Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee on an amendment to the Pharmaceuticals Directive (AM-RL) Annex XII –Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Pembrolizumab (Reassessment after the deadline: Urothelial carcinoma, CPS ≥ 10, first-line)

of 16 September 2021

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 studies 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 benefits,
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. Costs of therapy for the statutory health insurance,
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 pharmaceutical company submitted a dossier for the early benefit assessment for the active ingredient pembrolizumab to be assessed for the first time on 20 December 2018. For the resolution of 20 June 2019 made by the G-BA in this resolution, a time limit of 1 July 2020 was pronounced. At the pharmaceutical company's request, this time limit was extended until 1 April 2021 by the resolution of the G-BA of 5 March 2020.

In accordance with Section 4, paragraph 3 paragraph 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product pembrolizumab recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of

Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 23 March 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 July 2021 on the G-BA website at (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was also 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 (A21-34) prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. 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:

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

Urothelial carcinoma

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

Therapeutic indication of the resolution (resolution from 16.09.2021):

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10; first-line

- Carboplatin in combination with gemcitabine (cf. Annex VI concerning Section K of the Pharmaceuticals Directive)

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 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 Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. Comparative therapy should be part of the appropriate therapy in the therapeutic indication according to the generally accepted state of medical knowledge.

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

on 1. In terms of authorisation status and besides pembrolizumab, the active ingredients doxorubicin, methotrexate, and atezolizumab are available for the first-line treatment of locally advanced or metastatic urothelial carcinoma in patients not eligible for cisplatin.

on 2. A non-medicinal treatment is unsuitable as a comparator therapy in this therapeutic indication.

on 3. The following resolutions and guidelines of the G-BA exist regarding medicinal treatments in the present therapeutic indication:

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

- Atezolizumab,
  resolutions dated 16 March 2018 (initial assessment new therapeutic indication) and 20 June 2019 (reassessment due to new scientific knowledge/restriction on authorisation)

- Pembrolizumab,
  resolutions dated 16 March 2018 (initial assessment new therapeutic indication) and 20 June 2019 (reassessment due to new scientific knowledge/restriction on authorisation)

Resolutions on Annex VI (off-label use) of the Pharmaceuticals Directive:

- Combination therapy with carboplatin and gemcitabine, resolution dated 20 May 2021

on 4. The general state of medical knowledge, on which the finding of the G-BA is based, was illustrated by systematic research for guidelines as well as reviews of clinical studies in the present therapeutic indication.

In the first-line therapy of advanced, metastatic urothelial carcinoma, the guidelines unanimously recommend cisplatin in combination with gemcitabine.

However, a relevant number of patients are not eligible for cisplatin-containing chemotherapy. The combination therapy of carboplatin and gemcitabine recommended by guidelines, especially for this patient collective, is not approved in the present therapeutic indication but can be prescribed within the scope of off-label use (see Annex VI (Off-Label Use) of the Pharmaceuticals Directive).

However, patients who are not eligible for cisplatin should not be considered clinically as a uniform group. For patients with poor general condition, for example, a monochemotherapy is mentioned in guidelines as an alternative to gemcitabine with carboplatin. However, in the statements of medical experts in the present benefit assessment procedure, treatment with monochemotherapy was not considered to be of relevant importance in the reality of health care.

With the PD-L1 antibody atezolizumab, another treatment option is available that is approved in the present therapeutic indication. No additional benefit could be identified in the benefit assessment because no data were available that would have allowed an assessment of the additional benefit (resolution of 20.06.2019). The period of validity of the relevant resolution was limited. Therefore, atezolizumab is not considered as an appropriate comparator therapy presently.

Against this background, the G-BA has determined carboplatin in combination with gemcitabine (cf. Annex VI of the Pharmaceuticals Directive) as an appropriate comparator therapy for patients who are not eligible for cisplatin-containing chemotherapy.

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

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 for the treatment of adults with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

Justification:

For the renewed benefit assessment of pembrolizumab after the expiry of the limited period of validity of the initial resolution of 20 June 2019, the pharmaceutical company submits the results of the randomised, active-controlled, open-label, three-arm study KEYNOTE 361 with data cut-off of 29 April 2020. The presentation of the results from this study complies with the conditions of the limitation.

