GBA
Gemeinsamer
Bundesausschuss

Justification

for the Resolution of the Federal Joint Committee (GBA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Zolbetuximab (reassessment of an orphan drug after exceeding the 30 million euro limit: gastric or gastro-oesophageal junction (GEJ) adenocarcinoma, Claudin (CLDN) 18.2 positive, HER2-negative, first-line, combination with fluoropyrimidine- and platinum-containing chemotherapy)

of 5 November 2026

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1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (GBA) assess 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 GBA electronically, including all clinical studies the pharmaceutical company have 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 GBA 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 GBA decide 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 zolbetuximab (Vyloy) was listed for the first time on 1 November 2024 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Vyloy® for the treatment of gastric or gastro-oesophageal junction (GEJ) adenocarcinoma is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

At their session on 17 April 2025, the GBA decided on the benefit assessment of zolbetuximab in the therapeutic indication - first-line treatment of Claudin (CLDN) 18.2 positive, HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy - according to Section 35a SGB V.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 30 million in the last twelve calendar months, the pharmaceutical company must

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submit evidence in accordance with Chapter 5, Section 5, paragraphs 1 to 6 Rules of Procedure (VerfO) within three months of being requested to do so by the Federal Joint Committee, and in this evidence, must demonstrate the additional benefit compared to the appropriate comparator therapy.

By the letter dated 12 February 2026, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 15 May 2026, due to exceeding the €30 million turnover limit within the period from December 2024 to November 2025. Pursuant to Section 4, paragraph 3, number 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 6 of the Rules of Procedure, the pharmaceutical company submitted the final dossier to the GBA in due time on 12 May 2026.

The GBA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 17 August 2026 on the GBA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The GBA came to a decision on whether an additional benefit of zolbetuximab 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 GBA have 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 zolbetuximab.

In the light of the above, and taking into account the statements received and the oral hearing, the GBA have made 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 zolbetuximab (Vyloy) in accordance with the product information

Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive.

Therapeutic indication of the resolution (resolution of 5 November 2026):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

[1] General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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a) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression ≥ 1 (Combined Positive Score; CPS); first-line treatment

Appropriate comparator therapy for zolbetuximab in combination with fluoropyrimidine- and platinum-containing 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

b) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression < 1 (Combined Positive Score; CPS); first-line treatment

Appropriate comparator therapy for zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy:

- cisplatin + capecitabine

or

- oxaliplatin + capecitabine

or

- cisplatin + S-1 (tegafur/ gimeracil/ oteracil)

or

- cisplatin + 5-fluorouracil (only for patients with oesophageal adenocarcinoma)

or

- cisplatin + 5-fluorouracil + folinic acid (only for patients with oesophageal adenocarcinoma)

or

- epirubicin + cisplatin + capecitabine

or

- epirubicin + cisplatin + 5-fluorouracil

or

- epirubicin + oxaliplatin + capecitabine

or

- docetaxel + cisplatin + 5-fluorouracil

or

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- 5-fluorouracil + oxaliplatin + epirubicin (only for patients with oesophageal adenocarcinoma)

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the GBA 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 according to 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 GBA must be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy must 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 GBA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if they determine 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 for 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 for the therapeutic indication.

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

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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 zolbetuximab, medicinal products containing the active ingredients capecitabine, cisplatin, doxorubicin, epirubicin, 5-fluorouracil, folinic acid, mitomycin, tegafur/ gimeracil/ oteracil, nivolumab, pembrolizumab and tislelizumab are approved for 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:
- 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
- Tislelizumab: resolution of 18 June 2025

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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

In accordance with current guidelines, HER2 status, the PD-L1 Combined Positivity Score (CPS) and microsatellite instability (MSI) status are all significant for making the treatment decision in the present treatment setting.

With the marketing authorisation of the active ingredient tislelizumab, the Tumour Area Positivity (TAP) score was introduced as an additional score for determining PD-L1 expression in tumour tissue from gastric or gastro-oesophageal junction (GEJ) adenocarcinoma; this is not entirely comparable with the methods previously used. 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.

Based on the available evidence on therapy options depending on PD-L1 expression, it is differentiated into two sub-populations with a cut-off value of PD-L1 expression of CPS 1% on tumour cells:

a) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression ≥ 1 (Combined Positive Score; CPS); first-line treatment

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,

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the addition of an immune checkpoint inhibitor is recommended for patients with PD-L1 positive tumours.

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

By the resolution of 20 June 2024, the benefit assessment showed that an additional benefit of pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy compared with chemotherapy consisting of cisplatin + 5-fluorouracil, or cisplatin + capecitabine, or oxaliplatin + capecitabine is not proven as it was not possible to weigh up the benefits against the only minor advantage in the endpoint of overall survival due to data that could not be assessed in the endpoints of the morbidity, health-related quality of life and side effects categories.

By the resolution of 18 June 2025, the benefit assessment showed that an additional benefit of tislelizumab in combination with platinum- and fluoropyrimidine-based chemotherapy is not proven for the first-line treatment of gastric or gastro-oesophageal junction (GEJ) adenocarcinoma with a PD-L1 expression (TAP) ≥ 5%.

With regard to the addition of an immune checkpoint inhibitor to platinum- and fluoropyrimidine-based combination chemotherapy, the immune checkpoint inhibitors nivolumab and pembrolizumab were determined as the appropriate comparator therapy for the present benefit assessment procedure. In line with this, tislelizumab is not included in the appropriate comparator therapy for the present resolution.

The appropriate comparator therapy determined here includes several alternative therapy options. In this context, the 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 alternative therapy options are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics. The sole comparison with a therapy option that only represents a comparator therapy for part of the patient population is generally insufficient to demonstrate the additional benefit for the total population.

