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: advanced renal cell carcinoma, first-line, combination with lenvatinib)

of 7 July 2022

**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 is part of the Pharmaceuticals Directive.

## 2. Key points of the resolution

The active ingredient pembrolizumab (Keytruda) was listed for the first time on 15 August 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 15 November 2021, pembrolizumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 10 December 2021, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with

the new therapeutic indication (in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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 19 April 2022, 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:

## 2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

### 2.1.1 Approved therapeutic indication of pembrolizumab (Keytruda) in accordance with the product information

Keytruda, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults.

**Therapeutic indication of the resolution (resolution of 07.07.2022):**

see the approved therapeutic indication

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)

**Appropriate comparator therapy for pembrolizumab in combination with lenvatinib:**

- Pembrolizumab in combination with axitinib

b) Adults with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3)

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

**Appropriate comparator therapy for pembrolizumab in combination with lenvatinib:**

- Avelumab in combination with axitinib (only for patients with a poor risk profile)

*or*

- Nivolumab in combination with ipilimumab

*or*

- Pembrolizumab in combination with axitinib

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, medicinal products with the following active ingredients are available in relation to the authorisation status for the treatment of advanced renal cell carcinoma in previously untreated adults: Aldesleukin, avelumab, bevacizumab, cabozantinib, interferon alfa-2a[2], ipilimumab, lenvatinib, nivolumab, pazopanib, sunitinib, temsirolimus and tivozanib.

on 2. For patients in the present therapeutic indication, it is assumed that surgery and/or radiotherapy with curative objectives are not (or no longer) an option at the time of the treatment decision and that the treatment is palliative. Therefore, a non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication. The use of resection and/or radiotherapy as a palliative patient-individual therapy option for symptom control depending on the localization and symptomatology of the metastases remains unaffected.

[2] Interferon alfa-2a is out of distribution

on 3. The following resolutions on the applications of medicinal products are available:

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

- Cabozantinib in combination with nivolumab: resolution of 21 October 2021
- Nivolumab in combination with cabozantinib: resolution of 21 October 2021
- Avelumab in combination with axitinib: resolution of 14 May 2020
- Pembrolizumab in combination with axitinib: resolution of 14 May 2020
- Ipilimumab in combination with nivolumab: resolution of 15 August 2019
- Nivolumab in combination with ipilimumab: resolution of 15 August 2019
- Cabozantinib: resolution of 6 December 2018
- Tivozanib: resolution of 19 April 2018

Annex VI - Prescribability of approved medicinal products in non-approved therapeutic indications; Part B: Active ingredients that are not prescribable in off-label uses (last revised: March 2022).

Inhaled interleukin-2 (Proleukin®) for the treatment of renal cell carcinoma: resolution of 8 June 2016

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.

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

For the first-line treatment of advanced renal cell carcinoma, immune checkpoint inhibitor-based combination therapies have found their way into the therapy recommendations of the underlying current guidelines. The statements of the scientific-medical societies are consistent with this.

There are also current positive benefit assessments for the immune checkpoint inhibitor-based combination therapies:

Accordingly, compared with sunitinib, the G-BA identified an indication of a considerable additional benefit of the combination therapies of nivolumab and ipilimumab, approved in adults with previously untreated advanced renal cell carcinoma with an intermediate risk profile (IMDC score 1-2) and poor risk profile (IMDC score ≥ 3) by resolution of 15 August 2019.

For pembrolizumab in combination with axitinib, the resolution dated 14 May 2020 identified a hint for a considerable additional benefit over sunitinib for adults with previously untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0-2). For adults with a poor risk profile (IMDC score ≥ 3), there was indication of a considerable additional benefit over sunitinib.

According to the resolution of 14 May 2020, there is no additional benefit of avelumab in combination with axitinib over sunitinib for adults with previously untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0-2). For adults with a poor risk profile (IMDC score ≥ 3), a hint for a considerable additional benefit over sunitinib was identified.

In the guidelines and the written statements of the scientific-medical societies, a distinction is made between patients with a favourable, intermediate and poor risk profile on the basis of risk scores (IMDC score), and therapy recommendations are made separately according to the IMDC risk profile.

