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
Zolbetuximab (gastric or gastro-oesophageal junction (GEJ) adenocarcinoma)

of 17 April 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.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at their session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at their session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section

35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient zolbetuximab on 1 November 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 31 October 2024.

Zolbetuximab for the treatment of gastric or gastro-oesophageal junction (GEJ) adenocarcinoma is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 3 February 2025 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA adopted its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G24-32) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of zolbetuximab.

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

2.1 Additional benefit of the medicinal product

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 17 April 2025):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive

Indication of a minor additional benefit

Justification:

For the benefit assessment, the pharmaceutical company presented results from the phase III GLOW study and the open-label phase II FAST study as well as additionally presented results from the phase III SPOTLIGHT study. The GLOW study and the additionally presented SPOTLIGHT study are considered in the benefit assessment. In addition, as part of the written statement procedure, the pharmaceutical company subsequently submitted a meta-analysis, which is also taken into account for the benefit assessment. The FAST study presented in the dossier is not used for the benefit assessment, as it is unclear whether the population corresponds to the therapeutic indication.

GLOW study

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

254 subjects were randomised to the intervention arm (zolbetuximab + CAPOX) and 253 subjects to the control arm (placebo + CAPOX). Randomisation was performed, stratified by "region" (Asia; non-Asia), "number of organs with metastases" (0-2; ≥ 3) and "previous gastrectomy" (yes; no). The baseline characteristics were largely balanced between the treatment arms. The dosage of zolbetuximab in both studies corresponds to the recommended dose according to the product information.

Treatment with zolbetuximab should be continued until tumour progression, initiation of a new antineoplastic therapy, unacceptable toxicity, withdrawal of consent, decision of the medical investigator, "lost to follow-up" or end of study.

All subjects in the intervention arm and 98.4% in the control arm received at least one dose of the study medication. The safety population therefore differs slightly from the ITT population.

The study was conducted in study sites in Europe, North and South America as well as Asia; a German study site was not involved.

The primary endpoint of the study was progression-free survival (PFS). Other endpoints were overall survival and endpoints in the categories morbidity, health-related quality of life and side effects. For the benefit assessment, the results of the final data cut-off from 12.01.2024 are used.

SPOTLIGHT study

The SPOTLIGHT study is a double-blind, randomised, placebo-controlled phase III study to investigate the efficacy of zolbetuximab in combination with oxaliplatin, 5-fluorouracil and folinic acid (modified FOLFOX-6 regimen; mFOLOFX6) versus placebo in combination with mFOLFOX6.

283 subjects were randomised to the intervention arm (zolbetuximab + mFOLFOX6) and 282 subjects to the control arm (placebo + mFOLFOX6). Randomisation was performed, stratified by "region" (Asia; non-Asia), "number of organs with metastases" (0-2; ≥ 3) and "previous gastrectomy" (yes; no). The baseline characteristics were largely balanced between the treatment arms.

Treatment with zolbetuximab should be continued until tumour progression, initiation of a new antineoplastic therapy, unacceptable toxicity, withdrawal of consent, decision of the medical investigator, "lost to follow-up" or end of study.

At least one dose of the study medication was received by 98.6% of subjects in the intervention arm and in the control arm respectively. The safety population in both arms therefore differs slightly from the ITT population.

The study was conducted in study sites in Europe, North and South America, Australia as well as Asia; 11 study sites were located in Germany.

The primary endpoint of the study was progression-free survival (PFS). Other endpoints were overall survival and endpoints in the categories morbidity, health-related quality of life and side effects. For the benefit assessment, the results of the final data cut-off from 08.09.2023 are used.

FAST study

The FAST study is an open-label, randomised, placebo-controlled phase II study to investigate the efficacy and safety of zolbetuximab in combination with epirubicin, oxaliplatin and capecitabine (EOX) versus placebo in combination with EOX. The study is not used for the benefit assessment, as it is unclear whether the population corresponds to the therapeutic indication.

Zolbetuximab is approved for patients with HER2-negative gastric and GEJ adenocarcinomas whose tumours are CLDN-18.2-positive. As the study population in the FAST study was more comprehensive than the therapeutic indication, the pharmaceutical company depicted the modified ITT population (mITT) in the dossier using criteria analogous to the therapeutic indication. Patients with a positive HER2 status were excluded; patients with an unknown HER2 status were not excluded. Information on HER2 status was missing in a total of 88% of the mITT population of the FAST study.

