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
Amivantamab (new therapeutic indication: non-small cell lung cancer, EGFR Exon 19 deletions or Exon 21 L858R substitution mutations, pretreated, combination with carboplatin and pemetrexed)

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 23 February 2024, the pharmaceutical company filed an application to postpone the start of the benefit assessment procedure for the active ingredient amivantamab in the therapeutic indication "Rybrevant is indicated in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI)" in accordance with Section 35a paragraph 5b SGB V.

The pharmaceutical company expected marketing authorisation extensions for the active ingredient amivantamab within the period specified in Section 35a paragraph 5b SGB V for multiple therapeutic indications at different times.

At their session on 18 April 2024, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment

and the submission of a dossier for the benefit assessment for the therapeutic indication in question to four weeks after the marketing authorisation of the other therapeutic indication of the therapeutic indication covered by the application, at the latest six months after the first relevant date. The marketing authorisation for the other therapeutic indication covered by the application according to Section 35a paragraph 5b SGB V were granted within the 6-month period.

On 22 August 2024, amivantamab received the extension of the marketing authorisation for the therapeutic indication *"in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI)"*. The extension of the marketing authorisation for the therapeutic indication *"in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations"* was granted on 27 June 2024 and for the therapeutic indication *"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"* on 19 December 2024. These extensions of the marketing authorisation are 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, the pharmaceutical company have submitted a dossier in due time in accordance with Section 4, paragraph3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient amivantamab with the therapeutic indication

"Rybrevant is indicated in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI)"

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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 to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the 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:

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

2.1 Additional benefit of the medicinal product 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 carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI).

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:

a) Adults with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 0–1

Appropriate comparator therapy for amivantamab in combination with carboplatin and pemetrexed:

– Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel

b) Adults with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 2

Appropriate comparator therapy for amivantamab in combination with carboplatin and pemetrexed:

– Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) cf. Annex VI to Section K of the Pharmaceuticals Directive

or

– carboplatin in combination with nab-paclitaxel

or

– monotherapy with gemcitabine or vinorelbine (only for patients who are ineligible for platinum-based chemotherapy)

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.

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

On 1. In addition to amivantamab, the cytostatic agents cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, nab-paclitaxel, paclitaxel, pemetrexed, vindesine, vinorelbine, the antibodies atezolizumab, bevacizumab and tislelizumab as well as the protein kinase inhibitors gefitinib and osimertinib are approved for this therapeutic indication. Medicinal products explicitly approved for molecularly stratified therapy or for the treatment of NSCLC with exclusively squamous histology were not considered here. This is based on the assumption that patients will not be eligible for any further molecularly stratified therapy (directed against ALK, BRAF, KRAS G12C, METex14, RET or ROS1) at the time of therapy with amivantamab and that EGFR-mutated NSCLC is predominantly adenocarcinoma in histological terms. It is therefore also assumed that

therapy options that are explicitly indicated for squamous tumour histology are not regularly used in the currently planned therapeutic indication.

On 2. Non-medicinal treatment is not considered. For the planned therapeutic indication, it is assumed that there is neither an indication for definitive chemoradiotherapy nor for definitive local therapy.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Atezolizumab: resolutions of 02.04.2020 and 16.03.2018
- Dacomitinib: resolution of 17.10.2019
- Nintedanib: resolution of 18.06.2015
- Osimertinib: resolutions of 17.01.2019, 19.10.2017 and 15.09.2016
- Ramucirumab: resolution of 20.08.2020
- Tislelizumab: resolution of 18.06.2025

Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (off-label use):

- 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 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. A joint written statement from the German Society for Haematology and Medical Oncology (DGHO), the German Respiratory Society (DGP) and the Working Group for Internistic Oncology of the German Cancer Society (AIO) is available (hereinafter: the scientific-medical societies).

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.

It is assumed that patients will not be eligible for any (further) molecularly stratified therapy directed against ALK, BRAF, Exon 20, KRAS, METex14, NTRK, ROS1 or RET at the time of therapy with amivantamab in combination with carboplatin and pemetrexed.