For patients with favourable risk profile (IMDC score 0), combination therapy of pembrolizumab and axitinib is recommended. In addition, the combination of avelumab and axitinib (with a weaker recommendation grade) is also recommended.

For patients with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3), pembrolizumab in combination with axitinib and nivolumab in combination with ipilimumab are preferred. In addition, the combination of avelumab and axitinib is also recommended, with a weaker level of recommendation.

Patients with favourable, intermediate, and poor risk profiles have different prognosis and response to therapy, which translates into considerable differences in overall survival.

Against this background and taking into account the existing therapy recommendations separated according to risk profile (favourable; intermediate/poor) as well as the authorisation status of the medicinal products under consideration, the G-BA considers it appropriate to consider the patient populations with favourable risk profile and intermediate/poor risk profile separately, despite partially overlapping therapy recommendations.

Therefore, in the overall assessment of the available evidence, pembrolizumab in combination with axitinib represents the appropriate comparator therapy for patients with previously untreated, advanced renal cell carcinoma with a favourable risk profile (IMDC score 0).

For patients with previously untreated advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3), multiple treatment options with comparable evidence are available with pembrolizumab in combination with axitinib, nivolumab in combination with ipilimumab and avelumab in combination with axitinib (only for patients with poor risk profile) and are determined to be appropriate comparator therapies.

Furthermore, cabozantinib in combination with nivolumab is available for first-line treatment. In the benefit assessment, for adults with previously untreated, advanced renal cell carcinoma with a favourable risk profile (IMDC score 0), intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3) compared to the appropriate comparator therapy, it was determined that an additional benefit is not proven (resolution of the G-BA of 21 October 2021).

A final assessment of the therapeutic significance of cabozantinib in combination with nivolumab cannot be made at this time and therefore this treatment option is not currently determined to be an appropriate comparator therapy.

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 in combination with lenvatinib is assessed as follows:

a) Adults with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)

An additional benefit is not proven.

b) Adults with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3)

An additional benefit is not proven.

Justification:

Data basis

In the absence of direct comparator studies of pembrolizumab in combination with lenvatinib (pembrolizumab + lenvatinib) versus the appropriate comparator therapy for patient groups a) and b), the pharmaceutical company uses an adjusted indirect comparison according to the method of Bucher et al. for the proof of an additional benefit. For these indirect comparisons using the bridge comparator sunitinib, the pharmaceutical company includes for both patient populations a) and b) the CLEAR study on the pembrolizumab + lenvatinib side and the KEYNOTE 426 study on the pembrolizumab + axitinib side. The studies are randomised open-label, controlled, multicentre Phase III studies.

*CLEAR study*

The CLEAR study compared pembrolizumab + lenvatinib and lenvatinib in combination with everolimus versus sunitinib. The ongoing study is being conducted in 81 study sites across Australia, Europe, Asia and North America.

1,069 adults with advanced renal cell carcinoma with a clear cell component who had not received prior systemic therapy were enrolled in the study. Patients with renal cell carcinoma without a clear cell component, with a Karnofsky performance status (KPS) < 70% or with active brain metastases were excluded from study participation.

Patients were randomly assigned in a 1:1:1 ratio to treatment with lenvatinib + everolimus (N = 357) or pembrolizumab + lenvatinib (N = 355) or sunitinib (N = 357). Randomisation was stratified by region (Western Europe and North America vs rest of the world) and risk group according to Memorial Sloan-Kettering Cancer Center (MSKCC) (favourable vs intermediate vs poor). The treatment arm lenvatinib + everolimus is not relevant for the present benefit assessment.

The treatment with pembrolizumab + lenvatinib and sunitinib was largely carried out according to the requirements in the product information. Patients were treated until disease

progression, the occurrence of unacceptable toxicity or therapy discontinuation at the decision of the doctor or patient. Treatment with pembrolizumab was limited to 35 treatment cycles (about 2 years) in the study. At the time of the 3rd data cut-off (28.08.2020), 75 patients (21% in the pembrolizumab + lenvatinib arm) had reached this maximum treatment duration with pembrolizumab. After discontinuation of the study medication, there were no limitations with regard to subsequent therapies. A changeover to the treatment of another other study arm was not planned.

