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 20 insertion mutation, first-line, 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 submitted an application for postponement of the date for the start of the benefit assessment procedure for amivantamab in the therapeutic indication of non-small cell lung cancer (NSCLC) 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 27 June 2024, amivantamab received the extension of the marketing authorisation for the therapeutic indication "advanced NSCLC with activating EGFR Exon 20 insertion mutations". The extension of the marketing authorisation for the therapeutic indication "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)" was granted on 22 August 2024 and for "advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations" on 19 December 2024. The mentioned 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 submitted in due time a dossier on tislelizumab with the therapeutic indication "advanced NSCLC with activating EGFR Exon 20 insertion mutations" in accordance with Section 4, paragraph 3, number 3 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 2 of the Rules of Procedure of the G-BA (VerfO).

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 first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.

Therapeutic indication of the resolution (resolution of 17 July 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 with activating EGFR Exon 20 insertion mutations; first-line therapy

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

- Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)

  or

- 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

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, medicinal products with the active ingredients cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, nab-paclitaxel, paclitaxel, pemetrexed, vinorelbine, vindesine, bevacizumab, afatinib, dacomitinib, erlotinib, gefitinib, osimertinib and ramucirumab are approved in the present therapeutic indication.

Medicinal products explicitly approved for molecularly stratified therapy were not considered here, nor were medicinal products for the treatment of NSCLC with exclusively squamous histology. 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:

- Ramucirumab: resolution of 20.08.2020
- Dacomitinib: resolution of 17.10.2019
- Osimertinib: resolution of 17.01.2019
- Afatinib: resolution of 15.11.2015

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 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 by the German Society for Haematology and Medical Oncology (DGHO), the German Respiratory Society (DGP), the Working Group for Thoracic Oncology in the Working Group for Internal Oncology of the German Cancer Society (AIO) and the Working Group for Pneumological Oncology of the German Cancer Society (POA) is available.

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 6 guideline recommendations and the reality of care.

The present guidelines recommend that patients with EGFR Exon20 insertion mutations be treated analogue to the EGFR wild type, as Exon20 insertion mutations are generally not sensitive to tyrosine kinase inhibitors (TKIs). In their written statement, the scientific-medical societies also primarily address therapy options analogous to treatment of the EGFR wild type and refer in particular to immunotherapy using an immune checkpoint inhibitor and a combination of immune checkpoint inhibitor and chemotherapy. The scientific-medical societies recommend chemotherapy alone in the case of contraindications to immunotherapy.

However, immune checkpoint inhibitors are not approved for the first-line treatment of advanced NSCLC in patients with EGFR tumour mutations or are only approved after failure of a corresponding targeted therapy. The scientific-medical societies also state that it is unclear whether patients with EGFR Exon 20 insertion mutations respond to immune checkpoint inhibitors to the same extent as patients without predictive genomic aberrations. Overall, the immune checkpoint inhibitors (as monotherapy or in

combination with chemotherapy) are therefore currently not considered as an appropriate comparator therapy in the present therapeutic indication.

The G-BA therefore consider it appropriate to determine a platinum-based (cis- or carboplatin) combination chemotherapy with a third-generation cytostatic (pemetrexed, paclitaxel, gemcitabine, docetaxel and vinorelbine) as an appropriate comparator therapy for the first-line treatment of patients with advanced NSCLC with Exon 20 insertion mutations. The approved combination of carboplatin and nab-paclitaxel is another equally appropriate alternative.

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:

<u>Adults with advanced NSCLC and with activating EGFR Exon 20 insertion mutations; first-line therapy</u>

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company presented results from the ongoing, open-label, randomised, controlled phase III PAPILLON study comparing amivantamab in combination with carboplatin and pemetrexed versus carboplatin and pemetrexed. The study is being conducted in 131 study sites across Australia, Asia, Europe, North America and South America since December 2020.

Adults with locally advanced or metastatic, non-squamous NSCLC and activating EGFR Exon 20 insertion mutations were enrolled in the study. Patients were not allowed to have received any pretreatment for the locally advanced or metastatic NSCLC. Patients had to be in good general condition, corresponding to an Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) of 0 or 1.

A total of 308 patients were enrolled and randomly assigned in a 1:1 ratio to the intervention arm (N = 153) or to the comparator arm (N = 155).

Treatment in the intervention arm largely corresponds to the product information. The combination of carboplatin and pemetrexed in the comparator arm is not approved for this indication in the respective product information, but can be prescribed in accordance with Annex VI to Section K of the Pharmaceuticals Directive.

The primary endpoint of the PAPILLON study is progression-free survival (PFS). Secondary endpoints are collected in the categories of mortality, morbidity, health-related quality of life and side effects.

Two data cut-offs are available for the PAPILLON study:

- 1st data cut-off from 03.05.2023: pre-specified primary analysis of all endpoints, planned after the occurrence of 200 PFS events
- 2nd data cut-off from 31.10.2023: non pre-specified analysis on overall survival; required by the regulatory authorities

In addition, a further data cut-off is available, which was carried out as part of the 120-day safety update for the Food and Drug Administration (FDA). A final data cut-off for overall survival is planned for approximately 48 months after randomisation of the first patient (expected number of deaths: 210).