It is also assumed that the patients are generally eligible for active antineoplastic therapy, which is why best supportive care is not considered as an appropriate comparator therapy in the present case.

Furthermore, EGFR-mutated NSCLC is predominantly adenocarcinoma in histological terms, which is why it is assumed that therapy options that are explicitly indicated for squamous tumour histology are not regularly used in this therapeutic indication.

Based on the available evidence, in particular taking into account the S3 guideline on lung cancer[2], the G-BA consider it appropriate to divide the patient population into two patient groups depending on the ECOG performance status (ECOG-PS) according to the present therapeutic indication.

a) Patients with ECOG-PS 0–1

According to the S3 guideline on lung cancer[2], immunochemotherapy, in particular with atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, is an established standard for patients with ECOG-PS 0-1. In addition to chemotherapy with a platinum derivative in combination with pemetrexed, this immunochemotherapy is also recommended as a therapy option by the scientific-medical societies in their written statement. No additional benefit of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin was identified in the benefit assessment, as no suitable study data compared to the appropriate comparator therapy were available (G-BA's resolution of 2 April 2020). In this regard, it should be noted that the present indication only represents a sub-area of the therapeutic indication that was the subject of this benefit assessment.

Apart from the combination of atezolizumab, bevacizumab, paclitaxel and carboplatin, which is only suitable for patients with ECOG-PS 0-1, apart from tislelizumab, no other immune checkpoint inhibitor monotherapy or combination therapy after platinum-based therapy and targeted therapy with a tyrosine kinase inhibitor is approved for patients with an EGFR mutation.

Tislelizumab is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 15 September 2023). Based on the generally accepted state of medical knowledge, tislelizumab (monotherapy) is not determined to be an appropriate comparator therapy for the present resolution.

b) Patients with ECOG-PS 2

According to the guidelines, platinum-based combination chemotherapy with a third-generation cytostatic (vinorelbine, gemcitabine, docetaxel, paclitaxel or pemetrexed) is an established and recommended treatment option. In their written statement, the scientific-medical societies recommend chemotherapy with a platinum derivative in combination with pemetrexed. In contrast to cisplatin, carboplatin is not approved for the treatment of NSCLC, but can be prescribed for "off-label use" (see Annex VI to Section K of the Pharmaceuticals Directive). In terms of overall survival time, both platinum derivatives are considered to be equally effective. The choice is based primarily on the toxicity to be individually expected. Due to the increased toxicity of cisplatin, the G-BA consider it appropriate to determine carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) as an appropriate comparator therapy for patients with an ECOG-PS 2. The combination of carboplatin and nab-paclitaxel is also recommended.

Only for patients with ECOG-PS 2, who are ineligible for platinum-based chemotherapy, is monochemotherapy with gemcitabine or vinorelbine considered according to the available evidence.

[2] Guideline program in oncology (German Cancer Society, German Cancer Aid, Association of the Scientific-Medical Societies): S3 guideline - Prevention, diagnosis, therapy and after-care of lung cancer, long version 3.0, 2024, AWMF registry number: 020-007OL https://www.leitlinienprogramm-onkologie.de/leitlinien/lungenkarzinom/; accessed 20.06.2025

In the joint statement of the German Society for Haematology and Medical Oncology (DGHO), the German Society for Pneumology and Respiratory Medicine (DGP) and the Working Group for Internal Oncology of the German Cancer Society (AIO) on the present benefit assessment procedure, it was stated, that a therapy according to the IMpower150 regimen with atezolizumab in combination with bevacizumab, paclitaxel and carboplatin or a therapy with pemetrexed and platinum can be initiated in the absence of evidence of a specifically treatable resistance mutation.

In the overall assessment, the G-BA determined atezolizumab in combination with bevacizumab, paclitaxel and carboplatin as an appropriate comparator therapy for patient group a (patients with ECOG-PS 0-1). For patient group b (patients with ECOG-PS 2), carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed), carboplatin in combination with nab-paclitaxel and, for patients, who are ineligible for platinum-based chemotherapy, the mono-chemotherapies with gemcitabine or vinorelbine are determined as the appropriate comparator therapy.