The primary endpoint of the study is progression-free survival (PFS). Patient-relevant secondary endpoints are overall survival, symptomatology, health status, health-related quality of life, and adverse events (AEs).

Besides the MSKCC score, the IMDC[3] score was collected at the start of the study, allowing patients to be differentiated by risk profile according to the IMDC score. Relevant for the assessment of patient population a) is therefore the sub-population of patients with a favourable risk profile (IMDC score 0). With regard to the CLEAR study, these are 110 patients in the intervention arm and 124 patients in the comparator arm. With regard to the assessment-relevant patient population b) with patients with an intermediate (IMDC score 1 to 2) or poor risk profile (IMDC score ≥ 3), the CLEAR study comprises 243 patients in the intervention arm and 229 patients in the comparator arm.

In the CLEAR study, a total of 4 data cut-offs have been carried out so far: 1. data cut-off from 06.12.2018 as pre-specified 1st interim analysis; 2nd data cut-off from 15.11.2019 as pre-specified 2nd interim analysis; 3rd data cut-off from 28.08.2020 as pre-specified 3rd interim analysis and final analysis for the primary endpoint PFS; 4th data cut-off from 31.03.2021 as evaluation of overall survival for the marketing authorisation procedure. For the benefit assessment, the pharmaceutical company submits the CLEAR study evaluations for the 3rd data cut-off. For the endpoint of overall survival, evaluations will be supplemented by the 4th data cut-off. As part of the written statement procedure, the pharmaceutical company presents the results of the 4th data cut-off of the CLEAR study for the endpoint of overall survival separately for the relevant sub-populations.

*KEYNOTE 426 study*

The KEYNOTE 426 study compared pembrolizumab in combination with axitinib versus sunitinib.

Adults with advanced or metastatic clear cell renal cell carcinoma (stage IV according to the AJCC classification) were enrolled in the study. A total of 861 patients were randomly assigned in a 1:1 ratio to treatment with either pembrolizumab in combination with axitinib (intervention arm; N = 432) or sunitinib (comparator arm; N = 429). Randomisation was stratified by region (North America vs Western Europe vs rest of the World) and risk profile according to IMDC score (favourable vs intermediate vs poor) at start of the study. Patients were not allowed to have received any prior systemic therapy in an extensive-stage, and adjuvant or neoadjuvant therapy had to have been given more than 12 months prior to the start of the study. Patients should be in a good general condition (KPS ≥ 70%). Patients with non-clear cell renal cell carcinoma, with a KPS < 70% or with active brain metastases were excluded from study participation.

[3] International Metastatic Renal Cell Carcinoma Database Consortium

The treatments with pembrolizumab in combination with axitinib and sunitinib were carried out according to the requirements in the product information. Patients were treated until disease progression, the occurrence of unacceptable persistent toxicity, or discontinuation of therapy at the discretion of the doctor or study participant. Treatment in the intervention arm was limited by the maximum number of 35 treatment cycles allowed (approximately 2 years) with pembrolizumab. After discontinuation of the study medication, there were no limitations with regard to subsequent therapies. A changeover to the treatment of the other study arm was not planned in the course of the study.

The study, which is still ongoing, will assess overall survival as well as endpoints on symptomatology, health status, health-related quality of life and adverse events, among other things.

The IMDC score was collected in the study as a disease characteristic start of study, allowing patients to be differentiated by risk profile according to the IMDC score. Relevant for the assessment of patient population a) is therefore the sub-population of patients with a favourable risk profile (IMDC score 0). In the KEYNOTE 426 study, these are 138 patients in the intervention arm and 131 patients in the comparator arm. With regard to the assessment-relevant patient population b) with patients with an intermediate (IMDC 1 to 2) or poor risk profile (IMDC score ≥ 3), the KEYNOTE 426 study comprises 294 patients in the intervention arm and 298 patients in the comparator arm.

