Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Pembrolizumab (New Therapeutic Indication: Hodgkin lymphoma, pretreated patients, ≥ 3 years)

of 16 September 2021

Contents

1. Legal basis

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

1. Approved therapeutic indications,
2. Medical benefits,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Costs of therapy for the statutory health insurance,
6. Requirements for a quality-assured application.

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

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

2. Key points of the resolution

The 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 9 March 2021, pembrolizumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L334, 12.12.2008, p. 7).

On 16 September 2020, the pharmaceutical company submitted an application to merge the evaluation procedures of pembrolizumab according to Section 35a, paragraph 5b SGB V. At its session on 5 November 2020, the G-BA approved the application for the merger in compliance with Section 35a, paragraph 5b SGB V.

On 30 March 2021, the pharmaceutical company has submitted 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

"KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option. "

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The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de), on 1 July 2021, thus initiating the written statement procedure. In addition, an oral hearing was also held.

The G-BA came to a resolution on whether an additional benefit of pembrolizumab compared with 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, and the addenda to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of pembrolizumab.

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

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

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

KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Therapeutic indication of the resolution (resolution from 16.09.2021):

This is an indication extension for pembrolizumab as monotherapy for the treatment of paediatric patients, as well as an earlier treatment in adults with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

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

The indication for the treatment of adults in the therapeutic situation after the failure of autologous stem cell transplantation (ASCT) and treatment with brentuximab vedotin (BV), or after the failure of treatment with BV when ASCT is not an option, is the subject of the resolution on the benefit assessment of pembrolizumab dated 17.11.2017.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option

Appropriate comparator therapy:

- Therapy according to doctor's instructions

b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment 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 a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. Comparative therapy should be part of the appropriate therapy in the therapeutic indication according to the generally accepted state of medical knowledge.

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

on 1. In addition to pembrolizumab, the cytotoxic chemotherapies approved in the present therapeutic indication are doxorubicin, bleomycin, lomustine, vincristine, cyclophosphamide, dacarbazine, vindesine, etoposide, ifosfamide, procarbazine and vinblastine; and also the immune checkpoint inhibitor nivolumab; the glucocorticoids prednisone and prednisolone; and the antibody-drug conjugate brentuximab vedotin.

No medicinal therapies, with the exception of procarbazine, are approved for the treatment of relapsed and refractory classical Hodgkin lymphoma in children.

on 2. Radiotherapy, surgical resection, as well as allogeneic and autologous stem cell transplantation are considered non-medicinal treatments in the therapeutic indication.

on 3. The following resolutions or guidelines of the G-BA for medical products and non-medicinal treatments are available:

- Methods Hospital Treatment Policy: Allogeneic unrelated donor stem cell transplantation for Hodgkin lymphoma in adults, resolution of 20.12.2012
- Resolution of 16 May 2013 on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V – brentuximab vedotin
- Resolution of 19 January 2017 on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V – brentuximab vedotin
- Resolution of 15 June 2017 on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V – nivolumab
- Resolution of 17 November 2017 on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V – pembrolizumab

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

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.

The appropriate comparator therapy was determined separately for adult patients and for children and adolescent patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

a) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option

According to current guideline recommendations, patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option should be treated with brentuximab vedotin, vinblastine, vinorelbine, gemcitabine, bendamustine, lenalidomide, and etoposide.

The active ingredients vinorelbine, gemcitabine, bendamustine and lenalidomide are not approved for the present indication. There is a discrepancy between medicinal products approved in the indication and medicinal products used in health care/recommended in guidelines.

The following treatment options are considered adequate as comparators in a clinical study:

- radiotherapy,
- brentuximab vedotin,
- vinblastine,
- vinorelbine,
- gemcitabine,
- bendamustine,
- lenalidomide,
- etoposide,
- autologous stem cell transplantation (after remission has been achieved),
- allogeneic stem cell transplantation (after remission has been achieved).

From a clinical point of view, allogeneic or autologous stem cell transplantation are among the therapeutic options in this therapeutic indication, but they do not represent a regular standard. Since (further) autologous or allogeneic stem cell transplantation can be considered for a part of the patients with achieved remission, autologous and allogeneic stem cell transplantation is suitable as comparators in the context of therapy according to the doctor's instructions in the designated therapeutic indication for adults.

