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: biliary tract carcinomas, first-line, combination with gemcitabine and cisplatin)

of 20 June 2024

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

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

On 11 December 2023, pembrolizumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 29 December 2023, the pharmaceutical company has submitted a dossier in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication) in accordance with Section 4, paragraph 3, No.2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with

Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with the new therapeutic indication:

"KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults."

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The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 April 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

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

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

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

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

KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

Therapeutic indication of the resolution (resolution of 20 June 2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with locally advanced unresectable or metastatic biliary tract carcinoma; first-line treatment

Appropriate comparator therapy for pembrolizumab in combination with gemcitabine and cisplatin:

- Cisplatin in combination with gemcitabine (cf. Annex VI to Section K of the Pharmaceuticals Directive)

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. In addition to pembrolizumab, only the active ingredient durvalumab is approved for the present therapeutic indication.

on 2. Non-medicinal treatment is not considered.

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

- Durvalumab: resolution of 5 October 2023

Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (off-label use, last revised: 24 June 2023):

- XXI. Cisplatin in combination with gemcitabine for advanced carcinomas of the gall bladder and bile ducts: systemic, medicinal first-line chemotherapy with cisplatin plus gemcitabine in patients with locally advanced, unresectable, relapsed or metastatic carcinomas of the gall bladder and/or bile ducts.

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 indication according to Section 35a paragraph 7 SGB V (see “Information on Appropriate Comparator Therapy”).

Against the background of the therapy carried out in the intervention arm with pembrolizumab in combination with gemcitabine and cisplatin, it is assumed that the patients are eligible for intensive combination chemotherapy with regard to any comorbidity and the general condition.

In addition to pembrolizumab in combination with gemcitabine and cisplatin, durvalumab in combination with gemcitabine and cisplatin is also approved in the present therapeutic indication. In the benefit assessment, an indication of a minor additional benefit of durvalumab in combination with gemcitabine and cisplatin over cisplatin in combination with gemcitabine was identified by resolution of 5 October 2023.

In addition, the combination therapy of cisplatin and gemcitabine can be prescribed for advanced carcinomas of the gall bladder and biliary tract in accordance with Annex VI to Section K of the Pharmaceuticals Directive. This is based on an assessment by the Off-label expert group in the specialist area of oncology in accordance with Section 35c, paragraph 1 SGB V, according to which the combination of cisplatin and gemcitabine is associated with an prolongation of survival time compared to monotherapy with gemcitabine.

The S3 guideline and international guidelines recommend a combination therapy consisting of durvalumab, cisplatin and gemcitabine. This also corresponds to the written statements of the Drugs Commission of the German Medical Association (AkdÄ) and the scientific-medical societies (Working Group for Internal Oncology (AIO) of the German Cancer Society (DKG), German Society for Haematology and Medical Oncology (DGHO), German Society for Gastroenterology and Digestive and Metabolic Diseases (DGVS); hereinafter: scientific-medical societies) on the question of comparator therapy and the current statements of the scientific-medical societies in the present procedure.

In this regard, the scientific-medical societies stated in the present procedure that the previous standard in first-line systemic therapy was the combination of cisplatin and gemcitabine. However, this changed in 2023 with the marketing authorisation of durvalumab in combination with cisplatin and gemcitabine.

Taking into account the result of the benefit assessment completed by resolution of 5 October 2023 and the recently adapted guideline recommendations, durvalumab in combination with gemcitabine and cisplatin is still classified as a relatively new therapy option, which is not defined as an appropriate comparator therapy for the present benefit assessment.

For the above-mentioned reasons, the present benefit assessment procedure is based on cisplatin in combination with gemcitabine as the appropriate comparator therapy.

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

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

2.1.3 Extent and probability of the additional benefit

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

Adults with locally advanced unresectable or metastatic biliary tract carcinoma; first-line treatment

Indication of a minor additional benefit

Justification:

For the proof of the additional benefit of pembrolizumab, the pharmaceutical company presented the results of the KEYNOTE-966 study started in September 2019.