In the KEYNOTE 426 study, 4 data cut-offs have been carried out so far: 1. data cut-off from 24.08.2018 as pre-specified 1st interim analysis; 2nd data cut-off from 02.01.2019 at the request of the European Medicines Agency (EMA); 3rd data cut-off from 06.01.2020 as pre-specified 2nd interim analysis; final data cut-off from 11.01.2021. In the dossier, the pharmaceutical company presents evaluations for the 3rd data cut-off. As part of the written statement procedure, the pharmaceutical company also presents the results of the 4th data cut-off of the KEYNOTE 426 study for the endpoint of overall survival separately for the relevant sub-populations.

Assessment

A central prerequisite for an adjusted indirect comparison is the assumption of sufficient similarity between the studies.

In terms of design, the CLEAR and KEYNOTE 426 studies are similar, also with regard to the use of the bridge comparator sunitinib. With regard to the similarity of the relevant sub-populations, the pharmaceutical company makes the comparison of the patient characteristics on the basis of the total population of both studies and classifies them as similar. However, the pharmaceutical company does not provide any information on the relevant sub-populations - patient group a) with favourable risk profile (IMDC score 0); patient group b) with intermediate or poor risk profile. In this regard, the pharmaceutical company states that in both included studies, the risk profile was a stratification factor and therefore it can be assumed that homogeneous patient collectives exist not only with regard to the overall population in the comparison between the individual treatment arms, but also with regard to the sub-populations relevant for the benefit assessment. This approach is not appropriate as the similarity test should be carried out on the basis of the relevant sub-populations.

The sub-population with a favourable risk profile (IMDC score 0; patient group a) accounts for only a small percentage of the total population in both studies, 33% (CLEAR) and 31%

(KEYNOTE 426). The sub-population with an intermediate or poor risk profile (patient group b) makes up the majority of the total population in both studies with 66% (CLEAR) and 69% (KEYNOTE 426). However, the percentages are not large enough to assess the similarity between the sub-populations of the two studies based on the respective total population. In addition to data on patient characteristics, data on durations of treatment and observation as well as on pretreatments and follow-up therapies received are not available for the sub-populations. In the assessment, it can therefore not be deduced with sufficient certainty that the sub-populations are sufficiently similar for the indirect comparison.

Overall, therefore, there are no suitable data to assess the additional benefit of pembrolizumab in combination with lenvatinib. An additional benefit of pembrolizumab in combination with lenvatinib versus the appropriate comparator therapy is therefore not proven.

### 2.1.4 Summary of the assessment

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

"Keytruda, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults."

In the therapeutic indication to be considered, two patient populations were differentiated:

a) Adults with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)

and

b) Adults with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3).

On patient population a)

Pembrolizumab in combination with axitinib was determined to be the appropriate comparator therapy.

The pharmaceutical company presents an adjusted indirect comparison of pembrolizumab in combination with lenvatinib (CLEAR study) versus pembrolizumab in combination with axitinib (KEYNOTE-426 study) via the bridge comparator sunitinib.

A central prerequisite for an adjusted indirect comparison is the assumption of sufficient similarity between the studies. This includes the similarity of the patient population, which, however, could not be adequately assessed in the present assessment, as relevant information on the respective sub-populations from the CLEAR and KEYNOTE 426 studies is not available. Overall, the available data do not allow conclusion with sufficient certainty that the sub-populations are sufficiently similar for the indirect comparison.

Thus, no suitable data are available to assess the additional benefit of pembrolizumab in combination with lenvatinib in patient group a). An additional benefit of pembrolizumab in combination with lenvatinib versus the appropriate comparator therapy is therefore not proven.

On patient population b)

The following appropriate comparator therapy was determined:

- Avelumab in combination with axitinib (only for patients with a poor risk profile)

*or*

- Nivolumab in combination with ipilimumab

*or*

- Pembrolizumab in combination with axitinib

The pharmaceutical company presents an adjusted indirect comparison of pembrolizumab in combination with lenvatinib (CLEAR study) versus pembrolizumab in combination with axitinib (KEYNOTE-426 study) via the bridge comparator sunitinib.