In the dossier, the pharmaceutical company presented the pre-specified 1st data cut-off from 03.05.2023 in full. For the current 2nd data cut-off, they only presented results on overall survival.

On the usability of the study results presented in the dossier:

In accordance with the regulation in Chapter 5 Section 18 of the Rules of Procedure of the G-BA, the benefit assessment examines whether there is evidence of an additional benefit for the medicinal product compared to the appropriate comparator therapy. The validity and completeness of the information in the dossier is also checked. The dossier template in Annex II must be used for compiling the documents. The data according to Chapter 5 Section 9, paragraphs 1, 4 to 8 of the Rules of Procedure of the G-BA must be prepared and submitted in accordance with the requirements specified in Modules 1 to 5. If the benefit assessment shows that the preparation of the documents in the dossier deviates from the requirements specified in Section 9 to an extent that prevents a proper assessment of the additional benefit, the Federal Joint Committee may determine that the additional benefit is not proven, Chapter 5 Section 18, paragraph 1, sentence 4 of the Rules of Procedure of the G-BA.

IQWiG stated in the dossier assessment that the results of the PAPILLION study presented by the pharmaceutical company in the dossier for the pre-specified 1st data cut-off were not suitable for the benefit assessment.

IQWIG also states that the 2nd overall survival data cut-off from 31.10 2023 of the PAPILLION study was required by the EMA and represents the most recent data cut-off. Between the 1st and 2nd data cut-offs, there is an interval of approx. 6 months, which in this case corresponds to an approximately 40% longer follow-up period for overall survival. At the 1st data cut-off, 70 patients in the intervention arm (46%) and 24 patients in the control arm (15%) were still being treated with the study medication. For these patients, data on patient-relevant endpoints in the categories of mortality, morbidity, health-related quality of life and side effects were accordingly collected further. IQWiG subsequently concluded that the 2nd data cut-off contains a relevantly higher information content. For the benefit assessment, the 2nd data cut-off from 31.10.2023 is relevant. For this data cut-off, evaluations must be carried out and submitted for all relevant endpoints collected in accordance with the module template. This also applies if a data cut-off was originally planned only for the evaluation of individual endpoints. However, the pharmaceutical company only presented data on overall survival for the 2nd data cut-off. According to IQWiG's dossier assessment, the data cut-off is therefore incomplete and the evaluations in the pharmaceutical company's dossier are not suitable for the benefit assessment.

Overall, IQWiG concludes that the evaluations of the current 2nd data cut-off are relevant for the benefit assessment. These were not submitted in full by the pharmaceutical company. The dossier is therefore incomplete in terms of content. As a result, IQWiG was not able to carry out an adequate assessment of the study data.

In the written statement procedure, the pharmaceutical company stated that, in their view, no additional information could be expected from the 2nd data cut-off due to the maturity of the data in the 1st data cut-off . They also explain that a data cut-off can only be fully analysed if the data for all relevant endpoints collected for this data cut-off is also available in a correspondingly processed ("clean") format. For the 2nd data cut-off, only the endpoint of overall survival was processed and analysed. As part of the written statement procedure, no further evaluations of the 2nd data cut-off were submitted.

After detailed consideration of IQWiG's statements on the shortcomings in the dossier, the G-BA concur with IQWiG's assessment. In summary, it can be stated that the 2nd data cut-off represents the most recent and the relevant data cut-off for the benefit assessment. In this regard, the G-BA state that a significant information gain compared to the 1st data cut-off can be assumed for the 2nd data cut-off . The follow-up period for overall survival is around 40% longer for the 2nd data cut-off. Patient-reported endpoints were collected for 46% of patients in the intervention arm and 15% in the control arm, which is why, in addition to the endpoint of overall survival, the other patient-relevant endpoints of the 2nd data cut-off had to be prepared and evaluated by the pharmaceutical company in the dossier. As a result, the G-BA state that, in accordance with Chapter 5 Section 18, paragraph 1 of the Rules of Procedure of the G-BA, the preparation of the documents in the dossier deviates from the requirements specified in Chapter 5 Section 9 of the Rules of Procedure of the G-BA to an extent that prevents a proper assessment of the additional benefit.

It is therefore concluded that the data presented is incomplete overall, which prevents a proper assessment. An additional benefit is therefore not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of amivantamab finds its legal basis in Section 35a, paragraph 3, sentence 5 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

The final results from the ongoing PAPILLON study are still pending and are expected in the fourth quarter of 2025, according to the pharmaceutical company.

Since clinical data are expected which are relevant for the benefit assessment of the medicinal product, it is justified to limit the validity of the resolution until further scientific knowledge is available for the assessment of the additional benefit of amivantamab. The limitation enables the expected interim results from the PAPILLON study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V in a timely manner.

For this purpose, the G-BA consider a limitation for the resolution until 1 July 2026 to be appropriate.

