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 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

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) 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 G-BA 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 G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient amivantamab (Rybrevant) was listed for the first time on 15 January 2022 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 19 December 2024, amivantamab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 16 January 2025, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company have submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with

Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient amivantamab with the new therapeutic indication

"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"

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The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 May 2025 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of amivantamab 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. In order to determine the extent of the additional benefit, the G-BA 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 amivantamab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have come to the following assessment:

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

2.1.1 Approved therapeutic indication of Amivantamab (Rybrevant) in accordance with the product information

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 17.07.2025):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for amivantamab in combination with lazertinib:

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

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

  or

- Osimertinib

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

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

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

On 1. The cytostatic agents cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, nab-paclitaxel, paclitaxel, pemetrexed, vinorelbine and vindesine, the protein kinase inhibitors afatinib, dacomitinib, erlotinib, gefitinib, lazertinib and osimertinib as well as the antibodies amivantamab, bevacizumab and ramucirumab are approved in the present therapeutic indication. The marketing authorisations are partly based on the use as monotherapy or in certain combination therapies. In addition, off-label use of carboplatin can also be prescribed in this therapeutic indication.

Medicinal products explicitly approved for molecularly stratified therapy (with the exception of EGFR) were not considered, nor were medicinal products for the treatment of NSCLC with exclusively squamous histology.

On 2. Non-medicinal treatment is not considered. It is assumed that there is neither an indication for definitive chemoradiotherapy nor for definitive local therapy.

On 3. The following resolutions and guidelines of the G-BA are available for medicinal product treatment in the present therapeutic indication:

Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Ramucirumab: resolution of 20 August 2020
- Dacomitinib: resolution of 17 October 2019
- Osimertinib: resolutions of 17 January 2019 and 6 February 2025
- Afatinib: resolution of 15 November 2015

Resolution of the Federal Joint Committee (G-BA) on an amendment of the Pharmaceuticals Directive (AM-RL): Annex VI (off-label use), last revised 7 May 2025:

- Carboplatin-containing medicinal products for advanced non-small cell lung cancer (NSCLC) – combination therapy

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.

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

When determining the appropriate comparator therapy, it is assumed that patients will not be eligible for further molecularly stratified therapy (directed against ALK, BRAF, EGFR Exon 20, KRAS G12C, METex14, RET or ROS1) at the time of therapy with amivantamab in combination with lazertinib. Furthermore, EGFR-mutated NSCLC is predominantly adenocarcinoma in histological terms, which is why therapy options for squamous cell carcinoma are not regularly used in this therapeutic indication. It is also assumed that there is neither an indication for definitive chemoradiotherapy nor for definitive local therapy.

According to the present guidelines, an EGFR tyrosine kinase inhibitor should be offered in the first line of therapy in the presence of an activating EGFR mutation. The therapy recommendations here are based on the specific EGFR mutation. According to the S3 guideline, patients with EGFR Exon 19 deletion should preferably be offered osimertinib due to the survival data.

In the benefit assessment of osimertinib as monotherapy, a hint for a considerable additional benefit thereof over gefitinib or erlotinib was identified for patients with locally advanced or metastatic NSCLC with an EGFR Exon 19 deletion (resolution of 17 January 2019).

An indication of a major additional benefit of the active ingredient afatinib over cisplatin in combination with pemetrexed was shown in the benefit assessment for patients with locally advanced and/or metastatic NSCLC in the patient group with an EGFR Exon 19 deletion (resolution of 5 November 2015).

In contrast, the G-BA did not identify any additional benefit of the active ingredient dacomitinib over the appropriate comparator therapy following the benefit assessment for patients with locally advanced or metastatic NSCLC with an EGFR Exon 19 deletion (resolution of 17 October 2019).

With regard to the EGFR Exon 21 L858R substitution mutations, the S3 guideline recommends selecting the therapy, depending on the efficacy and toxicity of the approved protein kinase inhibitors (afatinib, dacomitinib, erlotinib, gefitinib, osimertinib, erlotinib in combination with bevacizumab, erlotinib in combination with ramucirumab), based on the survival and/or efficacy data.

