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 and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Amivantamab (new therapeutic indication: non-small cell lung cancer, EGFR Exon 19 deletions or Exon 21 substitution mutations (L858R), combination with lazertinib)

of 17 July 2025

At their session on 17 July 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. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Amivantamab in accordance with the resolution of 7 July 2022:

Amivantamab

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

New therapeutic indication (according to the marketing authorisation of 19 December 2024):

Rybrevant is indicated in combination with lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations.

Therapeutic indication of the resolution (resolution of 17 July 2025):

See new therapeutic indication according to marketing authorisation.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Adults with advanced NSCLC and EGFR Exon 19 deletions or Exon 21 L858R substitution mutations; first-line treatment

Appropriate comparator therapy:

- Afatinib (only for patients with the activating EGFR Exon 19 deletion mutation)

  or

- Osimertinib

Extent and probability of the additional benefit of amivantamab in combination with lazertinib compared with osimertinib:

Hint for a minor additional benefit

Study results according to endpoints:[1]

[1] Data from the dossier assessment of the IQWiG (A25-08) and from the addendum (A25-77), unless otherwise indicated.

Adults with advanced NSCLC and EGFR Exon 19 deletions or Exon 21 L858R substitution mutations; first-line treatment

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival.
Morbidity	↑	Advantages in the endpoints of diarrhoea and appetite loss.
Health-related quality of life	↓	Disadvantages in physical functioning and role functioning.
Side effects	↓	Disadvantages in the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs. In detail, disadvantages in specific AEs.
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		

MARIPOSA study:

- Multicentre, randomised, controlled, partially blinded phase III study
- Amivantamab in combination with lazertinib versus osimertinib versus lazertinib
- Relevant sub-population: Amivantamab in combination with lazertinib versus osimertinib
- Data cut-off from 04.12.2024

Mortality

Endpoint	Amivantamab + lazertinib		Osimertinib		Intervention versus control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI]; p value
Overall survival					
	429	n.r. [42.9; n.c.] *173 (40.3)*	429	36.7 [33.4; 41.0] *217 (50.6)*	0.75 [0.61; 0.92]; 0.005[a]

Effect modification by the "age" characteristic					
< 65	235	n.r. *76 (32.3)*	237	35.61 [31.05; 42.42] *123 (51.9)*	0.53 [0.40; 0.70]; < 0.001
≥ 65	194	35.61 [30.42; n.c.] *97 (50.0)*	192	37.72 [34.23; n.c.] *94 (49.0)*	1.11 [0.84; 1.48]; 0.467
				Interaction:	< 0.001

Morbidity

Symptomatic progression	No suitable data				
Symptomatology					
EORTC QLQ-C30 (confirmed deterioration[b])					
Fatigue	429	n.r. [40.5; n.c.] *117 (27.3)*	429	n.r. [42.4; n.c.] *115 (26.8)*	1.05 [0.81; 1.36]; 0.719
Nausea and vomiting	429	n.r. *28 (6.5)*	429	n.r. *39 (9.1)*	0.67 [0.41; 1.09]; 0.110
Pain	429	n.r. *78 (18.2)*	429	n.r. *67 (15.6)*	1.11 [0.80; 1.55]; 0.516
Dyspnoea	429	n.r. *55 (12.8)*	429	n.r. *53 (12.4)*	0.99 [0.68; 1.44]; 0.942
Insomnia	429	n.r. *55 (12.8)*	429	n.r. *62 (14.5)*	0.83 [0.57; 1.19]; 0.311
Appetite loss	429	n.r. *46 (10.7)*	429	n.r. *70 (16.3)*	0.63 [0.44; 0.92]; 0.017
Constipation	429	n.r. *58 (13.5)*	429	n.r. *44 (10.3)*	1.29 [0.87; 1.92]; 0.203
Diarrhoea	429	n.r. *26 (6.1)*	429	n.r. *56 (13.1)*	0.43 [0.27; 0.69]; < 0.001
NSCLC-SAQ (confirmed deterioration[c])					
Total score	429	n.r. *40 (9.3)*	429	n.r. *53 (12.4)*	0.74 [0.49; 1.12]; 0.156
Cough	429	n.r. *35 (8.2)*	429	n.r. *41 (9.6)*	-
Pain	429	n.r. *53 (12.4)*	429	n.r. *63 (14.7)*	-
Dyspnoea	429	n.r. *79 (18.4)*	429	n.r. *63 (14.7)*	-
Fatigue	429	n.r. *68 (15.9)*	429	n.r. *85 (19.8)*	-
Appetite loss	429	n.r. *67 (15.6)*	429	n.r. *96 (22.4)*	-

PGIS (confirmed deterioration[d])					
Symptomatology	429	n.r. *53 (12.4)*	429	n.r. [44.1; n.c.] *65 (15.2)*	0.75 [0.52; 1.08]; 0.128
Health status					
EQ-5D VAS (confirmed deterioration[e])					
	429	n.r. 42 (9.8)	429	n.r. 52 (12.1)	0.78 [0.52; 1.17]; 0.229