Overall, the named treatment options provide multiple therapeutic options for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option. No objective, patient-individual criteria can be identified that should be considered when deciding between therapy options in patients in the therapeutic indication. Therefore, the G-BA determines a therapy according to the doctor's instructions as an appropriate comparator therapy for which the comparators mentioned above can be taken into account. The additional benefit should be demonstrated in a multicomparator study.

b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

No medicinal therapies, except for procarbazine, are approved for the treatment of relapsed and refractory classical Hodgkin lymphoma in children. The active ingredients named in the therapy recommendations are also not approved for treating relapsed and refractory classical Hodgkin lymphoma in children, except procarbazine.

The following treatments are considered adequate comparators in a clinical study:

- chemotherapy (suitable induction and high-dose chemotherapy regimens in each case)
  - induction chemotherapy: platinum-containing regimens, ifosfamide-etoposide-containing regimens, gemcitabine-containing regimens)
  - high-dose chemotherapy: in particular, BEAM
- radiation,
- stem cell transplantation (autologous or allogeneic stem cell transplantation; after remission has been achieved),
- brentuximab vedotin in combination with appropriate chemotherapeutic agents, e.g. brentuximab vedotin in combination with bendamustine
- immune checkpoint inhibitors: nivolumab

In contrast to the original definition of the comparators considered adequate in the context of a clinical study for the population of paediatric patients, it is clarified with regard to the use of brentuximab vedotin that it should not be used in monotherapy, but only in combination with suitable chemotherapeutic agents. The amendment takes into account the statements presented by scientific-medical societies regarding the appropriate use of brentuximab vedotin in paediatric patients.

No objective, patient-individual criteria can be identified that should be taken into account when deciding between therapy options in patients in the therapeutic indication. Therefore, the G-BA determines a therapy according to the doctor's instructions as an appropriate comparator therapy for which the comparators mentioned above can be taken into account. The additional benefit should be demonstrated in a multicomparator study.

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

2.1.3 Extent and probability of the additional benefit

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

a1) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is the appropriate therapy as determined by doctor's instructions.

Hint of a considerable additional benefit

a2) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is not the appropriate therapy as determined by doctor's instructions.

An additional benefit is not proven.

(b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option

An additional benefit is not proven.

Justification:

Overall, brentuximab vedotin as monotherapy represents a relevant comparator therapy for adults, especially for patients with previous ASCT. In principle, however, another ASCT can be considered as a therapy option for adults with late relapse after an ASCT. For adults who are not eligible for SCT and are in later lines of therapy, additional treatment options are available. Therefore, the restriction of the comparator therapy to brentuximab vedotin in the KEYNOTE 204 study does not represent a complete implementation of therapy according to the doctor's instructions. Consequently, the KEYNOTE 204 study only allows statements on the additional benefit of pembrolizumab for adults for whom brentuximab vedotin is a suitable treatment option according to doctor's instructions. Therefore, the G-BA considers a subdivision of the patient population concerning the implementation of therapy according to the doctor's instructions to be appropriate:

a1) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is the appropriate therapy as determined by doctor's instructions.

and

a2) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is not the appropriate therapy as determined by doctor's instructions.

a1) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is the appropriate therapy as determined by doctor's instructions.

Study Description:

For the proof of the additional benefit of pembrolizumab compared to the appropriate comparator therapy, the pharmaceutical company has submitted results of the randomised, actively controlled open-label study KEYNOTE 204 comparing pembrolizumab with brentuximab vedotin.

The study included adult patients with relapsed (progression of the disease after the last therapy) or refractory (lack of partial or complete response after the last therapy) classical Hodgkin lymphoma (rrHL).

Patients should not be eligible for auto- or allo-SCT at the time of enrolment. A total of 204,304 patients were enrolled in the KEYNOTE study and randomised in a 1:1 ratio to treatment with pembrolizumab (151 patients) and brentuximab vedotin (153 patients). The characteristics of previous ASCT (yes vs no) and disease status after first-line therapy (primary refractory vs early relapse < 12 months after first-line therapy vs late relapse ≥ 12 months after first-line therapy) were used for stratification.

