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 Pembrolizumab (new therapeutic indication: endometrial carcinoma with MSI-H or with dMMR, pretreated)

of 19 January 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms 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 11 November 2021, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for pembrolizumab, amongst other indications, in the indication "endometrial carcinoma with MSI-H or dMMR, with disease progression on or following prior treatment with a platinum-containing therapy" in accordance with Section 35a paragraph 5b SGB V. The pharmaceutical company expected marketing authorisation extensions for the active ingredient pembrolizumab within the period specified in Section 35a paragraph 5b SGB V for several therapeutic indications at different times.

In its session on 6 January 2022, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment

and the submission of a dossier for the benefit assessment for the therapeutic indication in question to four weeks after the marketing authorisation of the last therapeutic indication of the therapeutic indications covered by the application, at the latest six months after the first relevant date. All marketing authorisations for the therapeutic indications covered by the application according to Section 35a paragraph 5b SGB V were granted within the 6-month period.

For the therapeutic indication "endometrial carcinoma with MSI-H or dMMR, with disease progression on or following prior treatment with a platinum-containing therapy", pembrolizumab received the extension of the marketing authorisation as a major type 2 variation as defined according to Annex 2 No. 2a to Regulation (EC) number 1234/2008 of the Commission from 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, p. 7) on 25 April 2022. In accordance with the resolution of 6 January 2022, the benefit assessment of the active ingredient pembrolizumab in this new therapeutic indication thus began at the latest within four weeks, i.e., at the latest on 20 July 2022, after the last approval, which took place on 22 June 2022, of pembrolizumab in the therapeutic indications for the treatment of "melanoma in patients aged 12 years and older".

On 18 July 2022, 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 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with the new therapeutic indication "endometrial carcinoma with MSI-H or dMMR, with disease progression on or following prior treatment with a platinum-containing therapy".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 November 2022 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 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 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:

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

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 as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation

Therapeutic indication of the resolution (resolution of 19.01.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with advanced or recurrent endometrial cancer with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR), who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation

Appropriate comparator therapy for pembrolizumab as monotherapy:

Therapy according to doctor's instructions

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In addition to pembrolizumab, the following active ingredients are approved for the present therapeutic indication: Cisplatin, dostarlimab, doxorubicin, medroxyprogesterone acetate, megestrol acetate and pembrolizumab in combination with lenvatinib.

on 2. A non-medicinal treatment option is not considered for the therapeutic indication in question.

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

- Pembrolizumab in combination with lenvatinib: Resolution of 7 July 2022
- Dostarlimab: Resolution of 2 December 2021

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 therapeutic indication according to Section 35a paragraph 7 SGB V.

Those therapy options that are independent of the MSI-H/dMMR status and thus, eligible for the unselected patient population in this respect are considered for the appropriate comparator therapy.

The guidelines indicate, among others, systemic chemotherapy, which can also be a platinum-containing re-therapy for the present treatment setting. According to the authorisation status, the active ingredients cisplatin and doxorubicin can be considered for this purpose. In addition, the guidelines recommend chemotherapy with carboplatin in combination with paclitaxel.

Furthermore, according to the statements of the scientific-medical societies in previous benefit assessment procedures, monotherapy with paclitaxel represents a relevant treatment option in the therapeutic indication.

The active ingredients carboplatin and paclitaxel are not approved for the present indication. There is a discrepancy between medicinal products approved in the indication and those used in health care/recommended by the guidelines.

Furthermore, according to guidelines, endocrine therapy can be considered as a treatment option for the present treatment setting.

Taking into account the advanced stage of the disease and treatment, the G-BA also considers best supportive care to be a treatment option.

According to the statements of the scientific-medical experts in the present benefit assessment procedure, the Immuncheckpoint inhibitors dostarlimab as monotherapy (for patients with MSI-H/dMMR status) or pembrolizumab in combination with lenvatinib (regardless of MSI-H/dMMR status) should be offered to patients with advanced endometrial carcinoma in recurrence or refractoriness after platinum-containing chemotherapy.

To date, no medicinal treatment other than the active ingredient dostarlimab has been specifically approved for the treatment of endometrial carcinoma with MSI-H or a dMMR.