Health-related quality of life

EORTC QLQ-C30 (confirmed deterioration[f])					
Global health status	429	n.r. *72 (16.8)*	429	*n.r.* *83 (19.3)*	0.84 [0.61; 1.16]; 0.301
Physical functioning	429	n.r. *101 (23.5)*	429	n.r. *69 (16.1)*	1.55 [1.14; 2.12]; 0.005
Role functioning	429	n.r. [40.9; n.c.] *118 (27.5)*	429	n.r. *83 (19.3)*	1.50 [1.13; 1.99]; 0.005
Emotional functioning	429	n.r. *43 (10.0)*	429	n.r. *57 (13.3)*	0.74 [0.49; 1.10]; 0.133
Cognitive functioning	429	n.r. *89 (20.7)*	429	n.r. *98 (22.8)*	0.90 [0.67; 1.20]; 0.461
Social functioning	429	n.r. *93 (21.7)*	429	n.r. *88 (20.5)*	1.05 [0.79; 1.41]; 0.723

Side effects

Endpoint	**Amivantamab + lazertinib**		**Osimertinib**		Intervention versus control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI]; p value[g]
Adverse events in total					
	421	421 (100.0)	428	426 (99.5)	–
Serious adverse events (SAE)					
	421	233 (55.3)	428	177 (41.4)	1.34 [1.17; 1.54]; < 0.001
Severe adverse events (CTCAE grade ≥ 3)					
	421	337 (80.0)	428	224 (52.3)	1.53 [1.38; 1.70]; < 0.001

Therapy discontinuation due to adverse events[h]					
	421	178 (42.3)	428	70 (16.4)	2.59 [2.03; 3.29]; < 0.001
Specific adverse events					
Infusion-related reactions	No suitable data				
Venous thromboembolism (severe AEs)[i]	421	51 (12.1)	428	17 (4.0)	3.06 [1.80; 5.21]; < 0.001
Pneumonitis/ ILD (PT, SAE)	421	13 (3.1)	428	13 (3.0)	1.03 [0.48; 2.20]; 0.945
Skin and subcutaneous tissue disorders (SOC, AEs)	421	388 (92.2)	428	279 (65.2)	1.41 [1.31; 1.52]; < 0.001
Conjunctivitis (PT, AEs)	421	48 (11.4)	428	10 (2.3)	4.84 [2.48; 9.44]; < 0.001
Constipation (PT, AEs)	421	130 (30.9)	428	70 (16.4)	1.89 [1.46; 2.44]; < 0.001
Vomiting (PT, AEs)	421	59 (14.0)	428	28 (6.5)	2.14 [1.40; 3.28]; < 0.001
Oedema, peripheral (PT, AEs)	421	162 (38.5)	428	29 (6.8)	5.70 [3.93; 8.26]; < 0.001
Mucosa inflammation (PT, AEs)	421	48 (11.4)	428	14 (3.3)	3.52 [1.97; 6.27]; < 0.001
Muscle spasms (PT, AEs)	421	84 (20.0)	428	36 (8.4)	2.38 [1.65; 3.42]; < 0.001
Pain in an extremity (PT, AEs)	421	72 (17.1)	428	30 (7.0)	2.45 [1.64; 3.66]; < 0.001
Myalgia (PT, AEs)	421	60 (14.3)	428	24 (5.6)	2.54 [1.61; 4.00]; < 0.001
Paraesthesia (PT, AEs)	421	61 (14.5)	428	27 (6.3)	2.31 [1.50; 3.56]; < 0.001
Eye disorders (SOC, AEs)	421	144 (34.2)	428	76 (17.8)	1.93 [1.51; 2.46]; < 0.001
Reproductive system and breast disorders (SOC, AEs)	421	43 (10.2)	428	20 (4.7)	2.21 [1.32; 3.68]; 0.002
Injury, poisoning and procedural complications (SOC, SAEs)	421	32 (7.6)	428	16 (3.7)	2.03 [1.13; 3.65]; 0.018
Paronychia (PT, severe AEs)	421	49 (11.6)	428	2 (0.5)	24.71 [6.11; 99.96]; < 0.001

