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:
colorectal cancer with MSI-H or with dMMR, after fluoropyrimidine-based combination therapy)

of 19 January 2023

**Contents**

## 1. Legal basis

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

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

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

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

## 2. Key points of the resolution

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

On 11 November 2021, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for pembrolizumab, amongst other indications, in the indication "unresectable or metastatic colorectal cancer with MSI-H or mismatch dMMR after previous fluoropyrimidine-based combination therapy" in accordance with Section 35a paragraph 5b SGB V. The pharmaceutical company expected marketing authorisation extensions for the active ingredient pembrolizumab within the period specified in Section 35a paragraph 5b SGB V for several therapeutic indications at different times.

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

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

For the therapeutic indication "unresectable or metastatic colorectal cancer with MSI-H or mismatch dMMR after previous fluoropyrimidine-based combination therapy", pembrolizumab received the extension of the marketing authorisation as a major type 2 variation as defined according to Annex 2 No. 2a to Regulation (EC) number 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7) on 25 April 2022. In accordance with the resolution of 6 January 2022, the benefit assessment of the active ingredient pembrolizumab in this new therapeutic indication thus began at the latest within four weeks, i.e. at the latest on 20 July 2022, after the last approval, which took place on 22 June 2022, of pembrolizumab in the therapeutic indications for the treatment of "melanoma in patients aged 12 years and older".

On 18 July 2022, the pharmaceutical company has submitted in due time a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with the new therapeutic indication "unresectable or metastatic colorectal cancer with MSI-H or mismatch dMMR after previous fluoropyrimidine-based combination therapy".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 November 2022 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of pembrolizumab compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of pembrolizumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

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

Keytruda as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings:

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

- treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy.

**Therapeutic indication of the resolution (resolution of 19.01.2023):**

See therapeutic indication according to marketing authorisation.

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with unresectable or metastatic colorectal cancer with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR); after previous fluoropyrimidine-based combination therapy

**Appropriate comparator therapy for pembrolizumab:**

A patient-individual therapy, depending on the type and number of previous therapies, RAS and BRAF mutational status, location of the primary tumour, general condition and risk of toxicity induced by anti-VEGF and anti-VEGFR agents, selecting:

- 5-fluorouracil in combination with folinic acid and irinotecan (FOLFIRI) with or without bevacizumab or aflibercept or ramucirumab
- 5-fluorouracil in combination with folinic acid and irinotecan (FOLFIRI) with or without cetuximab or panitumumab (only for patients with wild-type RAS)
- 5-fluorouracil in combination with folinic acid and oxaliplatin (FOLFOX) with or without bevacizumab
- Capecitabine in combination with oxaliplatin (CAPOX) with or without bevacizumab
- 5-fluorouracil in combination with folinic acid with or without bevacizumab
- Capecitabine with or without bevacizumab
- Irinotecan as monotherapy
- Panitumumab as monotherapy (only for patients with wild-type RAS)
- Cetuximab as monotherapy (only for patients with wild-type RAS)
- Trifluridine/ tipiracil
- Irinotecan in combination with cetuximab (only for patients with wild-type RAS)
- Encorafenib in combination with cetuximab (only for patients with BRAF-V600E mutation)

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. For the specific treatment setting of metastatic, mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer after previous fluoropyrimidine-based combination therapy, no active ingredients are explicitly approved apart from pembrolizumab as monotherapy and nivolumab in combination with ipilimumab. In addition, the active ingredients 5-fluorouracil, aflibercept, bevacizumab, calcium folinate, capecitabine, cetuximab, encorafenib, irinotecan, mitomycin, oxaliplatin, panitumumab, ramucirumab, regorafenib and trifluridine/tipiracil are available as monotherapy or as part of combination therapies for the treatment of metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy, which also includes dMMR or MSI-H patients.

on 2. A non-medicinal treatment cannot be considered in this treatment setting.

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

- Nivolumab - resolution of 20 January 2022
- Encorafenib - resolution of 17 December 2020
- Trifluridine/ tipiracil - resolution of 1 October 2020
- Ramucirumab - resolution of 1 September 2016
- Regorafenib - resolution of 17 March 2016
- Aflibercept - resolution of 15 August 2013

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

For the present therapeutic indication, it is assumed that there is no indication for curative treatment or that there is no primary or secondary resectability.

In addition, it is assumed for the present therapeutic indication that the patients receive an antineoplastic therapy in the respective treatment setting.

The treatment concept of metastatic colorectal cancer in the palliative treatment setting is characterised by the sequence of different lines of therapy. For first and second-line therapy, the guidelines provide defined treatment regimens that include fluoropyrimidine, oxaliplatin and/or irinotecan-containing chemotherapy regimens.