Dostarlimab as monotherapy for the treatment of recurrent or advanced endometrial carcinoma with MSI-H or a dMMR that is progressive during or after prior treatment with platinum-based therapy was approved on 21 April 2021. In its resolution of 2 December 2021, the G-BA, against the background that no suitable study data were available for the benefit assessment, did not determine an additional benefit of dostarlimab in this therapeutic indication compared with the appropriate comparator therapy. Dostarlimab is not determined to be an appropriate comparator therapy for this resolution.

The combination therapy pembrolizumab + lenvatinib has been approved since 26 November 2021 for the treatment of endometrial carcinoma during or after prior platinum-based therapy, i.e., regardless of MSI-H/dMMR status.

In its resolution of 7 July 2022, the G-BA identified an indication of a major additional benefit for pembrolizumab in combination with lenvatinib compared to doxorubicin or paclitaxel in the context of therapy according to a doctor's instructions.

The combination of active ingredients pembrolizumab + lenvatinib is still a relatively new treatment option in this therapeutic indication. The combination therapy pembrolizumab + lenvatinib is not determined to be an appropriate comparator therapy for this resolution.

Overall, the G-BA determines a therapy according to the doctor's instructions as an appropriate comparator therapy for this resolution.

As part of the therapy according to the doctor's instructions, endocrine therapy with the active ingredients medroxyprogesterone acetate, megestrol acetate as well as systemic chemotherapy, which can also be platinum-containing re-therapy, with cisplatin (monotherapy or in combination with doxorubicin), doxorubicin (monotherapy or in combination with cisplatin), paclitaxel (monotherapy) as well as carboplatin in combination paclitaxel and best supportive care alone are considered appropriate comparators.

Best Supportive Care (BSC) is understood as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

However, the possibility of the off-label use of the active ingredients in a clinical study does not allow any conclusions to be drawn about their appropriateness in the off-label use in the standard care of insured persons in the SHI system. Such an assessment would be reserved for the decision according to Section 35c SGB V. This does not affect an off-label prescription in specific cases according to the criteria of the established case law of the Federal Social Court on off-label use not regulated in the Pharmaceuticals Directive.

For the implementation of the therapy according to the doctor's instructions, the comparison for the benefit assessment should include several of the above-mentioned treatment options and adequately represent the therapies frequently used in the reality of care in Germany. The choice of comparators used must be justified in the dossier for the benefit assessment. Considering the number of treatment options available in the context of therapy according to the doctor's instructions, a single-

comparator comparison does not appear to be appropriate. However, this procedure would have to be justified separately should only a single-comparator comparison be carried out.

In view of the S3 guideline on endometrial carcinoma (September 2022), which was updated during the ongoing assessment process for pembrolizumab, the status of the treatment options in the present therapeutic indication, in particular the immune checkpoint inhibitors, may change in the course of a further development of the generally recognised state of medical knowledge. Against this background, and taking into account the statements of the scientific-medical experts regarding a change in the therapy recommendations in the present therapeutic indication due to the use of immune checkpoint inhibitors, a reassessment of the appropriate comparator therapy may be necessary in the foreseeable future.

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

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:

An additional benefit is not proven.

Justification:

Data basis

In the dossier for the benefit assessment, the pharmaceutical company submits the results of the marketing authorisation study on pembrolizumab for the present therapeutic indication. This is the KEYNOTE 158 study, which included pretreated patients with advanced (metastatic and / or unresectable) solid tumours.

In its written statement, the pharmaceutical company also submits a pooled analysis of the results of the single-arm studies KEYNOTE 158 and NCT02899793 in a non-adjusted indirect comparison to the results of the study KEYNOTE 775.

The pooled analysis of the single-arm studies in the non-adjusted indirect comparison to the results of the KEYNOTE 775 study is not used for the present assessment, as this comparison is subject to inherent uncertainty due to the lack of randomisation and does not represent an adequate method of indirect comparison.

KEYNOTE 158

The KEYNOTE 158 study is a since February 2016 ongoing multicentre, open-label, single-arm phase II study.

The patients in the study will be treated with pembrolizumab according to the product information. For the benefit assessment, the pharmaceutical company forms a sub-population of patients with endometrial carcinoma and MSI-H and disease progression during or after previous platinum-based therapy from cohorts D (endometrial carcinoma) and K (any advanced tumour (except colorectal cancer) with MSI-H) (N = 94).

