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 (new therapeutic indication: gastric or gastroesophageal junction adenocarcinoma, PD-L1 expression TAP score ≥ 5, HER2-, first-line, combination with platinum and fluoropyrimidine-based chemotherapy)

of 18 June 2025

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 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 "Gastric or gastroesophageal junction adenocarcinoma, PD-L1 expression TAP ≥ 5%, HER2-, first-line, combination with platinum and fluoropyrimidine-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 and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with HER-2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (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:

Adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%; first-line therapy

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

- Nivolumab in combination with fluoropyrimidine and platinum-based combination chemotherapy (only for tumours with PD-L1 expression (CPS) ≥ 5)

  or

- pembrolizumab in combination with fluoropyrimidine and platinum-based combination chemotherapy (only for tumours with PD-L1 expression (CPS) ≥ 1)

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 tislelizumab, medicinal products containing the active ingredients capecitabine, cisplatin, docetaxel, doxorubicin, epirubicin, 5-fluorouracil, folinic acid, mitomycin, tegafur/ gimeracil/ oteracil, nivolumab, pembrolizumab and zolbetuximab are approved for the present therapeutic indication.

Cisplatin is approved as a combination therapy via the active ingredients capecitabine, S-1 (tegafur/ gimeracil/ oteracil) and docetaxel. Oxaliplatin is approved as a combination therapy via the active ingredient capecitabine.

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:
- Tegafur/ gimeracil/ oteracil: Resolution of 20 December 2012
- Pembrolizumab: Resolutions of 5 May 2022 and 20 June 2024
- Nivolumab: Resolution of 19 May 2022
- Zolbetuximab: Resolution of 17 April 2025

On 4. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

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

In the present treatment setting, both the HER2 status and the PD-L1 combined positivity score (CPS) status are decisive for the treatment decision in accordance with current guidelines and written statements from the scientific-medical societies. The present therapeutic indication adds a further score - the tumour area positivity (TAP) score - for determining PD-L1 expression in the tumour tissue of gastric or gastroesophageal junction adenocarcinoma, 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, the previously used CPS value is used to determine the appropriate comparator therapy: In this regard, a TAP score ≥ 5% includes PD-L1 positive tumours with a CPS score ≥ 1 by definition.

Adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%; first-line therapy

For patients with negative HER2 status, the guidelines recommend platinum and fluoropyrimidine-based combination chemotherapy. With regard to the platinum component, the focus here is specifically on cisplatin and oxaliplatin.

The decision as to whether an immune checkpoint inhibitor should be added to this combination chemotherapy depends on the PD-L1-CPS status. Accordingly, the addition of an immune checkpoint inhibitor is recommended for patients with PD-L1 positive tumours. In this regard, the immune checkpoint inhibitors are considered according to their respective marketing authorisation – nivolumab for a PD-L1-CPS status ≥ 5 and pembrolizumab for a PD-L1-CPS status ≥ 1, in each case in combination with platinum and fluoropyrimidine-based chemotherapy.

Fluoropyrimidine and platinum-containing doublet or triplet combinations without the additional administration of PD-1 inhibitors are currently only suitable for patients with a PD-L1-CPS status < 1, but are not covered by the present therapeutic indication.

By resolution of 19 May 2022, in the benefit assessment of nivolumab in combination with fluoropyrimidine and platinum-containing combination chemotherapy for the first-line treatment of HER2-negative advanced or metastatic gastric, gastroesophageal junction or oesophageal adenocarcinomas in adults whose tumours express PD-L1 (Combined Positive Score [CPS] ≥ 5), a hint for a considerable additional benefit of the above combination chemotherapy over FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin) was identified.

By resolution of 20 June 2024, it was identified in the benefit assessment that an additional benefit of pembrolizumab in combination with fluoropyrimidine and platinum-based chemotherapy is not proven.

By resolution of 17 April 2025, the benefit assessment of zolbetuximab, which is approved in combination with fluoropyrimidine and platinum-containing chemotherapy as a medicinal product for the treatment of a rare disease for the first-line treatment of Claudin (CLDN) 18.2 positive and HER2 negative locally advanced inoperable or metastatic gastric or gastroesophageal junction adenocarcinoma, found an indication of minor additional benefit. The active ingredient zolbetuximab is a new treatment option in the present therapeutic indication, which specifically targets Claudin (CLDN) 18.2 positive tumours. The active ingredient was only recently approved (marketing authorisation on 19.09.2024). Based on the generally accepted state of medical knowledge, zolbetuximab is not determined to be an appropriate comparator therapy for the present resolution.