KEYNOTE-966 is an ongoing, multicentre, double-blind, randomised controlled phase III study, comparing pembrolizumab in combination with gemcitabine and cisplatin to cisplatin in combination with gemcitabine. Adults with advanced unresectable or metastatic biliary tract carcinoma who have not previously received systemic therapy for advanced unresectable or metastatic disease are being investigated.

The study consists of 2 cohorts: a global cohort and a Chinese extension cohort. For the benefit assessment, the pharmaceutical company only presented the global cohort. 1,069 patients were enrolled in this and randomised in a 1:1 ratio to either treatment with pembrolizumab in combination with gemcitabine and cisplatin (N = 533) or treatment with cisplatin in combination with gemcitabine (N = 536).

The study is being conducted in 185 study sites across Australia, Asia, Europe, North America and South America.

The present benefit assessment is based on the results of the final data cut-off from 15.12.2022.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall survival, there was a statistically significant difference to the advantage of pembrolizumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine.

Although the prolongation of survival time achieved is assessed as a relevant improvement, its extent is minimal.

Morbidity

Progression-free survival (PFS)

PFS was operationalised in the KEYNOTE-966 study as the time from randomisation to the first documentation of disease progression or death from any cause, whichever occurs first.

There is a statistically significant difference to the advantage pembrolizumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" was already assessed as an independent endpoint in the present study via the endpoint "overall survival". 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-BIL21)

The symptomatology of the patients is assessed in the study with the EORTC QLQ-C30 and the disease-specific additional module EORTC QLQ-BIL21.

For the benefit assessment, the pharmaceutical company submitted evaluations of the time to first deterioration by at least 10 points. These are used as basis for the present assessment.

In the EORTC QLQ-C30, for the endpoint of appetite loss, there was a statistically significant difference to the disadvantage of pembrolizumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine.

In the disease-specific additional module EORTC QLQ-BIL21, for the endpoints of fatigue, jaundice and side effect of the treatment, there was a statistically significant difference to the disadvantage of pembrolizumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine. With regard to the assessment of the results on the endpoint of side effect of the treatment, there are uncertainties both for the morbidity endpoint and for safety endpoints due to a possible double collection of these events.

Health status (assessed by EQ-5D VAS)

The health status is assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. Evaluations of the time to first deterioration by at least 15 points were submitted by the pharmaceutical company and used as a basis for the present assessment.

For the endpoint of health status, there is no statistically significant difference between the treatment groups.

Overall, in the morbidity endpoint category for pembrolizumab in combination with gemcitabine and cisplatin, there were disadvantages in the symptomatology for the endpoints of appetite loss, fatigue, jaundice and side effect of the treatment.

Quality of life

The quality of life of patients is assessed in the KEYNOTE-966 study using functional scales of the EORTC QLQ-C30 questionnaire and the disease-specific additional module EORTC QLQ-BIL21.

For the benefit assessment, evaluations of the time to first deterioration by at least 10 points were submitted by the pharmaceutical company and used as a basis for the present assessment.

There was no statistically significant difference between the treatment groups for any of the scales of the health-related quality of life.

Overall, there was neither an advantage nor a disadvantage of pembrolizumab in combination with gemcitabine and cisplatin with regard to health-related quality of life.

Side effects

Adverse events 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), therapy discontinuation due to AEs

There were no statistically significant differences between the treatment arms for the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs.

Specific AEs

Immune-mediated severe AEs (CTCAE grade ≥ 3)

For the endpoint of immune-mediated severe AEs, there was a statistically significant difference to the disadvantage of pembrolizumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine.

Immune-mediated SAEs

For the endpoint of immune-mediated SAEs, there was no statistically significant difference between the treatment groups.

Rash (UEs), cardiac disorders (SAEs), fever (SAEs) and reduced neutropenia (SAEs)

For the specific AEs of rash (AEs), cardiac disorders (SAEs), fever (SAEs) and neutropenia (SAEs), there was a statistically significant difference to the disadvantage of pembrolizumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine.

