Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients in Accordance with Section 35a SGB V Pembrolizumab (Reassessment Based on New Scientific Knowledge: Urothelial Carcinoma)

From 20 June 2019

Contents

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1. Legal basis

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

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for 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 shall pass a resolution 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 as an active ingredient of the medicinal product Keytruda® was first placed on the (German) market on 15 August 2015. The G-BA prompted a new benefit assessment in accordance with 35a, paragraph 1 SGB V in conjunction with Section 3, paragraph 1 no. 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) and Chapter 5, Section 13 Rules of Procedure (VerfO) for the active ingredient pembrolizumab at the request of its members in the resolution of 2 August 2018. The new benefit assessment was initiated on the basis of new scientific findings from the current KEYNOTE-361 (NCT02853305) study and a related change in the approved therapeutic indication of pembrolizumab by resolution of the EU Commission dated 6 July 2018.

The relevant date for the active ingredient pembrolizumab in accordance with Chapter 5, Section 8, paragraph 1, number 6 of the Rules of Procedure of the G-BA (VerfO) is 2. Januar 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1 number 6 VerfO. on 20 December 2018.

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The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 01 April 2019, 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 with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier evaluation prepared by the IQWiG, and the statements submitted in the written and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA 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 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 is indicated as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for pembrolizumab as monotherapy was determined as follows:

a) Urothelial carcinoma; patients who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (first line)

Chemotherapy according to the 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 practice unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the efficiency principle.

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, in principle, have a marketing authorisation for the therapeutic indication.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

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2. If non-medical 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-drug 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 active ingredients doxorubicin, methotrexate, and atezolizumab are authorised for the first-line treatment of urothelial carcinoma in patients not eligible for cisplatin.

On 2. Non-drug treatment is not indicated in this therapeutic situation.

On 3. The following resolutions and guidelines of the G-BA have been issued on drug therapies in the present therapeutic indication:

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

Atezolizumab: Resolution of 16 March 2018

Pembrolizumab: Resolution of 16 March 2018

On 4. The generally accepted state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

The guidelines unanimously recommend cisplatin in combination with gemcitabine for first-line treatment of advanced metastatic urothelial carcinoma.

However, a relevant number of patients are not eligible for cisplatin-containing chemotherapy. However, the combination therapy of carboplatin and gemcitabine recommended by the guidelines for this patient population in particular is not authorised for this therapeutic indication. However, patients who are unsuitable for cisplatin should not be considered clinically as a uniform group. For patients with poor general condition, for example, monochemotherapy is mentioned in the guidelines as an alternative to carboplatin with gemcitabin. However, in the written statements of medical experts in the present benefit assessment procedure, treatment with monochemotherapy, in particular with the active ingredients methotrexate and doxorubicin, was not given any relevant significance in the reality of care.

The PD-L1 antibody atezolizumab is another treatment option authorised in the present therapeutic indication. Because it is still quite new in the field of care, the therapeutic significance cannot yet be conclusively assessed. By resolution of 16 March 2018, no additional benefit could be identified for atezolizumab. The active ingredient is currently being subjected to a further benefit assessment procedure. Atezolizumab is not currently being considered as an appropriate comparator therapy.

Against this background, the G-BA has identified chemotherapy according to the doctor's instructions as an appropriate comparator therapy for the sub-population of patients who are not eligible for a cisplatin-containing chemotherapy. The active ingredients discussed in the above justification shall be taken into account.

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

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2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven for the treatment of locally advanced or metastatic urothelial carcinoma in adult patients who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

Justification:

In the dossier, the pharmaceutical company shall not present any results from directly comparative studies or studies suitable for an adjusted indirect comparison.

In order to demonstrate the additional benefit of pembrolizumab compared to the appropriate comparator therapy, the pharmaceutical company compares the results of single-arm studies or of individual arms of comparative studies in this partial therapeutic indication (non-adjusted). The results presented correspond as far as possible to the data submitted by the pharmaceutical company within the framework of the initial evaluation of the originally approved therapeutic indication.

Comparative results from the ongoing, open, controlled, and randomised KEYNOTE-361 Phase III study, which, in a three-armed design, compares pembrolizumab monotherapy with a combination therapy of pembrolizumab with gemcitabine plus cisplatin or carboplatin as well as a combination therapy of gemcitabine plus cisplatin or carboplatin, are not yet available. This study included adult patients with locally advanced or metastatic urothelial carcinoma who had not been pretreated in this disease stage. The restriction on authorisation of pembrolizumab was determined by a recommendation of the EMA[2] following a review of the study by an external Data Monitoring Committee (DMC) because reduced survival was observed in patients with a CPS <10 under pembrolizumab compared to carboplatin plus gemcitabine.