Overall, the G-BA therefore determined the appropriate comparator therapies to be nivolumab for tumours with PD-L1 expression (CPS) ≥ 5 and pembrolizumab for tumours with PD-L1 expression (CPS) ≥ 1, in each case in combination with fluoropyrimidine and platinum-based combination chemotherapy. 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.

Change of the appropriate comparator therapy

Compared to the originally determined appropriate comparator therapy, patient group b) "Adults with locally advanced, unresectable or metastatic HER2 negative gastric or gastroesophageal junction adenocarcinoma with a tumour PD-L1 expression ≥ 5% (tumour area positivity; TAP score) and < 1 (combined positive score; CPS); first-line therapy" is deleted in the present resolution.

This change was made because a simultaneous characterisation of the PD-L1 expression status of the tumour tissue as PD-L1 positive using a TAP score ≥ 5% and PD-L1 negative using a CPS score < 1 as a result of the benefit assessment procedure is considered to be a rather theoretical constellation that could only exist in individual cases. For this reason, the G-BA considers it appropriate to change the appropriate comparator therapy for the present resolution to the effect that patient group b) is deleted. In contrast to the originally defined patient group a), the patient population defined above is no longer based on the characteristic "≥ 1 (combined positive score; CPS)".

This change to the appropriate comparator therapy is in accordance with the corresponding statement of the pharmaceutical company. For the present assessment of the additional benefit of tislelizumab, the change has the consequence that the assessment of the additional benefit in the present therapeutic indication is based on a patient population and the appropriate comparator therapy originally determined for this patient population is used, which is not affected by the change.

2.1.3 Extent and probability of the additional benefit

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

Adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%; first-line therapy

An additional benefit is not proven.

Justification:

The pharmaceutical company presented results from the RATIONALE 305 study to prove the additional benefit.

Patients with locally advanced, unresectable or metastatic HER-2 negative gastric or gastroesophageal junction adenocarcinoma, whose disease had not previously been treated with systemic therapy, were enrolled in the completed, double-blind phase III RCT RATIONALE 305. Although the determination of PD-L1 expression in the tumour tissue was necessary for enrolment in the study, patients were enrolled in the study regardless of PD-L1 expression. As first-line treatment, 501 patients received tislelizumab and 496 patients received placebo – in each case, in combination with platinum and fluoropyrimidine-containing chemotherapy consisting of either oxaliplatin and capecitabine or cisplatin and 5-fluorouracil. In accordance with the marketing authorisation of tislelizumab, the sub-population of patients with a tumour PD-L1 expression TAP ≥ 5 % was used for the benefit assessment (N = 274 in the intervention arm vs N = 272 in the control arm).

Assessment:
The patients received platinum and fluoropyrimidine-based chemotherapy in the comparator arm of the study. For adults with a tumour PD-L1 expression ≥ 5% TAP score, the appropriate comparator therapy was determined to be chemoimmunotherapy consisting of nivolumab or pembrolizumab, in each case, in combination with fluoropyrimidine and platinum-based combination chemotherapy and depending on the extent of tumour PD-L1 expression. Thus, a comparison with the appropriate comparator therapy is not possible.

No assessable data are available as the data presented do not allow a comparison with the appropriate comparator therapy.

Conclusion

The G-BA therefore concluded that an additional benefit of tislelizumab in combination with platinum and fluoropyrimidine-based chemotherapy for the first-line treatment of adult patients with HER-2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5% is not proven.

2.1.4 Summary of the assessment

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

"Tevimbra, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with HER-2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%."

The G-BA determined the appropriate comparator therapy to be chemoimmunotherapy consisting of nivolumab or pembrolizumab, in each case, in combination with fluoropyrimidine and platinum-based combination chemotherapy.

Results from the completed, double-blind phase III RCT RATIONALE 305 were presented for the assessment.

No assessable data are available as the data presented do not allow a comparison with the appropriate comparator therapy.

The G-BA therefore concluded that an additional benefit of tislelizumab in combination with platinum and fluoropyrimidine-based chemotherapy is not proven.

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

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

The G-BA bases its resolution on the information provided by the pharmaceutical company.

It should be noted that the lower limit is an underestimate, as it does not take into account patients who show locally advanced, unresectable or metastatic carcinoma due to progression and who are therefore eligible for first-line treatment.

The upper limit is subject to uncertainty because, in addition to not taking progression into account, it can be assumed that the upper limit of the percentage of patients who are eligible for palliative first-line therapy in stage III is overestimated.

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: 1 April 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 gastric or gastroesophageal junction 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 (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.