The benefit assessments of afatinib (resolution of 5 November 2015), dacomitinib (resolution of 17 October 2019) and ramucirumab in combination with erlotinib (resolution of 20 October 2020) each showed no additional benefit over the appropriate comparator therapy for patients with EGFR Exon 21 L858R substitution mutations.

A hint for a considerable additional benefit of osimertinib as monotherapy over gefitinib or erlotinib was identified for patients with locally advanced or metastatic NSCLC with EGFR Exon 21 L858R substitution mutations (resolution of 17 January 2019).

Osimertinib in combination with pemetrexed and platinum-based chemotherapy is a new treatment option in the present therapeutic indication. The osimertinib combination therapy was only recently approved (marketing authorisation on 28.06.2024). In the benefit assessment, no additional benefit of osimertinib in combination with pemetrexed and platinum-based chemotherapy was proven (resolution of 6 February 2025). Osimertinib in combination with pemetrexed and platinum-based chemotherapy is therefore not determined as an appropriate comparator therapy.

In summary, the G-BA considers it appropriate to determine osimertinib or afatinib as the appropriate comparator therapy on the basis of the underlying evidence and the results of the benefit assessment. Afatinib is only indicated for patients with the activating EGFR Exon 19 deletions.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

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

Hint for a minor additional benefit

Justification:

MARIPOSA study

The MARIPOSA study is an ongoing, multicentre, partially blinded, randomised, controlled, three-arm phase III study comparing amivantamab + lazertinib (arm A) as well as osimertinib (arm B) and lazertinib (arm C) in monotherapy. The study arms amivantamab + lazertinib and osimertinib are relevant for the present benefit assessment. The comparison of amivantamab + lazertinib with osimertinib is unblinded.

The study has been conducted in 219 study sites in Europe, North and South America, Asia and Australia since October 2020.

Adults with newly diagnosed, locally advanced or metastatic NSCLC with EGFR Exon 19 deletion or Exon 21 L858R substitution and a good general condition (ECOG-PS = 0 or 1) were enrolled. Patients were not allowed to have received systemic therapy for the locally advanced or metastatic disease.

A total of 1,074 patients were randomised in a 2:2:1 ratio. The relevant study arms amivantamab + lazertinib and osimertinib for the present benefit assessment each comprised 429 patients. Stratification was based on mutation type (EGFR Exon 19 deletion vs EGFR Exon 21 L858R substitution), descent (Asian vs non-Asian) and presence of brain metastases (yes vs no).

In addition to the primary endpoint of progression-free survival, endpoints in the categories of mortality, morbidity, health-related quality of life and side effects were collected.

Data from the pre-specified data cut-off from 11.08.2023 and the data cut-off from 13.05.2024 required by the EMA as part of the marketing authorisation are available for the MARIPOSA study. The analyses of the final data cut-off from 04.12.2024 were submitted as part of the written statement procedure. The final data cut-off from 04.12.2024 was used for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

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

For the endpoint of overall survival, the total population showed a statistically significant survival advantage in favour of amivantamab in combination with lazertinib compared to osimertinib, the extent of which is assessed as a significant improvement.

There was an effect modification here due to the "age" characteristic. For subjects < 65 years, the subgroup analysis showed a statistically significant difference to the advantage of amivantamab in combination with lazertinib. However, for subjects ≥ 65 years, there was no statistically significant difference. These subgroup results are considered a relevant outcome of the present benefit assessment. They point out that older patients benefit less from the

therapy. However, they are considered inadequate to derive separate statements on the additional benefit in the overall assessment. Furthermore, the effect modification is not evident for other patient-relevant endpoints.

Morbidity

Symptomatic progression

Although the endpoint is basically patient-relevant, it is not suitable for the benefit assessment in the present operationalisation. Thus, there is no adequate information on the relevance of the individual component of symptom deterioration that requires clinical intervention to control the symptomatology. In addition, the symptoms that were to be included as events in the evaluation were not predefined. Thus, there are relevant uncertainties regarding the endpoint definition presented.

The endpoint of symptomatic progression is not used for the present benefit assessment.