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b) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression < 1 (Combined Positive Score; CPS); first-line treatment

The underlying evidence continues to mention fluoropyrimidine- and platinum-containing doublet or triplet combinations for PD-L1-negative patients (PD-L1 expression status of the tumour tissue CPS < 1) with locally advanced, unresectable or metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma, with HER2 status playing a decisive role in the treatment algorithm. For HER2-negative patients, the platinum component specifically refers to cisplatin and oxaliplatin, and the fluoropyrimidine component to 5-fluorouracil, capecitabine and S-1 (tegafur/ gimeracil/ oteracil).

The platinum- and fluoropyrimidine-based-based doublet or triplet combination therapies mentioned in the guidelines include both approved and unapproved medicinal products for the present therapeutic indication; these are equally recommended, and no preference can be inferred from the guidelines. It cannot be derived from the present evidence that the off-label use of medicinal products would generally be preferred to the use of medicinal products approved in the therapeutic indication according to the generally recognised state of medical knowledge. The requirements for exceptionally determining the off-label use of medicinal products as the appropriate comparator therapy in accordance with Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) are therefore not met.

In the overall analysis of the available evidence, the GBA therefore determine the approved platinum- and fluoropyrimidine-based doublet or triplet combination therapies as equally appropriate comparator therapies.

The appropriate comparator therapy determined here includes several alternative therapy options. In this context, the 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 alternative therapy options are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics. The sole comparison with a therapy option that only represents a comparator therapy for part of the patient population is generally insufficient to demonstrate the additional benefit for the total population.

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

Any change to the appropriate comparator therapy requires a decision by the GBA based on a prior review of the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO.

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2.1.3 Extent and probability of the additional benefit

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

a) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression ≥ 1 (Combined Positive Score; CPS); first-line treatment

An additional benefit is not proven.

b) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression < 1 (Combined Positive Score; CPS); first-line treatment

Hint of a minor additional benefit.

Justification:

a) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression ≥ 1 (Combined Positive Score; CPS); first-line treatment

For patients with PD-L1 expression ≥ 1 (CPS), the pharmaceutical company did not identify any suitable study. This is appropriate. No data on this patient population are therefore available for the benefit assessment. Consequently, an additional benefit of zolbetuximab in first-line treatment of patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression ≥ 1 (CPS) is not proven.

b) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression < 1 (Combined Positive Score; CPS); first-line treatment

This benefit assessment is based on the results for the relevant sub-population of patients with tumour PD-L1 expression of CPS < 1 from the pharmaceutical company's phase III GLOW study.

The GLOW study is an ongoing, double-blind, randomised, placebo-controlled phase III study to investigate the efficacy of zolbetuximab in combination with capecitabine and oxaliplatin (CAPOX) compared to placebo in combination with CAPOX.

A total of 254 subjects of the total population were randomised to the intervention arm (zolbetuximab + CAPOX) and 253 subjects to the control arm (placebo + CAPOX). These subjects had to have locally advanced unresectable or metastatic HER2-negative as well as Claudin 18.2 positive (defined as Claudin 18.2 expression in ≥ 75% of tumour cells with moderate to strong membrane staining) gastric or gastro-oesophageal junction adenocarcinoma, which had not been systemically treated.

Randomisation was stratified by region (Asia vs non-Asia), number of organs with metastases (0–2 vs ≥ 3) and previous gastrectomy (yes vs no). Treatment was given until disease progression, unacceptable toxicity or therapy discontinuation as decided by the doctor or patient. The study was conducted in study sites across Europe, North and South America as well as Asia; a German study site was not involved. In addition to the primary endpoint of progression-free survival (PFS), the secondary endpoints of the study included overall survival,

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as well as endpoints of the morbidity, health-related quality of life and side effects categories. For the benefit assessment, the results of the final data cut-off from 12 January 2024 are used.

Relevant sub-population of the GLOW study

Patients were enrolled in the GLOW study regardless of PD-L1 expression. For the present research question, the sub-population of patients harbouring tumours with PD-L1 expression < 1 (via CPS) is relevant. This comprises 84 subjects in the intervention arm and 88 subjects in the comparator arm, with patient characteristics being largely balanced between the treatment arms.

Limitations of the GLOW study

In accordance with the S3 guideline, the PD-L1 status must routinely be determined as one of the key therapy management biomarkers for planning the treatment of HER2-negative gastric and GEJ adenocarcinomas. PD-L1 testing was done retrospectively as it had not been carried out in the total population prior to enrolment in the study; nevertheless, 90 subjects (35.4%) in the intervention arm and 85 subjects (33.6%) in the control arm remained with an unknown CPS status. These subjects with unknown CPS status could not be included in the relevant sub-population for the present benefit assessment.

In the GLOW study, concomitant palliative radiotherapy was permitted only for peripheral bone metastases. Other palliative radiotherapy measures relevant to healthcare, particularly those aimed at local symptom control, were not included; it therefore remains unclear to what extent and for what percentage of patients these measures would have been indicated.

Antiemetic prevention is required for both zolbetuximab and the oxaliplatin contained in the CAPOX regimen. The GLOW study protocol highlighted the need for antiemetic prevention. However, the use of appropriate concomitant antiemetic treatment was, on the whole, inadequate in the study. Whilst a combination of a serotonin 5-HT3 receptor antagonist and dexamethasone is recommended for the moderately emetogenic CAPOX regimen, a quadruple prophylaxis comprising a serotonin 5-HT3 receptor antagonist, an NK1 antagonist, dexamethasone and, if applicable, olanzapine must be used due to the higher emetogenic risk associated with zolbetuximab.

Given that the active ingredients used in the study arms may place different demands on the respective antiemetic concomitant treatments, and that the study protocol did not contain any specific or binding guidelines on the selection of antiemetic treatment, the criteria used to make the patient-individual choice of antiemetic therapy remains unclear in the context of the double-blind GLOW study.