Treatment period:

Adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%; first-line therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tislelizumab in combination with cisplatin and 5-fluorouracil (5-FU)				
Tislelizumab	1 x every 21 days	17.4	1	17.4
Cisplatin	Day 1 of a 21-day cycle	17.4	1	17.4
5-FU	Day 1 – 5 of a 21-day cycle	17.4	5	87
Tislelizumab in combination with oxaliplatin and capecitabine				
Tislelizumab	21-day cycle	17.4	1	17.4
Oxaliplatin	Day 1 of a 21-day cycle	17.4	1	17.4
Capecitabine	2 x on day 1 – 14 of a 21-day cycle	17.4	14	243.6
Appropriate comparator therapy				
Nivolumab in combination with 5-fluorouracil (5-FU) + folinic acid + oxaliplatin (FOLFOX-4) (only for tumours with PD-L1 expression (CPS ≥ 5))				
Nivolumab	1 x every 14 days or 1 x every 21 days	26.1 or 17.4	1	26.1 or 17.4
5-FU	1 x on day 1 and 2 of a 14-day cycle	26.1	2	52.2
Folinic acid	1 x on day 1 and 2 of a 14-day cycle	26.1	2	52.2
Oxaliplatin	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Nivolumab in combination with 5-fluorouracil (5-FU) + folinic acid + oxaliplatin (mod. FOLFOX-6) (only for tumours with PD-L1 expression (CPS ≥ 5))				
Nivolumab	1 x every 14 days or	26.1 or 17.4	1	26.1 or 17.4

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x every 21 days			
5-FU	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Folinic acid	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Oxaliplatin	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Nivolumab in combination with capecitabine and oxaliplatin (XELOX) (only for tumours with PD-L1 expression (CPS ≥ 5))				
Nivolumab	1 x every 14 days or 1 x every 21 days	26.1 or 17.4	1	26.1 or 17.4
Capecitabine	2 x on day 1 - 14 of a 21 day cycle	17.4	14	243.6
Oxaliplatin	1 x on day 1 of a 21 day cycle	17.4	1	17.4
Pembrolizumab in combination with cisplatin and 5-fluorouracil (5-FU)				
Pembrolizumab	1 x every 21 days or 1 x every 42 days	17.4 or 8.7	1	17.4 or 8.7
Cisplatin[2]	Day 1 of a 21-day cycle	17.4	1	17.4
5-FU[2]	Day 1 – 5 of a 21-day cycle	17.4	5	87.0
Pembrolizumab in combination with oxaliplatin and capecitabine				
Pembrolizumab	1 x every 21 days or 1 x every 42 days	17.4 or 8.7	1	17.4 or 8.7

[2] 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
Oxaliplatin[2]	Day 1 of a 21-day cycle	17.4	1	17.4
Capecitabine[2]	2 x on day 1 – 14 of a 21-day cycle	17.4	14	243.6

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)[3].

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.

Adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%; first-line therapy

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					
Tislelizumab in combination with cisplatin and 5-fluorouracil (5-FU)					
Tislelizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
Cisplatin	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-FU	800 mg/m² = 1528 mg	1528 mg	1 x 2,500 mg	87.0	87.0 x 2,500 mg
Tislelizumab in combination with oxaliplatin and capecitabine					
Tislelizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
Oxaliplatin	130 mg/m²	248.3 mg	1 x 200 mg	17.4	17.4 x 200 mg

