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: cervical cancer, PD-L1 expression ≥ 1 (CPS), combination with chemotherapy with or without bevacizumab)

of 2 February 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 online 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 February 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 therapeutic indications, in the present indication "persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1" 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 multiple 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 "persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1", 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 "persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1".

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

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

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

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

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

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

Keytruda, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1.

Therapeutic indication of the resolution (resolution of 02.02.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; first-line

Appropriate comparator therapy:

Therapy according to doctor's instructions

b) Adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; after first-line chemotherapy and for whom further antineoplastic therapy is an option

Appropriate comparator therapy:

Therapy according to doctor's instructions

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.

3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. In addition to pembrolizumab in combination with chemotherapy with or without bevacizumab , the active ingredients bevacizumab, cemiplimab, bleomycin, carboplatin, cisplatin, ifosfamide, mitomycin and topotecan are approved in the present therapeutic indication.

on 2. For the present therapeutic indication, it is assumed that surgery and/or radiotherapy with a curative objective are not (or no longer) an option at the time of the treatment decision and that the treatment setting is palliative. In the present therapeutic indication, a non-medicinal treatment is therefore not considered.

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.

on 3. No corresponding resolutions or assessments are available.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic 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 care.

The present therapeutic indication addresses several lines of therapy. For first-line therapy of patients as well as for patients who have already received first-line chemotherapy, different therapy options can be considered according to the available evidence. Therefore, in the present therapeutic indication, a distinction is made between a) adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; first-line and b) adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; after first-line chemotherapy.

a) Adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; first-line

According to the guidelines, a platinum-containing combination chemotherapy is recommended for the present treatment setting within the framework of a medicinal therapy with palliative therapy intention.

The primary focus is on cisplatin as part of a combination therapy. However, cisplatin can be replaced by carboplatin, especially in cisplatin-pretreated patients or patients not eligible for cisplatin. In addition, the platinum-free therapy paclitaxel in combination with topotecan is recommended.

According to the available evidence, bevacizumab should be administered simultaneously with palliative combination chemotherapy consisting of cis-/carboplatin in combination with paclitaxel or paclitaxel in combination with topotecan.

The active ingredient paclitaxel is only approved for the present indication via the marketing authorisation of bevacizumab. Therefore, there is a discrepancy between medicinal products approved in the indication and those used in health care/ recommended in guidelines.

The active ingredient cemiplimab is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 18.11.2022). Based on the generally accepted state of medical knowledge, cemiplimab is not determined to be an appropriate comparator therapy for the present resolution.

In the overall assessment, the G-BA determines a therapy according to doctor's instructions as the appropriate comparator therapy for the present treatment setting.

In the context of a clinical study, the G-BA considers the following treatment options as suitable comparators for therapy according to doctor's instructions.

- Cisplatin in combination with paclitaxel ± bevacizumab
- Carboplatin in combination with paclitaxel ± bevacizumab (only for cisplatin-pretreated patients or not eligible for cisplatin)
- Cisplatin in combination with topotecan
- Carboplatin in combination with topotecan (only for cisplatin-pretreated patients or not eligible for cisplatin)
- Paclitaxel in combination with topotecan ± bevacizumab (only for patients not eligible for platinum-containing chemotherapy)

A single-comparator study is usually not sufficient for the implementation of the therapy according to the doctor's instructions in a direct comparative study. It is expected that the investigators will be able to choose from several treatment options (multi-comparator study).

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

b) Adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; after first-line chemotherapy and for whom further antineoplastic therapy is an option

For the palliative treatment setting after first-line chemotherapy, the guidelines recommend monotherapies with the active agents nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed and irinotecan. For patients with PD-L1 positive

metastatic cervical cancer, pembrolizumab is also named. In addition, best supportive care (BSC) is a therapy option.

Based on the present therapeutic indication, which provides for treatment with a combination therapy consisting of pembrolizumab and chemotherapy, with or without bevacizumab, it is assumed that further antineoplastic therapy is usually considered for the patients in the therapeutic indication. BSC is therefore not considered as an appropriate comparator therapy.

Individual active ingredient recommended in these guidelines are not approved in the present indication: nab-paclitaxel, vinorelbine, pemetrexed, irinotecan and pembrolizumab. The marketing authorisation of the active ingredients ifosfamide and topotecan is linked to the concomitant active ingredient cisplatin in the present therapeutic indication. Therefore, there is a discrepancy between medicinal products approved in the indication and those used in health care/ recommended in guidelines.

