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 Tislelizumab (oesophageal squamous cell carcinoma (OSCC), PD-L1 expression TAP score ≥ 5%, first-line, combination with platinum-based chemotherapy)

of 18 June 2025

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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 all 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 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 tislelizumab (Tevimbra) was listed for the first time on 1 September 2024 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 25 November 2024, tislelizumab was granted the extension of the marketing authorisation for the therapeutic indications "Gastric or gastroesophageal junction adenocarcinoma, PD-L1 expression TAP ≥ 5, HER2-, first-line, combination with platinum- and fluoropyrimidine-based chemotherapy" and "Oesophageal squamous cell carcinoma, PD-L1 expression TAP score ≥ 5%, first-line, combination with platinum-based chemotherapy" and "Oesophageal squamous cell carcinoma, after previous therapy". The extension of the marketing authorisation for the therapeutic indications "Non-small cell lung cancer, after previous therapy", "Non-small cell lung cancer, squamous, first-line, combination with carboplatin and either paclitaxel or nab-paclitaxel" and "Non-small cell lung cancer, non-squamous, PD-L1 expression ≥ 50%, first-line, combination with pemetrexed and platinum-containing chemotherapy" was granted on 8 July

2024. The mentioned extensions of the marketing authorisation are classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 20 December 2024, the pharmaceutical company submitted in due time a dossier on tislelizumab with the therapeutic indication "Oesophageal squamous cell carcinoma, PD-L1 expression TAP score ≥ 5%, first-line, combination with platinum-based chemotherapy" in accordance with Section 4, paragraph 3, number 3 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 2 of the Rules of Procedure of the G-BA (VerfO).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 April 2025 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 tislelizumab 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. 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 tislelizumab.

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 Tislelizumab (Tevimbra) in accordance with the product information

Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a TAP score ≥ 5%.

Therapeutic indication of the resolution (resolution of 18 June 2025):

See the approved therapeutic indication.

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with unresectable, locally advanced or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have a tumour cell PD-L1 expression ≥ 1% or a combined positive score (CPS) ≥ 10; first-line therapy

Appropriate comparator therapy for tislelizumab in combination with platinum-based chemotherapy:

- Nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy (only for patients with tumour cell PD-L1 expression ≥ 1%)

or

- nivolumab in combination with ipilimumab (only for patients with tumour cell PD-L1 expression ≥ 1%)

or

- pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy (only for patients with a combined positive score (CPS) ≥ 10)

b) Adults with unresectable, locally advanced or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have no tumour cell PD-L1 expression ≥ 1% and no combined positive score (CPS) ≥ 10; first-line therapy

Appropriate comparator therapy for tislelizumab in combination with platinum-based chemotherapy:

- Cisplatin in combination with 5-fluorouracil

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.

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

On 1. In addition to tislelizumab in combination with platinum-based chemotherapy, medicinal products with the active ingredients 5-fluorouracil, cisplatin, mitomycin, nivolumab in combination with fluoropyrimidine and platinum-based combination chemotherapy, nivolumab in combination with ipilimumab and pembrolizumab in combination with fluoropyrimidine and platinum-based chemotherapy are approved in the present therapeutic indication.

On 2. A non-medicinal treatment option is not considered for the therapeutic indication in question. This does not affect the use of radiotherapy as a supportive therapy option.

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

- Pembrolizumab (resolution of 5 May 2022)
- Nivolumab (resolutions of 20 October 2022)

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 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 (see "Information on Appropriate Comparator Therapy"). A joint written statement has been issued by the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS), the Working Group for Internal Oncology of the German Cancer Society (AIO), the German Cancer Society (DKG) and the German Society for Haematology and Medical Oncology (DGHO).