As part of the benefit assessment, the G-BA used epidemiological data on the distribution of HER2 status to estimate the percentage of patients with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma. As a result, it was found that a positive HER2 status is not so rare that it can be safely assumed that the percentage of HER2-negative subjects in the FAST study is at least 80%.

As part of the written statement procedure, the pharmaceutical company subsequently submitted further information on the percentage of HER2-positive patients in other studies. However, these were not systematically researched. Relevant information on the patients in the FAST study who had an unknown HER2 status was not subsequently submitted. It can therefore still not be safely assumed that the percentage of HER2-negative subjects in the FAST study is at least 80%.

Meta-analysis of the GLOW and SPOTLIGHT studies

The pharmaceutical company presented a meta-analysis of the GLOW and SPOTLIGHT studies as part of the written statement procedure. In addition to the results of the individual studies, the results of the meta-analysis are used as a basis for the benefit assessment.

Comparison between the GLOW and SPOTLIGHT studies

Patients in the intervention arm of the GLOW study were treated with zolbetuximab shorter by 2.6 months than those in the SPOTLIGHT study. The various components of chemotherapy were also administered over a shorter period of time in the GLOW study than in the SPOTLIGHT study, although the difference between the studies is smaller.

When comparing the baseline characteristics, it is noticeable that the percentage of patients from Asia was higher in the GLOW study (62.1%) than in the SPOTLIGHT study (31.3%). In the GLOW study, the tumour was located in the stomach in 84.4% of patients and in the GEJ in 15.6%. In the SPOTLIGHT study, tumours were slightly less common in the stomach (75.9%) and slightly more common in the GEJ (24.1%). In the GLOW study, 50.7% had a CPS status < 5; in the SPOTLIGHT study, the percentage was slightly higher at 60.7%. The other baseline characteristics of the studies were largely similar.

The differences in the results of the two studies could be due to both the differences in patient characteristics and the different chemotherapy regimens.

<u>Comparator therapies in the GLOW and SPOTLIGHT studies</u>

In the GLOW and SPOTLIGHT studies, 15.8% and 8.5% of patients in the comparator arm had a CPS status ≥ 5 and 33.6% and 30.1% of patients had an unknown CPS status. Recommendations from a current guideline indicate that a PD-1 inhibitor can be added to fluoropyrimidine/platinum-based chemotherapy in patients with HER2-negative and PD-L1-positive tumours (defined as CPS ≥ 1)[2]. As part of the written statement procedure, the clinical experts stated that the CPS status, in particular a CPS status ≥ 5, is relevant for the treatment decision in patient care. In this regard, treatment with a PD-1 inhibitor in addition to fluoropyrimidine/ platinum-based chemotherapy is available for patients with PD-L1-positive tumours (defined as CPS ≥ 1). The extent to which patients in the comparator arms of the studies would be eligible for treatment with an immune checkpoint inhibitor due to their CPS

[2] Rajdev, Lakshmi, Erin B. Kennedy, and Manish A. Shah. "Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline Q and A." JCO Oncology Practice 19.4 (2023): 197-200.

status in relation to the current healthcare context remains open, particularly due to the percentage of patients with an unknown CPS status.

The comparator therapy in the SPOTLIGHT study - the modified FOLFOX-6 regimen - does not currently have marketing authorisation in Germany.

Mortality

The overall survival is operationalised in the GLOW and SPOTLIGHT studies as the time from randomisation to death from any cause or end of study.

For the overall survival endpoint, the GLOW and SPOTLIGHT studies and the meta-analysis of these two studies showed a statistically significant difference between the treatment arms. Although the extent of the achieved prolongation in survival time is assessed as a relevant improvement, its extent is minimal.

Morbidity

Progression-free survival

Progression-free survival (PFS) was operationalised in the GLOW and SPOTLIGHT studies as the time from randomisation to occurrence of a radiological disease progression or death from any cause. The endpoint was collected by principal investigators on site and was assessed according to the RECIST criteria version 1.1. For the PFS endpoint, both the GLOW and SPOTLIGHT studies showed a statistically significant advantage of zolbetuximab in combination with CAPOX (GLOW study) or mFOLFOX6 (SPOTLIGHT study).