According to the approved therapeutic indication, only patients with relapsed or refractory classical Hodgkin lymphoma treated with ≥ 2 prior therapies are relevant. However, the KEYNOTE 204 study also included patients who were treated only with prior chemotherapy. For the benefit assessment, the results for the relevant sub-population were therefore taken from the subgroup analyses of the pharmaceutical company (patients with at least 2 previous therapies). The relevant sub-population includes 124 (82.1% of the total population) patients in the pembrolizumab arm and 125 (81.7% of the total population) patients in the brentuximab vedotin arm.

For the patients in the relevant sub-population, it can be assumed with sufficient certainty that brentuximab vedotin is the appropriate therapy according to the doctor's instructions, based on the specific inclusion and exclusion criteria of the KEYNOTE-204 study and the baseline characteristics.

The treatment with pembrolizumab as well as brentuximab vedotin in the KEYNOTE 204 study was largely carried out according to the information provided in the product information.

The primary endpoints of the KEYNOTE 204 study are progression-free survival (PFS) and overall survival. Patient-relevant secondary endpoints are symptomatology, health status, B symptoms, health-related quality of life, and adverse events.

Observation times for the endpoints side effects were collected for the period of treatment with the study medication (plus 30 days or 90 days for SAEs).

Endpoints on morbidity (excluding B symptoms) and health-related quality of life were collected up to a maximum of 1 year and at treatment discontinuation (plus 30 days). This results in incomplete data collection of these endpoints for the treatment period with the study medication for those patients who were treated for > 1 year in the KEYNOTE 204 study.

For the KEYNOTE 204 study, 2 data cut-offs are available presently:

- 1. Data cut-off (16.10.2018): a priori planned interim analysis 3 months after all patients were enrolled and 110 PFS events were observed
- 2. Data cut-off (16.01.2020): a priori planned interim analysis after approximately 176 PFS events

The KEYNOTE 204 study is still ongoing, and recruitment has been completed. The final analysis is planned when 146 deaths have occurred; so far, 43 deaths have occurred. In advance, 2 more interim analyses are planned. In the present benefit assessment, the study results for the 2nd data cut-off are assessed.

Extent and probability of the additional benefit

Mortality

For the endpoint overall survival, no data were available in the dossier, which is why the death rate was considered a substitute for the benefit assessment. The results on deaths were taken from the data on study discontinuations and are only available for the total population.

For overall mortality, there was no statistically significant difference between treatment groups considering the total population.

So far, the percentages of patients who died are very small; final analyses on the endpoint overall survival are still pending.

Morbidity

Health status (EQ-5D VAS)

In the KEYNOTE 204 study, health status was assessed using the EQ-5D VAS questionnaire for the relevant sub-population.

In the dossier, the pharmaceutical company presented responder analyses operationalised as the time to first deterioration, defined as a decrease in score by ≥ 7 points and ≥ 10 points compared with baseline. These responder analyses are used for the benefit assessment.

For patients in the KEYNOTE 204 study, there was no statistically significant difference between treatment groups for both a ≥ 7 point and ≥ 10 point decrease in score.

Therefore, there is neither an advantage nor a disadvantage for pembrolizumab about the endpoint health status.

Symptomatology

Symptoms were assessed in the KEYNOTE 204 study using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30.

For EORTC QLQ-C30 and -QLQ-C30, the pharmaceutical company submitted responder analysis for time to first deterioration (defined as an increase in score of at least 10 points from baseline) in the dossier for the benefit assessment.

For the endpoints exhaustion, pain and loss of appetite, there was a statistically significant difference in the benefit of pembrolizumab over brentuximab vedotin for the relevant sub-population.

In the overall assessment, although the reliability of data is limited, there are large positive effects on individual endpoints in some cases.

B symptoms

There is no significant difference between the treatment groups for the relevant sub-population for the endpoint time to the first occurrence of at least one B-symptom. With regard to the endpoint B symptoms, there is, therefore, neither an advantage nor a disadvantage for pembrolizumab.

Overall, there was a significant improvement in the symptomatology with pembrolizumab in the category morbidity compared to brentuximab vedotin.

Quality of life

The functional scales of the disease-specific questionnaire EORTC QLQ-C30 were used to assess health-related quality of life in the KEYNOTE 204 study. For the benefit assessment, the pharmaceutical company submitted responder analysis for time to first deterioration (defined as a decrease in score of at least 10 points from baseline) in the dossier.