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

With the German S3 guideline[2] and the ASCO guideline[3] (last revised: January 2023), two high-quality guidelines are available. According to the guidelines, the treatment decision in the first-line treatment of advanced, recurrent or metastatic oesophageal squamous cell carcinoma is largely determined by the tumour cell PD-L1 expression or the combined positive score (CPS) value. The present therapeutic indication adds a further score - the tumour area positivity (TAP) score - for determining PD-L1 expression in the tumour tissue of oesophageal squamous cell carcinomas, which is not entirely comparable with the previously used determination methods (tumour cell PD-L1 expression or CPS). Against this background and taking into account the authorisation status of the medicinal products under consideration, a distinction is made between two sub-populations for the determination of the appropriate comparator therapy depending on the previously used PD-L1 expression and CPS scores:

a) Adults with advanced, recurrent or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have a tumour cell PD-L1 expression ≥ 1% or a combined positive score (CPS) ≥ 10; first-line therapy

According to the guideline recommendations, pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy should be used for patients with metastatic or locally advanced, non-curatively treatable oesophageal squamous cell carcinoma with a PD-L1 CPS ≥ 10. In addition, the ASCO guideline recommends nivolumab in combination with platinum and fluoropyrimidine-based chemotherapy or nivolumab in combination with ipilimumab for patients with oesophageal squamous cell carcinoma with PD-L1 expression ≥ 1%. The therapies nivolumab in combination with platinum and fluoropyrimidine-based chemotherapy or nivolumab in combination with ipilimumab were not yet approved for oesophageal cancer at the time of the final coordination of the guideline commission of the German S3 guideline.

In the written statements, the scientific-medical societies state that the standard in the systemic first-line therapy of patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma depends on PD-L1 expression. Pembrolizumab in combination with platinum-containing chemotherapy and fluoropyrimidine is

[2] Guideline program in oncology (German Cancer Society, German Cancer Aid, Association of the Scientific-Medical Societies). Diagnosis and therapy of squamous cell carcinomas and oesophageal adenocarcinoma; S3 guideline, long version 3.1; June 2022

[3] Shah MA et al. Immunotherapy and targeted therapy for advanced gastroesophageal cancer: ASCO guideline. J Clin Oncol 2023:Jco2202331.

recommended at a CPS ≥ 10, as well as nivolumab in combination with platinum-containing chemotherapy and fluoropyrimidine and the chemotherapy-free option nivolumab in combination with ipilimumab (in each case, for tumour cell PD-L1 expression ≥ 1%). This significance of the checkpoint inhibitor combinations was confirmed in the statements of the scientific-medical societies in the present procedure.

The benefit assessment of pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy showed an indication of a considerable additional benefit for adults with CPS ≥ 10 compared with cisplatin in combination with 5-fluorouracil (resolution of 5 May 2022). The benefit assessment showed an indication of a considerable additional benefit of nivolumab in combination with platinum and fluoropyrimidine-based chemotherapy compared with cisplatin in combination with 5-fluorouracil for adults with tumour cell PD-L1 expression ≥ 1%. A hint for a considerable additional benefit of nivolumab in combination with ipilimumab compared to cisplatin in combination with 5-fluorouracil was identified for adults with a tumour cell PD-L1 expression ≥ 1% (resolutions of 20 October 2022).

In the overall assessment, the G-BA determined the above-mentioned therapy options as an appropriate comparator therapy in each case. In this context, individual therapy options only represent a comparator therapy for the part of the patient population that has the patient and disease characteristics specified in brackets. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

b) Adults with advanced, recurrent or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have no tumour cell PD-L1 expression ≥ 1% and no combined positive score (CPS) ≥ 10; first-line therapy

According to the S3 guideline recommendation, patients with metastatic or locally advanced, non-curatively treatable oesophageal squamous cell carcinoma with a CPS ≤ 10 may be treated with a combination therapy consisting of a platinum derivative and a fluoropyrimidine or a taxane as palliative systemic chemotherapy. According to the guideline, combination therapy of cisplatin with a fluoropyrimidine (5-fluorouracil or capecitabine) was often used in the underlying clinical studies. Capecitabine and oxaliplatin are not approved in the indication and are therefore not determined as appropriate comparator therapy.

In the written statements, the scientific-medical societies state that a combination chemotherapy of cisplatin and 5-fluorouracil is the standard for patients with a low PD-L1 expression corresponding to CPS < 10 or a tumour cell PD-L1 expression of 0. In addition, the scientific-medical societies state that the presumably equally effective combination therapy with FOLFOX - due to its lower toxicity - can also be recommended despite the unavailability of comparator data.