Overall, the available evidence and the statements of the scientific-medical societies in the benefit assessment procedure show that a specific standard therapy for patients with metastatic, dMMR or MSI-H colorectal cancer after previous fluoropyrimidine-based combination therapy cannot be specified.

Thus, in principle, those therapy options that represent a standard, regardless of the dMMR or MSI-H status, are considered as appropriate comparator therapy.

The present therapeutic indication addresses a treatment setting that may correspond to a second-line therapy as well as to a third-line therapy or a subsequent line of therapy, which is why the determination of the appropriate comparator therapy was based on these different treatment settings.

In the first or second-line therapy of metastatic colorectal cancer, the chemotherapy regimens 5-fluorouracil in combination with folinic acid and irinotecan (FOLFIRI) and 5-fluorouracil in combination with folinic acid and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPOX) are regularly used, which can be accordingly combined with anti-VEGF active ingredients (bevacizumab, aflibercept and ramucirumab) and anti-EGFR substances (cetuximab, panitumumab), depending on the marketing authorisation and mutational status. So far, the superiority of a specific sequence for the total population of patients with metastatic colorectal cancer has not been proven.

According to the unanimous therapy recommendations, a FOLFIRI-based therapy in the first-line should be followed by a FOLFOX-based therapy in the second line and a FOLFOX-based therapy in the first-line should be followed by a FOLFIRI-based therapy in the second line.

Aflibercept and ramucirumab are two anti-VEGF active ingredients that are approved in the present therapeutic indication and can be used after prior oxaliplatin-containing chemotherapy. In the benefit assessment, an indication of a minor additional benefit was found for aflibercept compared to FOLFIRI (resolution of 15 August 2013), while an additional benefit for ramucirumab compared to FOLFIRI was not proven (resolution of 1 September 2016).

For patients with BRAF-V600E mutation, the combination of active ingredients of encorafenib and cetuximab is also available. In the resolution of 17 December 2020, a hint for a considerable additional benefit was found for this combination of active ingredients compared to FOLFIRI + cetuximab or irinotecan + cetuximab.

For the treatment of patients with metastatic colorectal cancer in the third line and subsequent lines of therapy, two therapy options are available with trifluridine/ tipiracil and regorafenib, which are recommended in the guidelines for subsequent lines of therapy.

Within the scope of the benefit assessment, a hint for a minor additional benefit. was identified for trifluridine/ tipiracil compared to best supportive care with the resolution of 1 October 2020.

The active ingredient regorafenib was removed from the directory services according to Section 131 paragraph 4 SGB V in May 2016 and therefore does not represent an appropriate comparator therapy at the current time. This is due to the fact that a regular supply is not guaranteed in Germany. Furthermore, the benefit assessment for regorafenib did not determine any additional benefit compared to best supportive care (resolution of 17 March 2016).

In the case of a reduced general condition, certain intolerances or in more advanced treatment settings, monotherapies with capecitabine, irinotecan, cetuximab or

panitumumab as well as the combination therapies of irinotecan with cetuximab, capecitabine with bevacizumab and 5-fluorouracil with folinic acid with or without bevacizumab are available as further treatment options according to the marketing authorisations.

Furthermore, nivolumab in combination with ipilimumab is still a quite new treatment option available in care. In the benefit assessment, by resolution of 20 January 2022, no additional benefit was identified for the treatment of patients with metastatic colorectal cancer with mismatch repair deficiency or high microsatellite instability after prior fluoropyrimidine-based combination chemotherapy; no suitable data were available. Nivolumab in combination with ipilimumab is not determined to be an appropriate comparator therapy for the present resolution, taking into account the available evidence and the results of the benefit assessment.

With regard to the previously mentioned different therapy options that can be considered for an appropriate comparator therapy in the present therapeutic indication, the concrete treatment decision depends largely on patient-individual factors. These usually include the type and number of previous therapies, the RAS and BRAF mutational status, the location of the primary tumour, the general condition as well as the side effect profiles of the active ingredients and, in particular, the risk of toxicity induced by anti-VEGF and anti-VEGFR active ingredients.

In the overall assessment, therefore, a patient-individual therapy, depending on the type and number of previous therapies, the RAS and BRAF mutational status, the location of the primary tumour, the general condition and the risk of toxicity induced by anti-VEGF and anti-VEGFR active ingredients, was chosen from the above-mentioned therapy options under "Appropriate comparator therapy for pembrolizumab".

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

### 2.1.3 Extent and probability of the additional benefit

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

Adults with unresectable or metastatic colorectal cancer with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR); after previous fluoropyrimidine-based combination therapy

An additional benefit is not proven.

