Gemeinsamer Bundesausschuss

Justification

to 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 Pembrolizumab (New therapeutic indication: Unresectable non-epithelioid malignant pleural mesothelioma, first-line, combination with pemetrexed and platinum chemotherapy)

of 16 October 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess 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 studies the pharmaceutical company have 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 decide 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 pembrolizumab (Keytruda) was listed for the first time on 15 August 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 4 April 2025, pembrolizumab 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 from 12.12.2008, sentence 7).

On 23 April 2025, 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 due time 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 pembrolizumab with the new therapeutic indication

"KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma."

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 August 2025 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 pembrolizumab 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 have 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 pembrolizumab.

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 Pembrolizumab (Keytruda) in accordance with the product information

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma.

Therapeutic indication of the resolution (resolution of 16.10.2025):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with unresectable non-epithelioid malignant pleural mesothelioma; first-line therapy

Appropriate comparator therapy for pembrolizumab in combination with pemetrexed and platinum chemotherapy:

- Nivolumab in combination with ipilimumab

[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 pembrolizumab, medicinal products with the active ingredients ipilimumab, nivolumab and pemetrexed in combination with cisplatin are approved in the present therapeutic indication.

On 2. Non-medicinal treatment is not considered.

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

- Nivolumab: resolution of 16.12.2021

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 written statement from the Drugs Commission of the German Medical Association (AkdÄ) is available.

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

Overall, the evidence in the present therapeutic indication is limited. Relevant Cochrane reviews or systematic reviews could not be identified.

The present guideline recommends immunotherapy with nivolumab in combination with ipilimumab for the first-line treatment of newly diagnosed non-epithelioid pleural mesothelioma.

In their written statement, the AkdÄ also state that the treatment standard in the first-line therapy of unresectable non-epithelioid malignant pleural mesothelioma is a primary immune checkpoint inhibitor therapy with nivolumab in combination with ipilimumab.

By resolution of 16 December 2021, the G-BA found an indication of a considerable additional benefit of nivolumab in combination with ipilimumab compared with pemetrexed in combination with platinum chemotherapy for adults with unresectable, malignant pleural mesothelioma and non-epithelioid tumour histology.

In addition to nivolumab in combination with ipilimumab, the guideline also mentions pembrolizumab in combination with pemetrexed and platinum chemotherapy with a weaker recommendation as a further therapy option for the present indication. Pembrolizumab in combination with pemetrexed and platinum chemotherapy was ruled out as an appropriate comparator therapy with regard to the research question of the benefit assessment.

In the overall analysis, the G-BA determined a therapy with nivolumab in combination with ipilimumab as the appropriate comparator therapy for the first-line therapy of unresectable non-epithelioid malignant pleural mesothelioma.

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 pembrolizumab is assessed as follows:

Adult patients with unresectable non-epithelioid malignant pleural mesothelioma; first-line therapy

An additional benefit is not proven.

Justification:

For the proof of the additional benefit of pembrolizumab, the pharmaceutical company presented the results of the KEYNOTE 483 study.

KEYNOTE 483 is a completed, open-label, randomised phase II/III study which compared pembrolizumab in combination with pemetrexed and platinum chemotherapy (study arm A) versus pemetrexed in combination with platinum chemotherapy (study arm B) and versus pembrolizumab monotherapy (study arm C). Adults with unresectable, advanced and/or metastatic malignant pleural mesothelioma were examined. For phase II of the study, the study participants were stratified by histological subtype (epithelioid versus non-epithelioid) and randomised in a 1:1:1 ratio into one of three study arms. Phase II of the study was conducted from November 2016 to September 2022 in 19 study sites in Italy and Canada. Study arm C was discontinued following an interim analysis in July 2021. The study was then converted into a phase III study which compared study arm A with study arm B. Phase III of the study was conducted between January 2017 and November 2024 in 54 study sites in France, Italy and Canada.

For the benefit assessment, results of phase II and phase III of the KEYNOTE 483 study were presented for the on-label sub-population with non-epitheloid subtype. The pharmaceutical company's dossier shows that 52 patients received pembrolizumab in combination with pemetrexed and platinum chemotherapy and 56 patients received pemetrexed in combination with platinum chemotherapy.

The results of the final data cut-off from 16 September 2022 are available for the benefit assessment.

Assessment:

The data of the KEYNOTE 483 study are not suitable for the assessment of the additional benefit. Pemetrexed in combination with platinum chemotherapy and pembrolizumab as monotherapy form the comparator arms of the study. This does not correspond to the appropriate comparator therapy of nivolumab in combination with ipilimumab. Consequently, the appropriate comparator therapy has not been implemented, which means that no suitable data are available in the overall assessment for the assessment of the additional benefit of pembrolizumab in combination with pemetrexed and platinum chemotherapy. An additional benefit of pembrolizumab in combination with pemetrexed and platinum chemotherapy for

the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma is therefore not proven.