The active ingredient cemiplimab is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 18.11.2022). Based on the generally accepted state of medical knowledge, cemiplimab is not determined to be an appropriate comparator therapy for the present resolution.

In the overall assessment, the G-BA determines a therapy according to doctor's instructions as the appropriate comparator therapy for the present treatment setting.

In the context of a clinical study, the G-BA considers the following monotherapies as suitable comparators for therapy according to doctor's instructions.

- nab-paclitaxel
- Vinorelbine
- Ifosfamide
- Topotecan
- Pemetrexed
- Irinotecan
- Pembrolizumab (for patients with PD-L1 positive metastatic cervical cancer)

A single-comparator study is usually not sufficient for the implementation of the therapy according to the doctor’s instructions in a direct comparative study. It is expected that the investigators will be able to choose from several treatment options (multi-comparator study).

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

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:

a) Adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; first-line

   a1) Pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab, or in combination with carboplatin and paclitaxel with or without bevacizumab:

   Indication of a considerable additional benefit

   a2) Pembrolizumab in combination with chemotherapies other than cisplatin and paclitaxel with or without bevacizumab or carboplatin and paclitaxel with or without bevacizumab:

   An additional benefit is not proven.

b) Adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; after first-line chemotherapy and for whom further antineoplastic therapy is an option

For pembrolizumab in combination with chemotherapy with or without bevacizumab, an additional benefit is not proven.

Justification:

a) Adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; first-line

   a1) Pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab, or in combination with carboplatin and paclitaxel with or without bevacizumab:

   and

   a2) Pembrolizumab in combination with chemotherapies other than cisplatin and paclitaxel with or without bevacizumab or carboplatin and paclitaxel with or without bevacizumab:

For the proof of the additional benefit of pembrolizumab, the pharmaceutical company presented the results of the KEYNOTE 826 study.

KEYNOTE 826 is an ongoing, multicentre, double-blind, randomised controlled trial comparing pembrolizumab in combination with chemotherapy with or without bevacizumab versus placebo in combination with chemotherapy with or without bevacizumab. The chemotherapies used in KEYNOTE 826 are the combinations of active ingredients cisplatin and paclitaxel or carboplatin and paclitaxel. The choice of chemotherapy and treatment decision to treat with or without bevacizumab was made at the discretion of the principal investigator prior to randomisation.

The study included adult patients who had persistent, recurrent or metastatic cervical cancer (squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma) that had not been previously treated with systemic chemotherapy. The enrolment was independent of PD-L1 expression. The patients were not eligible for curative therapies such as surgery and/or radiation. Furthermore, the patients had to have an ECOG-PS of 0 or 1.

Patients whose tumours express PD-L1 with CPS ≥ 1 are relevant for the present benefit assessment.

A total of 617 patients were enrolled in the study and randomised in a 1:1 ratio to either treatment with pembrolizumab in combination with chemotherapy with or without bevacizumab (N = 308) or to treatment with placebo in combination with chemotherapy with or without bevacizumab (N = 309). The relevant sub-population with a tumour PD-L1 expression CPS ≥ 1 comprises 273 patients in the intervention arm and 275 patients in the control arm.

Randomisation was stratified by metastatisis (according to International Federation of Gynecology and Obstetrics [FIGO] 2009, stage IVB) at the time of diagnosis (yes vs no), principal investigator's decision to use bevacizumab (yes vs no) and PD-L1 status (CPS < 1 vs 1 ≤ CPS < 10 vs CPS ≥ 10).

Due to the implementation of the appropriate comparator therapy, only the active ingredients cisplatin and paclitaxel with or without bevacizumab and carboplatin and paclitaxel with or without bevacizumab are considered as chemotherapy in both the control and intervention arms. Therefore, no data are available for the combination of pembrolizumab with other chemotherapy concomitant active ingredients for the intervention arm.