The KEYNOTE 361 study is an ongoing Phase III study being conducted in 172 study centres in 21 countries. Included were 1010 adults with advanced or metastatic urothelial carcinoma without prior systemic chemotherapy. Randomisation was done in a 1:1:1 ratio into one of the three study arms, stratified by PD-L1 status (CPS ≥ 10% and CPS < 10%). Study participants were treated with pembrolizumab monotherapy, a combination of pembrolizumab and chemotherapy, or chemotherapy alone. The chemotherapy regimen consisted of a combination of cisplatin and gemcitabine or a combination of carboplatin and gemcitabine and was determined by the doctor's instructions prior to randomisation. The primary endpoints of the KEYNOTE 361 study were overall survival (OS) and progression-free survival (PFS). Endpoints on morbidity, quality of life and adverse events (AEs) were also collected.

According to the marketing authorisation, the results of the comparison between pembrolizumab monotherapy and chemotherapy (carboplatin in combination with gemcitabine) in the sub-population with PD-L1-expressing tumours (CPS ≥ 10) are considered for the present benefit assessment. Patients not eligible for cisplatin-containing therapy were defined according to the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 or Karnofsky performance status ≤ 70%, creatinine clearance ≤ 60 ml/min, hearing loss on audiometry ≥ grade 2, peripheral neuropathy ≥ grade 2, or heart failure by New York Heart Association (NYHA) class > III. This sub-population, which is relevant for the benefit assessment, comprises 56 subjects in the pembrolizumab arm and 64 people in the chemotherapy arm. The choice of carboplatin as a component of combination chemotherapy was due to renal insufficiency in approximately 70% of patients.

Extent and probability of the additional benefit

Mortality

Overall survival

Overall survival was the primary endpoint of the KEYNOTE 361 study. However, there were no statistically significant differences between the treatment groups for either endpoint.

Morbidity

Symptomatology

Symptomatology endpoints were assessed using the symptom scales of the EORTC QLQ-C30. For the endpoints dyspnoea, exhaustion, nausea and vomiting, diarrhoea, pain, insomnia, and constipation, there was no statistically significant difference between the treatment groups. For the endpoint appetite loss (PT, AE), there is a statistically significant difference to the disadvantage of pembrolizumab.

Against the background of the only slight effect for the endpoint appetite loss, no overall disadvantage is derived for the endpoint symptomatology.

Health status

The endpoint health status was assessed using the EQ-5D VAS. There is no statistically significant difference in the health status (EQ-5D VAS).

Progression-free survival

The endpoint progression-free survival was assessed in the study but not presented in the dossier for the sub-population considered in the benefit assessment.

Quality of life

EORTC QLQ-C30

Health-related quality of life was assessed using the functional scales of the EORTC QLQ-C30. There was no statistically significant difference between the treatment groups for the endpoints global health status, physical functioning, role functioning, role functioning, emotional functioning, cognitive functioning, and social functioning.

Side effects

Endpoints in the category side effects were collected for the period of treatment with the study medication plus 30 days (for AEs and severe AEs) or up to 90 days (for serious AEs).

Adverse events (AEs) in total

Nearly all study participants experienced an adverse event. These are only presented in a supplementary manner.

Serious adverse events (SAE)

There were no statistically significant differences between pembrolizumab and chemotherapy for the endpoint SAE.

Severe AEs (CTCAE grade ≥ 3)

For the endpoint severe AEs from CTCAE grade 3, a significant difference to the benefit of pembrolizumab can be observed. The rate of severe AEs is high in both treatment groups (72.7% pembrolizumab vs 88.7% chemotherapy). In the pembrolizumab arm, severe AEs occurred a median of 2.5 months later than in the chemotherapy arm.

Discontinuation due to AEs, immune-mediated SAEs and severe AEs (CTCAE grade ≥ 3)

For the endpoints discontinuation due to AE as well as immune-mediated SAEs and immune-mediated severe AEs (CTCAE grade ≥ 3) there are no statistically significant differences between the study arms.

Specific AEs

For gastrointestinal disorders (SOC, AE) and blood and lymphatic system disorders (SOC; severe AE, CTCAE grade ≥ 3), there is a statistically significant advantage of pembrolizumab over combination therapy with carboplatin and gemcitabine.

For the specific adverse events metabolism and nutrition disorders (SOC, severe AE, CTCAE grade ≥ 3) and vascular disorders (SOC, severe AE, CTCAE grade ≥ 3), there is a statistically significant difference to the disadvantage of pembrolizumab versus chemotherapy.

In the overall consideration of the results on side effects, the overall rates only show a positive effect of pembrolizumab compared to the combination of carboplatin and gemcitabine for severe AEs (CTCAE grade ≥ 3). There was no statistically significant difference in the overall rates of serious AEs and treatment discontinuations due to AEs. In detail, the consideration of the specific AEs reveals both advantages and disadvantages.