On the part of the intervention to be evaluated, the results of the KEYNOTE052 study were thus included in the descriptive comparison as they were for the initial evaluation. KEYNOTE052 is a multi-centre, non-randomised, open, single-arm, Phase II study investigating the efficacy and safety of pembrolizumab in patients with advanced, non-resectable, or metastatic urothelial cancer. A total of 370 patients who had not received previous systemic chemotherapy and were not eligible for cisplatin-based chemotherapy were included. Patients were considered ineligible for cisplatin-based chemotherapy if ECOG performance status was ≥ 2, creatinine clearance was below 60 ml/min, severe hearing loss or peripheral neuropathy was present, or heart function was limited. Patients who were eligible for curative therapies were excluded from the study.

In the study, the treatment with pembrolizumab was carried out in accordance with the summary of product characteristics in a fixed dosage of 200 mg every 3 weeks for a regular total of up to 24 weeks.

The primary endpoint was response according to RECIST criteria. Overall survival, progression-free survival, and duration of response were collected as secondary endpoints. Using the EORTC QLQ-C30 questionnaire and the visual analogue scale of the EQ-5D, the symptoms of the patients were collected exploratively. The health-related quality of life was investigated by means of the functional scales of the EORTC QLQ-C30.

In addition to the results submitted during the initial evaluation, an additional, more recent KEYNOTE-052 data cut-off (30 November 2017) was evaluated for this assessment.

[2] European Medicines Agency

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The pharmaceutical company uses the combination carboplatin and gemcitabine as a comparator therapy and has identified studies in which patients received the combination carboplatin and gemcitabine. Four of the studies used were single-armed (Bellmunt 2001 with 16 patients included, Carles 2000 with 17 patients, Linardou 2004 with 58 patients, and Sella 2012 with 23 patients). A single study arm of the 2012 De Santis study (119 patients) and the retrospective comparison of Kim 2015 (22 patients) were also considered.

Against the background of the special situation of medical treatment and provision of medical care in the therapeutic indication described above, the G-BA sees a factual medical reason that exceptionally justifies taking into account the data from the indirect comparison with carboplatin and gemcitabine.

If the combination of carboplatin and gemcitabine used as comparator in the studies has not been used in compliance with the authorisation, it is not possible to draw any conclusions about their usefulness in the application form exceeding authorisation 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.

Different endpoints were reported in the publications on the studies; there are only few data available on patient-relevant endpoints. Results on overall survival are available from only four studies; results on the endpoint categories morbidity and quality of life are completely absent. Results on adverse events were only reported selectively and are therefore incomplete.

In contrast to the procedure in the dossier for the initial evaluation of the KEYNOTE-052 study, the comparison presented is based on the sub-population of the study in accordance with the restricted marketing authorisation of pembrolizumab (patients with PD-L1 expression with CPS ≥ 10). This patient population included 110 of the 370 patients included in the study. In relation to the studies on comparator therapy, the pharmaceutical company uses the overall population of the studies for the initial evaluation as in the dossier. The pharmaceutical company also submits a matching-adjusted indirect comparison of overall survival and adverse events for the present benefit assessment.

Overall assessment

The data provided by the pharmaceutical company are not suitable to be able to derive an additional benefit of pembrolizumab compared to the appropriate comparator therapy.

On one hand, the comparison of individual arms from different studies presented by the pharmaceutical company is based on an incomplete data basis. This results in particular from the fact that in the comparative studies on carboplatin plus gemcitabine, only limited data on patient-relevant endpoints are available. On the other hand, the effects described are not sufficiently large to be able to rule out with sufficient certainty that the differences are solely due to bias. This applies in particular to the overall survival results of the non-adjusted comparison. The median overall survival for the population according to restricted marketing authorisation from the KEYNOTE-052 study was 18.5 months compared to 7.2–10 months under treatment with gemcitabine and carboplatin.

Because the fundamental criticism regarding the incomplete data basis remains as it was in the initial assessment, the assessment that the data submitted are unsuitable for deriving an additional benefit is valid. This is also unaffected by the additional submission of the Matching-adjusted indirect comparison.

Overall, for patients who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10, an additional benefit of pembrolizumab as monotherapy is not proven because of the limited data basis.

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2.1.4 Limitation of the period of validity of the resolution

a) Urothelial carcinoma; patients who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (first line)

The limitation of the period of validity of the resolution on the benefit assessment of pembrolizumab has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a, paragraph 1 SGB V.

The results of the currently ongoing KEYNOTE-361 study, on the basis of which the EMA modified the present approved therapeutic indication for pembrolizumab, are not yet available. In view of the fact that clinical data on patient-relevant endpoints and especially on overall survival relevant for the benefit assessment of the drug are expected in the future, the G-BA considers it appropriate to limit the period of validity of the resolution until further scientific evidence on the additional benefit of pembrolizumab is available. The limitation will permit the upcoming results from the KEYNOTE-361 study to be promptly incorporated into the benefit assessment of the drug in accordance with Section 35a SGB V.