Pembrolizumab was used in cycles of 3 weeks. Treatment with pembrolizumab was limited to a maximum treatment duration of 35 cycles (approximately 2 years), which deviates from the requirements in the product information, which stipulate therapy until cancer progression or until the occurrence of unacceptable toxicity. The combination chemotherapies in both study arms included paclitaxel and cisplatin or paclitaxel and carboplatin and were used in cycles of 3 weeks. The duration of treatment was limited to 6 cycles; however, chemotherapy could be continued beyond 6 cycles of treatment with the consent of the pharmaceutical company if the combination chemotherapy was tolerated and there was clinical benefit. The doses used in the combination chemotherapies were 175 mg/m² body surface area (BSA) paclitaxel, 50 mg/m² BSA cisplatin and an area under the curve (AUC) of 5 carboplatin. Paclitaxel is only approved for the present indication via the marketing authorisation of bevacizumab. Bevacizumab was used at a dosage of 15 mg/kg according to the product information.

In relation to the sub-population relevant to the benefit assessment, 15.2% of patients received combination chemotherapy consisting of cisplatin and paclitaxel and 81.2% of patients received combination chemotherapy consisting of carboplatin and paclitaxel. Of the patients who received combination chemotherapy of carboplatin and paclitaxel, at least 15.5% were treated with combination chemotherapy of carboplatin instead of cisplatin, contrary to the recommendation of the S3 guideline, although there was no medical rationale against the use of cisplatin.

Based on the benefit assessment dossier, it also remained unclear whether for the 38.5% of the relevant sub-population that did not receive combination therapy with bevacizumab, treatment with bevacizumab was unsuitable in principle. However, within the framework of the written statement procedure, the pharmaceutical company plausibly explained why the additional treatment with bevacizumab was unsuitable at the discretion of the principal investigator.

Treatment with the study medication continued until disease progression, unacceptable toxicity or intercurrent disease, or until patients received a maximum of 35 cycles of treatment with pembrolizumab or 6 cycles of treatment with chemotherapy.

The still ongoing study is being conducted at 151 study sites in 19 countries. Primary endpoints in the study are overall survival and progression-free survival (PFS). Patient-relevant secondary endpoints are endpoints in the categories morbidity, health-related quality of life and side effects.

For the benefit assessment, the results of the pre-specified interim analysis (370 PFS events in the relevant sub-population with a CPS ≥ 1) of the study are used (1st data cut-off of 3 May 2021).

Limitation of the KEYNOTE 826 study

The present marketing authorisation is based on the combination therapy of pembrolizumab with chemotherapy with or without bevacizumab. The chemotherapy is not specified in more detail here and the approved therapeutic indication is also not restricted to the chemotherapeutic agents cisplatin and paclitaxel or carboplatin and paclitaxel used in the KEYNOTE 826 study[2].

In the dossier for the benefit assessment, the pharmaceutical company submits the KEYNOTE 826 study, in which pembrolizumab is investigated in combination with cisplatin and paclitaxel with or without bevacizumab and in combination with carboplatin and paclitaxel with or without bevacizumab. Other chemotherapy concomitant active ingredients are not being investigated in the study.

Regarding the possibility of combination with chemotherapy other than that used in the KEYNOTE 826 study, the EMA states in the EPAR, among other things, that in first-line therapy the use of a platinum doublet with or without bevacizumab is the standard of care and the platinum-paclitaxel doublet is the most commonly used chemotherapy doublet worldwide. With regard to the active ingredient topotecan, it is stated that the use of topotecan in combination with paclitaxel and bevacizumab in first-line therapy is a further, but limited, therapy option and that topotecan is usually used as monotherapy in second- or third-line therapy.

Furthermore, the EPAR describes that in terms of efficacy, it appears unlikely that the additional benefit of pembrolizumab will change if pembrolizumab is added to another regimen that is considered effective for a particular disease/situation. In summary, the EPAR states that the risk-benefit ratio for general use "in combination with chemotherapy" can be considered positive.

Within the framework of the written statement procedure, the clinical assessment experts also explained that the chemotherapy combinations cisplatin/carboplatin in combination with paclitaxel with or without bevacizumab used in the study is the treatment standard in the therapeutic indication.

The pharmaceutical company submitted data for the benefit assessment only for pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab and in combination with carboplatin and paclitaxel with or without bevacizumab. However, the wording of the therapeutic indication "in combination with chemotherapy" does not exclude the use of pembrolizumab in combination with other chemotherapy options. In addition to

[2] https://www.ema.europa.eu/documents/variation-report/keytruda-h-c-003820-ii-0117-epar-assessment-report-variation_en.pdf

the platinum-paclitaxel-based chemotherapy regimen used by the pharmaceutical company in the study, other topotecan-based chemotherapy regimens are recommended in the guidelines.