Justification:

Data basis

In the dossier for the benefit assessment, the pharmaceutical company submits the results of the approval study on pembrolizumab. This is the KEYNOTE-164 study, which included patients with locally advanced unresectable or metastatic colorectal cancer with MSI-H or dMMR.

*KEYNOTE-164*

The KEYNOTE-164 study is a single-arm phase II study conducted between August 2015 and February 2021 in 34 study sites in North America, Europe, Asia and Australia with a total of 124 patients.

At the time of enrolment in the study, the patients had to have already been treated with standard therapy regimens. Depending on the previous therapy, the patients were divided into two cohorts (cohort A: pre-treated with fluoropyrimidine, oxaliplatin and irinotecan; cohort B: pre-treated with at least 1 standard systemic therapy [fluoropyrimidine in combination with oxaliplatin or irinotecan with or without anti-VEGF/EGFR monoclonal antibodies]).

The objective response rate (ORR) was the primary endpoint of the study. Further patient-relevant endpoints were collected on overall survival and side effects.

Comparator data:

As the pharmaceutical company has not identified a randomised controlled trial for a direct comparison, he is conducting an information search for further investigations. For his information gathering on further investigations, the pharmaceutical company divides into the following two questions:

- Patients after 1 previous systemic therapy (sub-population A1 according to the pharmaceutical company, hereinafter referred to as pharmaceutical company's question A1) and
- Patients after at least 2 previous systemic therapies (sub-population A2 according to the pharmaceutical company, hereinafter referred to as question A2 of the pharmaceutical company).

For these questions, the pharmaceutical company selects certain therapy options in each case, which are named by the G-BA within the framework of patient-individual therapy:

- Question A1 of the pharmaceutical company: Irinotecan- or oxaliplatin-based treatment regimen with or without anti-vascular endothelial growth factor (VEGF) or anti-epidermal growth factor receptor (EGFR) substances
- Question A2 of the pharmaceutical company: Trifluridine/ tipiracil

According to these two questions defined by the pharmaceutical company, a separate information collection was carried out. For question A1, the pharmaceutical company identified the retrospective study Tourgeron 2020, for question A2 the studies RECOURSE and TERRA. Subsequently, the pharmaceutical company carries out comparisons of individual arms of the KEYNOTE-164 study and the respective identified studies corresponding to the research question.

*Tougeron 2020 (Question A1)*

The Tourgeron 2020 study is a retrospective study of adult patients with metastatic colorectal cancer and MSI-H or dMMR. The analysis includes patients who received a corresponding diagnosis in the period from 2007 to 2017. The pharmaceutical company uses patients with chemotherapy with or without targeted therapy in the second line (N = 136) for the

comparison of individual arms. These patients received irinotecan (n = 89; 65 %), oxaliplatin (n = 33; 24 %) and other therapies (n = 8; 6 %) as second-line chemotherapy; no data is available for 6 patients. In addition, 103 (76%) patients received targeted therapy (anti-VEGF, anti-EGFR or regorafenib). Information on the dosage of the medication is not available.

Of the total of 124 patients included in the KEYNOTE-164 study, the pharmaceutical company uses a sub-population of 30 patients with prior systemic therapy for the comparison of individual arms and presents a comparison exclusively for the endpoint of overall survival. In addition to these results of the comparison of individual arms of different studies, the pharmaceutical entrepreneur additionally presents non-comparative results of the KEYNOTE-164 study.

*RECOURSE and TERRA (Question A2)*

The RECOURSE and TERRA studies are double-blind RCTs comparing trifluridine/tipiracil + best supportive care (BSC) with placebo + BSC. Both studies were part of the benefit assessment (reassessment after the deadline) of trifluridine/tipiracil in the treatment of pretreated colorectal cancer (resolution of 01.10.2020).

Both studies included patients with metastatic colorectal cancer with at least 2 previous standard treatment regimens for the metastatic stage, without information on MSI-H or dMMR status. A total of 800 (RECOURSE) and 406 (TERRA) patients were randomly assigned in a 2:1 ratio to treatment with trifluridine/tipiracil + BSC (534 and 271 patients in the RECOURSE and TERRA trials, respectively) or placebo + BSC (266 and 135 patients in the RECOURSE and TERRA studies, respectively).

For the comparison of individual arms, the pharmaceutical company uses all 534 patients of the trifluridine/tipiracil arm of the RECOURSE study and a sub-population consisting of 61 patents of the trifluridine/tipiracil arm of the TERRA study.