Symptomatology

EORTC QLQ-C30

Disease symptomatology was surveyed in the MARIPOSA study using the EORTC QLQ-C30 questionnaire. The evaluation of event proportions presented in the dossier was not suitable for the benefit assessment. With their statement, the pharmaceutical company submitted time-to-event analyses on the confirmed deterioration which were used as the basis for the present assessment.

For the endpoints of diarrhoea and appetite loss, there were statistically significant differences to the advantage of amivantamab in combination with lazertinib.

No differences were found for the other symptoms of fatigue, nausea and vomiting, pain, dyspnoea, constipation and insomnia.

NSCLC-SAQ

The evaluation of event proportions presented in the dossier was not suitable for the benefit assessment. With their statement, the pharmaceutical company submitted time-to-event analyses on the confirmed deterioration which were used as the basis for the present assessment.

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

PGIS

There was no statistically significant difference for the PGIS endpoint.

Health status

EQ-5D, visual analogue scale

The health status was surveyed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

There was no statistically significant difference between the treatment arms.

The overall assessment showed advantages for the symptoms of diarrhoea and appetite loss. In the morbidity endpoint category, an overall advantage of amivantamab in combination with lazertinib was therefore identified.

Quality of life

EORTC QLQ-C30

Disease symptomatology was surveyed in the MARIPOSA study using the EORTC QLQ-C30 questionnaire. The evaluation of event proportions presented in the dossier was not suitable for the benefit assessment. With their statement, the pharmaceutical company submitted time-to-event analyses on the confirmed deterioration which were used as the basis for the present assessment.

For the endpoints of physical functioning and role functioning, there was a statistically significant difference to the disadvantage of amivantamab in combination with lazertinib.

There were no differences for the endpoints of global health status, emotional functioning, cognitive functioning and social functioning.

The overall assessment showed disadvantages for the endpoints of physical functioning and role functioning. With regard to health-related quality of life, a disadvantage of amivantamab in combination with lazertinib is therefore derived.

Side effects

Adverse events (AEs) in total

In the MARIPOSA 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) and discontinuation due to AEs

For the endpoints of SAEs, severe AEs and discontinuation due to AEs, there was a statistically significant difference to the disadvantage of amivantamab in combination with lazertinib.

Specific AE

Infusion-related reactions

No suitable data are available for the endpoint of infusion-related reactions.

Venous thromboembolic event (severe AEs), skin and subcutaneous tissue disorders (AEs)

For the endpoints "Venous thromboembolic event" and "Skin and subcutaneous tissue disorders", there was a statistically significant difference to the disadvantage of amivantamab in combination with lazertinib.

Pneumonitis/ ILD (SAEs)

There was no statistically significant difference between the treatment groups.

Other specific AEs

There was a statistically significant difference between the treatment groups to the disadvantage of amivantamab in combination with lazertinib for the endpoints of conjunctivitis (AEs), constipation (AEs), vomiting (AEs), peripheral oedema (AEs), mucositis (AEs), muscle spasms (AEs), pain in an extremity (AEs), myalgia (AEs), paraesthesia (AEs), eye disorders (AEs), reproductive system and breast disorders (AEs), injury, poisoning and procedural complications (AEs), paronychia (severe AEs), investigations (severe AEs), metabolism and nutrition disorders (severe AEs), gastrointestinal disorders (severe AEs), general disorders and administration site conditions (severe AEs) and vascular disorders (severe AEs).

In the overall analysis of the endpoints on side effects, treatment with amivantamab in combination with lazertinib only showed negative effects. These are characterised by significant disadvantages in terms of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs. In detail, there were disadvantages for the specific AEs.

Overall assessment

Results from the MARIPOSA study on mortality, morbidity, health-related quality of life and side effects are available for the assessment of the additional benefit of amivantamab in combination with lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations. This RCT compared amivantamab in combination with lazertinib with osimertinib.