Overall, it can be concluded that the GLOW study did not adequately take into account the potentially differing requirements for antiemetic prevention in the two study arms, which stem from the differing emetogenic potential of the combinations of active ingredients used.

Clinical experts stated in the written statement procedure that antiemetic prevention through a combination of dexamethasone, serotonin 5-HT3 receptor antagonists, NK1 antagonists and olanzapine is now optimised for the use of zolbetuximab in the current healthcare context.

Extent and probability of the additional benefit

Mortality

In the GLOW study, overall survival was operationalised as the time between randomisation and death from any cause.

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For the endpoint of overall survival, there was a statistically significant difference between the treatment groups in favour of zolbetuximab in combination with CAPOX. The extent of the prolongation achieved in overall survival is assessed as a minor improvement.

Morbidity

Progression-free survival

In the GLOW study, progression-free survival was operationalised as the time from randomisation to the occurrence of radiological disease progression (as defined by RECIST version 1.1), assessed by a blinded independent review committee (IRC), or until death from any cause, whichever occurred first.

For the PFS endpoint, there was no statistically significant difference between the study arms.

The present PFS endpoint is a composite endpoint consisting of endpoints from the "mortality" and "morbidity" categories. The endpoint component "mortality" is already assessed via the endpoint "overall survival" as an independent endpoint. The "radiological progression of the disease" morbidity component is assessed according to RECIST criteria and thus not symptom-related, but only by means of imaging procedures.

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

Symptomatology (assessed using EORTC QLQ-C30 and EORTC QLQ-OG25)

In the GLOW study, disease symptomatology was assessed using the EORTC QLQ-C30 questionnaire and the EORTC QLQ-OG25 additional module. Presented responder analyses of the time to 1st deterioration by ≥ 10 points are used for the present benefit assessment.

For nausea and vomiting, which occur particularly in connection with the first loading dose of zolbetuximab, the relevant items of the EORTC QLQ-C30 could not be meaningfully interpreted in both study arms due to limitations relating to antiemetic treatment.

Pain intensity (assessed using the NRS)

In the GLOW study, pain intensity was assessed using the Numerical Rating Scale (NRS), in which patients rated their pain on an 11-point numerical rating scale to self-assess the intensity of the pain they were experiencing (0 = "no pain" to 10 = "worst pain imaginable").

Health status (using the visual analogue scale (VAS) of the EQ-5D)

The health status was assessed in the GLOW study using the visual analogue scale of the EQ-5D.

For the endpoints of symptomatology, pain intensity and health status, there was no statistically significant difference between the treatment groups in each case.

Quality of life

Health-related quality of life was assessed in the GLOW study using the EORTC QLQ-C30 questionnaire. Presented responder analyses of the time to 1st deterioration by ≥ 10 points are used for the present benefit assessment.

For the endpoints "global health status", "physical functioning", "role functioning", "cognitive functioning", "emotional functioning" and "social functioning" in the endpoint category of

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health-related quality of life, there was no statistically significant difference between the treatment arms in each case.

In the subgroup analyses, the "social functioning" scale showed an effect modification by the "age" characteristic, as assessed using the EORTC QLQ-C30. The analyses showed a statistically significant difference to the disadvantage of zolbetuximab + CAPOX for patients > 65 years of age, whilst no statistically significant difference between the treatment arms was observed for patients ≤ 65 years of age. The result for the total population was used for the assessment.

Overall, neither an advantage nor a disadvantage was thus identified for the endpoint category of health-related quality of life.

Side effects

Total adverse events (AEs)

In the GLOW study, almost all patients in the control and intervention arms experienced an AE. The results were only presented additionally.

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

For the endpoints of SAEs and severe AEs, there were no statistically significant differences between the treatment arms.

Therapy discontinuation due to AEs

For the endpoints of SAEs and severe AEs, there were no statistically significant differences between the treatment arms.

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Specific AEs

For the endpoint "decreased appetite", there was a statistically significant difference between the treatment arms to the disadvantage of zolbetuximab + CAPOX compared to CAPOX.

No suitable data are available on the side effects of nausea and vomiting, which occur particularly in connection with the first loading dose of zolbetuximab.

For the endpoints of SAEs, severe AEs and discontinuation due to AEs, the overall analysis of the results on side effects showed no statistically significant differences between the treatment arms. Detailed analysis showed a disadvantage of the specific AE "decreased appetite".

Overall, therefore, neither advantages nor disadvantages can be identified for the endpoint category of side effects.

Overall assessment

For the benefit assessment, results are available on mortality, morbidity, quality of life and side effects from the ongoing, double-blind, randomised, placebo-controlled phase III GLOW study, which compares zolbetuximab in combination with capecitabine and oxaliplatin (CAPOX) to placebo in combination with CAPOX.

For the endpoint of overall survival, the GLOW study showed a statistically significant advantage in favour of zolbetuximab. The extent of the prolongation achieved in overall survival is assessed as a minor improvement.

For the endpoints of symptomatology (assessed using the EORTC QLQ-C30 and the disease-specific additional module EORTC QLQ-OG25), pain intensity (assessed using the NRS) and health status (via the EQ-5D VAS) in the endpoint category of morbidity, there were no statistically significant differences between the treatment groups in each case.

For the endpoint category of health-related quality of life, which was assessed using the EORTC QLQ-C30, there was no statistically significant difference between the treatment groups.

For the endpoints of SAEs, severe AEs and discontinuation due to AEs, the results on side effects showed no statistically significant differences between the treatment arms. Detailed analysis showed a disadvantage of the specific AE "decreased appetite". The overall analysis of the results on side effects showed neither an advantage nor a disadvantage.