Of the total of 124 patients included in the KEYNOTE-164 study, the pharmaceutical company uses a sub-population of 94 patients with at least two previous systemic therapies for the comparison of individual arms and presents a comparison for the patient-relevant endpoints overall survival, serious adverse events (SAEs) and severe adverse events (AEs). For this purpose, the pharmaceutical company submits a comparison without adjustment and a matching-adjusted-indirect-comparison (MAIC) analysis, each without a bridge comparator. In addition, the pharmaceutical company presents non-comparative results of the KEYNOTE-164 study.

<u>Assessment</u>

The results of the single-arm KEYNOTE-164 study presented alone are unsuitable for assessing the additional benefit of pembrolizumab as they do not allow a comparison with the appropriate comparator therapy.

In order to classify an additional benefit of pembrolizumab, the pharmaceutical company conducts an information retrieval on further investigations and divides it into two questions. On the comparison page, the pharmaceutical company searches for his research question A1 exclusively for studies with irinotecan- or oxaliplatin-based treatment regimens with or without anti-VEGF or anti-EGFR substances; for their research question A2, the search on the comparison page is limited to studies with trifluridine/tipiracil.

This procedure is not appropriate, as the data presented do not address the research question of the benefit assessment, and the information retrieval related to the research question of

the present benefit assessment is incomplete due to a division into two patient groups and the associated restriction of the information retrieval to the treatment options selected by the pharmaceutical company.

Additionally, in the comparisons of individual arms submitted by the pharmaceutical company, results from different studies are compared without adjustment for potentially relevant effect modifiers or prognostic factors. These are subject to inherent uncertainty due to the lack of randomisation.

The MAIC analyses presented by the pharmaceutical company are unsuitable for the benefit assessment. In the case of non-randomised comparisons without a bridge comparator, only those procedures that are carried out using individual patient data, in contrast to MAIC analysis, are generally useful for confounder adjustment. In contrast, the MAIC analysis accounts for confounding based on aggregate data.

Furthermore, for question A1 of the pharmaceutical company, there is no effect on overall survival for which it can be safely excluded in the present situation of a comparison of individual arms that it does not result solely from a systematic bias due to confounding variables. Furthermore, a benefit-harm assessment is not possible because no results on side effects are available.

For question A2 of the pharmaceutical company, the pivotal criterion MSI-H or dMMR was only considered on the intervention side, but not on the comparison side.

In the literature, the statements of the scientific-medical societies and the testimonies of the clinical experts in the oral hearing, high-grade microsatellite instability (MSI-H) is considered to have a prognostic value in certain tumour stages, according to which this aspect can be potentially relevant for the comparability of certain patient populations.

Conclusion

Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of pembrolizumab as monotherapy in adult patients with locally advanced unresectable or metastatic colorectal cancer with MSI-H or dMMR after previous fluoropyrimidine-based combination therapy is not proven.

### 2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient pembrolizumab:

"Keytruda as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings: treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy."

The G-BA determined a patient-individual therapy as an appropriate comparator therapy, which comprises several active ingredients as monotherapy as well as in combination therapies and provides for a treatment decision depending on patient-individual factors, which include in particular the type and number of previous therapies, the RAS and BRAF mutational status, the localisation of the primary tumour, the general condition and the risk of toxicity induced by anti-VEGF and anti-VEGFR substances.

For the benefit assessment, the pharmaceutical company submitted the results from the Phase II KEYNOTE 164 study. This is an uncontrolled study and therefore, does not include a

comparator group. In addition, indirect comparisons of individual treatment options were submitted by the pharmaceutical company.

Overall, the presented adjusted and non-adjusted indirect comparisons are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of pembrolizumab as monotherapy in adult patients with locally advanced unresectable or metastatic colorectal cancer with MSI-H or dMMR after previous fluoropyrimidine-based combination therapy is not proven.

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

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

The G-BA bases its resolution on the patient numbers stated by IQWiG in the dossier assessment.

Although the pharmaceutical company's approach is largely comprehensible from a mathematical point of view, it is not comprehensible from a methodological point of view in some cases. The procedure of the pharmaceutical company tends to lead to an overestimation, whereas the number of patients in the SHI target population stated by the pharmaceutical company is subject to uncertainty in the overall view due to underestimations and unclear transferability of share values in other steps.

## 2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Keytruda (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 3 January 2023):

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

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of adults with unresectable metastatic colorectal cancer, specialists in internal medicine and gastroenterology, and other doctors from specialist groups participating in the Oncology Agreement.

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

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

## 2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 January 2023).

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

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and the maximum treatment duration, if specified in the product information.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements were applied (average body height: 1,72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[2].