The results for the endpoint of overall survival show a statistically significant difference with a clear advantage of amivantamab in combination with lazertinib. There was an effect modification here due to the "age" characteristic. For subjects < 65 years, the subgroup analysis showed a statistically significant difference to the advantage of amivantamab in combination with lazertinib. However, for subjects ≥ 65 years, there was no statistically significant difference. These subgroup results are considered a relevant outcome of the present benefit assessment. They point out that older patients benefit less from the therapy. However, they are considered inadequate to derive separate statements on the additional benefit in the overall assessment. Furthermore, the effect modification is not evident for other patient-relevant endpoints.

In the morbidity endpoint category, symptomatology (EORTC QLQ-C30, NSCLC-SAQ, PGIS) and health status (EORTC QLQ-C30, EQ-5D VAS) were surveyed, with positive effects for the endpoints of diarrhoea and appetite loss. Overall, an advantage of amivantamab in combination with lazertinib was derived.

With regard to health-related quality of life (EORTC QLQ-C30), an overall disadvantage can be identified due to negative effects on the endpoints of physical functioning and role functioning.

In terms of side effects, there were disadvantages of amivantamab in combination with lazertinib with regard to the endpoints of SAEs, severe AEs and therapy discontinuation due to AEs, as well as in detail for the specific AE "Venous thromboembolic event" and other specific AEs. In the category of side effects, clear disadvantages could therefore be identified overall.

In the overall analysis of the present results on the patient-relevant endpoints, the clear advantage in overall survival is offset by clear disadvantages in side effects. There are further advantages in the morbidity endpoint category and further disadvantages in the health-related quality of life. By a weighted decision in the overall assessment, the G-BA concluded that there was a minor additional benefit of amivantamab in combination with lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations.

Reliability of data (probability of additional benefit)

The randomised, multicentre, controlled MARIPOSA study forms the basis of the present benefit assessment.

Although the risk of bias at study level is classified as low overall, there are overarching uncertainties for all endpoint categories, as no adequate thrombosis prophylaxis to prevent venous thromboembolic events was carried out as part of the MARIPOSA study.

For the endpoint of overall survival, there is a low risk of bias. However, a relevant uncertainty in the reliability of data results for the total patient population due to the effect modification by the "age" characteristic.

The endpoint-specific risk of bias for the results of the patient-reported endpoints on morbidity and health-related quality of life is rated as high due to the lack of blinding.

Due to the lack of consideration of the symptoms underlying the infusion-related reactions, there are uncertainties for the evaluations in the endpoint category of side effects.

In summary, the G-BA derive a hint for the identified additional benefit with regard to the reliability of data.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient amivantamab.

The therapeutic indication assessed here is as follows: Amivantamab 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.

The G-BA determined afatinib (only for patients with the activating EGFR Exon 19 deletion mutation) or osimertinib as the appropriate comparator therapy.

The pharmaceutical company presented the MARIPOSA RCT, which compared amivantamab in combination with lazertinib versus osimertinib.

The results for the endpoint of overall survival show a statistically significant difference with a clear advantage of amivantamab in combination with lazertinib. There was an effect modification here due to the "age" characteristic. There was a statistically significant difference with an advantage for subjects < 65 years and no statistically significant difference for subjects ≥ 65 years. These results are considered a relevant result. They point out that older patients benefit less from the therapy. However, they are considered inadequate to derive separate statements on the additional benefit in the overall assessment. Furthermore, the effect modification is not evident for other patient-relevant endpoints.

In the endpoint category of morbidity, symptomatology (EORTC QLQ-C30, NSCLC-SAQ, PGIS) and health status (EORTC QLQ-C30, EQ-5D VAS) were surveyed. This results in an advantage overall.

With regard to health-related quality of life (EORTC QLQ-C30), a disadvantage was identified overall.

In terms of side effects, there were disadvantages of amivantamab in combination with lazertinib with regard to the endpoints of SAEs, severe AEs and therapy discontinuation due to AEs, as well as in detail for the specific AE "Venous thromboembolic event" and other specific AEs. In the category of side effects, clear disadvantages could therefore be identified overall.

In the overall analysis of the present results on the patient-relevant endpoints, the clear advantage in overall survival is offset by clear disadvantages in side effects. There are further advantages in the morbidity endpoint category and further disadvantages in the health-related quality of life. By a weighted decision, the G-BA therefore concluded that there was a minor additional benefit of amivantamab in combination with lazertinib.