In contrast to the question of the marketing authorisation, in which the benefit-risk ratio is assessed, the extent to which an extrapolation to further chemotherapy concomitant active ingredients could be made with regard to the present patient-relevant therapeutic effects must be assessed for the question of the benefit assessment.

There are no correspondingly significant data from the present benefit assessment procedure and also no findings according to the generally recognised state of medical knowledge that could lead to the assumption with sufficient certainty that the present results on patient-relevant therapeutic effects are transferable to other chemotherapy concomitant active ingredients.

In the present assessment of the G-BA, this leads to correspondingly different statements on the extent and probability of the additional benefit, on the one hand, for pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab, and secondly for pembrolizumab in combination with chemotherapies other than cisplatin and paclitaxel with or without bevacizumab or carboplatin and paclitaxel with or without bevacizumab.

b) Adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; after first-line chemotherapy and for whom further antineoplastic therapy is an option

No data are available to allow an assessment of the additional benefit.

Extent and probability of the additional benefit

a) Adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; first-line

a1) Pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab, or in combination with carboplatin and paclitaxel with or without bevacizumab:

Mortality

For the endpoint overall survival, there is a statistically significant difference to the advantage of pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab compared to the control arm.

The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

Morbidity

Progression-free survival (PFS)

The endpoint PFS is operationalised in the KEYNOTE 826 study as the time from randomisation to the first documentation of disease progression or death from any cause, whichever occurs first. The occurrence of disease progression is assessed using RECIST criteria (version 1.1) by a blinded, independent, central review committee.

There is a statistically significant difference between the treatment groups for the advantage of pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" was already assessed in the present study via the endpoint "overall survival" as an independent endpoint. The morbidity component assessment was not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST 1.1 criteria).

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS. The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology (collected using EORTC QLQ-C30 and EORTC QLQ-CX24)

In the KEYNOTE 826 study, the patients' symptomatology is assessed using the EORTC QLQ-C30 and the disease-specific additional module EORTC QLQ-CX24. In the dossier for the benefit assessment, the pharmaceutical company submitted responder analyses for this endpoint for the time until the 1st clinically relevant deterioration by ≥ 15 points compared to baseline.

For the EORTC questionnaires, only evaluations for the response criterion 10 points are to be presented in the dossier.

Within the framework of the written statement procedure, the pharmaceutical company submitted corresponding responder analyses for the 1st clinically relevant deterioration by ≥ 10 points compared to baseline. These are used as basis for the assessment.

For the symptoms dyspnoea and peripheral neuropathies, there are statistically significant differences to the disadvantage of pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab compared to the control arm.

Health status (assessed by EQ-5D VAS)

The health status is assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. In the dossier for the benefit assessment, the pharmaceutical company submitted responder analyses for this endpoint for the time until the 1st clinically relevant deterioration by ≥ 15 points compared to baseline, which are used as basis for the assessment.

There is a statistically significant difference for the endpoint health status to the benefit of pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab compared to the control arm.

Overall, no predominant advantage or disadvantage is found for the endpoint category morbidity based on an advantage in health status and disadvantages in the symptoms dyspnoea and peripheral neuropathies.

Quality of life

Health-related quality of life is assessed in the KEYNOTE 826 study using the EORTC QLQ-C30 questionnaire and the disease-specific additional module EORTC QLQ-CX24.

For the benefit assessment, the pharmaceutical company submitted responder analyses for this endpoint for the time until the 1st clinically relevant deterioration by ≥ 15 points compared to baseline.

For the EORTC questionnaires, only evaluations for the response criterion 10 points are to be presented in the dossier.

Within the framework of the written statement procedure, the pharmaceutical company submitted corresponding responder analyses for the 1st clinically relevant deterioration by ≥ 10 points compared to baseline. These are used as basis for the assessment.

For health-related quality of life, there is no statistically significant difference between the treatment arms. For the scale "sexual pleasure" of the EORTC QLQ-CX24 no usable data are available due to a too high percentage of missing values at the start of the study.

Side effects

Adverse events (AEs) in total

Adverse events occurred in almost all patients. The results for the endpoint "total adverse events" are only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3)

For the endpoints of SAEs and severe AEs (CTCAE grade ≥ 3), there are no statistically significant differences between the treatment arms.

Therapy discontinuations due to AEs

For the endpoint treatment discontinuations due to AEs (discontinuation of at least one active ingredient component), there was a statistically significant difference to the disadvantage of

pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab.