In addition to the primary endpoint objective response rate, endpoints of the categories mortality, morbidity, health-related quality of life and side effects were collected.

The study is being conducted in 55 study sites in Asia, Australia, Europe, North and South America.

Comparator data

The KEYNOTE 158 study is an uncontrolled study. Thus, this study does not include a comparator group which allows comparison of the results of treatment with pembrolizumab.

For the benefit assessment, the pharmaceutical company submits a comparison of individual arms of the studies KEYNOTE 158 (cohort D (endometrial carcinoma) and K (dMMR / MSI-H)) and KEYNOTE 775.

KEYNOTE 775 study

The KEYNOTE 775 study is a multicentre, randomised, active-controlled, open-label phase III study, ongoing since June 2018, comparing pembrolizumab in combination with lenvatinib to a therapy according to doctor's instructions of doxorubicin or paclitaxel.

The study enrolled adult patients with advanced or recurrent endometrial carcinoma and disease progression after prior systemic platinum-based chemotherapy.

The pharmaceutical company uses the sub-population of patients with dMMR in the doxorubicin or paclitaxel arm (N = 65) for the indirect comparison.

In addition to the primary endpoints of overall survival and progression-free survival, endpoints in the categories of morbidity, health-related quality of life and side effects are being collected.

The study is being conducted in 167 study sites in Asia, Australia, Europe, North and South America.

Assessment:

The results from the KEYNOTE 158 study alone are not suitable for assessing the additional benefit of pembrolizumab as they do not allow a comparison with the appropriate comparator therapy.

Methodology of the comparison of individual arms of different studies

In the dossier, the pharmaceutical company presents a non-adjusted indirect comparison of individual arms of the KEYNOTE 158 and KEYNOTE 775 studies for the endpoints overall survival and objective response rate. For the endpoints progression-free survival and severe adverse events, the pharmaceutical company compares the results of the two studies descriptively. The pharmaceutical company presents the results on symptomatology, health status and health-related quality of life of the KEYNOTE 158 study additionally.

The single-arm comparisons submitted by the pharmaceutical company are naïve comparisons without a bridge comparator and without adjustment for potentially relevant effect modifiers or prognostic factors. These comparisons have inherent uncertainty due to the lack of randomisation and are not an adequate method of indirect comparison. Moreover, there are no effects for which it can be safely excluded in the present setting of an indirect comparison without bridge comparator that they do not result solely from a systematic risk of bias due to confounding variables.

Conclusion:

Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of pembrolizumab as monotherapy in adult patients with advanced or recurrent endometrial carcinoma with MSI-H or a dMMR, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation is 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 is approved as monotherapy for the treatment of advanced or recurrent endometrial carcinoma with MSI-H or a dMMR, with disease progression on or following prior treatment with a platinum-containing therapy in any setting and when curative surgery or radiation is not an option.

The G-BA determined the appropriate comparator therapy to be a therapy according to the doctor's instructions that may include endocrine therapy, chemotherapy and best supportive care.

For the benefit assessment, the pharmaceutical company submitted the results from the KEYNOTE 158 study for the treatment with pembrolizumab. This is an uncontrolled study and therefore, does not include a comparator group.

For the assessment of the additional benefit, the pharmaceutical company submits a comparison of individual arms of the studies KEYNOTE 158 and KEYNOTE 775.

These comparisons have inherent uncertainty due to the lack of randomisation and are not an adequate method of indirect comparison. Moreover, there are no effects for which it can be safely ruled out that they do not result solely from systematic bias.

Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of pembrolizumab as monotherapy is not proven.

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

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

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of dostarlimab (resolution of 2 December 2021).

The range mentioned includes both the number of patients in the SHI target population stated by the pharmaceutical company and the number stated by the assessment expert. It must be taken into account that uncertainty must also be assumed for this range.

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: 3 January 2023):

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

Therapy with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with endometrial carcinoma.

Before initiation of therapy with pembrolizumab, the presence of microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) should be confirmed by a validated test in a tumour sample.

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: 1 January 2023).

Treatment period:

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.