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" was already assessed as an independent endpoint in the present study via the endpoint "overall survival". The morbidity component assessment was not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST version 1.1 criteria).

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

Symptomatology

Symptomatology was assessed using the EORTC QLQ-C30, EORTC QLQ-OG25 and EQ-5D-5L-VAS instruments. In addition, pain severity was assessed using a numerical rating scale (NRS). In the dossier, the pharmaceutical company submitted time-to-event analyses of the time to first deterioration.

The results were not presented due to low return rates at the end of treatment (< 70%) and in the follow-up phase (30- and 90-day follow-up). In order to fully map the effects of the intervention and control on the symptoms and to be able to adequately interpret/ compare the results, these data are required at the end of treatment especially because a deteriorated health status becomes more likely at the end of treatment or a deteriorated health status can lead to the end of treatment. There is no further information on reasons for censoring.

Quality of life

EORTC QLQ-C30

Health-related quality of life was assessed using the EORTC QLQ-C30 instrument. The pharmaceutical company presented time-to-event analyses of the time to first deterioration in the dossier.

The results were not presented due to low return rates at the end of treatment (< 70%) and in the follow-up phase (30- and 90-day follow-up). Furthermore, there is no information on reasons for censoring (detailed description in the section on symptomatology).

Side effects

Adverse events (AEs) in total

In the GLOW and SPOTLIGHT studies, AEs occurred in both study arms in almost all patients. The results were only presented additionally.

Serious adverse events (SAE)

For the endpoint, there was no statistically significant difference between the treatment groups.

Severe adverse events (CTCAE grade 3 or 4)

For the endpoint of severe AEs, the SPOTLIGHT study and the meta-analysis of the GLOW and SPOTLIGHT studies showed a statistically significant difference to the disadvantage of zolbetuximab in combination with mFOLFOX6 or chemotherapy.

Therapy discontinuation due to adverse events

For the endpoint of therapy discontinuation due to AEs, the meta-analysis of the GLOW and SPOTLIGHT studies showed a statistically significant difference to the disadvantage of zolbetuximab in combination with chemotherapy.

Specific AEs

In detail, for the severe AEs (with an incidence ≥ 5% or ≥ 10 subjects in at least one study arm), there were statistically significant disadvantages in the intervention arm for "Neutropenia, PT" (GLOW study), "Loss of appetite, PT" (GLOW study and meta-analysis), "Hypoalbuminaemia, PT" (SPOTLIGHT study) "Gastrointestinal disorders, SOC", "Asthenia, PT", "Metabolism and nutrition disorders, SOC" (SPOTLIGHT study and meta-analysis respectively), "Nausea, PT", "Vomiting, PT" (GLOW and SPOTLIGHT studies respectively as well as meta-analysis), and "Vascular disorders, SOC" (meta-analysis). There was a statistically significant advantage in the intervention arm for "Alanine aminotransferase increased, PT" (SPOTLIGHT study and meta-analysis).

For SAEs (with an incidence ≥ 5% or ≥ 10 subjects in at least one study arm), there were statistically significant disadvantages in the intervention arm for "Injury, poisoning and procedural complications, SOC" (meta-analysis) and "Loss of appetite, PT" (GLOW study) as well as statistically significant advantages for "Respiratory, thoracic and mediastinal disorders, SOC" (GLOW study).

For the AEs of special interest, there were statistically significant disadvantages in the intervention arm for "Nausea (AE regardless of severity grade)", "Nausea (severe AE)",

"Vomiting (AE regardless of severity grade)", "Vomiting (severe AE)", "Infusion-related reactions (AE regardless of severity grade)", "Infusion-related reactions (severe AE, CTCAE grade ≥ 3)", "Infusion-related reactions (SAE)" (GLOW and SPOTLIGHT studies respectively as well as meta-analysis) and "Stomach pain (severe AE)" (SPOTLIGHT study).

Conclusion on side effects

In the overall analysis, with regard to the endpoint category of side effects, disadvantages of zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy compared to placebo in combination with fluoropyrimidine- and platinum-containing chemotherapy were observed for the severe AEs in the SPOTLIGHT study, and disadvantages were observed for the severe AEs and therapy discontinuation due to AEs in the meta-analysis. In detail, there were disadvantages and some advantages for specific AEs.

