Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At their session on 17 April 2025, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient Zolbetuximab as follows:

Zolbetuximab

Resolution of: 17 April 2025
Entry into force on: 17 April 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 19 September 2024):

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 therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Zolbetuximab is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with 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.

The G-BA determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

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

Extent of the additional benefit and significance of the evidence of zolbetuximab:

Indication of a minor additional benefit

Study results according to endpoints:[1]

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

[1] Data from the dossier evaluation of the G-BA (published on 3. February 2025), and from the amendment to the dossier assessment from 28 March 2025, unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↓↓	Disadvantages for severe AEs and therapy discontinuation due to AEs (meta-analysis). In detail, there are disadvantages and individual advantages for specific AEs (GLOW and SPOTLIGHT studies, meta-analysis).
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

Studies:

GLOW study:

- multicentre, double-blind, placebo-controlled phase III study
- Zolbetuximab in combination with capecitabine in combination with oxaliplatin (CAPOX) **vs** placebo in combination with CAPOX
- Final data cut-off: 12.01.2024 (final OS analysis)

SPOTLIGHT study:

- multicentre, double-blind, placebo-controlled phase III study
- Zolbetuximab in combination with oxaliplatin + 5-fluorouracil + folinic acid (mFOLFOX6) **vs** placebo in combination with mFOLFOX6
- Final data cut-off: 08.09.2023 (final OS analysis)

Meta-analysis of the GLOW and SPOTLIGHT studies

Mortality

Endpoint	Zolbetuximab (GLOW: + CAPOX) (SPOTLIGHT: + mFOLFOX6)		Placebo (GLOW: + CAPOX) (SPOTLIGHT: + mFOLFOX6)		Zolbetuximab vs placebo
	N[a]	Median survival time in months [95% CI] *Patients with event n (%)*	N[a]	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[b] Absolute difference (AD)[c]
Overall survival					
GLOW	254	14.3 [12.1; 16.4] 180 (70.9)	253	12.2 [10.3; 13.7] 207 (81.8)	0.76 [0.62; 0.94] 0.009 AD: + 1.9 months
SPOTLIGHT	283	18.2 [16.1; 20.6] 197 (69.6)	282	15.6 [13.7; 16.9] 217 (77.0)	0.78 [0.64; 0.95] 0.015 AD: + 2.6 months
Meta-analysis	537	16.4 [15.0; 17.9] 377 (70.2)	535	13.7 [12.3; 15.3] 424 (79.3)	0.77 [0.67; 0.89] 0.0004 AD: + 2.7 months

Morbidity

Progression-free survival (PFS) (presented additionally)[d]					
GLOW	254	8.2 [7.3, 8.8] 153 (60.2)	253	6.8 [6.1, 8.1] 182 (71.9)	0.69 [0.55; 0.86] 0.0009 AD: + 1.4 months
SPOTLIGHT	283	11.0 [9.7; 12.5] 159 (56.2)	282	8.9 [8.2; 10.4] 187 (66.3)	0.73 [0.59; 0.91]; 0.0048 AD: + 2.1 months
Symptomatology					
EORTC QLQ-C30					
GLOW	No suitable data[e]				
SPOTLIGHT	No suitable data[e]				
EORTC QLQ-OG25					
GLOW	No suitable data[e]				
SPOTLIGHT	No suitable data[e]				
EQ-5D-5L-VAS					
GLOW	No suitable data[e]				
SPOTLIGHT	No suitable data[e]				

Pain severity using NRS	
GLOW	No suitable data[e]
SPOTLIGHT	No suitable data[e]

Health-related quality of life

EORTC QLQ-C30	
GLOW	No suitable data[e]
SPOTLIGHT	No suitable data[e]

Side effects

Endpoint **MedDRA system organ classes/ preferred terms/ AEs of special interest**	**Zolbetuximab (GLOW: + CAPOX) (SPOTLIGHT: + mFOLFOX6)**		**Placebo (GLOW: + CAPOX) (SPOTLIGHT: + mFOLFOX6)**		Zolbetuximab vs placebo
	N[a]	*Patients with event n (%)*	N[a]	*Patients with event n (%)*	Relative risk[f] [95% CI] p value[g]
Total adverse events (presented additionally)					
GLOW	254	251 (98.8)	249	244 (98.0)	-
SPOTLIGHT	279	278 (99.6)	278	277 (99.6)	-
Meta-analysis[h]	533	529 (99.3)	527	521 (98.9)	-
Serious adverse events (SAE)					
GLOW	254	123 (48.4)	249	126 (50.6)	0.97 [0.82; 1.16] 0.66
SPOTLIGHT	279	133 (47.7)	278	129 (46.4)	1.02 [0.86; 1.21] 0.77
Meta-analysis[h]	533	256 (48.0)	527	255 (48.4)	1.00 [0.88; 1.13] 0.96
Severe adverse events (CTCAE grade 3 or 4)					
GLOW	254	186 (73.2)	249	175 (70.3)	1.06 [0.95; 1.18] 0.43
SPOTLIGHT	279	244 (87.5)	278	219 (78.8)	1.12 [1.04; 1.21] 0.01
Meta-analysis[h]	533	430 (80.7)	527	394 (74.8)	1.10 [1.03; 1.17] 0.003
Therapy discontinuation due to adverse events					
GLOW	254	81 (31.9)	249	64 (25.7)	1.26 [0.95; 1.68]