Specific AEs

For the specific AEs immune-mediated SAEs, immune-mediated severe AEs (CTCAE grade ≥ 3) and skin and subcutaneous tissue disorders (severe AE, CTCAE grade ≥ 3), there is a statistically significant difference to the disadvantage of pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab.

The overall results on side effects show a disadvantage for pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab compared to placebo in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab in terms of therapy discontinuations due to AEs. In detail, there are disadvantages in the specific AEs.

Overall assessment

For the assessment of the additional benefit of pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab for the treatment of persistent, recurrent or metastatic cervical cancer with PD-L1-expressing tumours (Combined Positive Score [CPS] ≥ 1) in adults, results of the KEYNOTE 826 study are available for the endpoint categories mortality, morbidity, quality of life and side effects.

The ongoing study is comparing pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab versus placebo in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab.

Overall survival shows a statistically significant difference in to the advantage of pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab. The magnitude of the effect is assessed as a significant improvement.

For the endpoint category morbidity, no predominant advantage or disadvantage can be determined. There were disadvantages for the intervention in the symptoms dyspnoea and peripheral neuropathies (assessed with EORTC QLQ-C30 and EORTC QLQ-CX24) and an advantage in health status (assessed with EQ-5D VAS).

With regard to health-related quality of life (assessed with EORTC QLQ-C30 and EORTC QLQ-CX24), there is no statistically significant difference between the treatment arms, which means that neither an advantage nor a disadvantage can be determined for the quality of life overall.

In terms of side effects, pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab shows a disadvantage in treatment discontinuations due to adverse events. In detail, there are disadvantages for the specific adverse events.

In the overall analysis of the available results on the patient-relevant endpoints, the G-BA comes to the conclusion that the clear advantage in overall survival outweighs the

disadvantage in therapy discontinuations due to adverse events. There is a significant improvement in the therapy-relevant benefit that has not been achieved so far.

As a result, the G-BA identifies a considerable additional benefit for pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab for the treatment of persistent, recurrent or metastatic cervical cancer with PD-L1-expressing tumours (CPS ≥ 1) in adults compared to the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of an multicentre, randomised, controlled, double-blind study.

The risk of bias at the study level is rated as low.

The risk of bias of the result for the endpoint of overall survival is estimated to be low.

Uncertainties arise with regard to the guideline-compliant use of carboplatin in the KEYNOTE 826 study. Accordingly, in the relevant sub-population with CPS ≥ 1, 81.2 % of patients received combination chemotherapy consisting of carboplatin and paclitaxel. Of these patients, at least 15.5 % were treated with combination chemotherapy of carboplatin instead of cisplatin, contrary to the recommendation of the S3 guideline, although there was no medical rationale against the use of cisplatin.

Overall, the available data basis is subject to uncertainties. However, these uncertainties are not rated to be so high as to justify a downgrading of the reliability of data of the overall assessment. In particular, the risk of bias of the endpoint of overall survival is rated as low. Thus, the reliability of data for the additional benefit determined is classified in the category "indication".

a2) Pembrolizumab in combination with chemotherapies other than cisplatin and paclitaxel with or without bevacizumab or carboplatin and paclitaxel with or without bevacizumab:

No data are available to allow an assessment of the additional benefit.

b) Adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; after first-line chemotherapy and for whom further antineoplastic therapy is an option

No data are available to allow an assessment of the additional benefit.

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, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1."

In the therapeutic indication to be considered, 2 patient groups were distinguished:

a) Adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; first-line

b) Adult patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with CPS ≥ 1; after first-line chemotherapy and for whom further antineoplastic therapy is an option

Patient group a)

As only data from the KEYNOTE 826 study are available for the assessment for pembrolizumab + cisplatin + paclitaxel ± bevacizumab and pembrolizumab + carboplatin + paclitaxel ± bevacizumab compared to placebo + cisplatin + paclitaxel ± bevacizumab and placebo + carboplatin + paclitaxel ± bevacizumab , but not in combination with another chemotherapy, separate statements on the additional benefit are made in this regard:

a1) Pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab, or in combination with carboplatin and paclitaxel with or without bevacizumab

The appropriate comparator therapy was determined by G-BA to be a "therapy according to doctor's instructions".

For overall survival, there is an advantage for the patients in the intervention arm, which is assessed as a significant improvement.