Overall assessment/ conclusion

The results from the double-blind, placebo-controlled phase III GLOW and SPOTLIGHT studies as well as a meta-analysis of these two studies are available for the benefit assessment. In the GLOW study, zolbetuximab in combination with capecitabine in combination with oxaliplatin (CAPOX) was compared with placebo in combination with CAPOX and in the SPOTLIGHT study, zolbetuximab in combination with oxaliplatin + 5-fluorouracil + folinic acid (mFOLFOX6) was compared with placebo in combination with mFOLFOX6. Results on mortality, morbidity, quality of life and side effects are available in each case.

For the overall survival endpoint, there was a statistically significant difference to the advantage of zolbetuximab in combination with CAPOX or mFOLFOX6. Although the extent of the achieved prolongation in survival time is assessed as a relevant improvement, its extent is minimal.

No assessable data on morbidity and health-related quality of life are available.

With regard to side effects, disadvantages of zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy were observed for severe AEs in the SPOTLIGHT study and disadvantages were observed for severe AEs and therapy discontinuation due to AEs in the meta-analysis. In detail, disadvantages were predominantly observed for specific AEs in the GLOW and SPOTLIGHT studies as well as the meta-analysis.

In the overall analysis, the positive effect on overall survival is offset by disadvantages in terms of side effects. These disadvantages do not question the extent of the improvement in overall survival. No assessable data on morbidity and health-related quality of life are available. Overall, a minor additional benefit was therefore identified.

Significance of the evidence

This benefit assessment is based on the results of the double-blind, placebo-controlled phase III GLOW and SPOTLIGHT studies as well as the meta-analysis of these two studies.

The risk of bias is considered to be low at study level and for the endpoints of overall survival and side effects.

No assessable data on morbidity and health-related quality of life are available. In view of the fact that high significance is attributed to statements on quality of life especially in the advanced palliative situation, there is uncertainty regarding the significance of the evidence.

Overall, the G-BA derives an indication of the identified additional benefit with regard to the significance of the evidence.

2.1.3 Summary of the assessment

The present benefit assessment concerns the benefit assessment of the new medicinal product Vyloy with the active ingredient zolbetuximab.

Zolbetuximab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, was approved as an orphan drug for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive.

The results from the double-blind, placebo-controlled phase III GLOW and SPOTLIGHT studies as well as a meta-analysis of these two studies are available for the benefit assessment. The GLOW study compared zolbetuximab in combination with capecitabine in combination with oxaliplatin (CAPOX) with placebo in combination with CAPOX or mFOLFOX6, while the SPOTLIGHT study compared zolbetuximab in combination with oxaliplatin + 5-fluorouracil + folinic acid (mFOLFOX6) with the latter.

For the overall survival endpoint, there was a statistically significant difference to the advantage of zolbetuximab in combination with CAPOX or mFOLFOX6. Although the prolongation of survival time achieved is assessed as a relevant improvement, its extent is minimal.

No assessable data on morbidity and health-related quality of life are available.

In terms of side effects, there were disadvantages for severe AEs and therapy discontinuation due to AEs, as well as disadvantages for specific AEs.

In the overall analysis, the positive effect on overall survival is offset by disadvantages in terms of side effects. These disadvantages do not question the extent of the improvement in overall survival. No assessable data on morbidity and health-related quality of life are available. Overall, a minor additional benefit was therefore identified.

The significance of the evidence for the additional benefit identified is classified in the "indication" category overall.

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).

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of pembrolizumab (resolution of 20 June 2024).

The number of patients with a negative HER2 status from the pembrolizumab procedure (716 to 3,797 patients) is used as the basis for calculating the patient numbers for this resolution. In a subsequent calculation step, the patient population is narrowed down to patients with Claudin 18.2-positive tumours. 39.4% patients with Claudin 18.2-positive tumours therefore results in a number of 282 to 1,496 patients. Taking into account the percentage of SHI-insured patients (87.7%), the following step results in a number of 247 to 1,312 patients.

Due to uncertainties regarding the data basis in the target population in Germany both an overestimation and an underestimation of patient numbers are possible.

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: 24 January 2025):

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

Treatment with zolbetuximab 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 gastro-oesophageal junction carcinomas.