Given the minor improvement in overall survival and the fact that neither advantages nor disadvantages are observed in the endpoint categories of morbidity, health-related quality of life and side effects, the GBA, in the overall assessment, identify a minor additional benefit of zolbetuximab in first-line therapy of patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression < 1 (CPS).

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Reliability of data (probability of additional benefit)

This benefit assessment is based on the results of the relevant sub-population with a tumour PD-L1 expression < 1 (CPS) from the randomised, double-blind, multicentre, controlled GLOW study.
The cross-endpoint risk of bias of the GLOW study is estimated to be low.

For the endpoint of overall survival, the risk of bias is estimated to be high due to the high and differential percentage of non-administrative censoring events (intervention arm vs comparator arm 20% vs 14%), which meant that follow-up could not be completed until the data cut-off.

For all results on patient-reported endpoints of the morbidity and health-related quality of life categories, the risk of bias is classified as high, as the return rates for the questionnaires on patient-reported endpoints from both endpoint categories fall below 70% in the intervention arm and below 60% in the comparator arm as early as the start of the 7th treatment cycle (approximately 4.2 months after the start of treatment).

For the endpoints in the endpoint category of side effects, the risk of bias is rated as low; for the endpoint of discontinuation due to AEs, the reliability of data is limited.

In summary, the reliability of data for the additional benefit identified is classified in the "hint" category.

2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient zolbetuximab due to the exceeding of the EUR 30 million turnover limit. Zolbetuximab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive.

In the therapeutic indication under consideration, two patient groups are distinguished based on PD-L1 tumour expression < 1 and ≥ 1 (Combined Positive Score; CPS) respectively:

a) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression ≥ 1 (CPS); first-line treatment

The GBA determined the appropriate comparator therapy to be nivolumab or pembrolizumab, each in combination with platinum- and fluoropyrimidine-based combination chemotherapy.

The pharmaceutical company did not provide any data that would enable an assessment of the additional benefit, as no suitable study could be identified for this patient group. An additional benefit is therefore not proven.

b) Adults with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression < 1 (CPS); first-line treatment

The GBA determined several platinum-based doublet and triplet regimens as the appropriate comparator therapy.

For the benefit assessment, data are available from the GLOW study, which compared zolbetuximab + oxaliplatin + capecitabine (CAPOX) with CAPOX. Enrolment in the GLOW study

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was independent of PD-L1 expression. The relevant sub-population for this patient group is the sub-population of patients harbouring tumours with PD-L1 expression < 1 (CPS) from the GLOW study.

For the endpoint of overall survival, there was a statistically significant advantage in favour of zolbetuximab. The extent of the prolongation achieved in overall survival is assessed as a minor improvement.

For the endpoints of symptomatology (EORTC QLQ-C30 and EORTC QLQ-OG25), pain intensity (NRS) and health status (EQ-5D VAS) in the endpoint category of morbidity, there were no statistically significant differences between the treatment groups in each case.

For the endpoint category of health-related quality of life (EORTC QLQ-C30), there was no statistically significant difference between the treatment groups.

For the endpoints of SAEs, severe AEs and discontinuation due to AEs, the results on side effects showed no statistically significant differences between the treatment arms. Detailed analysis showed a disadvantage of the specific AE "decreased appetite". The overall analysis of the results on side effects showed neither an advantage nor a disadvantage.

Given the minor improvement in overall survival and the fact that neither advantages nor disadvantages are observed in the endpoint categories of morbidity, health-related quality of life and side effects, the GBA, in the overall assessment, identify a minor additional benefit of zolbetuximab in first-line therapy of adults with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression < 1 (CPS).

The reliability of data of the additional benefit identified is classified in the "hint" category.

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 GBA base their resolution on the information regarding the number of patients from the IQWiG's dossier assessment.

The adjustment to the figures submitted by the pharmaceutical company, as recommended by the IQWiG, is implemented for the purposes of this resolution. This takes into account a higher number of patients with HER2-negative gastric or GEJ adenocarcinoma and with palliative primary disease. Taking this higher baseline as a starting point, the percentages for Claudin 18.2 positive tumours – which are described differently in the literature – are taken into account by means of a range.

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a) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression ≥ 1 (Combined Positive Score; CPS); first-line treatment

Approximately 470 to 1,340 patients

b) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression < 1 (Combined Positive Score; CPS); first-line treatment

Approximately 620 to 1,700 patients

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 Vyloy (active ingredient: zolbetuximab) at the following publicly accessible link (last access: 15 July 2026):

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

Treatment with zolbetuximab must only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with gastric or gastro-oesophageal junction carcinomas, as well as specialists in internal medicine and gastroenterology and other specialists from other specialist groups participating in the Oncology Agreement.

Eligible patients must have a CLDN18.2-positive tumour status, defined as ≥ 75% of tumour cells with moderate to strong membranous CLDN18 immunohistochemical staining, tested by a CE-marked in vitro diagnostic device (IVD) with an appropriate intended use. If a CE-marked IVD is not available, an alternative validated test must be used.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 September 2026).