For the endpoints global health status, physical, emotional, social, and role functioning, there was a statistically significant difference in the benefit of pembrolizumab over brentuximab vedotin.

For the endpoint cognitive functioning, no statistically significant difference was detected between the study arms.

Overall, in the category quality of life, treatment with pembrolizumab showed consistent and significant positive effects on several endpoints with limited data reliability.

There is a clear advantage of pembrolizumab concerning health-related quality of life compared to treatment with brentuximab vedotin.

Side effects

Adverse events

In the KEYNOTE 204 study, 97.5% of patients experienced an adverse event in the intervention arm. In the comparator arm, this was 95.2% of patients. The results for the endpoint Total adverse events are only presented additionally.

Severe AEs (CTCAE grade ≥ 3)

For the endpoint severe AEs (CTCAE grade ≥ 3), there is a statistically significant difference in the benefit of pembrolizumab compared to brentuximab vedotin for the relevant sub-population.

SAEs and discontinuation due to AEs

For the endpoints SAEs and discontinuation due to AEs, there was no statistically significant difference between the treatment groups for the relevant sub-population.

Immune-mediated SAEs, immune-mediated severe AEs (CTCAE grade ≥ 3)

There was no statistically significant difference between the treatment groups for the endpoints immune-mediated SAEs and immune-mediated severe AE.

Specific AEs

Selection of specific AEs is not possible because data on frequent AEs, severe AEs (CTCAE grade ≥ 3) and SAEs are incomplete for the relevant sub-population. This results from the fact that the evaluations of the relevant sub-population were taken from the subgroup analyses of the pharmaceutical company. However, in the dossier subgroup, analyses are only available for frequent AEs / severe AEs / SAEs, for which a statistically significant difference between the treatment groups was shown in the overall population.

In the statement, the pharmaceutical company selectively submits data only for the neuropathies (PTs peripheral neuropathy and peripheral sensory neuropathy). The results on neuropathies are therefore not used for the benefit assessment.

Although a statistically significant advantage can be observed for pembrolizumab compared to brentuximab vedotin for severe AEs (CTCAE grade ≥ 3), this advantage is not sufficient in terms of its effect size to establish a difference relevant for the benefit assessment for the entire endpoint category.

Thus, neither a relevant advantage nor disadvantage can be identified for pembrolizumab compared to brentuximab vedotin in this endpoint category.

Overall assessment

For the assessment of the additional benefit of pembrolizumab compared to brentuximab vedotin, results on mortality (overall survival), morbidity (health status, symptomatology), health-related quality of life and side effects are available from the open-label, randomised, controlled study KEYNOTE 204.

About mortality, neither an advantage nor a disadvantage can be identified for pembrolizumab compared to brentuximab vedotin. So far, the percentages of patients who died are very small; final analyses on the endpoint overall survival are still pending.

In the morbidity category, positive effects of treatment with pembrolizumab were observed for the endpoints exhaustion, pain and appetite loss. Overall, these will be evaluated as a significant improvement in symptomatology.

For the health-related quality of life, positive effects of treatment with pembrolizumab were observed for the endpoints global health status, emotional, social, physical and role functioning. Overall, these are rated as a significant improvement in health-related quality of life.

For the endpoint category side effects, there was no statistically significant difference between the study arms for serious AEs, discontinuations due to AEs, endpoint immune-mediated SAEs, and immune-mediated severe AEs. There is a statistically significant difference in the benefit of pembrolizumab compared to brentuximab vedotin for severe adverse events (CTCAE grade ≥ 3). However, in terms of its effect size, this benefit is insufficient to establish a difference relevant to the benefit assessment for the entire endpoint category. Thus, neither a relevant advantage nor disadvantage can be identified for pembrolizumab compared to brentuximab vedotin in this endpoint category.

The overall assessment takes into account that there are significant advantages of pembrolizumab compared to brentuximab vedotin in the endpoint categories morbidity and quality of life.

In the overall assessment of the available results, the G-BA found a considerable additional benefit for pembrolizumab compared to brentuximab vedotin in the treatment of patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is the appropriate therapy according to doctor's instructions.