[3] 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	Average annual consumption by potency
	= 248.3 mg		+ 1 x 50 mg		+ 17.4 x 50 mg
Capecitabine	1000 mg/m² = 1800 mg	3600 mg	6 x 500 mg + 4 x 150 mg	243.6	1,461.6 x 500 mg + 974.4 x 150 mg
Appropriate comparator therapy					
Nivolumab in combination with 5-fluorouracil (5-FU) + folinic acid + oxaliplatin (FOLFOX-4) (only for tumours with PD-L1 expression (CPS ≥ 5))					
Nivolumab	240 mg or 360 mg	240 mg or 360 mg	2 x 120 mg or 3 x 120 mg	26.1 or 17.4	52.2 x 120 mg
5-FU	400 mg/m² = 764.0 mg	764.0 mg	1 x 1,000 mg	52.2	52.2 x 1000 mg
	600 mg/m² = 1146.0 mg	1146.0 mg	1 x 2,500 mg		52.2 x 2,500 mg
Folinic acid	200 mg/m² = 382.0 mg	382.0 mg	1 x 400 mg	52.2	52.2 x 400 mg
Oxaliplatin	85 mg/m² = 162.4 mg	162.4 mg	1 x 200 mg	26.1	26.1 x 200 mg
Nivolumab in combination with 5-fluorouracil (5-FU) + folinic acid + oxaliplatin (mod. FOLFOX-6) (only for tumours with PD-L1 expression (CPS ≥ 5))					
Nivolumab	240 mg or 360 mg	240 mg or 360 mg	2 x 120 mg or 3 x 120 mg	26.1 or 17.4	52.2 x 120 mg
5-FU	400 mg/m² = 764.0 mg	764.0 mg	1 x 1000 mg	26.1	26.1 x 1,000 mg
	2400 mg/m² = 4584.0 mg	4584.0 mg	1 x 5000 mg		26.1 x 5,000 mg
Folinic acid	400 mg/m² = 764.0 mg	764.0 mg	1 x 800 mg	26.1	26.1 x 800 mg
Oxaliplatin	85 mg/m² = 162.4 mg	162.4 mg	1 x 200 mg	26.1	26.1 x 200 mg
Nivolumab in combination with capecitabine and oxaliplatin (XELOX) (only for tumours with PD-L1 expression (CPS ≥ 5))					
Nivolumab	240 mg or	240 mg or	2 x 120 mg or	26.1 or	52.2 x 120 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	360 mg	360 mg	3 x 120 mg	17.4	
Capecitabine	1000 mg/m² = 1800 mg	3600 mg	6 x 500 mg + 4 x 150 mg	243.6	1461.6 x 500 mg + 974.4 x 150 mg
Oxaliplatin	130 mg/m² = 248.3 mg	248.3 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 mg + 17.4 x 50 mg
Pembrolizumab in combination with cisplatin and 5-fluorouracil (5-FU)					
Pembrolizumab	200 mg or 400 mg	200 mg or 400 mg	2 x 100 mg or 4 x 100 mg	17.4 or 8.7	34.8 x 100 mg
Cisplatin[2]	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-FU[2]	800 mg/m² = 1528 mg	1528 mg	1 x 2,500 mg	87.0	87.0 x 2,500 mg
Pembrolizumab in combination with oxaliplatin and capecitabine					
Pembrolizumab	200 mg or 400 mg	200 mg or 400 mg	2 x 100 mg or 4 x 100 mg	17.4 or 8.7	34.8 x 100 mg
Oxaliplatin[2]	130 mg/m² = 248.3 mg	248.3 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 mg + 17.4 x 50 mg
Capecitabine[2]	1000 mg/m² = 1800 mg	3600 mg	6 x 500 mg + 4 x 150 mg	243.6	1461.6 x 500 mg + 974.4 x 150 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 100 mg	1 CIS	€ 2,288.43	€ 1.77	€ 127.40	€ 2,159.26
Capecitabine 500 mg[4]	120 FCT	€ 151.84	€ 1.77	€ 11.12	€ 138.95
Capecitabine 150 mg[4]	120 FCT	€ 54.15	€ 1.77	€ 3.39	€ 48.99
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 2,500 mg[4]	1 SFI	€ 23.60	€ 1.77	€ 0.97	€ 20.86
Oxaliplatin 200 mg	1 CIS	€ 395.68	€ 1.77	€ 18.24	€ 375.67
Oxaliplatin 50 mg	1 CIS	€ 107.40	€ 1.77	€ 4.56	€ 101.07
Appropriate comparator therapy					
Calcium folinate 800 mg[4]	1 SFI	€ 451.32	€ 1.77	€ 34.80	€ 414.75
Calcium folinate 400 mg[4]	1 SFI	€ 242.59	€ 1.77	€ 18.29	€ 222.53
Capecitabine 500 mg[4]	120 FCT	€ 151.84	€ 1.77	€ 11.12	€ 138.95
Capecitabine 150 mg[4]	120 FCT	€ 54.15	€ 1.77	€ 3.39	€ 48.99
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 1,000 mg[4]	1 SII	€ 16.67	€ 1.77	€ 0.42	€ 14.48
5-fluorouracil 2,500 mg[4]	1 SFI	€ 23.60	€ 1.77	€ 0.97	€ 20.86
5-fluorouracil 5,000 mg[4]	1 SII	€ 34.02	€ 1.77	€ 1.80	€ 30.45
Nivolumab 120 mg	1 CIS	€ 1,539.71	€ 1.77	€ 84.64	€ 1,453.30
Oxaliplatin 200 mg	1 CIS	€ 395.68	€ 1.77	€ 18.24	€ 375.67
Oxaliplatin 50 mg	1 CIS	€ 107.40	€ 1.77	€ 4.56	€ 101.07
Pembrolizumab 100 mg	2 CIS	€ 4,962.26	€ 1.77	€ 280.10	€ 4,680.39

Abbreviations:
FCT = film-coated tablets, CIS = concentrate for the preparation of an infusion solution, SII = solution for injection/infusion, 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.

[4] Fixed reimbursement rate

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.

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:

Adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%; 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); 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 9 April 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the changed appropriate comparator therapy at its session on 10 December 2024.

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.

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	9 April 2024	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	10 December 2024	New 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