<u>Overall assessment</u>

For the reassessment of the benefit of pembrolizumab for the treatment of adults with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10, results on mortality, morbidity, health-related quality of life, and side effects are available from the KEYNOTE 361 study. In the ongoing study, pembrolizumab is being compared to the combination of carboplatin and gemcitabine. The study sub-population relevant to this assessment includes adults who are not eligible for cisplatin-containing therapy and whose tumours express PD-L1 (CPS ≥ 10). For the endpoint overall survival, no statistically significant difference was detected between the treatment groups.

Symptomatology endpoints were mapped using the symptom scales of the EORTC QLQ-C30. Statistically significant differences are only shown for the endpoint appetite loss, where a disadvantage of pembrolizumab is evident. There is no statistically significant difference in the health status (EQ-5D VAS).

There were no statistically significant differences between the treatment groups with regard to health-related quality of life, which was assessed using the functional scales of the EORTC QLQ-C30.

In the results on side effects, the overall rates show a positive effect of pembrolizumab compared to the combination of carboplatin and gemcitabine only for severe AEs (CTCAE grade ≥ 3). There was no statistically significant difference in the overall rates of serious AEs and treatment discontinuations due to AEs. In detail, the consideration of the specific AEs reveals both advantages and disadvantages.

In the overall analysis of the available results on patient-relevant endpoints, there is a statistically significant improvement only in side effects, based on the positive effect in one endpoint, severe AEs (CTCAE grade ≥ 3). In contrast, there were no relevant differences between the treatments in terms of overall survival, symptomatology, health status and health-related quality of life. Against this background, the present positive effect on side effects is not considered sufficient to establish an overall relevant and not only minor improvement of the therapy-relevant benefit.

As a result of a weighing decision, the G-BA thus states that an additional benefit is not proven for pembrolizumab as monotherapy for the treatment of adults with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

2.1.4 Summary of the assessment

This assessment is the reassessment of the benefit of pembrolizumab in the therapeutic indication "treatment of adults with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10" after the expiration of the period of validity of the initial resolution on 20 June 2019. For this benefit assessment, the pharmaceutical company submitted the results of the randomised, active-controlled, open-label, three-arm study KEYNOTE 361 with a data cut-off of 29 April 2020. The study sub-population relevant to this assessment includes adults who are not eligible for cisplatin-containing therapy and whose tumours express PD-L1 (CPS ≥ 10).

Chemotherapy consisting of carboplatin in combination with gemcitabine was determined to be the appropriate comparator therapy.

However, there were no statistically significant differences between the treatment groups for the overall survival.

Regarding the data on morbidity, there is no relevant difference between the treatments, both in terms of symptomatology and health status.

However, there were no statistically significant differences between the treatment groups for the health-related quality of life.

The results on side effects show a statistically significant difference in favour of pembrolizumab compared to chemotherapy based on the positive effect in one endpoint, severe adverse events (CTCAE grade ≥ 3).

In view of the fact that there are no relevant differences between the treatments in terms of overall survival, symptomatology, health status or health-related quality of life, the positive effect on side effects is not considered sufficient to establish a relevant and not only minor improvement in the treatment-relevant benefit.

As a result of a weighing decision, the G-BA thus states that an additional benefit is not proven for pembrolizumab as monotherapy for the treatment of adults with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

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 from the dossier of the pharmaceutical company. The derivation of the patient numbers is basically comprehensible, but is also subject to uncertainties that tend to lead to an underestimation.

On the one hand, the pharmaceutical company only considers evaluations with patients with locally advanced or metastatic urothelial carcinoma in stage IV according to the UICC classification as well as the coded diagnosis of urinary bladder cancer (according to ICD-10: C67). This does not include those diagnosed with an earlier stage tumour and were later found to have progressed to stage IV, or whose initially unknown tumour entity.

In addition, some sources show a high percentage of cases in which the tumour stage was not reported. The pharmaceutical company takes this uncertainty into account when stating the number of cases. However, a deviation from the distribution used by the pharmaceutical company would result if cases with an unknown stage were excluded.

Furthermore, the pharmaceutical company uses only one study to estimate the proportion of cisplatin-ineligible subjects, which considers renal function as the only criterion. However, further relevant criteria for the exclusion of cisplatin as a therapeutic option have been published and are also referred to in the S3 guideline on urinary bladder cancer.[2,3] Their inclusion would lead to a higher percentage of patients not eligible for cisplatin than stated by the pharmaceutical company.