Reliability of data (probability of additional benefit)

The present evaluation is based on the results of an open-label, randomised controlled study. The cross-endpoint risk of bias is rated as low for the study.

In the endpoint categories morbidity and health-related quality of life, the results for the EORTC QLQ-C30 can be assumed to have a high risk of bias. On the one hand, this is due to the lack of blinding in the subjective endpoint survey and, on the other hand, to the sharply declining return rates of the questionnaire throughout the study, which were differential between the study arms.

For the endpoints on symptomatology and health-related quality of life, systematically shortened observation times are available because the survey on the EORTC QLQ C30 questionnaire was conducted until disease progression or up to a maximum of 1 year, as well as at therapy discontinuation and 30 days after that. Thus, complete surveys for the entire treatment period are not available for a relevant percentage of the study population that was potentially still at risk after 1 year of treatment. Therefore, it is unclear what the effects are for the entire treatment phase.

Further uncertainty arises from the fact that systematically processed data on relevant specific side effects of pembrolizumab are not available for the relevant sub-population. The pharmaceutical company submitted only selectively chosen data for the neuropathies.

The European Medicines Agency's assessment report states that the treatment effect of pembrolizumab in both the KEYNOTE 204 and KEYNOTE 087 studies compared to brentuximab vedotin tended to be less pronounced in patients in European study sites than in patients in non-European study sites. For the benefit assessment, no evaluations were submitted by the pharmaceutical company concerning the location of the study centres (Europe versus outside Europe). This results in uncertainty regarding the transferability of the study results to the health care context in Germany.

For this reason, in the overall assessment, the reliability of data on the additional benefit identified is classified as a hint.

a2) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is not the appropriate therapy as determined by doctor's instructions.

Justification:
No data are available to assess the additional benefit of pembrolizumab compared with the appropriate comparator therapy in adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is not the appropriate therapy as determined by doctor's instructions.

b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option

Justification:

There are no RCTs directly comparing pembrolizumab with the appropriate comparator therapy for the paediatric target population (children ≥ 3 years of age).

For the benefit assessment of pembrolizumab in children ≥ 3 years and adolescents with relapsed or refractory classical Hodgkin lymphoma, the pharmaceutical company intends to transfer the results in adults to children and adolescents using the data from the KEYNOTE 051 study. The KEYNOTE 051 study is an open-label, 1-arm phase 1 / 2 study investigating pembrolizumab as monotherapy in children and adolescents with various oncological indications. Only children and adolescents with relapsed and refractory classical Hodgkin lymphoma treated with at least 2 previous therapies are relevant for the benefit assessment. This sub-population was included in the cohort with a programmed cell death ligand 1 (PD-L1)-positive advanced relapsed or refractory solid tumour / other lymphomas (PD-L1-positive cohort) and was followed up after the introduction of the 7th amendments in the cohort with relapsed or refractory classical Hodgkin lymphoma (hereafter referred to as r/r c-HL cohort).

The r/r cHL cohort included children and adolescents ≥ 3 years and ≤ 18 years of age, regardless of PD-L1 status, who had either refractory classical Hodgkin lymphoma after first-line therapy or high-risk and relapsed classical Hodgkin lymphoma after first-line therapy or relapsed or refractory classical Hodgkin lymphoma after second-line therapy.

The relevant population with relapsed or refractory classical Hodgkin lymphoma is composed as follows:

- 22 patients with relapsed or refractory classical Hodgkin lymphoma, of which
  - 15 patients in the PD-L1 positive cohort and
  - 7 patients in the r/r-cHL cohort
- 3 of the 22 patients have only 1 prior therapy and are not relevant to the present therapeutic indication. It is unclear which cohort these patients were included in

The primary endpoint of the KEYNOTE 051 study is the objective response rate. Secondary patient-relevant endpoints are overall survival, B-symptomatology, and adverse events.

For the evidence transfer from adults with relapsed or refractory classical Hodgkin lymphoma (KEYNOTE 204 study) to children and adolescents, the pharmaceutical company attempts to transfer the findings to the additional benefit pembrolizumab in adults to children and adolescents using all endpoints for which there are results in both studies.