The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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

a) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression ≥ 1 (Combined Positive Score; CPS); first-line treatment

Courtesy translation – only the German version is legally binding.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed:				
Zolbetuximab in combination with oxaliplatin, folinic acid and 5-fluorouracil (mFOLFOX6)				
Zolbetuximab (initial single dose)				
Zolbetuximab	On day 1 1 x on day 1	1	1	1
Zolbetuximab (maintenance doses)				
Zolbetuximab	From day 21 1 x every 21 days	16.4	1	16.4
	or			
	From day 14 1 x every 14 days	25.1	1	25.1
in combination with mFOLFOX6				
Oxaliplatin	1 x on day 1, 15 and 29 of a 42-day cycle	8.7	3	26.1
Folinic acid/ leucovorin	1 x on day 1, 15 and 29 of a 42-day cycle	8.7	3	26.1
5-FU	Bolus and continuous infusion: 1 x on day 1, 15 and 29 of a 42-day cycle	8.7	3	26.1
Zolbetuximab in combination with oxaliplatin and capecitabine (CAPOX)				
Zolbetuximab (initial single dose)				
Zolbetuximab	On day 1 1 x on day 1	1	1	1
Zolbetuximab (maintenance doses)				
Zolbetuximab	From day 21 1 x every 21 days	16.4	1	16.4
	or			
	From day 14 1 x every 14 days	25.1	1	25.1
in combination with CAPOX				
Oxaliplatin	1 x every 21 days	17.4	1	17.4

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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 1 x every 21 days	26.1 or 17.4	1	26.1 or 17.4
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

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cisplatin	Day 1 – 5 of a 21-day cycle	17.4	5	87.0
5-FU	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
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

b) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression < 1 (Combined Positive Score; CPS); first-line treatment

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed:				
Zolbetuximab in combination with oxaliplatin, folinic acid and 5-fluorouracil (mFOLFOX6)				
Zolbetuximab (initial single dose)				
Zolbetuximab	On day 1 1 x on day 1	1	1	1
Zolbetuximab (maintenance doses)				
Zolbetuximab	From day 21 1 x every 21 days	16.4	1	16.4
	or			
	From day 14 1 x every 14 days	25.1	1	25.1
in combination with mFOLFOX6				
Oxaliplatin	1 x on day 1, 15 and 29 of a 42-day cycle	8.7	3	26.1
Folinic acid	1 x on day 1, 15 and 29 of a 42-day cycle	8.7	3	26.1

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
5-FU	Bolus and continuous infusion: 1 x on day 1, 15 and 29 of a 42-day cycle	8.7	3	26.1
Zolbetuximab in combination with oxaliplatin and capecitabine (CAPOX)				
Zolbetuximab (initial single dose)				
Zolbetuximab	<u>On day 1</u> 1 x on day 1	1	1	1
Zolbetuximab (maintenance doses)				
Zolbetuximab	<u>From day 21</u> 1 x every 21 days	16.4	1	16.4
	or			
	<u>From day 14</u> 1 x every 14 days	25.1	1	25.1
in combination with CAPOX				
Oxaliplatin	1 x every 21 days	17.4	1	17.4
Capecitabine	1 x on day 1-14 of a 21-day cycle	17.4	14	243.6
Appropriate comparator therapy				
Cisplatin in combination with capecitabine				
Cisplatin	1 x every 21 days	17.4	1	17.4
Capecitabine	2 x on day 1 - 14 of a 21-day cycle	17.4	14	243.6
Oxaliplatin in combination with capecitabine				
Oxaliplatin	1 x on 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
Cisplatin + S-1 (tegafur/ gimeracil/ oteracil)				
Cisplatin	1 x per 28-day cycle for 6 cycles	6.0	1	6.0
S-1 (tegafur/ gimeracil/ oteracil)	2 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0
Cisplatin in combination with 5-fluorouracil (5-FU)				

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
(only for patients with oesophageal adenocarcinoma)				
Cisplatin	1 x on day 1 of a 21-day cycle	17.4	1	17.4
5-FU	1 x on day 1 - 5 of a 21-day cycle	17.4	5	87.0
Cisplatin in combination with 5-fluorouracil (5-FU) and folinic acid (only for patients with oesophageal adenocarcinoma)				
Cisplatin	1 x on day 1 of a 21-day cycle	17.4	1	17.4
5-FU	1 x on day 1 - 5 of a 21-day cycle	17.4	5	87.0
Folinic acid	1 x on day 1 of a 21-day cycle	17.4	1	17.4
Epirubicin in combination with cisplatin and capecitabine				
Epirubicin	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
Capecitabine	1 x daily per 21-day cycle	17.4	21	365
Epirubicin in combination with cisplatin and 5-fluorouracil (5-FU)				
Epirubicin	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-FU	1 x daily per 21-day cycle	17.4	21	365
Epirubicin in combination with oxaliplatin and capecitabine				
Epirubicin	1 x on day 1 of a 21-day cycle	17.4	1	17.4

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Oxaliplatin	1 x on day 1 of a 21-day cycle	17.4	1	17.4
Capecitabine	2 x daily per 21-day cycle	17.4	21	365
Epirubicin in combination with oxaliplatin and 5-fluorouracil (5-FU) (only for patients with oesophageal adenocarcinoma)				
Epirubicin	1 x on day 1 of a 21-day cycle	17.4	1	17.4
Oxaliplatin	1 x on day 1 of a 21-day cycle	17.4	1	17.4
5-FU	1 x daily per 21-day cycle	17.4	21	365
Docetaxel in combination with cisplatin and 5-fluorouracil (5-FU) (only for patients with oesophageal adenocarcinoma)				
Docetaxel	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-FU	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 "2025 Microcensus – body measurements of the population" were applied (average body height: 1.73 m; average body weight: 78.3 kg). This results in a body surface area of 1.92 m² (calculated according to Du Bois 1916)[2].