2.1.4 Summary of the assessment

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

"KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma."

Nivolumab in combination with ipilimumab was determined to be the appropriate comparator therapy.

The pharmaceutical company presented results of the open-label phase II/III KEYNOTE 483 study which compared pembrolizumab in combination with pemetrexed and platinum chemotherapy versus pemetrexed in combination with platinum chemotherapy and versus pembrolizumab monotherapy. Both comparator arms of the study do not correspond to the appropriate comparator therapy. Thus, no suitable data are available. As a result, it was concluded that an additional benefit of pembrolizumab in combination with pemetrexed and platinum chemotherapy for the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma is not proven.

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

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

The resolution is based on the information provided by the pharmaceutical company. Uncertainties exist in particular in the lower limit for the percentage of patients with non-epithelioid histology and for patients with unresectable, malignant pleural mesothelioma, as well as in the underestimated upper limit for the percentage of patients who may be eligible for first-line systemic therapy. Overall, uncertainties in patient numbers can be assumed.

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 Keytruda (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 19 September 2025):

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

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of patients with pleural mesothelioma, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and other doctors from specialist groups participating in the Oncology Agreement.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with pembrolizumab as well as on infusion-related reactions.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of 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]

The dosage according to the target AUC of carboplatin is calculated using the Calvert formula and the estimation of renal function with the Cockcroft-Gault equation using the average height (women: 166 cm, men: 179 cm), the average weight (women 69.2 kg, men 85.8 kg) and

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

the average age of women and men in Germany in 2021 (women: 46 years, men: 43.4 years)[3] and the mean standard serum creatinine concentration (women: 0.75 mg/dl, men: 0.9 mg/dl)[4].
The mean value (AUC 5-6 = 770.8 mg) formed from these doses for women (AUC 5 = 637 mg, AUC 6 = 764.4 mg) and men (AUC 5 mg/ml/min = 764.5 mg, AUC 6 mg/ml/min = 917.4 mg) was used as the basis for calculating the costs of carboplatin.

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

According to the product information of nivolumab, the recommended dosage of nivolumab in combination therapy with ipilimumab is 360 mg every 21 days, and the dosage of ipilimumab is 1 mg/kg every 42 days.

According to the product information of pemetrexed, the recommended dosage of pemetrexed is 500 mg/m² body surface area (BSA) every 21 days, and the dosage of cisplatin is 75 mg/m² BSA also every 21 days.

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.

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.

[3]Federal Institute for Population Research, Average age of the population in Germany (1871-2021) https://www.bib.bund.de/DE/Fakten/Fakt/B19-Durchschnittsalter-Bevoelkerung-ab-1871.html
[4]DocCheck Flexikon – Serum creatinine, URL: https://flexikon.doccheck.com/de/Serumkreatinin [last access: 05.08.2025]

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				
Pembrolizumab in combination with pemetrexed and cisplatin				
Pembrolizumab	1 x every 21 days	17.4	1	17.4
	or			
	1 x every 42 days	8.7	1	8.7
Pemetrexed	1 x every 21 days	17.4	1	17.4
Cisplatin	1 x every 21 days	17.4	1	17.4
Pembrolizumab in combination with pemetrexed and carboplatin				
Pembrolizumab	1 x every 21 days	17.4	1	17.4
	or			
	1 x every 42 days	8.7	1	8.7
Pemetrexed	1 x every 21 days	17.4	1	17.4
Carboplatin	1 x every 21 days	17.4	1	17.4
Appropriate comparator therapy				
Nivolumab in combination with ipilimumab				
Nivolumab	1 x per 21-day cycle	17.4	1	17.4
Ipilimumab	1 x per 42-day cycle	8.7	1	8.7

Consumption:

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					
Pembrolizumab in combination with pemetrexed and cisplatin					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
Pemetrexed	500 mg/m^2 BSA = 955 mg	955 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg
Cisplatin	75 mg/m^2 BSA = 143.3 mg	143.3 mg	1 x 50 mg + 1 x 100 mg	17.4	17.4 x 50 mg + 17.4 x 100 mg
Pembrolizumab in combination with pemetrexed and carboplatin					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
Pemetrexed	500 mg/m^2 BSA = 955 mg	955 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg
Carboplatin	AUC 5-6 mg/ml/min = 770.8 mg	770.8 mg	1 x 600 mg + 1 x 150 mg + 1 x 50 mg	17.4	17.4 x 600 mg + 17.4 x 150 mg + 17.4 x 50 mg
Appropriate comparator therapy					
Nivolumab in combination with ipilimumab					
Nivolumab	360 mg	360 mg	2 x 100 mg + 4 x 40 mg	17.4	34.8 x 100 mg + 69.6 x 40 mg
Ipilimumab	1 mg/kg BW = 77.7 mg	77.7 mg	2 x 50 mg	8.7	17.4 x 50 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 reference prices 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					
Pembrolizumab 100 mg	2 CIS	€ 4,962.26	€ 1.77	€ 280.10	€ 4,680.39
Pemetrexed 1,000 mg	1 CIS	€ 1,124.81	€ 1.77	€ 52.84	€ 1,070.20
Cisplatin 100 mg	1 CIS	€ 76.59	€ 1.77	€ 3.10	€ 71.72
Cisplatin 50 mg	1 CIS	€ 47.71	€ 1.77	€ 1.73	€ 44.21
Carboplatin 600 mg	1 CIS	€ 300.84	€ 1.77	€ 13.74	€ 285.33
Carboplatin 150 mg	1 CIS	€ 83.06	€ 1.77	€ 3.40	€ 77.89
Carboplatin 50 mg	1 CIS	€ 34.66	€ 1.77	€ 1.11	€ 31.78
Appropriate comparator therapy					
Nivolumab 40 mg	1 CIS	€ 520.90	€ 1.77	€ 28.21	€ 490.92
Nivolumab 100 mg	1 CIS	€ 1,285.26	€ 1.77	€ 70.53	€ 1,212.96
Ipilimumab 50 mg	1 CIS	€ 3,489.23	€ 1.77	€ 195.98	€ 3,291.48
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 August 2025

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.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product

is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

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
Medicinal product to be assessed:							
Pembrolizumab in combination with pemetrexed and platinum chemotherapy							
Pembrolizumab + pemetrexed + cisplatin							
Pemetrexed							
17.4 cycles of 21 days each							
Dexamethasone 2 x 4 mg[5]	100 x 4 mg TAB	€ 79.54	€ 1.77	€ 5.40	€ 72.37	52.2	€ 75.55
Folic acid[6] 350 – 1,000 µg/day	100 x 400 µg TAB	€ 17.60	€ 0.88	€ 1.98	€ 14.74	365.0	€ 53.80 – € 107.60
Vitamin B12 1,000 µg/day, every 3 cycles	10 x 1,000 µg AMP	€ 8.19	€ 0.41	€ 0.37	€ 7.41	6.8	€ 5.04
Cisplatin							
17.4 cycles of 21 days each 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.							
Hydration and forced diuresis							
Mannitol 10% Inf. sol., 37.5 g/day	10 x 500 ml INF	€ 105.54	€ 5.28	€ 4.26	€ 96.00	17.4	€ 167.04

[5] Fixed reimbursement rate

[6] The cost calculation for folic acid is based on the single dose of 400 µg of the non-divisible tablets available for cost calculation related to a dose range of 400 - 800 µg per day, even if a dose range of 350 - 1,000 µg is given in the product information.

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
Sodium chloride 0.9% Inf. sol., 3 – 4.4 l/day	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	17.4	€ 104.66 – € 174.44
Pembrolizumab + pemetrexed + carboplatin							
Pemetrexed							
17.4 cycles of 21 days each							
Dexamethasone 2 x 4 mg[7]	100 x 4 mg TAB	€ 79.54	€ 1.77	€ 5.40	€ 72.37	52.2	€ 75.55
Folic acid[8] 350 – 1,000 µg/day	100 x 400 µg TAB	€ 17.60	€ 0.88	€ 1.98	€ 14.74	365.0	€ 53.80 – € 107.60
Vitamin B12 1,000 µg/day, every 3 cycles	10 x 1,000 µg AMP	€ 8.19	€ 0.41	€ 0.37	€ 7.41	6.8	€ 5.04

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.

[7] Fixed reimbursement rate

[8] The cost calculation for folic acid is based on the single dose of 400 µg of the non-divisible tablets available for cost calculation related to a dose range of 400 - 800 µg per day, even if a dose range of 350 - 1,000 µg is given in the product information.

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 designate 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 have 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 have 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 have 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:

Adult patients with unresectable non-epithelioid malignant pleural mesothelioma; first-line therapy

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 pembrolizumab (Keytruda); Keytruda 25 mg/ml concentrate for the preparation of an infusion solution 100 mg/ 4 ml; last revised: September 2025

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 their session on 29 March 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 their session on 23 April 2025.

On 23 April 2025, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 24 April 2025 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 pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 17 July 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 August 2025. The deadline for submitting statements was 22 August 2025.

The oral hearing was held on 8 September 2025.

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 7 October 2025, and the proposed draft resolution was approved.

At their session on 16 October 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	29 March 2022	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	23 April 2025	New determination of the appropriate comparator therapy
Working group Section 35a	3 September 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	8 September 2025	Conduct of the oral hearing
Working group Section 35a	17 September 2025; 1 October 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	7 October 2025	Concluding discussion of the draft resolution
Plenum	16 October 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 October 2025

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

Prof. Hecken