The combination chemotherapy FOLFOX is not approved for the present indication and is therefore not determined as an appropriate comparator therapy. The S3 guideline points out that a life-prolonging effect of systemic palliative chemotherapy for oesophageal squamous cell carcinoma is not certain. For the determination of the appropriate comparator therapy, it is assumed that the patients are eligible for cisplatin-containing chemotherapy.

In the overall assessment, the G-BA determined cisplatin in combination with 5-fluorouracil 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 tislelizumab is assessed as follows:

a) Adults with unresectable, locally advanced or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have a tumour cell PD-L1 expression ≥ 1% or a combined positive score (CPS) ≥ 10; first-line therapy

An additional benefit is not proven.

b) Adults with unresectable, locally advanced or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have no tumour cell PD-L1 expression ≥ 1% and no combined positive score (CPS) ≥ 10; first-line therapy

An additional benefit is not proven.

Justification:

The pharmaceutical company submitted the results of the randomised controlled trial RATIONALE 306 for the patient population b) for the benefit assessment of tislelizumab in combination with platinum-based chemotherapy for the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a TAP score ≥ 5%.

RATIONALE 306

The RATIONALE 306 study is a double-blind phase III study comparing tislelizumab in combination with platinum-based chemotherapy versus placebo in combination with platinum-based chemotherapy (hereinafter: chemotherapy). Chemotherapy was allocated according to the principal investigator with selection of cisplatin or oxaliplatin + 5-fluorouracil, cisplatin or oxaliplatin + capecitabine or cisplatin or oxaliplatin + paclitaxel prior to randomisation.

Patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma with PD-L1-expressing tumours (TAP score ≥ 5%) who had not yet received systemic therapy in stage IV of the disease were enrolled in the study. Of the total of 649 patients enrolled in the study, 326 patients were randomised to the intervention arm and 323 patients to the control arm.

The study was conducted at 162 study sites in Europe, Asia, Australia and North America between 2018 and 2024.

For the benefit assessment, results for the data cut-off of the 3-year follow-up from 24.11.2023 were presented.

On the assignment of the patients to patient populations a) and b) with regard to PD-L1 expression:

In the present study, the PD-L1 expression of the tumours was determined exclusively using the TAP score. The TAP score is a new method in the therapeutic indication for determining PD-L1 expression in tumour tissue. Until now, PD-L1 expression in tumour tissue has been determined as tumour cell PD-L1 expression or CPS value, in accordance with the previous marketing authorisations of PD-1/PD-L1 inhibitors.

In the dossier for the benefit assessment, the pharmaceutical company formed 2 patient groups and assigned patients with a TAP score ≥ 10% to patient group a) and patients with a TAP score ≥ 5% to < 10% to patient group b). They state that this assignment was made in accordance with the G-BA's appropriate comparator therapy.

The G-BA divided the patient population according to the therapeutic indication into the patient group a) with the characteristics "with a tumour cell PD-L1 expression ≥ 1% or a combined positive score (CPS) ≥ 10)" and b) with the characteristics "no tumour cell PD-L1 expression ≥ 1% and no combined positive score (CPS) ≥ 10". The characteristics "tumour cell PD-L1 expression" and "CPS value" named in the patient groups were not taken into account in the pharmaceutical company's division of the patient groups (exclusive consideration of the TAP score). This approach was not justified by the pharmaceutical company in the benefit assessment dossier. For the assignment of the threshold values or the agreement of the characteristics of TAP score and CPS, the pharmaceutical company only refers in Module 3 of the dossier to a study that compares TAP score and CPS in gastric and gastroesophageal junction adenocarcinomas as well as in oesophageal squamous cell carcinomas and finds a high agreement between TAP score and CPS. Information on the comparability of TAP score and tumour cell PD-L1 expression was not provided with the dossier.

It was confirmed in the oral hearing that all 3 scores for measuring PD-L1 expression in tumour tissue are currently determined and reported in clinical practice. Clinical experts have stated in this regard that there are only minor deviations between the TAP score and the CPS and that the values are considered sufficiently comparable in clinical practice according to the current state of knowledge. Regarding the comparability of tumour cell PD-L1 expression and the CPS score, it was estimated in the oral hearing that they are not comparable.