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:

a) Adults with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 0–1

An additional benefit is not proven.

b) Adults with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 2

An additional benefit is not proven.

Justification:

For the benefit assessment, no direct comparator studies of amivantamab in combination with carboplatin and pemetrexed versus the appropriate comparator therapy were presented by the pharmaceutical company in the dossier. Furthermore, no indirect comparison was submitted.

The pharmaceutical company referred to the label-enabling MARIPOSA-2 study in the dossier. This is an ongoing, open-label, randomised, multicentre phase III study comparing amivantamab in combination with lazertinib, carboplatin and pemetrexed (arm A) and amivantamab in combination with carboplatin and pemetrexed (arm C) with a chemotherapy consisting of carboplatin and pemetrexed (arm B). Arm C is decisive for this benefit

assessment. The study has been conducted in 247 study sites in Europe, North America, South America and Asia since November 2021.

Adult patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletion or Exon 21 L858R substitution mutation and ECOG-PS 0-1 were enrolled in the study. Patients had to show disease progression under at least one previous line of therapy, including a tyrosine kinase inhibitor.

A total of 131 patients were randomly assigned to treatment with amivantamab in combination with carboplatin and pemetrexed (arm C) and 263 patients to treatment with a chemotherapy consisting of carboplatin and pemetrexed (arm B). Stratification factors for randomisation were Asian descent (yes or no), history of brain metastases (yes or no) and osimertinib line of therapy (first-line or second-line).

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.

In the written statement procedure, the pharmaceutical company submitted the results for the second data cut-off from 26.04.2024. This is the pre-specified interim analysis after 300 deaths.

Assessment:

The data from the MARIPOSA-2 study are unsuitable for the assessment of the additional benefit. In the comparator arm (arm B), patients were treated with a chemotherapy consisting of carboplatin and pemetrexed. This does not correspond to the appropriate comparator therapy for patient group a (ECOG-PS 0-1). In contrast, only patients with an ECOG-PS 0-1 were enrolled in the MARIPOSA-2 study although the chemotherapy in arm B corresponded to the appropriate comparator therapy for patient group b (ECOG-PS 2). Thus, no comparison with the respective appropriate comparator therapy is possible for both patient groups.

In the overall assessment, no suitable data that would allow an assessment of the additional benefit of amivantamab in combination with carboplatin and pemetrexed are therefore available. The additional benefit of amivantamab in combination with carboplatin and pemetrexed versus the appropriate comparator therapy is therefore not proven.

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 carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI).

In the therapeutic indication to be considered, two patient groups were distinguished:

a) Adults with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 0–1

b) Adults with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 2

The pharmaceutical company presented results from the phase III MARIPOSA-2 study, which compared amivantamab in combination with carboplatin and pemetrexed (arm C) with a chemotherapy consisting of carboplatin and pemetrexed (arm B).

Patient group a

The G-BA determined atezolizumab in combination with bevacizumab, carboplatin and paclitaxel as the appropriate comparator therapy. In the comparator arm of the MARIPOSA-2 study, patients were treated with a chemotherapy consisting of carboplatin and pemetrexed. This does not correspond to the appropriate comparator therapy for patient group a (ECOG-PS 0-1). No suitable data are therefore available for an assessment of the additional benefit of amivantamab. An additional benefit is not proven.

Patient group b

The G-BA determined various chemotherapy (combinations) as the appropriate comparator therapy. Only patients with ECOG-PS 0-1 were enrolled in the study although the chemotherapy consisting of carboplatin and pemetrexed in the comparator arm of the MARIPOSA-2 study corresponded to the appropriate comparator therapy for patient group b (ECOG-PS 2). No suitable data are therefore available for an assessment of the additional benefit of amivantamab. An additional benefit is not proven.

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).