For the endpoint categories of morbidity and health-related quality of life, there are no differences between the treatment arms that are relevant for the assessment.

With regard to side effects, patients in the intervention arm experienced a disadvantage in discontinuing therapy due to adverse events. In detail, there are disadvantages for the specific adverse events.

Overall, the clear advantage in overall survival outweighs the disadvantage in treatment discontinuation due to adverse events.

The data basis is subject to some uncertainties, which, however, are not rated to be so high as to justify a downgrading of the reliability of data.

As a result, an indication of a considerable additional benefit is identified for pembrolizumab in combination with cisplatin and paclitaxel with or without bevacizumab or in combination with carboplatin and paclitaxel with or without bevacizumab .

a2) Pembrolizumab in combination with chemotherapies other than cisplatin and paclitaxel with or without bevacizumab or carboplatin and paclitaxel with or without bevacizumab

No data are available to allow an assessment of the additional benefit. An additional benefit is not proven.

Patient group b)

No data are available to allow an assessment of the additional benefit. An additional benefit 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 information from the dossier of the pharmaceutical company.

However, the number of patients submitted by the pharmaceutical company is subject to uncertainties. These result primarily from an insufficient consideration of progression events, especially for the calculation of the lower limit, and an underestimated percentage for patients after first-line chemotherapy for whom further antineoplastic therapy is an option.

The number of patients for whom further antineoplastic therapy is considered after first-line chemotherapy is underestimated.

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: 16 December 2022):

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

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

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: 15 January 2023).

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

The therapy regimen presented corresponds to the regimen used in the approval study of the therapeutic indication under consideration. The corresponding dosage information was taken from module 3 of the benefit assessment dossier and from the product information, section 5.1, of the pharmaceutical company.

The average body measurements of adult females were applied for dosages, depending on body weight (BW) or body surface area (BSA) (average body height: 1,66 m; average body weight: 68.7 kg)[3]. This results in a body surface area of 1.76 m² (calculated according to Du Bois 1916).

For the calculation of the AUC dosage data of carboplatin, the mean age of women in Germany of 44.5 years[4], a gender factor of women of 0.85[5] and a mean serum creatinine concentration of 0.75 mg/dl[6] were also used.

Chemotherapy component in combination with pembrolizumab

The marketing authorisation of pembrolizumab in combination with chemotherapy is not restrictive with regard to the chemotherapy component. Explanatory comments in this regard are set out in the European Medicines Agency (EMA) assessment report (EPAR).[7]

Thus, a variety of different chemotherapies and treatment regimens may be considered with respect to the chemotherapy component. Therefore, the treatment costs for "pembrolizumab in combination with chemotherapy other than that mentioned in the approval study" are reported as not determinable.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Patient population a) + b)				
Pembrolizumab	1 x every 21 days	17.4	1	17.4
	or			
	1 x every 42 days	8.7	1	8.7
in combination with				
cisplatin + paclitaxel ± bevacizumab				
Cisplatin	1 x in a 21-day cycle	17.4	1	17.4

[3] Federal Health Reporting. Average body measurements of the population (2017), www.gbe-bund.de

[4] Federal Statistical Office (DESTATIS). Body measurements by age group and sex. 2022, https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Tabellen/liste-koerpermasse.htm

[5] Carboplatin AUC Calculator, https://www.thecalculator.co/health/Carboplatin-AUC-Calculator-631.html

[6] DocCheck Medical Services GmbH. DocCheck Flexikon - Serum creatinine. 2022, https://flexikon.doccheck.com/de/Serumkreatinin#

[7] https://www.ema.europa.eu/documents/variation-report/keytruda-h-c-003820-ii-0117-epar-assessment-report-variation_en.pdf

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Paclitaxel	1 x in a 21-day cycle	17.4	1	17.4
Bevacizumab	1 x in a 21-day cycle	17.4	1	17.4
Carboplatin + paclitaxel ± bevacizumab				
Carboplatin	1 x in a 21-day cycle	17.4	1	17.4
Paclitaxel	1 x in a 21-day cycle	17.4	1	17.4
Bevacizumab	1 x in a 21-day cycle	17.4	1	17.4
Chemotherapy other than the one mentioned in the approval study				
Other chemotherapy	Not determinable			
Appropriate comparator therapy				
Patient population a) Therapy according to doctor's instructions[8] - Cisplatin + paclitaxel + bevacizumab				
Cisplatin	1 x in a 21-day cycle	17.4	1	17.4
Paclitaxel	1 x in a 21-day cycle	17.4	1	17.4
Bevacizumab	1 x in a 21-day cycle	17.4	1	17.4
- Cisplatin + topotecan				
Cisplatin	1 x in a 21-day cycle	17.4	1	17.4
Topotecan	3 x on day 1, 2 and 3 of a 21-day cycle	17.4	3	52.2
- Carboplatin + paclitaxel + bevacizumab				