Eligible patients should 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 agent (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 requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 April 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 locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive; 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				
Zolbetuximab in combination with oxaliplatin, folinic acid and 5-fluorouracil (mFOLFOX6)				
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 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-fluorouracil (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

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 locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive; 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					
Zolbetuximab in combination with oxaliplatin, folinic acid and 5-fluorouracil (mFOLFOX6)					
Zolbetuximab (initial single dose)					
Zolbetuximab	800 mg/m² = 1,528.0 mg	1,528.0 mg	16 x 100 mg	1	16 x 100 mg
Zolbetuximab (maintenance doses)					
Zolbetuximab	600 mg/m² = 1,146.0 mg	1,146.0 mg	12 x 100 mg	16.4	196.8 x 100 mg
	or				
	400 mg/m² = 764.0 mg	764.0 mg	8 x 100 mg	25.1	200.8 x 100 mg
in combination with mFOLFOX6					
Oxaliplatin	85 mg/m² = 162.4 mg	162.4 mg	1 x 200 mg	26.1	26.1 x 200 mg
Folinic acid	400 mg/m² = 764.0 mg	764.0 mg	1 x 800 mg	26.1	26.1 x 800 mg
5-fluorouracil (5-FU)	*Bolus* 400 mg/m² = 764.0 mg	764.0 mg	1 x 1000 mg	26.1	26.1 x 1000 mg
	Continuous infusion 2400 mg/m²	4584.0 mg	1 x 5000 mg		26.1 x 5000 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
	= 4584.0 mg				
Zolbetuximab in combination with oxaliplatin and capecitabine (CAPOX)					
Zolbetuximab (initial single dose)					
Zolbetuximab	800 mg/m² = 1,528.0 mg	1528.0 mg	16 x 100 mg	1	16 x 100 mg
Zolbetuximab (maintenance doses)					
Zolbetuximab	600 mg/m² = 1,146.0 mg	1,146.0 mg	12 x 100 mg	16.4	196.8 x 100 mg
	or				
	400 mg/m² = 764.0 mg	764.0 mg	8 x 100 mg	25.1	200.8 x 100 mg
in combination with CAPOX					
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
Capecitabine	1000 mg/m² = 1800.0 mg	3600.0 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:

Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive; first-line therapy

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 100mg	3 PII	€ 1,983.53	€ 1.77	€ 109.99	€ 1,871.77
Calcium folinate[4] 800 mg	1 SFI	€ 304.65	€ 1.77	€ 23.20	€ 279.45
Capecitabine[4] 150 mg	120 FCT	€ 54.15	€ 1.77	€ 3.39	€ 48.76
Capecitabine[4] 500 mg	120 FCT	€ 151.84	€ 1.77	€ 11.11	€ 138.96
5-fluorouracil[4] 5,000 mg	1 SFI	€ 34.02	€ 1.77	€ 1.80	€ 30.45
5-fluorouracil[4] 1,000 mg	1 SII	€ 16.67	€ 1.77	€ 0.42	€ 14.48
Oxaliplatin 50 mg	1 CIS	€ 107.06	€ 1.77	€ 4.54	€ 100.75
Oxaliplatin 200 mg	1 CIS	€ 396.85	€ 1.77	€ 18.30	€ 376.78
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; SII = solution for injection/infusion; SFI = solution for injection; PII = powder for the preparation of a solution for injection or infusion					

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Costs for additionally required SHI services:

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

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

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 information on this, which is why the necessary costs cannot be quantified.							

[4] Fixed reimbursement rate

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 locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive; 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 zolbetuximab (Vyloy); Vyloy 100 mg powder for a concentrate for the preparation of an infusion solution; last revised: January 2025

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

On 31 October 2024, the pharmaceutical company submitted a dossier for the benefit assessment of zolbetuximab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 3 February 2025 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting

statements was 24 February 2025.

The oral hearing was held on 10 March 2025.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 28 March 2025.

A new version of the G-BA's dossier assessment was prepared on 28 March 2025. This version 1.1 of 28 March 2025 replaces version 1.0 of the dossier assessment of 3 February 2025 and was brought to the attention of the Subcommittee on Medicinal Products at its session on 8 April 2025. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 8 April 2025, and the draft resolution was approved.

At their session on 17 April 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	28 January 2025	Information of the benefit assessment of the G-BA
Working group Section 35a	4 March 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 March 2025	Conduct of the oral hearing
Working group Section 35a	18 March 2025 1 April 2025	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	8 April 2025	Concluding discussion of the draft resolution
Plenum	17 April 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 17 April 2025

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

Prof. Hecken