For these reasons, the pharmaceutical company's approach of assigning patients to patient groups a) and b) solely on the basis of the TAP score and not on the basis of the tumour cell PD-L1 expression and CPS scores established in the therapeutic indication for determining PD-L1 expression is considered inappropriate, in particular due to the lack of consideration of tumour cell PD-L1 expression.

Cut-off of the sub-population relevant for the benefit assessment for patient group b):

For the benefit assessment, the pharmaceutical company performed a cut-off of the study population for patient group b). The sub-population presented by the pharmaceutical company comprises 30 patients with PD-L1 expression (TAP score) ≥ 5% to < 10% who received the appropriate comparator therapy cisplatin + 5-fluorouracil. The pharmaceutical company points out in the dossier that the randomisation is broken due to the cut-off of the relevant sub-population.

a) Adults with unresectable, locally advanced or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have a tumour cell PD-L1 expression ≥ 1% or a combined positive score (CPS) ≥ 10; first-line therapy

The pharmaceutical company presented no data compared with the appropriate comparator therapy for the assessment of the additional benefit of tislelizumab in combination with platinum-based chemotherapy for patient group a).

An additional benefit for patients whose tumours express PD-L1 with a TAP score ≥ 5% and also have a tumour cell PD-L1 expression ≥ 1% or a combined positive score (CPS) ≥ 10 is therefore not proven.

b) Adults with unresectable, locally advanced or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have no tumour cell PD-L1 expression ≥ 1% and no combined positive score (CPS) ≥ 10; first-line therapy

The pharmaceutical company submitted the RATIONALE 306 study for the assessment of the additional benefit of tislelizumab in combination with platinum-based chemotherapy for patient group b). The pharmaceutical company performed a cut-off of the relevant patient population for the benefit assessment. The sub-population presented by the pharmaceutical company comprises 30 patients with PD-L1 expression (TAP score) ≥ 5% to < 10% who received the appropriate comparator therapy cisplatin + 5-fluorouracil.

In the RATIONALE 306 study, PD-L1 expression in tumour tissue was determined exclusively using the TAP score, as described above. Overall, the pharmaceutical company was unable to provide evidence that the sub-population they submitted had the characteristics "no tumour cell PD-L1 expression ≥ 1% and no CPS ≥ 10". The sub-population of the RATIONALE 306 study presented by the pharmaceutical company cannot be used for the benefit assessment especially due to the lack of consideration of the characteristic of tumour cell PD-L1 expression.

There are therefore no suitable data for an assessment of the additional benefit of tislelizumab in combination with platinum-based chemotherapy compared with the appropriate comparator therapy. An additional benefit for the patients whose tumours express PD-L1 with a TAP score ≥ 5% and also have no tumour cell PD-L1 expression ≥ 1% and no combined positive score (CPS) ≥ 10 is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is a benefit assessment of a new therapeutic indication for the active ingredient tislelizumab.

The therapeutic indication assessed here is as follows:

"Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a TAP score ≥ 5%."

In the therapeutic indication to be considered, 2 patient groups were distinguished by PD-L1 expression of the tumours:

a) Adults with unresectable, locally advanced or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have a tumour cell PD-L1 expression ≥ 1% or a combined positive score (CPS) ≥ 10; first-line therapy

b) Adults with unresectable, locally advanced or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have no tumour cell PD-L1 expression ≥ 1% and no combined positive score (CPS) ≥ 10; first-line therapy

Patient group a)

Treatment with the active ingredients nivolumab in combination with fluoropyrimidine and platinum-based combination chemotherapy or nivolumab in combination with ipilimumab or pembrolizumab in combination with fluoropyrimidine and platinum-based combination chemotherapy was determined as the appropriate comparator therapy.

No data compared to the appropriate comparator therapy were available for the benefit assessment. An additional benefit is therefore not proven.