A central prerequisite for an adjusted indirect comparison is the assumption of sufficient similarity between the studies. This includes the similarity of the patient population, which, however, could not be adequately assessed in the present assessment, as relevant information on the respective sub-populations from the CLEAR and KEYNOTE 426 studies is not available. Overall, the available data do not allow conclusion with sufficient certainty that the sub-populations are sufficiently similar for the indirect comparison.

Thus, no suitable data are available to assess the additional benefit of pembrolizumab in combination with lenvatinib in patient group b). An additional benefit of pembrolizumab in combination with lenvatinib versus the appropriate comparator therapy is therefore not proven.

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

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

The G-BA based its resolution on the patient numbers from the recently conducted benefit assessment of cabozantinib in combination with nivolumab (resolution of 21 October 2021). Despite uncertainties, this number was seen in a largely plausible order of magnitude.

The number of patients of the upper limit determined by the pharmaceutical company is within the range indicated in the previous procedure of cabozantinib in combination with nivolumab. In contrast, the number of patients of the lower limit tends to be underestimated due to the low relapse rate assumed by the pharmaceutical company. Therefore, the G-BA considers it appropriate to use the number of patients from the resolution on cabozantinib in combination with nivolumab.

## 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: 20 April 2022):
https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf

Treatment with pembrolizumab in combination with lenvatinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology as well as specialists in internal medicine and nephrology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of adults with renal cell carcinoma.

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.

In the CLEAR study, only patients with renal cell carcinoma with clear cell histology were examined. No data are available for patients with non-clear cell renal cell carcinoma.

## 2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 June 2022).

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 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.

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.

Treatment period:

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Pembrolizumab in combination with lenvatinib | | | | |
| Pembrolizumab | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| | or | | | |
| | 1 x per 42-day cycle | 8.7 | 1 | 8.7 |
| Lenvatinib | continuously, 1 x daily | 365 | 1 | 365 |
| Appropriate comparator therapy | | | | |
| a) Adults with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0) | | | | |

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| Pembrolizumab in combination with axitinib | | | | |
| Pembrolizumab | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| | or | | | |
| | 1 x per 42-day cycle | 8.7 | 1 | 8.7 |
| Axitinib | continuously, 2 x daily | 365 | 1 | 365 |
| b) Adults with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3) | | | | |
| Avelumab in combination with axitinib (only for patients with a poor risk profile) | | | | |
| Avelumab | 1 x per 14-day cycle | 26.1 | 1 | 26.1 |
| Axitinib | continuously, 2 x daily | 365 | 1 | 365 |
| Nivolumab in combination with ipilimumab | | | | |
| *Initial treatment* | | | | |
| Nivolumab | 1 x per 21-day cycle | 4 | 1 | 4 |
| Ipilimumab | 1 x per 21-day cycle | 4.0 | 1 | 4 |
| *Follow-up treatment* | | | | |
| Nivolumab | 1 x per 14 day cycle (3 weeks after last dose of initial treatment) | 20.1 | 1 | 20.1 |
| | or | | | |
| | 1 x per 28 day cycle (6 weeks after last dose of initial treatment) | 9.3 | 1 | 13.0 |
| Pembrolizumab in combination with axitinib | | | | |
| Pembrolizumab | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| | or | | | |
| | 1 x per 42-day cycle | 8.7 | 1 | 8.7 |
| Axitinib | continuously, 2 x daily | 365 | 1 | 365 |

Consumption:

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg)[4].