Overall, for the reasons stated above, the numbers of patients not eligible for cisplatin-containing therapy whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 are likely to be higher than determined by the pharmaceutical company and, therefore, a potential underestimation exists. Notwithstanding this, the patient numbers calculated in this way represent the best available estimate at present.

[2] Guideline program in oncology (German Cancer Society, German Cancer Aid, Association of the Scientific Medical Societies): S3 guideline Early detection, diagnosis, treatment, and after-care of urinary bladder cancer, long version 2.0, 2020, AWMF registration number 032/038OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/harnblasenkarzinom/ (retrieved on: 23.04.2021).

[3] Galsky, M.D., et al., Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. J Clin Oncol, 2011. 29(17): p. 2432-8.

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: 2 July 2021):

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 and urology, and specialists participating in the Oncology Agreement experienced in the treatment of adults with urothelial carcinoma.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient card. The training material for health professionals and the patient card contain, in particular, instructions on the management of immune-mediated side effects potentially occurring with pembrolizumab as well as on infusion-related reactions. The prescribing doctor must discuss with the patient the risks of therapy with KEYTRUDA. The patient card should be made available to the patient.

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 September 2021).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is patient-individual 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.

Costs of the appropriate comparator therapy:

The dosing instructions and treatment duration from the resolution dated 20 May 2021, regarding Annex VI (Off-Label Use), and the median patient characteristics of the study population from the de Santis et al. (2012) publication were used as the basis for calculation.[4] Thus, the median glomerular filtration rate (GFR) of 50 ml/min of the studied patient group was used to calculate the carboplatin dose.

The average body measurements were applied for dosages depending on body weight or surface (average body height: 1.72 m, average body weight: 77 kg). This results in a body surface area of 1.9 m² (calculated according to Du Bois 1916)[5].

[4] De Santis, et al. (2012). Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. Journal of clinical, 30(2), 191–199.

[5] Federal Statistical Office, Wiesbaden 2018: https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Publikationen/Downloads-Gesundheitszustand/koerpermasse-5239003179004.pdf?__blob=publicationFile.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Pembrolizumab	once every 21 days	17.4	1	17.4
	or			
	once every 42 days	8.7	1	8.7
Appropriate comparator therapy				
Carboplatin in combination with gemcitabine				
Carboplatin	once every 21 days	4-6	1	4-6
Gemcitabine	Day 1 and 8, cycle restart on day 22	8-12	1	8-12

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ day of treatment	Usage by potency/ day of treatment	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
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8
Appropriate comparator therapy					
Carboplatin in combination with gemcitabine					
Carboplatin	4.5 x [GFR+25] mg over 1 hour	337.5 mg	2 x 150 mg, 1 x 50 mg	4-6	8 to 12 x 150 mg, 4 to 6 x 50 mg
Gemcitabine	1,000 mg/m^2	1,900 mg	1 x 2,000 mg	8-12	8 to 12 x 2,000 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 Sections 130 and 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. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

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	1 CIS	€ 3 037.06	€ 1.77	€ 170.17	€ 2 865.12

Appropriate comparator therapy					
Carboplatin in combination with gemcitabine					
Carboplatin 150 mg/15 ml	1 CIS	€ 82.79	€ 1.77	€ 3.40	€ 77.62
Carboplatin 50 mg/5 ml	1 CIS	€ 34.38	€ 1.77	€ 1.11	€ 31.50
Gemcitabine 2,000 mg/50 ml	1 CIS	€ 193.96	€ 1.77	€ 8.68	€ 183.51
Abbreviations: CIS = concentrate for the preparation of an infusion solution.					

LAUER-TAXE® last revised: 1 September 2021

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 considered 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 standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe)(Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 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 sales 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.

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 25 September 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 26 March 2021, 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 5 VerfO.

By letter dated 26 March 2021 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 29 June 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 01 July 2021. The deadline for submitting written statements was 22 July 2021.

The oral hearing was held on 9 August 2021.

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 the 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 September 2021, and the proposed resolution was approved.

At its session on 16 September 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Sub-committee Medicinal product	25 September 2018	Determination of the appropriate comparator therapy
Working group Section 35a	4 August 2021	Information on statements received; preparation of the oral hearing
Sub-committee Medicinal product	9 August 2021	Conduct of the oral hearing
Working group Section 35a	18 August 2021 1 September 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Sub-committee Medicinal product	7 September 2021	Final discussion of the draft resolution
Plenum	16 September 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 September 2021

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

Prof. Hecken