Patient group b)

Treatment with cisplatin in combination with 5-fluorouracil was determined as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company presented the results of the RATIONALE 306 study. The pharmaceutical company was unable to provide evidence that the sub-population they submitted had the characteristics "no tumour cell PD-L1 expression ≥ 1% and no CPS ≥ 10". The sub-population of the RATIONALE 306 study presented by the pharmaceutical company cannot be used for the benefit assessment especially due to the lack of consideration of the characteristic of tumour cell PD-L1 expression. There are therefore no suitable data for an assessment of the additional benefit of tislelizumab in combination with platinum-based chemotherapy compared with the appropriate comparator therapy. An additional benefit is therefore not proven.

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

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

The resolution is based on information provided by the pharmaceutical company in the dossier on the benefit assessment. The information on patient numbers is subject to uncertainty. On the one hand, the pharmaceutical company takes into account a cross-gender percentage in their derivation for the percentage of patients with oesophageal squamous cell carcinoma. When determining the percentage of patients with locally advanced, unresectable or metastatic disease, there are uncertainties regarding the percentages of staging and progression events. On the other, there are uncertainties due to the exclusive consideration of the TAP score by the pharmaceutical company. For patient group a) with "tumour cell PD-L1 expression ≥ 1% or CPS ≥ 10", the pharmaceutical company does not consider the threshold value of tumour cell PD-L1 expression ≥ 1%. It is unclear whether patients with a tumour cell PD-L1 expression ≥ 1% and a TAP score ≥ 5% remain unconsidered. For patient group b) with "no tumour cell PD-L1 expression ≥ 1% and no CPS ≥ 10", it is unclear whether patients were

considered or not considered by non-consideration of tumour cell PD-L1 expression < 1% and exclusive consideration of TAP ≥ 5% to < 10% instead (comparable to CPS ≥ 5 to < 10).

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 Tevimbra (active ingredient: tislelizumab) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 11 June 2025):

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

Therapy with tislelizumab 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 oesophageal carcinoma.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (including patient identification card). The training material contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with tislelizumab.

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 2025).

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

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

5-fluorouracil is usually used in combination with cisplatin [...] according to the product information[4].

[4] Fluorouracil Accord 50 mg/ml solution for injection/infusion

Cisplatin is often used in the combination therapy with 5-fluorouracil at a dosage of 100 mg/m² cisplatin and 1,000 mg/m² body surface area 5-fluorouracil in 3-week cycles[5,6,7]. For the cost calculation of cisplatin in combination with 5-fluorouracil, the specified dosage regimen is shown as an example.

a) Adults with unresectable, locally advanced or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have a tumour cell PD-L1 expression ≥ 1% or a combined positive score (CPS) ≥ 10; first-line therapy

and

b) Adults with unresectable, locally advanced or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have no tumour cell PD-L1 expression ≥ 1% and no combined positive score (CPS) ≥ 10; first-line therapy

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				
Patient groups a) and b)				
Tislelizumab in combination with platinum-based chemotherapy				
Tislelizumab	1 x on day 1 of a 21-day cycle	17.4	1	17.4
Cisplatin	1 x on day 1 of a 21-day cycle	17.4	1	17.4
5-fluorouracil	1 x on day 1-5 of a 21-day cycle	17.4	5	87.0
Appropriate comparator therapy				
Patient group a)				

[5] S3 guideline - oncology guideline programme "Diagnostics and therapy of squamous cell carcinomas and adenocarcinomas of the oesophagus", long version 4.0 December 2023

[6] Grünberger B, Raderer M, Schmidinger M, Hejna M. Palliative chemotherapy for recurrent and metastatic oesophageal cancer. Anticancer Res. 2007 Jul-Aug;27(4C):2705-14. PMID: 17695436