1. For the number of German patients with lung cancer, the incidence for 2020 (56,690 patients)[3] is used as the basis for the calculations. The current publications lack projected data. This is why later developments cannot be presented here. Several calculation steps are used to narrow down this patient group to the target population.
2. The percentage of lung cancer patients with NSCLC is between 73.6% and 83.6%[4, 5] (41,724 to 47,393 patients).

[3] Robert Koch Institute, Society of Epidemiological Cancer Registries in Germany. Cancer in Germany for 2019/2020. 2023

[4] Benefit assessment according to Section 35a SGB V, A21-27, selpercatinib, 11.06.2021

[5] Institute for Quality and Efficiency in Health Care. IQWiG reports – No. 798. Examination of the usability of the Scientific Use File of the German Centre for Cancer Registry Data (ZfKD) in the context of determining the SHI target population. 2019.

3. Of these, 46.6% of patients are in stage IV at initial diagnosis[6]. Of the remaining 53.4% of patients who are in stage I-IIIB, 37.7% will progress to stage IV in 2022[7]. The percentage of patients in stage IIIB/IIIC is 4.5% to 6.1%[8]. The total number of patients is 32,274 to 36,659.
4. A systematic first-line therapy is given in 76.9% to 96.1% of cases[4] (24,818 - 35,229 patients).
5. The percentage of patients with activating EGFR mutation is 10.3% to 14.1%[9] (2,556 to 4,967 patients).
    a. Of these, 41.7% to 61.9% have an Exon 19 deletion (1,066 to 3,075 patients). Of these, 10.5% received afatinib in first-line therapy (112 to 323 patients), 71.2% thereof received second-line therapy (80 to 230 patients). Of these, 65.6% do not have a T790M mutation (52 to 151 patients).[10, 11, 12, 13]
    b. A further 89.5% of patients with Exon 19 deletion received osimertinib as first-line therapy (954 to 2,752 patients).[10]
    c. Finally, 27.3% to 31.7% of patients with an EGFR mutation have an Exon 21 L858R substitution mutation (698 to 1,575 patients). Of these, 100% receive osimertinib as first-line therapy.[10, 12]
    d. Of the patients pretreated with osimertinib, 64.9% to 77.2% received second-line therapy (1,072 to 3,340 patients).[14, 15, 16]
6. This results in a total of 1,124 to 3,491 patients.
7. Of these, 77.2% have an ECOG PS 0-1 (868 to 2,695 patients), 22.8% have an ECOG PS ≥ 2 (256 to 796 patients).[10]
8. With 87.28% of patients in statutory health insurance[17], the target population comprises approximately 760 to 2,350 patients with an ECOG-PS 0-1 and approximately 225 to 695 patients with an ECOG-PS ≥ 2.

[6] Benefit assessment according to Section 35a SGB V, A23-29 | A23-31, durvalumab and tremelimumab, 29.06.2023
[7] 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)
[8] Benefit assessment according to Section 35a SGB V, A23-37, cemiplimab, 28.04.2023
[9] Benefit assessment according to Section 35a SGB V, A21-86, osimertinib, 29.09.2021
[10] AIO studies. CRISP interim analysis: NSCLC stage IV, IIIB/C palliative. Database cut 30.09.2023. 2023.
[11] Gahr S, Stoehr R, Geissinger E et al. EGFR mutational status in a large series of Caucasian European NSCLC patients: data from daily practice. Br J Cancer 2013; 109(7): 1821-1828. https://doi.org/10.1038/bjc.2013.511.
[12] Faehling M, Schwenk B, Kramberg S et al. Oncogenic driver mutations, treatment, and EGFR-TKI resistance in a Caucasian population with non-small cell lung cancer: survival in clinical practice. Oncotarget 2017; 8(44): 77897-77914. https://doi.org/10.18632/oncotarget.20857.
[13] Park K, Bennouna J, Boyer M et al. Sequencing of therapy following first-line afatinib in patients with EGFR mutation-positive non-small cell lung cancer. Lung Cancer 2019; 132: 126-131. https://doi.org/10.1016/j.lungcan.2019.04.014.
[14] Johnson & Johnson. Additional analyses of the MARIPOSA study. 2024.
[15] Planchard D, Janne PA, Cheng Y et al. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. N Engl J Med 2023; 389(21): 1935-1948. https://doi.org/10.1056/NEJMoa2306434.
[16] Ramalingam SS, Vansteenkiste J, Planchard D et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med 2020; 382(1): 41-50. https://doi.org/10.1056/NEJMoa1913662.
[17] Federal Ministry of Health. Statutory health insurance - members, co-insured dependants and sickness absence rate - monthly figures January - October 2024. 2024.