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Pembrolizumab in combination with lenvatinib | | | | | |
| 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 |
| Lenvatinib | 20 mg | 20 mg | 2 x 10 mg | 365.0 | 730 x 10 mg |
| Appropriate comparator therapy | | | | | |
| a) Adults with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0) | | | | | |
| Pembrolizumab in combination with axitinib | | | | | |
| 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 |
| Axitinib | 5 mg | 10 mg | 2x 5 mg | 365 | 730 x 5 mg |
| b) Adults with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3) | | | | | |
| Avelumab in combination with axitinib (only for patients with a poor risk profile) | | | | | |
| Avelumab | 800 mg | 800 mg | 4 x 200 mg | 26.1 | 104.4 x 200 mg |
| Axitinib | 5 mg | 10 mg | 2x 5 mg | 365 | 730 x 5 mg |
| Nivolumab in combination with ipilimumab | | | | | |
| *Initial treatment* | | | | | |
| Nivolumab | 3 mg/kg BW | 231 mg | 2 x 120 mg | 4 | 8 x 120 mg |
| Ipilimumab | 1 mg/kg BW | 77 mg | 2 x 50 mg | 4 | 8 x 50 mg |

[4] 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 |
|---|---|---|---|---|---|
| *Follow-up treatment* | | | | | |
| Nivolumab | 240 mg | 240 mg | 2 x 120 mg | 20.1 | 40.2 x 120 mg |
| | or | | | | |
| | 480 mg | 480 mg | 4 x 120 mg | 9.3 | 37.2 x 120 mg |
| Pembrolizumab in combination with axitinib | | | | | |
| 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 |
| Axitinib | 5 mg | 10 mg | 2x 5 mg | 365 | 730 x 5 mg |

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

**Costs of the medicinal products:**

| Designation of the therapy | Packaging size | Costs (pharmacy sales price) | Rebate Section 130 SGB V | Rebate Section 130a SGB V | Costs after deduction of statutory rebates |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Pembrolizumab 100 mg | 1 CIS | € 3,037.30 | € 1.77 | € 170.17 | € 2,865.36 |
| Lenvatinib 10 mg | 30 HC | € 1,496.84 | € 1.77 | € 82.25 | € 1,412.82 |
| Appropriate comparator therapy | | | | | |
| Avelumab 200 mg | 1 CIS | € 834.79 | € 1.77 | € 45.59 | € 787.43 |
| Axitinib 5 mg | 56 FCT | € 3,597.38 | € 1.77 | € 0.00 | € 3,595.61 |
| Ipilimumab 50 mg | 1 CIS | € 3,489.20 | € 1.77 | € 195.98 | € 3,291.45 |
| Nivolumab 120 mg | 1 CIS | € 1,546.93 | € 1.77 | € 85.05 | € 1,460.11 |
| Pembrolizumab 100 mg | 1 CIS | € 3,037.30 | € 1.77 | € 170.17 | € 2,865.36 |

| 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 |
|---|---|---|---|---|---|
| Abbreviations: FCT = film-coated tablets, HC = hard capsules, CIS = concentrate for the preparation of an infusion solution | | | | | |

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

According to the avelumab product information, patients are required to be premedicated with an antihistamine and paracetamol prior to the first 4 infusions of avelumab. The product information does not provide any specific information why the necessary costs cannot be quantified.

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 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 calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

## 4. Process sequence

At its session on 6 October 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 10 December 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 2 VerfO.

By letter dated 10 December 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. In a letter dated 22 December 2021, the G-BA informed IQWiG about the prolongation of the benefit assessment procedure agreed in the Subcommittee on Medicinal Products on 21 December 2021.

The dossier assessment by the IQWiG was submitted to the G-BA on 5 April 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 19 April 2022. The deadline for submitting written statements was 10 May 2022.

The oral hearing was held on 23 May 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 28 June 2022, and the proposed resolution was approved.

At its session on 7 July 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal products | 6 October 2020 | Determination of the appropriate comparator therapy |
| Subcommittee on Medicinal Products | 21 December 2021 | Prolongation of the benefit assessment procedure determined |
| Working group Section 35a | 18 May 2022 | Information on written statements received; preparation of the oral hearing |
| Subcommittee Medicinal products | 23 May 2022 | Conduct of the oral hearing |
| Working group Section 35a | 1 June 2022<br>15 June 2022<br>22 June 2022 | Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure |
| Subcommittee Medicinal products | 28 June 2022 | Concluding discussion of the draft resolution |
| Plenum | 7 July 2022 | Adoption of the resolution on the amendment of Annex XII AM-RL |

Berlin, 7 July 2022

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

Prof. Hecken