[7] Bleiberg H, Conroy T, Paillot B, Lacave AJ, Blijham G, Jacob JH, Bedenne L, Namer M, De Besi P, Gay F, Collette L, Sahmoud T. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer. 1997 Jul;33(8):1216-20. doi: 10.1016/s0959-8049(97)00088-9. PMID: 9301445.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Nivolumab in combination with fluoropyrimidine and platinum-based combination chemotherapy				
Nivolumab	1 x per 14-day cycle	26.1	1	26.1
	or			
	1 x per 28-day cycle	13.0	1	13.0
Cisplatin[8]	1 x per 28-day cycle	13.0	1	13.0
5-fluorouracil[8]	1 x on day 1-5 of a 28-day cycle	13.0	5	65.0
Nivolumab in combination with ipilimumab				
Nivolumab	1 x per 14-day cycle	26.1	1	26.1
	or			
	1 x per 21-day cycle	17.4	1	17.4
Ipilimumab	1 x per 42-day cycle	8.7	1	8.7
Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Cisplatin[9]	1 x per 21-day cycle	17.4	1	17.4
5-fluorouracil[9]	1 x on day 1-5 of a 21-day cycle	17.4	5	87.0
Patient group b)				
Cisplatin + 5-fluorouracil				

[8] Shown as an example, based on the information under 5.1 in the product information for nivolumab.

[9] Shown as an example, based on the information under 5.1 in the product information for pembrolizumab.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
5-fluorouracil	1 x on day 1-5 of a 21-day cycle	17.4	5	87.0

Consumption:

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)[10].

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.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Patient groups a) and b)					
Tislelizumab in combination with platinum-based chemotherapy					
Tislelizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
Cisplatin	60 mg/m² = 114.6 mg – 80 mg/m² = 152.8 mg	114.6 mg – 152.8 mg	1 x 100 mg + 2 x 10 mg – 1 x 100 mg + 1 x 50 mg	17.4	17.4 x 100 mg + 34.8 x 10 mg – 17.4 x 100 mg +

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
			+ 1 x 10 mg		17.4 x 50 mg + 17.4 x 10 mg
5-fluorouracil	750 mg/m² = 1,432.5 mg – 800 mg/m² = 1,528 mg	1,432.5 mg – 1,528 mg	1 x 2,500 mg	87.0	87.0 x 2500 mg
Appropriate comparator therapy					
Patient group a)					
Nivolumab in combination with fluoropyrimidine and platinum-based combination chemotherapy					
Nivolumab	240 mg	240 mg	2 x 120 mg	26.1	52.2 x 120 mg
	or				
	480 mg	480 mg	4 x 120 mg	13.0	52.0 x 120 mg
Cisplatin[11]	80 mg/m² = 152.8 mg	152.8 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	13.0	13.0 x 100 mg + 13.0 x 50 mg + 13.0 x 10 mg

[11] Shown as an example, based on the information under 5.1 in the product information for nivolumab.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
5-fluorouracil[11]	800 mg/m² = 1,528 mg	1,528 mg	1 x 2,500 mg	65.0	65.0 x 2,500 mg
Nivolumab in combination with ipilimumab					
Nivolumab	3 mg/kg BW = 233.1 mg	233.1 mg	2 x 120 mg	26.1	52.2 x 120 mg
	or				
	360 mg	360 mg	3 x 120 mg	17.4	52.2 x 120 mg
Ipilimumab	1 mg/kg BW = 77.7 mg	77.7 mg	2 x 50 mg	8.7	17.4 x 50 mg
Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy					
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[12]	80 mg/m² = 152.8 mg	152.8 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	17.4	17.4 x 100 mg + 17.4 x 50 mg + 17.4 x 10 mg
5-fluorouracil[12]	800 mg/m² = 1,528 mg	1,528 mg	1 x 2,500 mg	87.0	87.0 x 2,500 mg
Patient group b)					
Cisplatin + 5-fluorouracil					
Cisplatin	100 mg/m² = 191 mg	191 mg	2 x 100 mg	17.4	34.8 x