With regard to the reliability of data, a hint for the identified additional benefit is derived.

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).

For the number of German patients with lung cancer, the incidence for 2020 (56,690 patients)[2] is used as the basis for the calculations. The current publications lack projected data. This is why later developments cannot be presented here.

The following calculation steps are used to narrow down this patient group to the target population:

1. The percentage of lung cancer patients with NSCLC is between 73.6% and 83.6%[3] (41,723 to 47,392 patients).
2. Of these, 46.6% of patients are in stage IV at initial diagnosis[4]. Of the remaining 53.4% of patients who are in stage I-IIIB, 37.7% will progress to stage IV in 2022[5]. The percentage of patients in stage IIIB/IIIC is 4.5% to 6.1%[6]. The total number of patients is 32,273 to 36,658.
3. First-line therapy is given in 76.9% to 96.1%[3] of cases (24,818 - 35,228 patients).
4. 63.1% to 78.6% of stage IIIB/IV NSCLC patients[7] (15,660 to 27,689 patients) had non-squamous histology.
5. The percentage of patients with activating EGFR mutation is 10.3% to 14.1%[8] (1,613 to 3,904 patients).
6. The percentage of patients with activating EGFR L858R mutations or Exon 19 deletion is 85.6% - 88.7%[8] (1,381 to 3,463 patients).
7. Taking into account the percentage of SHI-insured patients of 87.28%, there are 1,205 to 3,023 patients in the first-line therapy.

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 Rybrevant (active ingredient: amivantamab) at the following publicly accessible link (last access: 15 May 2025):

https://www.ema.europa.eu/en/documents/product-information/rybrevant-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

[2] Robert Koch Institute, Society of Epidemiological Cancer Registries in Germany. Cancer in Germany for 2019/2020. 2023
[3] Benefit assessment according to Section 35a SGB V, A21-27, selpercatinib, 11.06.2021
[4] Benefit assessment according to Section 35a SGB V, A23-29 | A23-31, durvalumab and tremelimumab, 29.06.2023
[5] Tumour Registry Munich ICD-10 C34: Non-small cell. BC Survival [online]. 2022. URL: https://www.tumorregister-muenchen.de/facts/surv/sC34N_G-ICD-10-C34-Nicht-kleinzell.-BC-Survival.pdf; 37.7% (for the longest possible observation period of 15 years)
[6] Benefit assessment according to Section 35a SGB V, A23-37, cemiplimab, 28.04.2023
[7] Benefit assessment according to Section 35a SGB V, A19-84, atezolizumab, 02.04.2020
[8] Benefit assessment according to Section 35a SGB V, A21-86, osimertinib, 29.09.2021

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.

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 July 2025).

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 for the maximum treatment duration, if specified in the product information.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of 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).[9]

The annual treatment costs shown refer to the first year of treatment.

Treatment period:

Adults with advanced NSCLC and EGFR Exon 19 deletions or Exon 21 L858R substitution mutations; 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				
Amivantamab in combination with lazertinib				
Amivantamab (subcutaneous administration)	Week 1 to 4: 1 x every 7 days From week 5: 1 x per 14-day cycle	28.1	Week 1 to 4: 4 From week 5: 1	28.1

[9] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Amivantamab (intravenous administration)	Week 1 to 4: 1 x every 7 days From week 5: 1 x per 14-day cycle	28.1	Week 1 to 4: 4 From week 5: 1	28.1
Lazertinib	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Afatinib				
Afatinib	Continuously, 1 x daily	365.0	1	365.0
Osimertinib				
Osimertinib	Continuously, 1 x daily	365.0	1	365.0

Consumption:

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.