For this purpose, the G-BA considers a limitation of the resolution until 1 July 2020 to be appropriate.

Conditions of the limitation:

For the renewed benefit assessment after the deadline, the study results for all patient-relevant endpoints from the current KEYNOTE-361 study should be included in the dossier.

The G-BA is able, in principle, to revise the limitation if it has been presented with clear justification that it is insufficient or too long.

In accordance with Section 3, number 7 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of the drug pembrolizumab shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline proving an additional benefit of pembrolizumab in relation to the appropriate comparator therapy (Section 4, paragraph 3, number 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 5 VerfO). If the dossier is not submitted or submitted incompletely, the G-BA may come to the finding that an additional benefit is not proven.

The possibility that a benefit assessment for the medicinal product pembrolizumab can be carried out at an earlier point in time for other reasons (cf Chapter 5, Section 1, paragraph 2, numbers 2 – 4 VerfO) remains unaffected by this.

2.1.5 Summary of the assessment

The present assessment is a renewed benefit assessment of the active ingredient pembrolizumab on the basis of an application based on new scientific knowledge according to Section 13 (Chapter 5, Section 13, paragraph 1, sentence 1 VerfO).

The renewed benefit assessment refers exclusively to the use of pembrolizumab as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in the following patient groups:

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a) Urothelial carcinoma; patients who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (first line)

About patient group a)

The appropriate comparator therapy for pembrolizumab as monotherapy was determined by the G-BA as follows:

Chemotherapy according to the doctor's instructions

For this patient group, the pharmaceutical company presents the results of the KEYNOTE-052 single-arm Phase II study on the treatment with pembrolizumab in patients with advanced or metastatic urothelial carcinoma. In a non-adjusted comparison, these are compared with the results of studies on combination therapy with carboplatin and gemcitabine.

Against the background of the special situation of medical treatment and provision of medical care in the therapeutic indication, the G-BA sees a factual medical reason that exceptionally justifies taking into account the data from the indirect comparison with carboplatin and gemcitabine.

No conclusions can be drawn from this as to the usefulness of the combination of carboplatin and gemcitabine in the application form exceeding authorisation in the standard care of insured persons in the SHI system.

The comparison presented is based on the sub-population of the KEYNOTE-052 study in accordance with the restricted marketing authorisation (patients with PD-L1 expression with CPS ≥ 10), taking into account a more recent data cut-off compared to the initial evaluation of pembrolizumab. In relation to the studies on comparator therapy, the overall population of the studies is used. The pharmaceutical company also submits a matching-adjusted indirect comparison for the present benefit assessment.

The data provided by the pharmaceutical company were not suitable to be able to derive an additional benefit of pembrolizumab compared to the appropriate comparator therapy because of the incomplete data basis of the comparison submitted. The effects described were also not sufficiently large to be able to rule out with sufficient certainty that the differences were solely due to bias. This applies in particular to the overall survival results of the non-adjusted comparison.

Overall, for patients who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10, an additional benefit of pembrolizumab as monotherapy is not proven because of the limited data basis.

The resolution is limited until 1 July 2020. The results of the currently ongoing KEYNOTE-361 study, on the basis of which the EMA modified the present approved therapeutic indication for pembrolizumab, are not yet available. For the renewed benefit assessment after the deadline, the study results for all patient-relevant endpoints from the currently ongoing KEYNOTE-361 study should be included in the dossier.

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 information from the dossier of the pharmaceutical company for patients ineligible for cisplatin-based therapy whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10. The patient numbers listed in the present resolution are consistent with the information provided in the resolution on the benefit assessment of pembrolizumab (resolution of 16 March 2018) with additional consideration of a corresponding proportion of patients whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

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The derivation of patient numbers is comprehensible in principle; however, is also fraught with uncertainties that tend to lead to underestimation. There are uncertainties, in particular with regard to the proportion of patients who are not eligible for cisplatin-containing therapy. In the American registry study on which the data were based, only patients diagnosed with bladder carcinoma were considered. Urothelial carcinomas of other urinary organs were not considered. Even more relevant, however, was the fact that only patients with impaired renal function were considered ineligible for cisplatin therapy and were therefore included in the registry study. Further contraindications for cisplatin-containing therapy such as the presence of peripheral neuropathy, existing hearing damage and, in particular, heart failure, were not considered.

Furthermore, there are uncertainties with regard to the proportion of patients with tumours with a PD-L1 expression with a combined positive score (CPS) ≥ 10 because the proportional value used refers exclusively to the KEYNOTE-045 and -052 approval studies of pembrolizumab and is therefore subject to uncertainty because of the selectivity of the study populations.