Liver abscess (severe AEs)

For the endpoint of liver abscess (severe AEs), there was a statistically significant difference to the advantage of pembrolizumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine.

In the overall assessment of the results on side effects, there was neither an advantage nor a disadvantage of pembrolizumab in combination with gemcitabine and cisplatin. In detail, one advantage and some disadvantages were observed in the specific AEs.

Overall assessment

For the assessment of the additional benefit of pembrolizumab in combination with gemcitabine and cisplatin, results are available from the KEYNOTE-966 study for comparison with cisplatin in combination with gemcitabine for the endpoint categories of mortality, morbidity, quality of life and side effects.

For overall survival, there was a statistically significant difference to the advantage of pembrolizumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine. Although the prolongation of survival time achieved is assessed as a relevant improvement, its extent is minimal.

In the morbidity endpoint category (surveyed using the EORTC QLQ-C30, EORTC QLQ-BIL21 and EQ 5D-VAS), pembrolizumab in combination with gemcitabine and cisplatin showed disadvantages in symptomatology for the endpoints of appetite loss, fatigue, jaundice and side effects of treatment.

With regard to the endpoint categories of health-related quality of life (surveyed using EORTC QLQ-C30 and EORTC QLQ-BIL21) and side effects, there were neither advantages nor disadvantages of pembrolizumab in combination with gemcitabine and cisplatin. In detail, one advantage and some disadvantages were observed in the specific AEs for side effects.

In the overall analysis of the present results on the patient-relevant endpoints, the advantage in overall survival is offset by disadvantages in symptomatology. However, these are not considered to be as such, so as to justify a downgrade the extent of the additional benefit.

As a result, pembrolizumab in combination with gemcitabine and cisplatin for first-line therapy of adults with unresectable or metastatic biliary tract cancer (BTC) is found to have a minor additional benefit compared to cisplatin in combination with gemcitabine.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the multicentre, randomised, controlled, double-blind KEYNOTE-966 study.

At the study level, the risk of bias is considered low.

The risk of bias for the endpoint of overall survival is rated as low.

For the other endpoint categories of morbidity, quality of life and side effects, the respective endpoint-specific risk of bias is also estimated to be low.

In the overall assessment, the reliability of data for the additional benefit determined is classified in the "indication" category.

2.1.4 Summary of the assessment

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

"KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults."

The G-BA determined cisplatin in combination with gemcitabine (cf. Annex VI to Section K of the Pharmaceuticals Directive) as the appropriate comparator therapy.

For the assessment, the pharmaceutical company submits the still ongoing, double-blind phase III KEYNOTE-966 study for the comparison of pembrolizumab in combination with gemcitabine and cisplatin versus cisplatin in combination with gemcitabine.

For overall survival, there was a statistically significant advantage for patients in the intervention arm. Although the prolongation of survival time achieved is assessed as a relevant improvement, its extent is minimal.

In the morbidity endpoint category, there were disadvantages in symptomatology (appetite loss, fatigue, jaundice and side effects of treatment).

With regard to the endpoint categories of health-related quality of life and side effects, there are neither advantages nor disadvantages of pembrolizumab in combination with gemcitabine and cisplatin. In detail, there were disadvantages and one advantage in the specific AEs for side effects.

As a result, based on the advantage in overall survival, the G-BA identified an indication of a minor additional benefit of pembrolizumab in combination with gemcitabine and cisplatin compared with cisplatin in combination with gemcitabine.

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

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

The resolution is based on the information from the dossier of the pharmaceutical company. These patient numbers are underestimated.

The significant reasons for this are the exclusion of patients who progressed to a locally advanced, unresectable or metastatic stage in the year under review and the exclusion of patients who did not receive first-line therapy but are eligible for it.

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: 29 May 2024):

https://www.ema.europa.eu/en/documents/overview/keytruda-epar-medicine-overview_en.pdf

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology as well as specialists in internal medicine and gastroenterology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with biliary tract carcinomas.
In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with pembrolizumab as well as on infusion-related reactions.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 June 2024).