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					
Amivantamab in combination with lazertinib					
Amivantamab (subcutaneous administration)	Week 1 – 4 1,600 mg From week 5: 1,600 mg	Week 1 – 4 1,600 mg From week 5: 1,600 mg	Week 1 – 4 1 x 1,600 mg From week 5: 1 x 1,600 mg	28.1	28.1 x 1,600 mg
Amivantamab (intravenous administration)	Week 1 Day 1: 350 mg Week 1 Day 2: 700 mg Week 2 – 4 1,050 mg	Week 1 Day 1: 350 mg Week 1 Day 2: 700 mg Week 2 – 4 1,050 mg	Week 1 Day 1: 1 x 350 mg Week 1 Day 2: 2 x 350 mg Week 2 – 4 3 x 350 mg	28.1	84.3 x 350 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	From week 5: 1,050 mg	From week 5: 1,050 mg	From week 5: 3 x 350 mg		
Lazertinib	240 mg	240 mg	1 x 240 mg	365	365 x 240 mg
Appropriate comparator therapy					
Afatinib					
Afatinib	40 mg	40 mg	1 x 40 mg	365.0	365 x 40 mg
Osimertinib as monotherapy					
Osimertinib	80 mg	80 mg	1 x 80 mg	365.0	365 x 80 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Amivantamab 350 mg (IV)	1 CIS	€ 1,847.18	€ 1.77	€ 102.20	€ 1,743.21
Amivantamab 1,600 mg (SC)	1 SFI	€ 5,426.22	€ 1.77	€ 306.60	€ 5,117.85
Lazertinib 240 mg	28 FCT	€ 9,642.47	€ 1.77	€ 547.39	€ 9,093.31
Appropriate comparator therapy					
Afatinib 40 mg	28 FCT	€ 2,515.27	€ 1.77	€ 140.35	€ 2,373.15
Osimertinib 80 mg	30 FCT	€ 5,760.15	€ 1.77	€ 325.67	€ 5,432.71
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection					

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Costs for additionally required SHI services:

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

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

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

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:							
Amivantamab in combination with lazertinib							
Amivantamab							
Dexamethasone [10] 20 mg IV *(week 1 day 1)* 10 mg IV *(week 1 day 2)*	10 x 4 mg SFI	€ 16.92	€ 1.77	€ 0.44	€ 14.71	2	€ 14.71
Dimetindene IV 1 mg/10 kg BW = 7.8 mg, IV	5 x 4 mg SFI	€ 26.24	€ 1.77	€ 6.92	€ 17.55	28.1	€ 197.26
Paracetamol 500 - 1,000 mg, PO[11]	20 TAB x 500 mg 10 TAB x 1,000 mg	€ 3.47 € 3.32	€ 0.17 € 0.17	€ 0.15 € 0.14	€ 3.15 € 3.01	28.1	€ 4.43 – € 8.46

[10] Fixed reimbursement rate

[11] The cost calculation for paracetamol is based on the single dose of 500 mg of the non-divisible tablets available for cost calculation related to a dose range of 500 – 1,000 mg per day, even if a dose range of 650 – 1,000 mg is given in the product information.

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 special agreement on contractual unit costs of retail pharmacist services (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 designate 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 have 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 have 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 have 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 advanced NSCLC and EGFR Exon 19 deletions or Exon 21 L858R substitution mutations; first-line treatment

Each of the designated medicinal products is an active ingredient that is specifically named as a concomitant active ingredient in the product information for the assessed medicinal product. Corresponding text extract from the product information for the assessed medicinal product: "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".

For the designated medicinal products, the requirements of Section 35a, paragraph 3, sentence 4 SGB V are also fulfilled.

References:
Product information for amivantamab (Rybrevant); Rybrevant® 350 mg concentrate for the preparation of an infusion solution; last revised: April 2025

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

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 December 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at their session on 17 December 2024.

On 16 January 2025, the pharmaceutical company submitted a dossier for the benefit assessment of amivantamab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 22 January 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient amivantamab.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 April 2025, and the written statement procedure was initiated with publication on the G-BA website on 2 May 2025. The deadline for submitting statements was 23 May 2025.

The oral hearing was held on 10 June 2025.

By letter dated 11 June 2025, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 27 June 2025.

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

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

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

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	12 December 2023	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	17 December 2024	New determination of the appropriate comparator therapy
Working group Section 35a	3 June 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 June 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	17 June 2025; 2 July 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	8 July 2025	Concluding discussion of the draft resolution

Plenum	17 July 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 17 July 2025

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

Prof. Hecken