Dyspnoea	No suitable data				
Investigations (SOC, severe AEs)	421	65 (15.4)	428	42 (9.8)	1.57 [1.09; 2.26]; 0.015
Metabolism and nutrition disorders (SOC, severe AEs)	421	66 (15.7)	428	33 (7.7)	2.03 [1.37; 3.01]; < 0.001
Gastrointestinal disorders (SOC, severe AEs)	421	41 (9.7)	428	19 (4.4)	2.21 [1.30; 3.74]; 0.003
General disorders and administration site conditions (SOC, severe AEs)	421	40 (9.5)	428	22 (5.1)	1.85 [1.12; 3.05]; 0.017
Vascular disorders (SOC, severe AEs)	421	34 (8.1)	428	20 (4.7)	1.73 [1.01; 2.96]; 0.044

a Hazard ratio (incl. 95% CI and p value) calculated using the Cox proportional hazards model; stratified by mutation type (EGFR Exon 19-Del or EGFR Exon 21-L858R sub), descent (Asian, non-Asian) and history of brain metastases (yes, no).
b An increase by ≥ 10 points compared to the start of the study in at least 2 consecutive and all subsequent surveys, without subsequent improvement until the end of the observation, is considered a clinically relevant, confirmed deterioration (scale range: 0 to 100).
c An increase by ≥ 3 points of the scale range in the total score compared to the start of the study, without subsequent improvement until the end of the observation, is considered a clinically relevant, confirmed deterioration (range of values for the total score: 0 to 20).
d An increase by ≥ 1 point compared to the start of the study, without subsequent improvement until the end of the observation, is considered a clinically relevant, confirmed deterioration (scale range: 1 to 6).
e A decrease by ≥ 15 points compared to the start of the study, without subsequent improvement until the end of the observation, is considered a clinically relevant, confirmed deterioration (scale range: 0 to 100).
f A decrease by ≥ 10 points compared to the start of the study, without subsequent improvement until the end of the observation, is considered a clinically relevant, confirmed deterioration (scale range: 0 to 100).
g Cochran-Mantel-Haenszel method; stratified by mutation type (EGFR Exon 19-Del or EGFR Exon 21-L858R sub), descent (Asian, non-Asian) and history of brain metastases (yes, no)
h Discontinuation of at least 1 active ingredient component
i Operationalised via the SMQ "Thromboembolic events" with CTCAE grade ≥ 3; results largely determined by the PTs "Deep vein thrombosis", "Venous thrombosis of an extremity" and "Pulmonary embolism"

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; ILD = interstitial lung disease; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; NSCLC-SAQ = Non-small Cell Lung Cancer Symptom Assessment Questionnaire; n.r. = not reached; PGIS = Patient Global Impression of Severity; SOC = system organ class; PT = preferred term; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale

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

<u>Adults with advanced NSCLC and EGFR Exon 19 deletions or Exon 21 L858R substitution mutations; first-line treatment</u>

Approx. 1,250 to 3,025 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 Rybrevant (active ingredient: amivantamab) at the following publicly accessible link (last access: 15 May 2025):

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

Treatment with amivantamab in combination with lazertinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of patients with non-small cell lung cancer, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and other doctors from specialist groups participating in the Oncology Agreement.

EGFR mutational status
Prior to a therapy with Rybrevant, the EGFR mutational status must be detected in the tumour tissue or plasma samples using a validated test method.

Venous thromboembolic (VTE) events with concomitant use of lazertinib
In patients receiving Rybrevant (if applicable as a subcutaneous dosage form) in combination with lazertinib, prophylactic anticoagulation should be initiated at the time of therapy initiation to prevent VTE events.

4. Treatment costs

Annual treatment costs:

Adults with advanced NSCLC and EGFR Exon 19 deletions or Exon 21 L858R substitution mutations; first-line treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Amivantamab in combination with lazertinib	
Amivantamab	€ 143,811.59 - € 146,952.60
Lazertinib	€ 118,537.79
Total	€ 262,349.38 - € 265,490.39
Additionally required SHI services	€ 216.40 - € 220.43
Appropriate comparator therapy:	
Afatinib	
Afatinib	€ 30,935.71
Osimertinib	
Osimertinib	€ 66,097.97

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

Costs for additionally required SHI services: not applicable

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: Amivantamab in combination with lazertinib					
Amivantamab (IV)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	28.1	€ 2,810
Lazertinib	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	28.1	€ 2,810

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:

<u>Adults with advanced NSCLC and EGFR Exon 19 deletions or Exon 21 L858R substitution mutations; first-line treatment</u>

The following medicinal products with new active ingredients that can be used in a combination therapy with amivantamab in the therapeutic indication of the resolution on the basis of the marketing authorisation under Medicinal Products Act are named (active ingredients and invented names) in accordance with Section 35a, paragraph 3, sentence 4 SGB V:

- Lazertinib (Lazcluze)

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.

II. **In Annex XIIa of the Pharmaceuticals Directive, the following information shall be added in alphabetical order:**

"Active ingredient of the assessed medicinal product

Amivantamab

Resolution according to Section 35a paragraph 3 SGB V from

17 July 2025

Therapeutic indication of the resolution

Rybrevant is indicated in combination with lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations.

Patient group a

Adults with advanced NSCLC and EGFR Exon 19 deletions or Exon 21 L858R substitution mutations; first-line treatment

Naming of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V (active ingredients and invented names[2])

Lazertinib (Lazcluze)

Period of validity of the designation (since... or from... to)

Since 17 July 2025

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 July 2025.

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

Berlin, 17 July 2025

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

Prof. Hecken