					0.12
SPOTLIGHT	279	125 (44.8)	278	107 (38.5)	1.16 [0.95; 1.41] 0.13
Meta-analysis[h]	533	206 (39.0)	527	171 (32.4)	1.19 [1.01; 1.40] 0.03
Severe adverse events according to MedDRA (with an incidence ≥ 5% or ≥ 10 subjects in at least one study arm and statistically significant difference between the treatment arms; SOC and PT)					
Neutropenia, PT					
GLOW	254	18 (7.1)	249	7 (2.8)	2.03 [0.84; 4.94] 0.03
Gastrointestinal disorders, SOC					
SPOTLIGHT	279	102 (36.6)	278	56 (20.1)	1.79 [1.35; 2.37] < 0.0001
Meta-analysis[h]	533	177 (33.2)	527	118 (22.4)	1.47 [1.20; 1.80] 0.0002
Nausea, PT					
GLOW	254	22 (8.7)	249	6 (2.4)	2.59 [1.15; 5.84] 0.0022
SPOTLIGHT	279	45 (16.1)	278	19 (6.8)	2.15 [1.29; 3.57] 0.0006
Meta-analysis[h]	533	67 (12.6)	527	25 (4.7)	2.26 [1.47; 3.49] 0.0002
Vomiting, PT					
GLOW	254	31 (12.2)	249	9 (3.6)	2.78 [1.40; 5.51] 0.0004
SPOTLIGHT	279	45 (16.1)	278	17 (6.1)	2.42 [1.44; 4.08] 0.0001
Meta-analysis[h]	533	76 (14.3)	527	26 (4.9)	2.55 [1.68; 3.86] < 0.0001
Asthenia, PT					
SPOTLIGHT	279	21 (7.5)	278	7 (2.5)	2.32 [1.04; 5.18] 0.01
Meta-analysis[h]	533	28 (5.3)	527	10 (1.9)	2.13 [1.08; 4.20] 0.03
Alanine aminotransferase increased, PT					
SPOTLIGHT	279	2 (0.7)	278	10 (3.6)	0.38 [0.10; 1.46] 0.02
Meta-analysis[h]	533	4 (0.8)	527	17 (3.2)	0.35 [0.13; 0.95] 0.04
Metabolism and nutrition disorders, SOC					

SPOTLIGHT	279	66 (23.7)	278	35 (12.6)	1.74 [1.18; 2.56] 0.0008
Meta-analysis[h]	533	107 (20.1)	527	68 (12.9)	1.47 [1.10; 1.96] 0.01
Loss of appetite, PT					
GLOW	254	17 (6.7)	249	4 (1.6)	3.25 [1.27; 8.34] 0.0033
Meta-analysis[h]	533	34 (6.4)	527	13 (2.5)	2.23 [1.17; 4.26] 0.01
Hypoalbuminaemia, PT					
SPOTLIGHT	279	12 (4.3)	278	2 (0.7)	3.74 [1.01; 13.80] 0.01
Respiratory, thoracic and mediastinal disorders, SOC					
GLOW	254	11 (4.3)	249	22 (8.8)	0.55 [0.26; 1.16] 0.04
Vascular disorders, SOC					
Meta-analysis[h]	533	21 (3.9)	527	13 (2.5)	1.83 [1.06; 3.14] 0.03
SAEs according to MedDRA (with an incidence ≥ 5% or ≥ 10 subjects in at least one study arm and statistically significant difference between the treatment arms; SOC and PT)					
Injury, poisoning and procedural complications, SOC					
Meta-analysis[h]	533	21 (3.9)	527	6 (1.1)	2.37 [1.09; 5.12] 0.03
Loss of appetite, PT					
GLOW	254	10 (3.9)	249	3 (1.2)	2.28 [0.79; 6.58] 0.04
Respiratory, thoracic and mediastinal disorders, SOC					
GLOW	254	10 (3.9)	249	23 (9.2)	0.61 [0.29; 1.30] 0.02
Adverse events of special interest (with statistically significant difference between the treatment arms)					
Nausea (AE regardless of severity grade)					
GLOW	254	175 (68.9)	249	125 (50.2)	1.36 [1.17; 1.57] < 0.0001
SPOTLIGHT	279	230 (82.4)	278	171 (61.5)	1.25 [1.13; 1.39] < 0.0001
Meta-analysis[h]	533	405 (76.0)	527	296 (56.2)	1.28 [1.18; 1.40] < 0.0001
Nausea (severe AE)					

