resolution.

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.

2.1.3 Extent and probability of the additional benefit

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

Adults with unresectable or metastatic urothelial carcinoma; first-line treatment

An additional benefit is not proven.

Justification:

On the CA209-901 study (CheckMate 901)

The pharmaceutical company has presented the results of the randomised, open-label phase III CA209-901 study (CheckMate 901) to prove the additional benefit. From the four-arm study, only the two treatment arms in which nivolumab + cisplatin + gemcitabine was compared with cisplatin + gemcitabine were relevant for the present benefit assessment.

For the ongoing multicentre study, which began in January 2018, two planned data cut-offs are available for the two study arms used, nivolumab + cisplatin + gemcitabine and cisplatin + gemcitabine: an interim analysis after 267 overall survival events and a final analysis after 356 overall survival events. 304 patients were included and randomly allocated in a 1:1 ratio to each of the study arms used. The primary endpoints are overall survival and progression-free survival (PFS); secondary endpoints are collected in the categories of morbidity, health-related quality of life and side effects.

Implementation of the appropriate comparator therapy:

In accordance with the appropriate comparator therapy, patients with unresectable or metastatic urothelial carcinoma who are progression-free after treatment with cisplatin + gemcitabine in first-line therapy should receive maintenance treatment with avelumab. According to the study design and study protocol, maintenance treatment with avelumab was not explicitly planned for patients without progression after chemotherapy, so that not all patients received maintenance treatment with avelumab.

In their written statement, the pharmaceutical company presented figures showing that a relevant percentage of patients in the control arm of the study were not treated with avelumab maintenance treatment in accordance with the appropriate comparator therapy: Accordingly, in the control arm of the study relevant for the benefit assessment, approx. 60% of patients (182 of 304 patients in the ITT population) were eligible for maintenance treatment with avelumab, but only approx. 7% of patients (22 patients treated with avelumab within 10 weeks of at least 4 cycles of chemotherapy and subsequent freedom from progression) received maintenance treatment with avelumab. Patients were eligible for maintenance treatment with avelumab if they were progression-free following at least 4 cycles of

chemotherapy with cisplatin + gemcitabine. This results in a relevant percentage of patients amounting to approx. 50% who were not adequately treated with avelumab maintenance treatment despite being eligible for it.

In summary, the results presented from the CheckMate 901 studies are unsuitable for assessment of the additional benefit because the appropriate comparator therapy in the control arm with cisplatin + gemcitabine was not implemented for a relevant proportion of patients.

Conclusion

In the CheckMate 901 study, around 50% of patients in the control arm with cisplatin + gemcitabine were not adequately treated with avelumab despite being eligible for maintenance treatment with avelumab, which meant that the appropriate comparator therapy was not implemented for a relevant proportion of patients. No assessable data are thus available for the benefit assessment.

The G-BA therefore concluded that an additional benefit is not proven for nivolumab in combination with cisplatin and gemcitabine in the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient nivolumab. The therapeutic indication assessed here is as follows:

"OPDIVO in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma."

The G-BA determined cisplatin in combination with gemcitabine followed by avelumab as maintenance treatment (maintenance treatment with avelumab only for patients who are progression-free) as the appropriate comparator therapy.

For the assessment, results from the relevant study arms nivolumab + cisplatin + gemcitabine and cisplatin + gemcitabine of the CheckMate 901 study are available.

In the CheckMate 901 study, around 50% of patients in the control arm with cisplatin + gemcitabine were not adequately treated with avelumab despite being eligible for maintenance treatment with avelumab, which meant that the appropriate comparator therapy was not implemented for a relevant proportion of patients. For this reason, the data presented are unsuitable for the benefit assessment.

The G-BA therefore concluded that an additional benefit is not proven for nivolumab in combination with cisplatin and gemcitabine in the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the information provided by the pharmaceutical company.

This information is subject to uncertainty resulting from the fact that the determination of the percentages of disease stages according to the system of the International Union Against Cancer (Union Internationale Contre le Cancer, UICC) also includes cases with an unknown stage and that the proportion of progression from the upper limit of stage I to stage II or stage III may be higher.

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: 5 September 2024):

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

Treatment with nivolumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology and urology, and specialists participating in the Oncology Agreement experienced in the treatment of adults with urothelial carcinoma.

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 2024).

The costs for the first year of treatment are shown for the cost representation in the resolution.

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 the maximum treatment duration, if specified in the product information.

Treatment period:

Adults with unresectable or metastatic urothelial carcinoma; first-line treatment

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 in combination with cisplatin and gemcitabine				
Nivolumab	1 x every 21 days	6	1	6
Cisplatin	1 x on day 1 or day 2 per 21-day cycle	6	1	6
Gemcitabine	1 x on day 1 + 8 per 21-day cycle	6	2	12
Maintenance treatment with nivolumab				
Nivolumab	1 x every 14 days or 1 x every 28 days	17.1 or 8.5	1	17.1 or 8.5
Appropriate comparator therapy				
Cisplatin in combination with gemcitabine				
Cisplatin	1 x on day 1 or day 2 per 28-day cycle	4 – 6	1	4 – 6
Gemcitabine	1 x on day 1, 8 and 15 per 28-day cycle	4 – 6	3	12 – 18
Maintenance treatment with avelumab				
Avelumab	1 x every 14 days	18.1 – 14.1	1	18.1 – 14.1

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body

weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[2].