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: 3 July 2025):

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

Treatment with amivantamab 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.

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).

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

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.

The dosage regimens used in the MARIPOSA-2 approval study will be used for amivantamab in combination with carboplatin and pemetrexed.

The dosage of carboplatin as part of the combination therapy of the medicinal product to be assessed (amivantamab in combination with carboplatin and pemetrexed) is calculated using the Calvert formula and the estimation of renal function using the Cockcroft-Gault equation, whereby average values of age (women: 46 years, men: 43.4 years)[18], body height (women: 166 cm, men: 179 cm)[19], body weight (women: 69.2 kg, men: 85.8 kg)[19] and the mean standard serum creatinine concentration (women: 0.75 mg/dl, men: 0.90 mg/dl)[20] for women and men in Germany in 2021 are used.

The mean value (AUC 5 = 700.8 mg) formed from these doses for women (AUC 5 = 637 mg) and men (AUC 5 = 764.5 mg) was used as the basis for calculating the cost of carboplatin.

[18] Federal Institute for Population Research, average age of the population in Germany (1871-2021) https://www.bib.bund.de/DE/Fakten/Fakt/B19-Durchschnittsalter-Bevoelkerung-ab-1871.html

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

[20] DocCheck Flexikon – Serum creatinine, URL: https://flexikon.doccheck.com/de/Serumkreatinin [last access: 05.05.2025]

A cycle duration of 3 weeks is used as the basis for carboplatin as a component of the appropriate comparator therapy. For the use of carboplatin in the off-label indication "combination therapy for advanced NSCLC", Annex VI of the Pharmaceuticals Directive specifies the following dosage: up to 500 mg/m² BSA (body surface area) or AUC 6.0 (area under the curve).

During the subcutaneous administration of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, atezolizumab is initially administered in an induction phase lasting four or six cycles in combination with bevacizumab, paclitaxel and carboplatin every three weeks, followed by a maintenance phase in combination with bevacizumab every three weeks.

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)[19]. This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916).

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.

Treatment period:

a) Adults with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 0–1

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 carboplatin and pemetrexed				
Amivantamab	Week 1 to 4: 1 x every 7 days From week 7: 1 x per 21-day cycle	19.4	Week 1 to 4: 4 From week 7: 1	19.4
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel				
Induction therapy				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Atezolizumab	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
Bevacizumab	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
Carboplatin	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
Paclitaxel	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
Maintenance treatment				
Atezolizumab	1 x per 21-day cycle	11.4 - 13.4	1	11.4 - 13.4
Bevacizumab	1 x per 21-day cycle	11.4 - 13.4	1	11.4 - 13.4

b) Adults with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 2

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 carboplatin and pemetrexed				
Amivantamab	Week 1 to 4: 1 x every 7 days From week 7: 1 x per 21-day cycle	19.4	Week 1 to 4: 4 From week 7: 1	19.4
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) cf. Annex VI to Section K of the Pharmaceuticals Directive				
Carboplatin	1 x per 21-day cycle	17.4	1	17.4

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Gemcitabine	2 x per 21-day cycle	17.4	2	34.8
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Vinorelbine	2 x per 21-day cycle	17.4	2	34.8
Carboplatin in combination with nab-paclitaxel				
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
nab-paclitaxel	3 x per 21-day cycle	17.4	3	52.2
Monotherapy with gemcitabine or vinorelbine (only for patients who are ineligible for platinum-based chemotherapy)				
Gemcitabine	3 x per 28-day cycle	13.0	3	39.0
Vinorelbine	1 x every 7 days	52.1	1	52.1