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

[2] Federal Health Reporting. Average body measurements of the population (2025, both sexes), www.gbe-bund.de

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a) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression ≥ 1 (Combined Positive Score; CPS); first-line treatment

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:					
Zolbetuximab in combination with oxaliplatin, folinic acid and 5-fluorouracil (mFOLFOX6)					
Zolbetuximab (initial single dose)					
Zolbetuximab	800 mg/m² = 1,536.0 mg	1,536.0 mg	5 x 300 mg + 1 x 100 mg	1	5 x 300 mg + 1 x 100 mg
Zolbetuximab (maintenance doses)					
Zolbetuximab	600 mg/m² = 1,152.0 mg	1,152.0 mg	4 x 300 mg	16.4	65.6 x 300 mg
	or				
	400 mg/m² = 768.0 mg	768.0 mg	2 x 300 mg + 2 x 100 mg	25.1	50.2 x 300 mg + 50.2 x 100 mg
in combination with mFOLFOX6					
Oxaliplatin	85 mg/m² = 163.2 mg	163.2 mg	1 x 200 mg	26.1	26.1 x 200 mg
Folinic acid	400 mg/m² = 768.0 mg	768.0 mg	1 x 800 mg	26.1	26.1 x 800 mg
5-FU	*Bolus* 400 mg/m² = 768.0 mg	768.0 mg	1 x 1,000 mg	26.1	26.1 x 1,000 mg
	Continuous infusion 2,400 mg/m² = 4,608.0 mg	4,608.0 mg	1 x 5,000 mg		26.1 x 5,000 mg
Zolbetuximab in combination with oxaliplatin and capecitabine (CAPOX)					
Zolbetuximab (initial single dose)					
Zolbetuximab	800 mg/m² = 1,536.0 mg	1,536.0 mg	5 x 300 mg + 1 x 100 mg	1	5 x 300 mg + 1 x 100 mg
Zolbetuximab (maintenance doses)					
Zolbetuximab	600 mg/m² = 1,152.0 mg	1,152.0 mg	4 x 300 mg	16.4	65.6 x 300 mg
	or				
	400 mg/m² = 768.0 mg	768.0 mg	2 x 300 mg + 2 x 100 mg	25.1	50.2 x 300 mg + 50.2 x 100 mg
in combination with CAPOX					

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Oxaliplatin	130 mg/m² = 249.6 mg	249.6 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 mg + 17.4 x 50 mg
Capecitabine	1,000 mg/m² = 1,800.0 mg	2 x 1,800.0 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 = 768.0 mg	768.0 mg	1 x 1,000 mg	52.2	52.2 x 1,000 mg
	600 mg/m² = 1,152.0 mg	1,152.0 mg	1 x 2,500 mg		52.2 x 2,500 mg
Folinic acid	200 mg/m² = 384.0 mg	384.0 mg	1 x 400 mg	52.2	52.2 x 400 mg
Oxaliplatin	85 mg/m² = 163.2 mg	163.2 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 = 768.0 mg	768.0 mg	1 x 1,000 mg	26.1	26.1 x 1,000 mg
	2,400 mg/m² = 4,608.0 mg	4,608.0 mg	1 x 5,000 mg		26.1 x 5,000 mg
Folinic acid	400 mg/m² = 768.0 mg	768.0 mg	1 x 800 mg	26.1	26.1 x 800 mg
Oxaliplatin	85 mg/m² = 163.2 mg	163.2 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 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

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Capecitabine	1,000 mg/m² = 1,800 mg	3,600 mg	6 x 500 mg + 4 x 150 mg	243.6	1,461.6 x 500 mg + 974.4 x 150 mg
Oxaliplatin	130 mg/m² = 249.6 mg	249.6 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	80 mg/m² = 153.6 mg	153.6 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	87.0	87.0 x 100 mg + 87.0 x 50 mg + 87.0 x 10 mg
5-FU	800 mg/m² = 1,536 mg	1,536 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	130 mg/m² = 249.6 mg	249.6 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 mg + 17.4 x 50 mg
Capecitabine	1,000 mg/m² = 1,800 mg	3,600 mg	6 x 500 mg + 4 x 150 mg	243.6	1,461.6 x 500 mg + 974.4 x 150 mg

b) <u>Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive with a PD-L1 expression < 1 (Combined Positive Score; CPS); first-line treatment</u>

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:					
Zolbetuximab in combination with oxaliplatin, folinic acid and 5-fluorouracil (mFOLFOX6)					
Zolbetuximab (initial single dose)					
Zolbetuximab	800 mg/m² = 1,536.0 mg	1,536.0 mg	5 x 300 mg + 1 x 100 mg	1	5 x 300 mg + 1 x 100 mg
Zolbetuximab (maintenance doses)					

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Zolbetuximab	600 mg/m² = 1,152.0 mg	1,152.0 mg	4 x 300 mg	16.4	65.6 x 300 mg
	or				
	400 mg/m² = 768.0 mg	768.0 mg	2 x 300 mg + 2 x 100 mg	25.1	50.2 x 300 mg + 50.2 x 100 mg
in combination with mFOLFOX6					
Oxaliplatin	85 mg/m² = 163.2 mg	163.2 mg	1 x 200 mg	26.1	26.1 x 200 mg
Folinic acid	400 mg/m² = 768.0 mg	768.0 mg	1 x 800 mg	26.1	26.1 x 800 mg
5-FU	*Bolus* 400 mg/m² = 768.0 mg	768.0 mg	1 x 1,000 mg	26.1	26.1 x 1,000 mg
	Continuous infusion 2,400 mg/m² = 4,608.0 mg	4,608.0 mg	1 x 5,000 mg		26.1 x 5,000 mg
Zolbetuximab in combination with oxaliplatin and capecitabine (CAPOX)					
Zolbetuximab (initial single dose)					
Zolbetuximab	800 mg/m² = 1,536.0 mg	1,536.0 mg	16 x 100 mg	1	16 x 100 mg
Zolbetuximab (maintenance doses)					
Zolbetuximab	600 mg/m² = 1,152.0 mg	1,152.0 mg	12 x 100 mg	16.4	196.8 x 100 mg
	or				
	400 mg/m² = 768.0 mg	768.0 mg	8 x 100 mg	25.1	200.8 x 100 mg
in combination with CAPOX					
Oxaliplatin	130 mg/m² = 249.6 mg	249.6 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 mg + 17.4 x 50 mg
Capecitabine	1,000 mg/m² = 1,800.0 mg	3,600.0 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					
Cisplatin in combination with capecitabine					
Cisplatin	80 mg/m² = 153.6 mg	153.6 mg	1 x 100 mg + 1 x 50 mg	17.4	17.4 x 100 mg + 17.4 x 50 mg