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 monotherapy | | | | |
| Pembrolizumab | continuously, 1 x every 21 days | 17.4 | 1 | 17.4 |
| | continuously, 1 x every 42 days | 8.7 | 1 | 8.7 |
| Appropriate comparator therapy | | | | |
| FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) ± bevacizumab | | | | |
| FOLFOX 4 | | | | |
| Oxaliplatin | 1 x on day 1 of a 14-day cycle | 12 | 1 | 12 |
| Folinic acid | 1 x on day 1 + 2 of a 14-day cycle | 12 | 2 | 24 |
| 5-fluorouracil | 1 x on day 1 + 2 of a 14-day cycle | 12 | 2 | 24 |

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

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| plus bevacizumab if necessary | | | | |
| Bevacizumab | 1 x on day 1 of a 14-day cycle | 26.1 | 1 | 26.1 |
| FOLFOX 6 | | | | |
| Oxaliplatin | 1 x on day 1 of a 14-day cycle | 12 | 1 | 12 |
| Folinic acid | 1 x on day 1 of a 14-day cycle | 12 | 1 | 12 |
| 5-fluorouracil | 1 x on day 1 of a 14-day cycle | 12 | 1 | 12 |
| FOLFIRI (5-fluorouracil, folinic acid, irinotecan) ± bevacizumab or aflibercept or ramucirumab or cetuximab or panitumumab[3] | | | | |
| FOLFIRI | | | | |
| Irinotecan | 1 x on day 1 of a 14-day cycle | 26.1 | 1 | 26.1 |
| Folinic acid | 1 x on day 1 of a 14-day cycle | 26.1 | 1 | 26.1 |
| 5-fluorouracil | 1 x on day 1 of a 14-day cycle | 26.1 | 1 | 26.1 |
| plus bevacizumab or aflibercept or ramucirumab or cetuximab or panitumumab if necessary | | | | |
| Bevacizumab | 1 x on day 1 of a 14-day cycle | 26.1 | 1 | 26.1 |
| Aflibercept | 1 x on day 1 of a 14-day cycle | 26.1 | 1 | 26.1 |
| Ramucirumab | 1 x on day 1 of a 14-day cycle | 26.1 | 1 | 26.1 |
| Cetuximab | 1 x every 7 days | 52.1 | 1 | 52.1 |

[3] In view of different FOLFIRI protocols, the information from the Cyramza® (ramucirumab) product information, last revised August 2020, Zaltrap® (aflibercept), as of November 2020 and Peeters et al. 2010 (DOI: 10.1200/JCO.2009.27.6055) is used.

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| Panitumumab | 1 x on day 1 of a 14-day cycle | 26.1 | 1 | 26.1 |
| 5-fluorouracil + folinic acid ± bevacizumab | | | | |
| 5-fluorouracil (de Gramont) | | | | |
| Folinic acid | 1 x on day 1 + 2 of a 14-day cycle | 26.1 | 2 | 52.2 |
| 5-fluorouracil | 1 x on day 1 + 2 of a 14-day cycle | 26.1 | 2 | 52.2 |
| plus bevacizumab if necessary | | | | |
| Bevacizumab | 1 x on day 1 of a 14-day cycle | 26.1 | 1 | 26.1 |
| Capecitabine ± bevacizumab | | | | |
| Capecitabine | 2 x daily on day 1 - 14 of an 21-day cycle | 17.4 | 14 | 243.6 |
| plus bevacizumab if necessary | | | | |
| Bevacizumab | 1 x on day 1 of a 21-day cycle | 17.4 | 1 | 17.4 |
| CAPOX (capecitabine + oxaliplatin) ± bevacizumab | | | | |
| CAPOX | | | | |
| Oxaliplatin | 1 x on day 1 of a 21-day cycle | 8 | 1 | 8 |
| Capecitabine | 2 x on day 1-14 of a 21-day cycle | 8 | 14 | 112 |
| plus bevacizumab if necessary | | | | |
| Bevacizumab | 1 x on day 1 of a 21-day cycle | 17.4 | 1 | 17.4 |
| Irinotecan ± cetuximab | | | | |
| Irinotecan | 1 x on day 1 of a 21-day cycle | 17.4 | 1 | 17.4 |
| plus cetuximab if necessary | | | | |

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| Cetuximab | 1 x every 7 days | 52.1 | 1 | 52.1 |
| Trifluridine/ tipiracil | | | | |
| Trifluridine/ tipiracil | 2 x daily on day 1-5 and 8-12 of a 28-day cycle | 13 | 10 | 130 |
| Cetuximab | | | | |
| Cetuximab | 1 x every 7 days | 52.1 | 1 | 52.1 |
| Panitumumab | | | | |
| Panitumumab | 1 x on day 1 of a 14-day cycle | 26.1 | 1 | 26.1 |
| Encorafenib + cetuximab | | | | |
| Encorafenib | 1 x daily | 365 | 1 | 365 |
| Cetuximab | 1 x every 7 days | 52.1 | 1 | 52.1 |