Consumption:

a) Adults with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 0–1

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Amivantamab in combination with carboplatin and pemetrexed					
Amivantamab	Week 1 Day 1: 350 mg Week 1 Day 2: 1,050 mg	Week 1 Day 1: 350 mg Week 1 Day 2: 1,050 mg	Week 1 Day 1: 1 x 350 mg Week 1 Day 2: 3 x 350 mg	19.4	93 x 350 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
	Week 2 – 4 1,400 mg From week 7: 1,750 mg	Week 2 – 4 1,400 mg From week 7: 1,750 mg	Week 2 – 4 4 x 350 mg From week 7: 5 x 350 mg		
Carboplatin	AUC 5 = 700.8 mg	700.8 mg	1 x 150 mg + 1 x 600 mg	17.4	17.4 x 150 mg + 17.4 x 600 mg
Pemetrexed	500 mg/m^2 = 955 mg	955 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg
Appropriate comparator therapy					
Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel					
Induction therapy					
Atezolizumab	1,875 mg	1,875 mg	1 x 1,875 mg	4.0 – 6.0	4.0 x 1,875 mg – 6.0 x 1,875 mg
Bevacizumab	7.5 mg/kg = 582.8 mg	582.8 mg	2 x 400 mg	4.0 – 6.0	8.0 x 400 mg – 12.0 x 400 mg
	or				
	15 mg/kg = 1,165.5 mg	1,165.5 mg	3 x 400 mg	4.0 – 6.0	12.0 x 400 mg – 18.0 x 400 mg
Carboplatin	500 mg/m^2 = 955 mg	955 mg	2 x 450 mg + 2 x 50 mg	4.0 – 6.0	8.0 x 450 mg + 8.0 x 50 mg – 12.0 x 450 mg + 12.0 x 50 mg
Paclitaxel	175 mg/m^2 = 334.3 mg	334.3 mg	1 x 150 mg + 2 x 100 mg	4.0 – 6.0	4.0 x 150 mg + 8.0 x 100 mg – 6.0 x 150 mg + 12.0 x 100 mg
Maintenance treatment					
Atezolizumab	1,875 mg	1,875 mg	1 x 1,875 mg	11.4 – 13.4	11.4 x 1,875 mg – 13.4 x 1,875 mg
Bevacizumab	7.5 mg/kg	582.8 mg	2 x 400 mg	11.4	22.8 x 400 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
	= 582.8 mg			– 13.4	– 26.8 x 400 mg
	or				
	15 mg/kg = 1,165.5 mg	1,165.5 mg	3 x 400 mg	11.4 – 13.4	34.2 x 400 mg – 40.2 x 400 mg