The costs for the first year of treatment are shown for the cost representation in the resolution.

The two pembrolizumab doses of 200 mg every 3 weeks or 400 mg every 6 weeks recommended according to the product information are listed in the cost representation.

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.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body

weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[2].

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed:				
Pembrolizumab in combination with gemcitabine and cisplatin				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Gemcitabine	2 x per 21-day cycle	17.4	2	34.8
Cisplatin	2 x per 21-day cycle	17.4	2	34.8
Appropriate comparator therapy				
Cisplatin in combination with gemcitabine (cf. Annex VI to Section K of the Pharmaceuticals Directive)				
Cisplatin	2 x per 21-day cycle	8	2	16
Gemcitabine	2 x per 21-day cycle	8	2	16

[2] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Pembrolizumab in combination with gemcitabine and cisplatin					
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
Cisplatin	25 mg/m^2 BSA = 47.8 mg	47.8 mg	1 x 50 mg	34.8	34.8 x 50 mg
Gemcitabine	1,000 mg/m^2 BSA = 1,910 mg	1,910 mg	1 x 2,000 mg	34.8	34.8 x 2,000 mg
Appropriate comparator therapy					
Cisplatin in combination with gemcitabine (cf. Annex VI to Section K of the Pharmaceuticals Directive)					
Cisplatin	25 mg/m^2 BSA = 47.8 mg	47.8 mg	1 x 50 mg	16	16 x 50 mg
Gemcitabine	1,000 mg/m^2 BSA = 1,910 mg	1,910 mg	1 x 2,000 mg	16	16 x 2,000 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

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	€ 2,974.82	€ 2.00	€ 166.60	€ 2,806.22
Cisplatin 50 mg	1 CIS	€ 47.73	€ 2.00	€ 4.61	€ 41.12
Gemcitabine 2,000 mg	1 CIS	€ 194.23	€ 2.00	€ 8.68	€ 183.55
Appropriate comparator therapy					
Cisplatin 50 mg	1 CIS	€ 47.73	€ 2.00	€ 4.61	€ 41.12
Gemcitabine 2,000 mg	1 CIS	€ 194.23	€ 2.00	€ 8.68	€ 183.55
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 June 2024

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.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

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	Costs/ patient/ year
Medicinal product to be assessed							
Cisplatin							
17.4 cycles of 21 days each							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin.							

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	Costs/ patient/ year
The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	34.8	€ 317.03
Sodium chloride 0.9% inf. sol., 3 l - 4.4 l/day	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58	34.8	€ 340.14 -
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		€ 526.21
Appropriate comparator therapy							
Cisplatin							
8 cycles of 21 days each							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	16	€ 182.20
Sodium chloride 0.9% inf. sol., 3 l - 4.4 l/day	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58	16	€ 162.90 - € 260.64
Abbreviations: INF = infusion solution							

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 agents 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 do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (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 Designation of 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 the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates 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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with locally advanced unresectable or metastatic biliary tract carcinoma; first-line treatment

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for pembrolizumab (Keytruda); Keytruda 25 mg/ml concentrate for the preparation of an infusion solution; last revised: March 2024

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 24 October 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The working group Section 35a adapted the appropriate comparator therapy at its session on 6 December 2023.

On 29 December 2023, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 3 January 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 March 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 April 2024. The deadline for submitting statements was 23 April 2024.

The oral hearing was held on 6 May 2024.

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 11 June 2024, and the proposed resolution was approved.

At its session on 20 June 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 October 2023	Implementation of the appropriate comparator therapy
Working group Section 35a	6 December 2023	Implementation of the appropriate comparator therapy
Working group Section 35a	30 April 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 May 2024	Conduct of the oral hearing
Working group Section 35a	15 May 2024 5 June 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	11 June 2024	Concluding discussion of the draft resolution
Plenum	20 June 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 June 2024

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

Prof. Hecken