Consumption:

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Pembrolizumab monotherapy | | | | | |
| Pembrolizumab (21-day cycle) | 200 mg | 200 mg | 2 x 100 mg | 17.4 | 34.8 x 100 mg |
| Pembrolizumab (42-day cycle) | 400 mg | 400 mg | 4 x 100 mg | 8.7 | |
| Appropriate comparator therapy | | | | | |
| FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) ± bevacizumab | | | | | |
| FOLFOX 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 |
|---|---|---|---|---|---|
| Oxaliplatin | 85 mg/m² | 161.5 mg | 1 x 200 mg | 12 | 12 x 200 mg |
| Folinic acid | 200 mg/m² | 380 mg | 1 x 400 mg | 24 | 24 x 400 mg |
| 5-fluorouracil | 400 mg/m² | 760 mg | 1 x 1,000 mg | 24 | 24 x 1,000 mg |
| | 600 mg/m² | 1,140 mg | 1 x 1,000 mg<br>1 x 250 mg | 24<br>24 | 24 x 1,000 mg<br>24 x 250 mg |
| plus bevacizumab if necessary | | | | | |
| Bevacizumab | 5 mg/kg BW - | 385 mg - | 1 x 400 mg- | 26.1 | 26.1 x 400 mg- |
| | 10 mg/kg BW | 770 mg | 2 x 400 mg | | 52.2 x 400 mg |
| FOLFOX 6 | | | | | |
| Oxaliplatin | 85 mg/m² | 161.5 mg | 1 x 200 mg | 12 | 12 x 200 mg |
| Folinic acid | 400 mg/m² | 760 mg | 1 x 800 mg | 12 | 12 x 800 mg |
| 5-fluorouracil | 400 mg/m² | 760 mg | 1 x 1,000 mg | 12 | 12 x 1,000 mg |
| | 2,400 mg/m² | 4,560 mg | 1 x 5,000 mg | 12 | 12 x 5,000 mg |
| FOLFIRI (5-fluorouracil, folinic acid, irinotecan) +/- bevacizumab or aflibercept or ramucirumab or cetuximab or panitumumab | | | | | |
| FOLFIRI | | | | | |
| Irinotecan | 180 mg/m² | 342 mg | 1 x 300 mg +<br>2 x 40 mg | 26.1 | 26.1 x 300 mg +<br>52.2 x 40 mg |
| Folinic acid | 400 mg/m² | 760 mg | 1 x 800 mg | 26.1 | 26.1 x 800 mg |
| 5-fluorouracil | 400 mg/m² | 760 mg | 1 x 1,000 mg | 26.1 | 26.1 x 1,000 mg |
| | 2,400 mg/m² | 4,560 mg | 1 x 5,000 mg | 26.1 | 26.1 x 5,000 mg |
| plus bevacizumab or aflibercept or ramucirumab or cetuximab or panitumumab if necessary | | | | | |

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Bevacizumab | 5 mg/kg BW | 385 mg | 1 x 400 mg | 26.1 | 26.1 x 400 mg |
| Aflibercept | 4 mg/kg | 308 mg | 2 x 200 mg | 26.1 | 52.2 x 200 mg |
| Ramucirumab | 8 mg/kg | 616 mg | 1 x 500 mg +<br>2 x 100 mg | 26.1 | 26.1 x 500 mg +<br>52.2 x 100 mg |
| Cetuximab | Initial dose in week 1: 400 mg/m² BSA | 760 mg | 1 x 500 mg +<br>3 x 100 mg | 1 | 52.1 x 500 mg +<br>3 x 100 mg |
| | From week 2:<br>250 mg/m² BSA | 475 mg | 1 x 500 mg | 51.1 | |
| Panitumumab | 6 mg/kg BW | 462 mg | 1 x 400 mg +<br>1 x 100 mg | 26.1 | 26.1 x 400 mg +<br>26.1 x 100 mg |
| 5-fluorouracil + folinic acid ± bevacizumab | | | | | |
| 5-fluorouracil (de Gramont) | | | | | |
| Folinic acid | 200 mg/m² | 380 mg | 1 x 400 mg | 52.2 | 52.2 x 400 mg |
| 5-fluorouracil | 400 mg/m² | 760 mg | 1 x 1,000 mg | 52.2 | 52.2 x 1,000 mg |
| | 600 mg/m² | 1,140 mg | 1 x 1,000 mg<br>1 x 250 mg | 52.2<br>52.2 | 52.2 x 1,000 mg<br>52.2 x 250 mg |
| plus bevacizumab if necessary | | | | | |
| Bevacizumab | 5 mg/kg BW | 385 mg | 1 x 400 mg | 26.1 | 26.1 x 400 mg |
| Capecitabine ± bevacizumab | | | | | |