GLOW	254	22 (8.7)	249	6 (2.4)	2.59 [1.15; 5.84] 0.002
SPOTLIGHT	279	45 (16.1)	278	19 (6.8)	2.15 [1.29; 3.57] 0.0006
Meta-analysis[h]	533	67 (12.6)	527	25 (4.7)	2.26 [1.47; 3.49] 0.0002
Vomiting (AE regardless of severity grade)					
GLOW	254	169 (66.5)	249	79 (31.7)	2.06 [1.68; 2.53] < 0.0001
SPOTLIGHT	279	188 (67.4)	278	103 (37.1)	1.80 [1.51; 2.14] < 0.0001
Meta-analysis[h]	533	357 (67.0)	527	182 (34.5)	1.90 [1.67; 2.17] < 0.0001
Vomiting (severe AE)					
GLOW	254	31 (12.2)	249	9 (3.6)	2.78 [1.40; 5.51] 0.0004
SPOTLIGHT	279	45 (16.1)	278	17 (6.1)	2.42 [1.44; 4.08] 0.0001
Meta-analysis[h]	533	76 (14.3)	527	26 (4.9)	2.55 [1.68; 3.86] < 0.0001
Abdominal pain (severe AE)					
SPOTLIGHT	279	18 (6.5)	278	7 (2.5)	2.18 [0.87; 5.46] 0.03
Infusion-related reactions (AE regardless of severity grade)					
GLOW	254	91 (35.8)	249	25 (10.0)	2.96 [1.96; 4.48] < 0.0001
SPOTLIGHT	279	125 (44.8)	278	33 (11.9)	3.38 [2.37; 4.82] < 0.0001
Meta-analysis[h]	533	216 (40.5)	527	58 (11.0)	3.20 [2.44; 4.18] < 0.0001
Infusion-related reactions (severe AE, CTCAE grade ≥ 3)					
GLOW	254	17 (6.7)	249	1 (0.4)	4.43 [1.34; 14.67] 0.0002
SPOTLIGHT	279	20 (7.2)	278	2 (0.7)	3.99 [1.18; 13.46] < 0.0001
Meta-analysis[h]	533	37 (6.9)	527	3 (0.6)	4.21 [1.79; 9.88] 0.001
Infusion-related reactions (SAE)					

GLOW	254	9 (3.5)	249	0	4.52 [1.17; 17.51] 0.002
SPOTLIGHT	279	8 (2.9)	278	0	4.64 [1.01; 21.42] 0.004
Meta-analysis[h]	533	17 (3.2)	527	0 (0.0)	4.57 [1.66; 12.60] 0.003

a. The number corresponds to those subjects who were used to calculate the respective statistics.
b. HR based on Cox proportional hazards model, stratified by the stratification factors of randomisation ("region", "number of organs with metastases", "previous gastrectomy"); p value based on stratified two-tailed log-rank test, stratified by the stratification factors of randomisation.
c. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
d. Primary endpoint of the GLOW and SPOTLIGHT studies
e. No suitable data available; for justification, see sections 3.3 and 3.4 of the present dossier assessment
f. Estimation using the stratified logit method with zero cell correction, stratified by the stratification factors of randomisation ("region" (Asia; non-Asia), "number of organs with metastases" (0-2; ≥ 3), "previous gastrectomy" (yes; no)).
g. p value based on stratified log-rank test.
h. Based on fixed effects, no heterogeneity was found.

Abbreviations used:
AD = absolute difference; CAPOX = capecitabine + oxaliplatin; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; n.d.: no data available; CI = confidence interval; mFOLFOX6 = modified FOLFOX-6 regimen (oxaliplatin + 5-fluorouracil + folinic acid); N = number of patients evaluated; n = number of patients with (at least one) event; n.a. = not assessable; n.r. = not reached; n.a. = not applicable; (S)AE = (serious) adverse event; vs = versus

2. Number of patients or demarcation of patient groups eligible for treatment

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

Approx. 250 – 1,310 patients

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.

4. Treatment costs

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	Annual treatment costs/ patient
Medicinal product to be assessed:	
Zolbetuximab in combination with oxaliplatin, folinic acid and fluorouracil (mFOLFOX6)	
Zolbetuximab	€ 132,770.88 - € 135,266.58
Oxaliplatin	€ 9,833.96
Folinic acid	€ 7,299.65
Fluorouracil (5-FU)	€ 1,172.67
Total	€ 151,077.16 - € 153,572.86
Zolbetuximab in combination with oxaliplatin and capecitabine (CAPOX)	
Zolbetuximab	€ 132,770.88 - € 135,266.58
Oxaliplatin	€ 8,309.02
Capecitabine	€ 2,090.33
Total	€ 143,170.23 - € 145,665.93

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 April 2025)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed					
Zolbetuximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4	€ 1,740
				or	
				26.1	€ 2,610
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	26.1	€ 2,610
				or	
				17.4	€ 1,740
Folinic acid	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	26.1	€ 2,610
5-FU *Bolus*	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	26.1	€ 2,610
5-FU *22 h infusion*	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	26.1	€ 2,610

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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. 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.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 17 April 2025.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 17 April 2025

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

Prof. Hecken