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
			+ 1 x 10 mg		+ 17.4 x 10 mg
Capecitabine	1,000 mg/m² = 1,800 mg	3,600 mg	6 x 500 mg + 4 x 150 mg	243.6	1,461.6 x 500 mg + 974.4 x 150 mg
Oxaliplatin in combination with capecitabine					
Oxaliplatin	130 mg/m² = 249.6 mg	249.6 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 mg + 17.4 x 50 mg
Capecitabine	1,000 mg/m² = 1,800 mg	3,600 mg	6 x 500 mg + 4 x 150 mg	243.6	1,461.6 x 500 mg + 974.4 x 150 mg
Cisplatin + S-1 (tegafur/ gimeracil/ oteracil)					
Cisplatin	75 mg/m² = 144.0 mg	144.0 mg	1 x 100 mg + 1 x 50 mg	6.0	6.0 x 100 mg + 6.0 x 50 mg
S-1 (tegafur/ gimeracil/ oteracil)	25 mg/m² = 48 mg	2 x 48 mg = 100 mg	4 x 15 mg + 2 x 20 mg	273.0	1,092 x 15 mg + 546 x 20 mg
Cisplatin in combination with 5-fluorouracil (5-FU) (only for patients with oesophageal adenocarcinoma)					
Cisplatin	80 mg/m² = 153.6 mg	153.6 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 = 1,536.0 mg	1,536.0 mg	2 x 1,000 mg	87.0	174.0 x 1,000 mg
Cisplatin in combination with 5-fluorouracil (5-FU) and folinic acid (only for patients with oesophageal adenocarcinoma)					
Cisplatin	80 mg/m² = 153.6 mg	153.6 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 = 1,536.0 mg	1,536.0 mg	2 x 1,000 mg	87.0	174.0 x 1,000 mg
Folinic acid	400 mg/m² = 768.0 mg	768.0 mg	1 x 800 mg	17.4	17.4 x 800 mg
Epirubicin in combination with cisplatin and capecitabine (ECX)					
Epirubicin	50 mg/m² = 96.0 mg	96.0 mg	1 x 100 mg	17.4	17.4 x 100 mg
Cisplatin	60 mg/m² = 115.2 mg	115.2 mg	1 x 100 mg + 2 x 10 mg	17.4	17.4 x 100 mg + 34.8 x 10 mg
Capecitabine	625 mg/m² = 1,200.0 mg	1,200.0 mg	4 x 500 mg + 4 x 150 mg	365	1,460 x 500 mg + 1,460 x 150 mg

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Epirubicin in combination with cisplatin and 5-fluorouracil (5-FU) (ECF)					
Epirubicin	50 mg/m² = 96.0 mg	96.0 mg	1 x 100 mg	17.4	17.4 x 100 mg
Cisplatin	60 mg/m² = 115.2 mg	115.2 mg	1 x 100 mg + 2 x 10 mg	17.4	17.4 x 100 mg + 34.8 x 10 mg
5-FU	200 mg/m² = 384.0 mg	384.0 mg	1 x 500 mg	365	365 x 500 mg
Epirubicin in combination with oxaliplatin and capecitabine (EOF)					
Epirubicin	50 mg/m² = 96.0 mg	96.0 mg	1 x 100 mg	17.4	17.4 x 100 mg
Oxaliplatin	130 mg/m² = 249.6 mg	249.6 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 mg + 17.4 x 50 mg
Capecitabine	625 mg/m² = 1,200.0 mg	2,400.0 mg	4 x 500 mg + 4 x 150 mg	365	1,460 x 500 mg + 1,460 x 150 mg
Epirubicin in combination with oxaliplatin and 5-fluorouracil (5-FU) (only for patients with oesophageal adenocarcinoma)					
Epirubicin	50 mg/m² = 96.0 mg	96.0 mg	1 x 100 mg	17.4	17.4 x 100 mg
Oxaliplatin	130 mg/m² = 249.6 mg	249.6 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 mg + 17.4 x 50 mg
5-FU	200 mg/m² = 384.0 mg	384.0 mg	1 x 500 mg	365	365 x 500 mg
Docetaxel in combination with cisplatin and 5-fluorouracil (5-FU) (only for patients with oesophageal adenocarcinoma)					
Docetaxel	75 mg/m² = 144.0 mg	144.0 mg	1 x 160 mg	17.4	17.4 x 160 mg
Cisplatin	75 mg/m² = 144.0 mg	144.0 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	750 mg/m² = 1,440.0 mg	1,440.0 mg	2 x 1,000 mg	87.0	174.0 x 1,000 mg

Costs:

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

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of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