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Capecitabine | 1,250 mg/m² = 2,375 mg | 4600 mg | 8 x 500 mg +<br>2 x 300 mg | 243.6 | 1,948.8 x 500 mg +<br>487.2 x 300 mg |
| plus bevacizumab if necessary | | | | | |
| Bevacizumab | 7.5 mg/kg BW | 577.5 mg | 1 x 400 mg +<br>2 x 100 mg | 17.4 | 17.4 x 400 mg +<br>34.8 x 100 mg |
| CAPOX (capecitabine + oxaliplatin) ± bevacizumab | | | | | |
| CAPOX | | | | | |
| Oxaliplatin | 130 mg/m² | 247 mg | 1 x 200 mg +<br>1 x 50 mg | 8 | 8 x 200 mg +<br>8 x 50 mg |
| Capecitabine | 1,000 mg/m² = 1,900 mg | 3,800 mg | 8 x 500 mg | 112 | 896 x 500 mg |
| plus bevacizumab if necessary | | | | | |
| Bevacizumab | 7.5 mg/kg BW | 577.5 mg | 1 x 400 mg +<br>2 x 100 mg | 17.4 | 17.4 x 400 mg +<br>34.8 x 100 mg |
| Irinotecan +/- cetuximab | | | | | |
| Irinotecan | 350 mg/m² | 665 mg | 1 x 500 mg +<br>2 x 100 mg | 17.4 | 17.4 x 500 mg +<br>34.8 x 100 mg |
| plus cetuximab if necessary | | | | | |
| Cetuximab | Initial dose in week 1: 400 mg/m² BSA | 760 mg | 1 x 500 mg +<br>3 x 100 mg | 1 | 52.1 x 500 mg +<br>3 x 100 mg |

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| | From week 2: 250 mg/m² | 475 mg | 1 x 500 mg | 51.1 | |
| Trifluridine/ tipiracil | | | | | |
| Trifluridine/ tipiracil | 35 mg/m²<br><br>(65 mg) | 130 mg | 6 x 15 mg +<br><br>2 x 20 mg | 130 | 780 x 15 mg +<br><br>260 x 20 mg |
| Cetuximab | | | | | |
| Cetuximab | Initial dose in week 1: 400 mg/m² BSA | 760 mg | 1 x 500 mg +<br><br>3 x 100 mg | 1 | 52.1 x 500 mg +<br><br>3 x 100 mg |
| | From week 2: 250 mg/m² | 475 mg | 1 x 500 mg | 51.1 | |
| Panitumumab | | | | | |
| Panitumumab | 6 mg/kg BW | 462 mg | 1 x 400 mg +<br><br>1 x 100 mg | 26.1 | 26.1 x 400 mg +<br><br>26.1 x 100 mg |
| Encorafenib + cetuximab | | | | | |
| Encorafenib | 300 mg | 300 mg | 4 x 75 mg | 365 | 1460 x 75 mg |
| Cetuximab | Initial dose in week 1: 400 mg/m² BSA | 760 mg | 1 x 500 mg +<br><br>3 x 100 mg | 1 | 52.1 x 500 mg +<br><br>3 x 100 mg |
| | From week 2:<br><br>250 mg/m² | 475 mg | 1 x 500 mg | 51.1 | |