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	continuously, 1 x every 21 days	17.4	1	17.4
	or			
	continuously, 1 x every 42 days	8.7	1	8.7
Appropriate comparator therapy				
Therapy according to doctor's instructions[2]				
Medroxyprogesterone acetate	continuously, 1 - 3 x daily	365	1	365
Megestrol acetate	continuously, 1 x day	365	1	365
Cisplatin monotherapy				
Cisplatin	continuously, 1 x every 21 - 28 days	13.0 - 17.4	1	13.0 - 17.4
	or			
	continuous, day 1 - 5 every 21 - 28 days	13.0 - 17.4	5	65.0 - 87.0
Doxorubicin monotherapy				
Doxorubicin	continuously, 1 x every 21 days	7	1	7
Cisplatin + doxorubicin[3]				

[2] The active ingredients paclitaxel and carboplatin in combination with paclitaxel are also suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products.

[3] Nomura H et al.: Japanese Gynaecologic Oncology Group. Effect of Taxane Plus Platinum Regimens vs Doxorubicin Plus Cisplatin as Adjuvant Chemotherapy for Endometrial Cancer at a High Risk of Progression: A Randomised Clinical Trial. JAMA Oncol. 2019 Jun 1;5(6):833-840. doi: 10.1001/jamaoncol.2019.0001.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cisplatin	continuously, 1 x every 21 days	6	1	6
Doxorubicin	continuously, 1 x every 21 days	6	1	6
Best supportive care[4]	Different from patient to patient			

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.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

The product information on medroxyprogesterone acetate specifies the most common dosage of 300 - 600 mg per day for the treatment of endometrial carcinoma. A dosage of 250 mg - 500 mg is presented for the present calculation.

The study by Nomura et al. (2019)[5] is used to calculate the dosage of the combination therapy of cisplatin and doxorubicin.

The average body measurements were applied for dosages depending on body weight (BW) or body surface area (BSA), (average body height of an adult female: 1.66 m, average body weight of an adult female: 68.7 kg). This results in a body surface area of 1.76 m² (calculated according to Du Bois 1916)[6]

The maximum cumulative total dose of doxorubicin is 450 - 550 mg/m² BSA. On this basis, an approximate treatment duration of 7 cycles is used for monotherapy with doxorubicin.

[4] In the case of a comparison with best supportive care, also to be used additionally for the medicinal product to be assessed.

[5] Nomura H et al.: Japanese Gynaecologic Oncology Group. Effect of Taxane Plus Platinum Regimens vs Doxorubicin Plus Cisplatin as Adjuvant Chemotherapy for Endometrial Cancer at a High Risk of Progression: A Randomised Clinical Trial. JAMA Oncol. 2019 Jun 1;5(6):833-840. doi: 10.1001/jamaoncol.2019.0001.

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
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
Appropriate comparator therapy					
Therapy according to doctor's instructions[7]					
Medroxy-progesterone acetate	125 mg – 250 mg	300 mg - 600 mg	1 x 250 mg + 1 x 500 mg	365	365 x 250 mg - 365 x 500 mg
Megestrol acetate	80 mg – 320 mg	80mg - 320mg	0.5 x 160 mg[8] + 2 x 160 mg	365	182.5 x 160 mg - 730 x 160 mg
Cisplatin monotherapy					
Cisplatin	50 mg/m2 – 120 mg/m2 = 88.0 mg – 211.2 mg	88.0mg - 211.2mg	1 x 100 mg - 2 x 100 mg + 2 x 10 mg	13.0 - 17.4	(13.0 x 100 mg - 26.0 x 100 mg + 26.0 x 10 mg) - 17.4 x 100 mg - 34.8 x 100 mg + 34.8 x 10 mg)
	or				
	15 mg/m2 – 20 mg/m2 = 26.4 mg – 35.2 mg	26.4mg - 35.2mg	1 x 50 mg - 1 x 50 mg	65.0 - 87.0	65.0 x 50 mg - 87.0 x 50 mg
Doxorubicin monotherapy					

[7] The active ingredients paclitaxel and carboplatin in combination with paclitaxel are also suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products.