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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:					
Zolbetuximab 100 mg	1 PCI	€ 537.42	€ 1.77	€ 29.09	€ 506.56
Zolbetuximab 300 mg	1 PCI	€ 1,586.27	€ 1.77	€ 87.26	€ 1,497.24
Capecitabine 150 mg	120 FCT	€ 54.92	€ 1.77	€ 3.39	€ 49.76
Capecitabine 500 mg	120 FCT	€ 152.62	€ 1.77	€ 11.12	€ 139.73
Fluorouracil 1,000 mg	1 IIS	€ 17.45	€ 1.77	€ 0.42	€ 15.26
Fluorouracil 5,000 mg	1 IIS	€ 34.80	€ 1.77	€ 1.80	€ 31.23
Folinic acid 800 mg	5 SFI	€ 2221.88	€ 1.77	€ 176.51	€ 2043.60
Oxaliplatin 50 mg	1 CIS	€ 108.17	€ 1.77	€ 4.56	€ 101.84
Oxaliplatin 200 mg	1 CIS	€ 396.45	€ 1.77	€ 18.24	€ 376.44
Appropriate comparator therapy					
Capecitabine 150 mg	120 FCT	€ 54.92	€ 1.77	€ 3.39	€ 49.76
Capecitabine 500 mg	120 FCT	€ 152.62	€ 1.77	€ 11.11	€ 139.74
Cisplatin 10 mg	1 CIS	€ 20.44	€ 1.77	€ 1.06	€ 17.61
Cisplatin 50 mg	1 CIS	€ 48.48	€ 1.77	€ 1.73	€ 44.98
Cisplatin 100 mg	1 CIS	€ 77.36	€ 1.77	€ 3.10	€ 72.49
Docetaxel 160 mg	1 CIS	€ 262.43	€ 1.77	€ 11.88	€ 248.78
Epirubicin 100 mg	1 CIS	€ 301.62	€ 1.77	€ 13.74	€ 286.11
Fluorouracil 500 mg	1 IIS	€ 14.93	€ 1.77	€ 0.22	€ 12.94
Fluorouracil 1,000 mg	1 IIS	€ 17.45	€ 1.77	€ 0.42	€ 15.26
Fluorouracil 2,500 mg	1 SFI	€ 24.37	€ 1.77	€ 0.00	€ 22.60
Fluorouracil 5,000 mg	1 IIS	€ 34.80	€ 1.77	€ 1.80	€ 31.23
Folinic acid 400 mg	5 SFI	€ 1,185.05	€ 1.77	€ 0.00	€ 1,183.28
Folinic acid 800 mg	5 SFI	€ 2221.88	€ 1.77	€ 0.00	€ 2043.60
Nivolumab 120 mg	1 CIS	€ 1,513.18	€ 1.77	€ 83.11	€ 1428.30
Oxaliplatin 50 mg	1 CIS	€ 108.17	€ 1.77	€ 4.56	€ 101.84
Oxaliplatin 200 mg	1 CIS	€ 396.45	€ 1.77	€ 18.24	€ 376.44
Pembrolizumab 100 mg	2 CIS	€ 4,854.03	€ 1.77	€ 273.88	€ 4578.38
S 1 (tegafur/ gimeracil/ oteracil) 15 mg	84 HC	€ 344.92	€ 1.77	€ 18.43	€ 324.72
S 1 (tegafur/ gimeracil/ oteracil) 20 mg	84 HC	€ 455.87	€ 1.77	€ 24.57	€ 429.53
Abbreviations: FCT = film-coated tablets; IIS = solution for injection/ infusion; SFI = solution for injection; HC = hard capsules; PCI = powder for a concentrate for the preparation of an infusion solution					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there

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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.

The calculation of the additionally required SHI services is based on packs in distribution with the LAUER-TAXE® last revised on 15 September 2025 and fee structure items (FSI) - last revised in the 3rd quarter of 2025 of the uniform value scale (UVS 2025/Q3).

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:							
Zolbetuximab							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before administration of zolbetuximab. The product information for zolbetuximab does not provide any specific details in this regard, which is why the necessary costs cannot be quantified.							
Appropriate comparator therapy:							
Cisplatin *(pembrolizumab + cisplatin + 5-FU)* *(cisplatin + capecitabine)* *(cisplatin + 5-FU)* *(cisplatin + 5-FU + folinic acid)* *(epirubicin + cisplatin + capecitabine)* *(epirubicin + cisplatin + 5-FU)* *(docetaxel + cisplatin + 5-FU)*							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Mannitol 10% Inf. Sol., 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% Inf. Sol., 3 l - 4.4 l/day	10 x 500 ml INF	€ 13.28	€ 0.66	€ 0.96	€ 11.66	17.4	€ 104.66 - € 159.84
	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05		
Cisplatin (cisplatin + tegafur/ gimeracil/ oteracil*)*							
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.							

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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:							
Zolbetuximab							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before administration of zolbetuximab. The product information for zolbetuximab does not provide any specific details in this regard, which is why the necessary costs cannot be quantified.							
Mannitol 10% Inf. Sol., 37.5 g/day	10 x 250 ml INF	€ 87.05	€ 4.35	€ 7.94	€ 74.76	6.0	€ 74.76
Sodium chloride 0.9% Inf. Sol., 3 l - 4.4 l/day	6 x 1,000 ml INF	€ 25.09	€ 1.25	€ 2.05	€ 21.79	6.0	€ 40.10 – € 60.15
	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05		

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic 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-apply 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.

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 12 August 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

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On 12 May 2026, the pharmaceutical company submitted a dossier for the benefit assessment of zolbetuximab to the GBA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 6 VerfO.

By the letter dated 13 May 2026 in conjunction with the resolution of the GBA 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 GBA commissioned the IQWiG to assess the dossier concerning the active ingredient zolbetuximab.

The dossier assessment by the IQWiG was submitted to the GBA on 12 August 2026, and the written statement procedure was initiated with publication on the GBA website on 17 August 2026. The deadline for submitting written statements was 7 September 2026.

The oral hearing was held on 21 September 2026.

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 Subcommittee's session on 27 October 2026, and deliberation of the draft resolution was concluded.

At their session on 5 November 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	12 August 2025	Determination of the appropriate comparator therapy
Working group Section 35a	15 September 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	21 September 2026	Conduct of the oral hearing
Working group Section 35a	29 September 2026 13 October 2026	Consultation on the dossier assessment by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	27 October 2026	Concluding discussion of the draft resolution

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Plenum	5 November 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 5 November 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Dr Optendrenk

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