[11] Shown as an example, based on the information under 5.1 in the product information for nivolumab.
[12] Shown as an example, based on the information under 5.1 in the product information for pembrolizumab.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
					100 mg
5-fluorouracil	1,000 mg/m² = 1,910 mg	1,910 mg	1 x 2,500 mg	87.0	87.0 x 2,500 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 reference prices 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					
Tislelizumab 200 mg	1 CIS	€ 2,288.43	€ 1.77	€ 127.40	€ 2,159.26
Cisplatin 100 mg	1 CIS	€ 76.59	€ 1.77	€ 3.10	€ 71.72
Cisplatin 50 mg	1 CIS	€ 47.71	€ 1.77	€ 1.73	€ 44.21
Cisplatin 10 mg	1 CIS	€ 17.53	€ 1.77	€ 0.30	€ 15.46
5-fluorouracil [13] 2,500 mg	1 SFI	€ 23.60	€ 1.77	€ 0.97	€ 20.86
Appropriate comparator therapy					
Cisplatin 100 mg	1 CIS	€ 76.59	€ 1.77	€ 3.10	€ 71.72
Cisplatin 50 mg	1 CIS	€ 47.71	€ 1.77	€ 1.73	€ 44.21
Cisplatin 10 mg	1 CIS	€ 17.53	€ 1.77	€ 0.30	€ 15.46
Ipilimumab 50 mg	1 CIS	€ 3,489.23	€ 1.77	€ 195.98	€ 3,291.48

[13] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
5-fluorouracil[13] 2,500 mg	1 SFI	€ 23.60	€ 1.77	€ 0.97	€ 20.86
Nivolumab 120 mg	1 CIS	€ 1,539.71	€ 1.77	€ 84.64	€ 1,453.30
Pembrolizumab 100 mg	2 CIS	€ 4,962.26	€ 1.77	€ 280.10	€ 4,680.39
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection					

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Costs for additionally required SHI services:

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

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

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							

[13] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
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.							
Hydration and forced diuresis *17.4 cycles* *(Tislelizumab in combination with platinum-based chemotherapy)*							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 105.54	€ 5.28	€ 4.26	€ 96.00	17.4	€ 167.04
Sodium chloride 0.9% infusion solution, 3 - 4.4 l/day	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	17.4	€ 104.66 – € 174.44
Appropriate comparator therapy							
Cisplatin							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Hydration and forced diuresis *13.0 cycles* *(Nivolumab in combination with fluoropyrimidine and platinum-based combination chemotherapy)* *Cisplatin in combination with 5-fluorouracil*							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 105.54	€ 5.28	€ 4.26	€ 96.00	13.0	€ 124.80
Sodium chloride 0.9% infusion solution, 3 - 4.4 l/day	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	13.0	€ 78.20 – € 130.33
Hydration and forced diuresis *17.4 cycles* *(Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy)* *Cisplatin in combination with 5-fluorouracil*							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 105.54	€ 5.28	€ 4.26	€ 96.00	17.4	€ 167.04

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
Sodium chloride 0.9% infusion solution, 3 - 4.4 l/day	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	17.4	€ 104.66 – € 174.44
Abbreviations: INF = infusion solution							

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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 October 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 are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 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 requirements 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:

a) Adults with unresectable, locally advanced or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have a tumour cell PD-L1 expression ≥ 1% or a combined positive score (CPS) ≥ 10; first-line therapy

   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 tislelizumab (Tevimbra); BeiGene Tevimbra 100 mg concentrate for the preparation of an infusion solution; last revised: November 2024

b) Adults with unresectable, locally advanced or metastatic, non-curatively treatable oesophageal squamous cell carcinoma, whose tumours express PD-L1 with a TAP score ≥ 5% and also have no tumour cell PD-L1 expression ≥ 1% and no combined positive score (CPS) ≥ 10; first-line therapy

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

Product information for tislelizumab (Tevimbra); BeiGene Tevimbra 100 mg concentrate for the preparation of an infusion solution; last revised: November 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 their session on 21 February 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 20 December 2024, the pharmaceutical company submitted a dossier for the benefit assessment of tislelizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 20 December 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 tislelizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 March 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 April 2025. The deadline for submitting statements was 22 April 2025.

The oral hearing was held on 5 May 2025.

On 6 May 2025, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 7 May 2025 replaces version 1.0 of the dossier assessment dated 28 March 2025. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

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 2025, and the proposed draft resolution was approved.

At their session on 18 June 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	21 February 2023	Determination of the appropriate comparator therapy
Working group Section 35a	29 April 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	5 May 2025	Conduct of the oral hearing
Working group Section 35a	13 May 2025 3 June 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	11 June 2025	Concluding discussion of the draft resolution
Plenum	18 June 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 18 June 2025

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

Prof. Hecken