[8] Costs are only shown for the combination of active ingredients cisplatin + paclitaxel + bevacizumab, cisplatin + topotecan, carboplatin + paclitaxel + bevacizumab and paclitaxel + topotecan + bevacizumab. In addition to these, the following combinations of active ingredients cisplatin + paclitaxel, carboplatin + paclitaxel, carboplatin + topotecan and paclitaxel + topotecan also represent suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. However, these combinations of active ingredients products are not approved in the present therapeutic indication, and therefore, no costs are presented for these combinations of active ingredients.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Carboplatin	1 x in a 21-day cycle	17.4	1	17.4
Paclitaxel	1 x in a 21-day cycle	17.4	1	17.4
Bevacizumab	1 x in a 21-day cycle	17.4	1	17.4
- Paclitaxel + topotecan + bevacizumab				
Paclitaxel	1 x in a 21-day cycle	17.4	1	17.4
Topotecan	3 x on day 1, 2 and 3 of a 21-day cycle	17.4	3	52.2
Bevacizumab	1 x in a 21-day cycle	17.4	1	17.4
Patient population b) Therapy according to doctor's instructions[9]				

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Patient population a) + b)					
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
in combination with					
cisplatin + paclitaxel ± bevacizumab					

[9] For the present benefit assessment, the monotherapies with nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan, pembrolizumab (for patients with PD-L1 positive metastatic cervical cancer) represent a suitable comparator in the context of a therapy according to doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication (as monotherapies), and therefore, no costs are presented for these medicinal products.

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Cisplatin	50 mg/m² = 88 mg	88 mg	1 x 100 mg	17.4	17.4 x 100 mg
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 x 300 mg + 1 x 30 mg	17.4	17.4 x 300 mg + 17.4 x 30 mg
Bevacizumab	15 mg/kg BW	1,030.5 mg	2 x 400 mg + 3 x 100 mg	17.4	34.8 x 400 mg + 52.2 x 100 mg
Carboplatin + paclitaxel ± bevacizumab					
Carboplatin	AUC 5 = 641.4 mg	641.4 mg	1 + 600 mg + 1 x 50 mg	17.4	17.4 x 600 mg +
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 x 300 mg + 1 x 30 mg	17.4	17.4 x 300 mg + 17.4 x 30 mg
Bevacizumab	15 mg/kg BW	1,030.5 mg	2 x 400 mg + 3 x 100 mg	17.4	34.8 x 400 mg + 52.2 x 100 mg
Chemotherapy other than the one mentioned in the approval study					
Other chemotherapy	Not determinable				
Appropriate comparator therapy					
Patient population a) Therapy according to doctor's instructions[8] - Cisplatin + paclitaxel + bevacizumab					
Cisplatin	50 mg/m² = 88 mg	88 mg	1 x 100 mg	17.4	17.4 x 100 mg
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 x 300 mg + 1 x 30 mg	17.4	17.4 x 300 mg + 17.4 x 30 mg
Bevacizumab	15 mg/kg BW	1,030.5 mg	2 x 400 mg + 3 x 100 mg	17.4	34.8 x 400 mg + 52.2 x 100 mg
- Cisplatin + topotecan					
Cisplatin	50 mg/m² = 88 mg	88 mg	1 x 100 mg	17.4	17.4 x 100 mg
Topotecan	0.75 mg/m² = 1.32 mg	1.32 mg	1 x 2 mg	52.2	52.2 x 2 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
- Carboplatin + paclitaxel + bevacizumab					
Carboplatin	AUC 5 = 641.4 mg	641.4 mg	1 + 600 mg + 1 x 50 mg	17.4	17.4 x 600 mg + 17.4 x 50 mg
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 x 300 mg + 1 x 30 mg	17.4	17.4 x 300 mg + 17.4 x 30 mg
Bevacizumab	15 mg/kg BW	1,030.5 mg	2 x 400 mg + 3 x 100 mg	17.4	34.8 x 400 mg + 52.2 x 100 mg
- Paclitaxel + topotecan + bevacizumab					
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 x 300 mg + 1 x 30 mg	17.4	17.4 x 300 mg + 17.4 x 30 mg
Topotecan	0.75 mg/m² = 1.32 mg	1.32 mg	1 x 2 mg	52.2	52.2 x 2 mg
Bevacizumab	15 mg/kg BW	1,030.5 mg	2 x 400 mg + 3 x 100 mg	17.4	34.8 x 400 mg + 52.2 x 100 mg
Patient population b) Therapy according to doctor's instructions[9]					
Therapy according to doctor's instructions	No data available				