The pharmaceutical company justifies the transfer of results from adults to children and adolescents based on the comparability of both populations concerning the mechanism of action of pembrolizumab, the clinical picture of relapsed or refractory classical Hodgkin lymphoma, as well as based on similarly directed effects of pembrolizumab with regard to efficacy and safety in adults as well as children and adolescents. A comparable clinical picture and comparable efficacy and safety are important minimum requirements for the G-BA for a transfer of evidence.

Taken together, however, the concrete implementation of evidence transfer by the pharmaceutical company is not considered appropriate for the important reasons described below:

For an evidence transfer in the benefit assessment, the appropriate comparator therapy defined by the G-BA must be identical for both children and adults as a further decisive criterion. In the KEYNOTE 204 study in adult patients with relapsed or refractory classical Hodgkin lymphoma, brentuximab vedotin was used as a comparator. According to the statements of the scientific-medical societies at the oral hearing, brentuximab vedotin monotherapy is not a suitable, appropriate comparator therapy in the designated therapeutic indication in children. Instead, brentuximab vedotin should only be used in the therapeutic indication in children in combination with suitable chemotherapeutic agents (see also under Derivation of the appropriate comparator therapy, point 4). Thus, the appropriate comparator therapy for the adult and paediatric population differs regarding the medicinal product brentuximab vedotin. Thus, a transfer of evidence from the adult study to the paediatric population is not possible.

In addition, the adult and paediatric study populations differ in that a relevant percentage of the paediatric population has already been pretreated with brentuximab vedotin. There is no additional benefit for adult patients pretreated with brentuximab vedotin (resolution of 17.11.2017; pembrolizumab in Hodgkin lymphoma) that could be transferred to the paediatric population.

The standards to be applied for the acceptance of evidence based on a low degree of evidence will also consider the specificities and limitations of the conduct of paediatric clinical studies.

Overall, based on the evidence transfer, no additional benefit of pembrolizumab compared with the appropriate comparator therapy can be derived in children and adolescents.

Considering the severity of the disease and the statements of the scientific-medical societies, pembrolizumab may be a relevant therapeutic option for paediatric patients with relapsed or refractory classical Hodgkin lymphoma in individual cases in the patient-individual assessment.

2.1.4 Summary of the assessment

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

"KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option."

In the therapeutic indication to be considered, 3 patient groups were distinguished:

a1) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is the appropriate therapy as determined by doctor's instructions.

a2) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is not the appropriate therapy as determined by doctor's instructions.

(b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option

Patient populations a1)

The appropriate comparator therapy was determined to be a therapy according to doctor's instructions.

In the context of therapy, according to doctor's instructions, the treatment options radiotherapy, brentuximab vedotin, vinblastine, vinorelbine, gemcitabine, bendamustine, lenalidomide, etoposide, as well as autologous and allogeneic stem cell transplantation (in each case after remission has been achieved) were designated as suitable comparators.

For the patients considered in patient population a1, brentuximab vedotin is the appropriate therapy according to doctor's instructions.

For this patient group, the pharmaceutical company presents the open randomised controlled study KEYNOTE 204, in which pembrolizumab was compared with brentuximab vedotin.

About mortality, neither an advantage nor a disadvantage can be identified for pembrolizumab compared to brentuximab vedotin. So far, the percentages of patients who died are very small; final analyses on the endpoint overall survival are still pending.

For the endpoint categories morbidity and health-related quality of life, positive effects of treatment with pembrolizumab are shown, which are assessed as a significant improvement overall.

In the overall assessment of the endpoint category side effects, neither relevant advantages nor disadvantages can be identified for the benefit assessment for pembrolizumab compared to brentuximab vedotin.

In the overall assessment of the available results, the G-BA found a considerable additional benefit for pembrolizumab compared to brentuximab vedotin in the treatment of patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell

transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is the appropriate therapy according to doctor's instructions.

The risk of bias is considered high. Thus, a hint can be derived regarding the reliability of data.

Patient populations a2)

The appropriate comparator therapy was determined to be a therapy according to doctor's instructions.

In the context of therapy, according to doctor's instructions, the treatment options radiotherapy, brentuximab vedotin, vinblastine, vinorelbine, gemcitabine, bendamustine, lenalidomide, etoposide, as well as autologous and allogeneic stem cell transplantation (in each case after remission has been achieved) were designated as suitable comparators.