[8] As of 01.01.2023, megestrol acetate is only available on the German market in 160 mg pack, which is why a division of the tablets must be assumed here in exceptional cases. The tablets can be divided into equal doses.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Doxorubicin	60 mg/m² = 105.6 mg – 75 mg/m² = 132 mg	105.6 mg – 132 mg	1 x 100 mg + 1 x 10 mg - 1 x 150 mg	7	7 x 100 mg + 7 x 10 mg - 7 x 150 mg
Cisplatin + doxorubicin					
Cisplatin	50 mg/m2 BSA = 88 mg	88 mg	1 x 100 mg	6	6 x 100 mg
Doxorubicin	60 mg/m2 = 105.6 mg	105.6 mg	1 x 100 mg + 1 x 10 mg	6	6 x 100 mg + 6 x 10 mg
Best supportive care[9]	Different from patient to patient				

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.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Cost (pharmacy discount 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	1 CIS	€ 2,974.79	€ 1.77	€ 285.60	€ 2,687.42
Appropriate comparator therapy					
Cisplatin 100 mg	1 CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
Cisplatin 50 mg	1 CIS	€ 47.70	€ 1.77	€ 4.61	€ 41.32
Cisplatin 10 mg	1 CIS	€ 17.49	€ 1.77	€ 0.30	€ 15.42

[9] In the case of a comparison with best supportive care, also to be used additionally for the medicinal product to be assessed.

Designation of the therapy	Packaging size	Cost (pharmacy discount price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Doxorubicin 150 mg[10]	1 SFI	€ 418.32	€ 1.77	€ 0.00	€ 416.55
Doxorubicin 100 mg[10]	1 CIS	€ 285.75	€ 1.77	€ 0.00	€ 283.98
Doxorubicin 10 mg[10]	1 CIS	€ 40.28	€ 1.77	€ 2.29	€ 36.22
Medroxyprogesterone acetate 500 mg	100 TAB	€ 355.73	€ 1.77	€ 32.69	€ 321.27
Medroxyprogesterone acetate 250 mg	50 TAB	€ 104.80	€ 1.77	€ 8.88	€ 94.15
Megestrol acetate 160 mg	84 TAB	€ 1154.18	€ 1.77	€ 108.48	€ 1,043.93
Best supportive care[11]	Different from patient to patient				
Abbreviations: HC = hard capsules, SFI = solution for injection, CIS = concentrate for the preparation of an infusion solution, TAB = tablets					

LAUER-TAXE® last revised: 1 January 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.

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.

[10] Fixed reimbursement rate

[11] In the case of a comparison with best supportive care, also to be used additionally for the medicinal product to be assessed.

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 does not provide any specific information why the necessary costs cannot be quantified.							
Hydration/ diuresis							
Cisplatin (monotherapy)							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	13.0 - 17.4 or 65.0 - 87.0	€ 118.43 - € 158.51 or € 592.15 – 792.57
Sodium chloride 0.9% Inf. Solution, 3 l - 4.4 l/day	10 x 1000 ml INF	€ 34.68	€ 1.73	€ 1.08	€ 31.87	13.0 - 17.4 or 65.0 - 87.0	(€ 124.29 - € 191.82) - (€ 166.36 - € 256.74) or € 621.47 - € –959.08) - (€ 831.81 - € 1,283.69)
	10 x 500 ml INF	€ 23.12	€ 1.16	€ 1.89	€ 20.07		
Cisplatin (combination therapy)							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	6	€ 54.66
Sodium chloride 0.9% Inf. Solution, 3 l - 4.4 l/day	10 x 1000 ml INF	€ 34.68	€ 1.73	€ 1.08	€ 31.87	6	€ 57.37 - € 88.53
	10 x 500 ml INF	€ 23.12	€ 1.16	€ 1.89	€ 20.07		

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 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 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 Pembrolizumab

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall 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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 10 March 2021, 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 25 January 2022.

On 18 July 2022, 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, number 2 VerfO.

By letter dated 25 July 2022 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 28 October 2022, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2022. The deadline for submitting written statements was 22 November 2022.

The oral hearing was held on 5 December 2022.

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 January 2023, and the proposed resolution was approved.

At its session on 19 January 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	10 March 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	25 January 2022	New implementation of the appropriate comparator therapy

Working group Section 35a	29 November 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	5 December 2022	Conduct of the oral hearing
Working group Section 35a	13 December 2022 3 January 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	10 January 2023	Concluding discussion of the draft resolution
Plenum	19 January 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 January 2023

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

Prof. Hecken