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

Adults with unresectable or metastatic urothelial carcinoma; first-line treatment

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 in combination with cisplatin and gemcitabine					
Nivolumab	360 mg	360 mg	3 x 120 mg	6	18 x 120 mg
Cisplatin	70 mg/m² = 133.7 mg	133.7 mg	1 x 100 mg + 1 x 50 mg	6	6 x 100 mg + 6 x 50 mg
Gemcitabine	1,000 mg/m² = 1,910 mg	1,910 mg	2 x 1,000 mg	12	24 x 1,000 mg
Maintenance treatment with nivolumab					
Nivolumab	240 mg or 480 mg	240 mg or 480 mg	2 x 120 mg or 4 x 120 mg	17.1 or 8.5	34 x 120 mg
Appropriate comparator therapy					
Cisplatin in combination with gemcitabine					
Cisplatin	70 mg/m² = 133.7 mg	133.7 mg	1 x 100 mg + 1 x 50 mg	4 - 6	4 x 100 mg + 4 x 50 mg – 6 x 100 mg + 6 x 50 mg
Gemcitabine	1,000 mg/m² = 1,910 mg	1,910 mg	2 x 1,000 mg	12 – 18	24 x 1,000 mg – 36 x 1,000 mg
Maintenance treatment with avelumab					
Avelumab	800 mg	800 mg	4 x 200 mg	18.1 – 14.1	72.4 x 200 mg – 56.4 x 200 mg

[2] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a 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 reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Adults with unresectable or metastatic urothelial carcinoma; first-line treatment

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 in combination with cisplatin and gemcitabine						
Nivolumab 120 mg	1	CIS	€ 1,546.96	€ 2.00	€ 85.05	€ 1,459.91
Cisplatin 100 mg	1	CIS	€ 76.59	€ 2.00	€ 3.10	€ 71.49
Cisplatin 50 mg	1	CIS	€ 47.71	€ 2.00	€ 1.73	€ 43.98
Gemcitabine 1,000 mg	1	PIS	€ 102.35	€ 2.00	€ 10.62	€ 89.73
Appropriate comparator therapy						
Cisplatin and gemcitabine						
Cisplatin 100 mg	1	CIS	€ 76.59	€ 2.00	€ 3.10	€ 71.49
Cisplatin 50 mg	1	CIS	€ 47.71	€ 2.00	€ 1.73	€ 43.98
Gemcitabine 1,000 mg	1	PIS	€ 102.35	€ 2.00	€ 10.62	€ 89.73
Maintenance treatment with avelumab						
Avelumab 200 mg	1	CIS	€ 834.82	€ 2.00	€ 45.59	€ 787.23
Abbreviations: CIS = concentrate for the preparation of an infusion solution, PIS = powder for the preparation of an infusion solution						

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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.

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	Treatment days/ year	Costs/ patient/ year
Cisplatin							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Medicinal product to be assessed							
Nivolumab in combination with cisplatin and gemcitabine (6 cycles)							
Mannitol 10% infusion solution, 37.5 g/day	10 x 250 ml INF	€ 87.05	€ 4.35	€ 7.94	€ 74.76	6.0	€ 74.76
Sodium chloride 0.9% infusion solution, 3 l - 4.4 l/day	6 x 1,000 ml INF	€ 25.09	€ 1.25	€ 2.05	€ 21.79	6.0	€ 40.10 – € 60.15
	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05		
Appropriate comparator therapy							
Cisplatin and gemcitabine (4 - 6 cycles)							
Mannitol 10% infusion solution, 37.5 g/day	10 x 250 ml INF	€ 87.05	€ 4.35	€ 7.94	€ 74.76	4.0 – 6.0	€ 74.76
Sodium chloride 0.9% infusion solution, 3 l - 4.4 l/day	6 x 1,000 ml INF	€ 25.09	€ 1.25	€ 2.05	€ 21.79	4.0 – 6.0	€ 41.84 – € 60.15
	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05		
Abbreviation: INF = infusion solution							

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Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 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 agents 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 are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy 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 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 requirements in the product information of the assessed medicinal product.

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

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

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the

reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

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

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

Exception to the designation

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

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

Adults with unresectable or metastatic urothelial carcinoma; first-line treatment

No medicinal product with new active ingredients that can be used in a combination therapy and 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: June 2024

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 September 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 5 June 2024.

On 19 June 2024, 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 1, sentence 2 VerfO.

By letter dated 27 June 2024 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 20 September 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 October 2024. The deadline for submitting statements was 22 October 2024.

The oral hearing was held on 11 November 2024.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 10 December 2024, and the proposed draft resolution was approved.

At its session on 19 December 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	6 September 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	28 March 2023	New determination of the appropriate comparator therapy
WG	5 June 2024	New determination of the appropriate comparator therapy
Working group Section 35a	5 November 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 November 2024	Conduct of the oral hearing,
Working group Section 35a	19.11.2024; 03.12.2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	10 December 2024	Concluding discussion of the draft resolution
Plenum	19 December 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 December 2024

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

Prof. Hecken