b) <u>Adults with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 2</u>

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Amivantamab in combination with carboplatin and pemetrexed					
Amivantamab	<u>Week 1 Day 1:</u> 350 mg <u>Week 1 Day 2:</u> 1,050 mg <u>Week 2 – 4</u> 1,400 mg <u>From week 7:</u> 1,750 mg	<u>Week 1 Day 1:</u> 350 mg <u>Week 1 Day 2:</u> 1,050 mg <u>Week 2 – 4</u> 1,400 mg <u>From week 7:</u> 1,750 mg	<u>Week 1 Day 1:</u> 1 x 350 mg <u>Week 1 Day 2:</u> 3 x 350 mg <u>Week 2 – 4</u> 4 x 350 mg <u>From week 7:</u> 5 x 350 mg	19.4	93 x 350 mg
Carboplatin	AUC 5 = 700.8 mg	700.8 mg	1 x 150 mg + 1 x 600 mg	17.4	17.4 x 150 mg + 17.4 x 600 mg
Pemetrexed	500 mg/m^2 = 955 mg	955 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg
Appropriate comparator therapy					
Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) cf. Annex VI to Section K of the Pharmaceuticals Directive					
Carboplatin	500 mg/m^2 = 955 mg	955 mg	2 x 450 mg + 2 x 50 mg	17.4	34.8 x 450 mg + 34.8 x 50 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Docetaxel	75 mg/m² = 143.3 mg	143.3 mg	1 x 160 mg	17.4	17.4 x 160 mg
Gemcitabine	1,250 mg/m² = 2,387.5 mg	2,387.5 mg	2 x 200 mg + 2 x 1000 mg	34.8	69.6 x 200 mg + 69.6 x 1,000 mg
Paclitaxel	175 mg/m² = 334.3 mg	334.3 mg	2 x 100 mg + 1 x 150 mg	17.4	34.8 x 100 mg + 17.4 x 150 mg
Pemetrexed	500 mg/m² = 955 mg	955 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg
Vinorelbine	25 mg/m² – 30 mg/m² = 47.8 mg – 57.3 mg	47.8 mg – 57.3 mg	1 x 50 mg – 1 x 50 mg + 1 x 10 mg	34.8	34.8 x 50 mg – 34.8 x 50 mg + 34.8 x 10 mg
Carboplatin in combination with nab-paclitaxel					
Carboplatin	500 mg/m² = 955 mg	955 mg	2 x 450 mg + 2 x 50 mg	17.4	34.8 x 450 mg + 34.8 x 50 mg
nab-paclitaxel	100 mg/m² = 191 mg	191 mg	2 x 100 mg	52.2	104.4 x 100 mg
Monotherapy with gemcitabine or vinorelbine (only for patients who are ineligible for platinum-based chemotherapy)					
Gemcitabine	1,000 mg/m² = 1,910 mg	1,910 mg	2 x 1,000 mg	39.0	78 x 1,000 mg
Vinorelbine	25 mg/m² – 30 mg/m² = 47.8 mg – 57.3 mg	47.8 mg – 57.3 mg	1 x 50 mg – 1 x 50 mg + 1 x 10 mg	52.1	52.1 x 50 mg – 52.1 x 50 mg + 52.1 x 10 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:

a) Adults with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 0–1

and

b) Adults with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 2

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	1 CIS	€ 1,847.18	€ 1.77	€ 102.20	€ 1,743.21
Carboplatin 150 mg	1 CIS	€ 83.04	€ 1.77	€ 3.40	€ 77.87
Carboplatin 600 mg	1 CIS	€ 300.84	€ 1.77	€ 13.74	€ 285.33
Pemetrexed 1,000 mg	1 CIS	€ 1,124.81	€ 1.77	€ 52.84	€ 1,070.20
Appropriate comparator therapy					
Atezolizumab 1,875 mg	1 SFI	€ 4,129.23	€ 1.77	€ 232.53	€ 3,894.93
Bevacizumab 400 mg	1 CIS	€ 671.80	€ 1.77	€ 36.57	€ 633.46
Carboplatin 450 mg	1 CIS	€ 228.27	€ 1.77	€ 10.30	€ 216.20
Carboplatin 50 mg	1 CIS	€ 34.70	€ 1.77	€ 1.11	€ 31.82
Docetaxel 160 mg	1 CIS	€ 515.78	€ 1.77	€ 23.94	€ 490.07
Gemcitabine 1,000 mg	1 PIF	€ 102.35	€ 1.77	€ 10.62	€ 89.96
Gemcitabine 200 mg	1 PIF	€ 28.85	€ 1.77	€ 0.83	€ 26.25
nab-paclitaxel 100 mg	1 PIS	€ 429.36	€ 1.77	€ 19.84	€ 407.75
Paclitaxel 100 mg	1 CIS	€ 289.47	€ 1.77	€ 13.20	€ 274.50
Paclitaxel 150 mg	1 CIS	€ 428.54	€ 1.77	€ 19.80	€ 406.97
Pemetrexed 1,000 mg	1 CIS	€ 1,124.81	€ 1.77	€ 52.84	€ 1,070.20
Vinorelbine 50 mg	1 CIS	€ 152.64	€ 1.77	€ 6.71	€ 144.16
Vinorelbine 10 mg	1 CIS	€ 38.90	€ 1.77	€ 1.31	€ 35.82
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PIF = powder for the preparation of an infusion solution, PIS = powder for the preparation of an infusion suspension					