For the patients considered in patient population a2, brentuximab vedotin is not the appropriate therapy according to doctor's instructions.

No data are available to assess the additional benefit of pembrolizumab compared with the appropriate comparator therapy in adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is not the appropriate therapy as determined by doctor's instructions.

Therefore, an additional benefit is not proven for pembrolizumab.

Patient population b)

The appropriate comparator therapy was determined to be a therapy according to doctor's instructions.

In the context of therapy, according to the doctor's instructions, the treatment options chemotherapy (in each case suitable induction and high-dose chemotherapy regimens), radiation, autologous or allogeneic stem cell transplantation in each case after achieved remission, brentuximab vedotin in combination with suitable chemotherapeutic agents as well as nivolumab were named as suitable comparators.

The pharmaceutical company intends to transfer the results in adults for the benefit assessment of pembrolizumab in children ≥ 3 years and adolescents with relapsed or refractory classical Hodgkin lymphoma (KEYNOTE 204) to children and adolescents using the data from the KEYNOTE 051 study. The KEYNOTE 051 study is an open-label, 1-arm phase 1 / 2 study investigating pembrolizumab as monotherapy in children and adolescents with various oncological indications.

The concrete implementation of the evidence transfer by the pharmaceutical company is not considered appropriate since the appropriate comparator therapy for children and adults defined by the G-BA is not identical with regard to the use of brentuximab vedotin. In the KEYNOTE 204 study in adult patients with relapsed or refractory classical Hodgkin lymphoma, brentuximab vedotin as monotherapy was used as a comparator. According to the statements of the scientific-medical societies at the oral hearing, brentuximab vedotin monotherapy is not a suitable, appropriate comparator therapy in the designated therapeutic indication in children. Instead, brentuximab vedotin should be used in the therapeutic indication in children only in combination with appropriate chemotherapeutic agents. Thus, the appropriate

comparator therapy for the adult and paediatric population differs regarding the medicinal product brentuximab vedotin. Thus, a transfer of evidence from the adult study to the paediatric population is not possible. Therefore, an additional benefit is not proven.

Pembrolizumab may represent, in individual cases, a relevant therapeutic option in the present therapeutic indication for paediatric patients.

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 number of patients in the SHI target population derived by the pharmaceutical company in the present procedure represents an underestimate because patients who were newly diagnosed before the year under review and who fall into the target population of pembrolizumab in the year under review were not taken into account.

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: 26 May 2021):

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

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, or specialists in paediatrics and adolescent medicine specialising in paediatric haematology and oncology experienced in the treatment of patients with classical Hodgkin lymphoma (cHL).

In addition, for the treatment of children and adolescents, the requirements for paediatric oncology must be observed according to the guideline.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient pass. The training material for health professionals and the patient pass contain, in particular, instructions on the management of immune-mediated side effects potentially occurring with KEYTRUDA as well as on infusion-related reactions.

The prescribing doctor must discuss with the patient the risks of therapy with KEYTRUDA. The patient pass should be made available to the patient.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 September 2021).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-

individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The (daily) doses in the product information were used as the calculation basis.

The average body measurements were applied for dosages depending on body weight or surface (average body height of adults: 1.72 m, average adult body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916). An average body weight of 16.2 kg was used for children aged 3 years and an average bodyweight of 67.0 kg for adolescents aged 17 years.[2]

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
a) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option				
Pembrolizumab	1 x per 21 day cycle	17.4 cycles	1	17.4
	or			
	1 x per 42 day cycle	8.7 cycles	1	8.7
b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.				
Pembrolizumab	1 x per 21 day cycle	17.4 cycles	1	17.4
Appropriate comparator therapy				
a) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option				
Therapy according to doctor's instructions[a]				
Brentuximab vedotin	1 x per 21 day cycle	17.4 cycles	1	17.4

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Vinblastine	max. 1 x per 7 day cycle[3]	52.1 cycles	1	52.1
Radiotherapy	patient-individual			
allogeneic stem cell transplantation	patient-individual			
autologous stem cell transplantation	patient-individual			
b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.				
Therapy according to doctor's instructions[b]	patient-individual			
[a] Costs are presented only for the active ingredients brentuximab vedotin and vinblastine. In addition to these, the medicinal products etoposide, vinorelbine, gemcitabine, bendamustine and lenalidomide also represent suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products. [b] All medicinal therapies that represent a suitable comparator for the present benefit assessment in the context of therapy according to doctor's instructions are not approved in the present therapeutic indication, which is why no costs are presented for these medicinal products				

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
a) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option					

3 According to product information (Teva, last revision January 2020), it is recommended not to use vinorelbine more frequently than once in a 7-day period. The administration can also take place less frequently.