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 | € 2,974.79 | € 1.77 | € 285.60 | € 2,687.42 |
| Appropriate comparator therapy | | | | | |
| Bevacizumab 100 mg | 1 CIS | € 396.98 | € 1.77 | € 36.61 | € 358.60 |
| Bevacizumab 400 mg | 1 CIS | € 1,553.30 | € 1.77 | € 146.43 | € 1,405.10 |
| Capecitabine 300 mg[4] | 30 FCT | € 36.33 | € 1.77 | € 1.98 | € 32.58 |
| Capecitabine 500 mg[4] | 120 FCT | € 151.81 | € 1.77 | € 11.11 | € 138.93 |
| Capecitabine 500 mg[4] | 60 FCT | € 87.64 | € 1.77 | € 6.04 | € 79.83 |
| Cetuximab 500 mg | 1 INF | € 1,545.20 | € 1.77 | € 145.64 | € 1,397.84 |
| Cetuximab 100 mg | 1 INF | € 318.18 | € 1.77 | € 29.13 | € 287.28 |
| 5-fluorouracil 5,000 mg[4] | 1 SFI | € 33.99 | € 1.77 | € 1.80 | € 30.42 |
| 5-fluorouracil 1,000 mg[4] | 1 SFI | € 16.64 | € 1.77 | € 0.42 | € 14.45 |
| 5-fluorouracil 250 mg[4] | 1 SFI | € 12.85 | € 1.77 | € 0.12 | € 10.96 |
| Folinic acid 400 mg[4] | 5 SFI | € 793.25 | € 1.77 | € 61.85 | € 729.63 |
| Folinic acid 400 mg[4] | 1 SFI | 165.46 | € 1.77 | € 12.20 | € 151.49 |
| Folinic acid 800 mg[4] | 5 SFI | € 1,499.02 | € 1.77 | € 117.67 | € 1,379.58 |
| Folinic acid 800 mg[4] | 1 SFI | € 304.62 | € 1.77 | € 23.20 | € 279.65 |
| Irinotecan 40 mg | 1 CIS | € 85.56 | € 1.77 | € 9.41 | € 74.38 |
| Irinotecan 100 mg | 1 CIS | € 196.36 | € 1.77 | € 8.78 | € 185.81 |
| Irinotecan 300 mg | 1 CIS | € 573.90 | € 1.77 | € 71.20 | € 500.93 |
| Irinotecan 500 mg | 1 CIS | € 940.09 | € 1.77 | € 44.08 | € 894.24 |

[4] Fixed reimbursement rate

| 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 |
|---|---|---|---|---|---|
| Oxaliplatin 200 mg | 1 CIS | € 399.29 | € 1.77 | € 18.41 | € 379.11 |
| Oxaliplatin 200 mg | 1 CIS | € 628.26 | € 1.77 | € 29.28 | € 597.21 |
| Oxaliplatin 50 mg | 1 CIS | € 164.89 | € 1.77 | € 7.29 | € 155.83 |
| Panitumumab 400 mg | 1 CIS | € 2,657.13 | € 1.77 | € 254.50 | € 2,400.86 |
| Panitumumab 100 mg | 1 CIS | € 681.62 | € 1.77 | € 63.62 | € 616.23 |
| Ramucirumab 500 mg | 1 CIS | € 2,141.31 | € 1.77 | € 204.00 | € 1,935.54 |
| Ramucirumab 100 mg | 1 CIS | € 441.14 | € 1.77 | € 40.80 | € 398.57 |
| Aflibercept 200 mg | 1 CIS | € 769.87 | € 1.77 | € 30.00 | € 738.10 |
| Tipiracil/trifluridine 15 mg | 60 FCT | € 2,348.73 | € 1.77 | € 93.46 | € 2,253.50 |
| Tipiracil/trifluridine 20 mg | 60 FCT | € 3,112.42 | € 1.77 | € 124.62 | € 2,986.03 |
| Encorafenib 75 mg | 168 HC | € 6,235.15 | € 1.77 | € 252.00 | € 5,981.38 |
| Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; IIS = injection/infusion solution; SFI = solution for injection; INF = infusion solution | | | | | |

LAUER-TAXE® last revised: 1 January 2023

Costs for additionally required SHI services:

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

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

According to the product information on cetuximab (Erbitux), patients must be pretreated with an antihistamine and a corticosteroid for at least 1 hour prior to the first administration of cetuximab. This premedication is also recommended before all further infusions. The product information does not provide any specific information why the necessary costs cannot be quantified for the premedication.

Other SHI services:

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

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

### 2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Pembrolizumab

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

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

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

## 3. Bureaucratic costs calculation

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

## 4. Process sequence

At its session on 23 February 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 21 April 2022.

On 18 July 2022, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 2 VerfO.

By letter dated 25 July 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 October 2022, and the written statement procedure was initiated with publication on the G-BA website on 8 November 2022. The deadline for submitting written statements was 22 November 2022.

The oral hearing was held on 5 December 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 10 January 2023, and the proposed resolution was approved.

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

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal product | 23 February 2021 | Determination of the appropriate comparator therapy |
| Subcommittee Medicinal product | 21 April 2022 | New implementation of the appropriate comparator therapy |
| Working group Section 35a | 29 November 2022 | Information on written statements received; preparation of the oral hearing |
| Subcommittee Medicinal product | 5 December 2022 | Conduct of the oral hearing |
| Working group Section 35a | 13 December 2022<br>3 January 2023 | Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure |
| Subcommittee Medicinal product | 10 January 2023 | Concluding discussion of the draft resolution |

| | | |
|---|---|---|
| Plenum | 19 January 2023 | Adoption of the resolution on the amendment of Annex XII AM-RL |

Berlin, 19 January 2023

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

Prof. Hecken