Overall, for the reasons mentioned, it can be assumed that the numbers of patients ineligible for a cisplatin-based therapy whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 are higher than those determined by the pharmaceutical company. There is therefore a potential underestimation. Notwithstanding this, the patient numbers thus determined represent the best estimate currently available.

2.3 Requirements for a quality-assured application

The requirements of 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: 27 March 2019):

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

Only specialists in internal medicine, haematology, and oncology with experience treating patients with urothelial carcinoma, specialists in urology, and specialists participating in the Oncology Agreement may initiate and monitor treatment with pembrolizumab.

In accordance with the specifications of the EMA regarding additional measures for risk minimisation, the pharmaceutical company must provide training material and a patient card. Patients are requested to carry their patient cards with them at all times. The training material for health professionals and the patient card shall include, in particular, instructions on how to deal with the potential immune-mediated adverse reactions to pembrolizumab as well as infusion reactions.

2.4 Treatment costs

The treatment costs are based on the contents of the summary of product characteristics and the information listed in the LAUER-TAXE® (last revised: 1 June 2019).

If no maximum therapy duration is specified in the summary of product characteristics, the treatment duration is assumed to be one year, even if the actual therapy duration is patient-individualized and/or is shorter on average.

Costs of the appropriate comparator therapy

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The evidence for therapeutic options in the treatment of patients not eligible for cisplatin is limited overall. In the guidelines that explicitly recommend chemotherapy for these patients, the combination of carboplatin with gemcitabine is recommended. This combination is not authorised for the present indication. For patients with poor general condition, for example, monochemotherapy is mentioned as an alternative. However, in the written statements of medical experts in the present benefit assessment procedure, this was not given any relevant significance in the reality of care. Chemotherapy takes place according to the doctor's instructions. The active ingredients discussed in the justification of the appropriate comparator therapy must be taken into account.

Against this background, the G-BA considers it inappropriate to reflect the treatment costs on the basis of the costs for individual therapy options and notes that the treatment costs are patient-individualized.

Treatment duration:

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, every 3 weeks	17	1	17
	or			
	or every 6 weeks	8.5	1	8.5
Appropriate comparator therapy				
Patient population a) Urothelial carcinoma; patients who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (first line)				
Chemotherapy according to the doctor's instructions	patient-individualized			

Usage and consumption:

Designation of the therapy	Dosage	Dosage/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 × 100 mg	17	34 × 100 mg
	or				
	400 mg	400 mg	4 × 100 mg	8.5	34 × 100 mg

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Designation of the therapy	Dosage	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Patient population a) Urothelial carcinoma; patients who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (first line)					
Chemotherapy according to the doctor's instructions	patient-individualized				

Costs:

To facilitate comparability, the pharmaceutical costs were approximated both on the basis of the pharmacy sales price level and also the price less 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. Having determined the number of packs of a particular potency, the pharmaceutical costs were then calculated on the basis of the costs per pack less the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package 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 IFK	€ 3,234.94	€ 1.77	€ 181.48	€ 3,051.69
Appropriate comparator therapy					
Chemotherapy according to the doctor's instructions	patient-individualized				
Abbreviations. IFC = Concentrate for the preparation of an infusion solution					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 01 June 2019

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 drug to be evaluated and the appropriate comparator therapy according to the summary of product characteristics, the costs incurred for this must be taken into account as costs for additional SHI services required.

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

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additional SHI services required had to be taken into account.

Other services covered by SHI funds:

The auxiliary tax (contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy retail 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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (last revised: According to the special agreement on contractual unit costs of retail pharmacist services([Hilfstaxe) (last revised: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy retail price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for production 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.

3. Bureaucratic costs

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its meeting on 15 August 2017.

Because of new scientific findings, the appropriate comparator therapy established by the G-BA was reviewed. The Subcommittee on Medicinal Products redetermined the appropriate comparator therapy at its meeting on 25 September 2018.

On 20 December 2018 , 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 6 VerfO.

By letter dated 21 December 2018 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 27 March 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1. April 2019. The deadline for submitting written statements was 23 April 2019.

The oral hearing was held on 6 May 2019.

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

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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 meetings.

The evaluation of the written statements received and the oral hearing was discussed at the meeting of the subcommittee on 12 June 2019, and the proposed resolution was approved.

At its meeting on 20 June 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Meeting	Date	Subject of consultation
Subcommittee Medicinal products	15 August 2017	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	25 September 2018	Redefinition of the appropriate comparator therapy
Working group Section 35a	29 April 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 May 2019	Conduct of the oral hearing
Working group Section 35a	14 May 2019 21 May 2019 4 June 2019	Consultation on the dossier assessment by the IQWiG and the evaluation of the written statement procedure
Subcommittee Medicinal products	12 June 2019	Concluding discussion of the proposed resolution
Plenum	20 June 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 June 2019

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

Prof. Hecken

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