Costs:

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
Concomitant active ingredient:					
Bevacizumab 400 mg	1 CIS	€ 1,553.30	€ 1.77	€ 146.43	€ 1,405.10
Bevacizumab 100 mg	1 CIS	€ 396.98	€ 1.77	€ 36.61	€ 358.60
Carboplatin 600 mg	1 CIS	€ 300.81	€ 1.77	€ 13.74	€ 285.30
Carboplatin 50 mg	1 CIS	€ 34.63	€ 1.77	€ 1.11	€ 31.75
Cisplatin 100 mg	1 CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
Paclitaxel 30 mg	1 CIS	€ 94.12	€ 1.77	€ 3.93	€ 88.42
Paclitaxel 300 mg	1 CIS	€ 847.45	€ 1.77	€ 39.68	€ 806.00
Appropriate comparator therapy					
Patient population a) Therapy according to doctor's instructions					
Bevacizumab 400 mg	1 CIS	€ 1,553.30	€ 1.77	€ 146.43	€ 1,405.10
Bevacizumab 100 mg	1 CIS	€ 396.98	€ 1.77	€ 36.61	€ 358.60
Carboplatin 600 mg	1 CIS	€ 300.81	€ 1.77	€ 13.74	€ 285.30
Carboplatin 50 mg	1 CIS	€ 34.63	€ 1.77	€ 1.11	€ 31.75
Cisplatin 100 mg	1 CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
Paclitaxel 30 mg	1 CIS	€ 94.12	€ 1.77	€ 3.93	€ 88.42
Paclitaxel 300 mg	1 CIS	€ 847.45	€ 1.77	€ 39.68	€ 806.00
Topotecan 2 mg	1 CIS	€ 160.96	€ 1.77	€ 7.10	€ 152.09
Patient population b) Therapy according to doctor's instructions					
Not applicable					
Abbreviations: 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.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Cost/ patient/ year
Medicinal product to be assessed (concomitant active ingredient) and appropriate comparator therapy							
Cisplatin							
Antiemetic treatment							
In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information does not provide any specific information why the necessary costs cannot be quantified.							
Hydration/ diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	17.4	€ 158.51
Sodium chloride 0.9% Inf. Solution, 3 l - 4.4 l/day	10 x 1000 ml INF	€ 34.68	1.73	€ 1.08	€ 31.87	17.4	€ 166.36 - € 256.74
	10 x 500 ml INF	€ 23.12	1.16	€ 1.89	€ 20.07		
Paclitaxel							
Dexamethasone 20 mg[10]	50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08	17.4	€ 40.74
Dimetindene IV 1 mg/10 kg	5 x 4 mg SFI	€ 23.67	€ 1.77	€ 5.81	€ 16.09	17.4	€ 111.99
Cimetidine 300 mg IV	10 CIS x 200 mg	€ 19.77	€ 1.77	€ 0.40	€ 17.60	17.4	€ 61.25
Abbreviation: SFI = solution for injection; INF = infusion solution; TAB = tablets							

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[10] Fixed reimbursement rate

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.

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 07 December 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 26 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 26 July 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 October 2022, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2022. The deadline for submitting written statements was 22 November 2022.

The oral hearing was held on 19 December 2022.

By letter dated 21 December 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 13 January 2023.

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 24 January 2023, and the proposed resolution was approved.

At its session on 2 February 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 December 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	26 April 2022	New implementation of the appropriate comparator therapy
Working group Section 35a	13 December 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	19 December 2022 21. December	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	3 January 2023 17 January 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee	24 January 2023	Concluding discussion of the draft resolution

Medicinal products		
Plenum	2 February 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 February 2023

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

Prof. Hecken