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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							
Amivantamab in combination with carboplatin and pemetrexed							
Dexamethasone[21] 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	19.4	€ 136.19
Paracetamol 500 - 1,000 mg, PO[21,22]	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	19.4	€ 3.06 – € 5.84
Pemetrexed							
17.4 cycles of 21 days each Amivantamab in combination with carboplatin and **pemetrexed**							
Dexamethasone 2 x 4 mg[21]	100 x 4 mg TAB	€ 79.54	€ 1.77	€ 5.40	€ 72.37	52.2	€ 75.55
Folic acid[23] 350 – 1,000 µg/day	100 x 400 µg TAB	€ 17.60	€ 0.88	€ 1.98	€ 14.74	365.0	€ 53.80 – € 107.60
Vitamin B12[21] 1,000 µg/day, every 3 cycles	10 x 1,000 µg AMP	€ 8.19	€ 0.41	€ 0.37	€ 7.41	6.8	€ 5.04
Appropriate comparator therapy							
Paclitaxel							

[21] Fixed reimbursement rate

[22] 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.

[23] The cost calculation for folic acid is based on the single dose of 400 µg of the non-divisible tablets available for cost calculation related to a dose range of 400 - 800 µg per day, even if a dose range of 350 - 1,000 µg is given in the product information.

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
4 - 6 cycles Atezolizumab + bevacizumab + **paclitaxel** + carboplatin							
Dexamethasone[21] 2 x 20 mg PO	10 x 20 mg TAB	€ 32.42	€ 1.77	€ 0.00	€ 30.65	4 – 6	€ 30.65 – € 52.32
	20 x 20 mg TAB	€ 54.09	€ 1.77	€ 0.00	€ 52.32		
Dimetindene IV 1 mg/10 kg BW = 7.8 mg	5 x 4 mg SFI	€ 26.24	€ 1.77	€ 6.92	€ 17.55	4 – 6	€ 35.10 – € 52.65
Cimetidine 300 mg IV	10 x 200 mg AMP	€ 22.56	€ 1.77	€ 1.42	€ 19.37	4 – 6	€ 19.37 – € 38.74
Paclitaxel							
17.4 cycles of 21 days each Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or **paclitaxel** or pemetrexed) cf. Annex VI to Section K of the Pharmaceuticals Directive							
Dexamethasone[21] 2 x 20 mg PO	50 x 20 mg TAB	€ 118.88	€ 1.77	€ 0.00	€ 117.11	17.4	€ 81.51
Dimetindene IV 1 mg/10 kg BW = 7.8 mg	5 x 4 mg SFI	€ 26.24	€ 1.77	€ 6.92	€ 17.55	17.4	€ 122.15
Cimetidine 300 mg IV	10 x 200 mg AMP	€ 22.56	€ 1.77	€ 1.42	€ 19.37	17.4	€ 67.41
Pemetrexed							
17.4 cycles of 21 days each Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or **paclitaxel** or pemetrexed) cf. Annex VI to Section K of the Pharmaceuticals Directive							
Dexamethasone[21] 2 x 4 mg	100 x 4 mg TAB	€ 79.54	€ 1.77	€ 5.40	€ 72.37	52.2	€ 75.55
Folic acid[23] 350 – 1,000 µg/day	100 x 400 µg TAB	€ 17.60	€ 0.88	€ 1.98	€ 14.74	365.0	€ 53.80 – € 107.60
Vitamin B12[21] 1,000 µg/day, every 3 cycles	10 x 1,000 µg AMP	€ 8.19	€ 0.41	€ 0.37	€ 7.41	6.8	€ 5.04
Abbreviations: INF = infusion solution; AMP = ampoules; SFI = solution for injection; TAB = tablets							

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:

a) Adults with advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 0–1

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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

b) Adults with advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI); ECOG-PS 2

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

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 13 August 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.

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	13 August 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
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