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
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
b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.					
Pembrolizumab	2 mg/ kg = 32.4 mg - 134 mg	32.4 mg - 134 mg	1 x 100 mg- 2 x 100 mg	17.4	17.4 x 100 mg- 34.8 x 100 mg
Appropriate comparator therapy					
a) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option					
Therapy according to doctor's instructions[a]					
Brentuximab vedotin	1.8 mg/kg = 138.6 kg	138.6 kg	3 x 50 mg	17.4	52.2 x 50 mg
Vinblastine	4 mg/m2 - 6 mg/m2	7.6 mg - 11.4 mg	1 x 10 mg- 2 x 10 mg	52.1	52.1 x 10 mg- 104.2 x 10 mg
Radiotherapy	patient-individual				
allogeneic stem cell transplantation	patient-individual				
autologous stem cell transplantation	patient-individual				
b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.					

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Therapy according to doctor's instructions[b]	patient-individual				

[a] Costs are presented only for the active ingredients brentuximab vedotin and vinblastine. In addition to these, the medicinal products etoposide, vinorelbine, gemcitabine, bendamustine and lenalidomide also represent suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products.

[b] All medicinal therapies that represent a suitable comparator for the present benefit assessment in the context of therapy according to a doctor's instructions are not approved in the present therapeutic indication, which is why no costs are presented for these medicinal products

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
a) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and					

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
b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.					
Pembrolizumab 100 mg	1 CIS	€ 3,037.06	€ 1.77	€ 170.17	€ 2,865.12
Appropriate comparator therapy					
a) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option					
Therapy according to doctor's instructions[a]					
Brentuximab vedotin 50 mg	1 PIC	€ 3,429.04	€ 1.77	€ 192.56	€ 3,234.71
Vinblastine 10 mg	1 VIA	€ 129.90	€ 1.77	€ 15.04	€ 113.09
Radiotherapy	patient-individual				
allogeneic stem cell transplantation	patient-individual				
autologous stem cell transplantation	patient-individual				
b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.					
Therapy according to doctor's instructions[b]	patient-individual				
[a] Costs are presented only for the active ingredients brentuximab vedotin and vinblastine. In addition to these, the medicinal products etoposide, vinorelbine, gemcitabine, bendamustine and lenalidomide also represent suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products. [b] All medicinal therapies that represent a suitable comparator for the present benefit assessment in the context of therapy according to a doctor's instructions are not approved in the present therapeutic indication, which is why no costs are presented for these medicinal products					
Abbreviations: VIA = vials; CIS = concentrate for the preparation of an infusion solution; PIC = powder for the preparation of an infusion solution concentrate					

LAUER-TAXE® last revised: 1 September 2021

Costs for additionally required SHI services:

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

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

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

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe)(Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but instead follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy sales price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 26 May 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy defined by the G-BA took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 7 April 2021.

On 30 March 2021, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 31 March 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 June 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 01 July 2021. The deadline for submitting written statements was 22 July 2021.

The oral hearing was held on 9 August 2021.

By letter dated 09 August 2021, the IQWiG was commissioned with a supplementary assessment. The addenda prepared by IQWiG was submitted to the G-BA on 23 August 2021.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 September 2021, and the proposed resolution was approved.

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

Chronological course of consultation

Session	Date	Subject of consultation
Sub-committee Medicinal product	26 May 2020	Determination of the appropriate comparator therapy
Sub-committee Medicinal product	7 April 2021	New determination of the appropriate comparator therapy
Working group Section 35a	4 August 2021	Information on statements received; preparation of the oral hearing
Sub-committee Medicinal product	9 August 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 August 2021 1 September 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Sub-committee	7 September 2021	Final discussion of the draft resolution

Medicinal product		
Plenum	16 September 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 September 2021

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

Prof. Hecken