Conditions of the limitation:

For the new benefit assessment after expiry of the deadline, the results from the final analysis on overall survival as well as on all other patient-relevant endpoints from the PAPILLON study must be presented in the dossier.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 paragraph 1, number 5 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of the medicinal product with the active ingredient amivantamab recommences when the deadline has expired. For this purpose, the pharmaceutical company must present a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of amivantamab in comparison with the appropriate comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit is considered as being not proven.

The possibility that a benefit assessment for the medicinal product with the active ingredient amivantamab can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, Nos. 2 to 6 or No. 8 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

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

"Rybrevant is indicated in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations."

The appropriate comparator therapy was determined to be cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) or 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.

Results from the ongoing, open-label, randomised, controlled phase III PAPILLON study comparing amivantamab in combination with carboplatin and pemetrexed versus carboplatin and pemetrexed were presented in the dossier. The results for the 1st data cut-off were completely presented, but only results on overall survival were presented for the current 2nd data cut-off required by the EMA.

The follow-up period of the 2nd data cut-off was around 40% longer compared to the 1st data cut-off. At the 1st data cut-off, 46% of patients in the intervention arm and 15% of patients in the control arm were still undergoing treatment. For these patients, data on patient-relevant endpoints in the categories of mortality, morbidity, health-related quality of life and side effects were accordingly collected further. The 2nd data cut-off thus contains a relevantly higher information content. However, this data cut-off is incomplete in the dossier.

It is therefore concluded that the data presented is incomplete overall, which prevents a proper assessment. An additional benefit is therefore not proven.

The validity of the resolution is limited to 1 July 2026.

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 suitability for a platinum-based therapy exists in 70%-90% of patients (10,962 to 24,920 patients).
6. The percentage of patients with activating EGFR mutation is 10.3% to 14.1%[8] (1,129 to 3,513 patients).
7. The percentage of patients with EGFR Exon 20 insertion mutations is 7.0%[9] (79 to 246 patients).
8. Taking into account the percentage of SHI-insured patients of 87.28%, there are 69 to 215 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: 14 April 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

[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
[9] Percentage from the dossier of the pharmaceutical company

specialists in pulmonary medicine and other doctors from specialist groups participating in the Oncology Agreement.

EGFR Exon 20 insertion mutation testing
Prior to a therapy with Rybrevant, positive EGFR Exon 20 insertion mutational status must be detected 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 June 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 PAPILLON 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 body height (women: 166 cm, men: 179 cm)[12], body weight (women: 69.2 kg, men: 85.8 kg)[12], age (women: 46 years, men: 43.4 years)[10] and the mean standard serum creatinine concentration (women: 0.75 mg/dl, men: 0.9 mg/dl)[11] 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.

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).

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

[10] 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

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

weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[12].

Cisplatin is dosed differently, depending on the concomitant active ingredient. According to the product information of the concomitant medicinal products, the single dose of cisplatin in combination with vinorelbine or gemcitabine is 75 - 100 mg/m² BSA, in combination with docetaxel and pemetrexed 75 mg/m² BSA and in combination with paclitaxel 80 mg/m² BSA.

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:

Adults with advanced NSCLC and with activating EGFR Exon 20 insertion mutations; first-line therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
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				
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)				
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
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

[12] 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
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 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
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

Consumption:

Adults with advanced NSCLC and with activating EGFR Exon 20 insertion mutations; first-line therapy

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Amivantamab in combination with carboplatin and pemetrexed					
Amivantamab	Week 1 Day 1: 350 mg Week 1 Day 2:	Week 1 Day 1: 350 mg Week 1 Day 2:	Week 1 Day 1: 1 x 350 mg Week 1 Day 2:	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	Average annual consumption by potency
	1,050 mg Week 2 – 4 1,400 mg From week 7: 1,750 mg	1,050 mg Week 2 – 4 1,400 mg From week 7: 1,750 mg	3 x 350 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/m² = 955 mg	955 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg
Appropriate comparator therapy					
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)					
Cisplatin	75 mg/m² = 143.3 mg	143.3 mg	1 x 50 mg + 1 x 100 mg	17.4	17.4 x 50 mg + 17.4 x 100 mg
	80 mg/m² = 152.8 mg	152.8 mg	1 x 10 mg + 1 x 50 mg + 1 x 100 mg	17.4	17.4 x 10 mg + 17.4 x 50 mg + 17.4 x 100 mg
	100 mg/m² = 191 mg	191 mg	2 x 100 mg	17.4	34.8 x 100 mg
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 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/m² = 955 mg	955 mg	2 x 450 mg + 2 x 50 mg	17.4	34.8 x 450 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
					34.8 x 50 mg
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

Costs:

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

Costs of the medicinal products:

Adults with advanced NSCLC and with activating EGFR Exon 20 insertion mutations; first-line therapy

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
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					
Carboplatin 50 mg	1 CIS	€ 34.70	€ 1.77	€ 1.11	€ 31.82
Carboplatin 450 mg	1 CIS	€ 228.27	€ 1.77	€ 10.30	€ 216.20
Cisplatin 10 mg	1 CIS	€ 17.53	€ 1.77	€ 0.30	€ 15.46
Cisplatin 50 mg	1 CIS	€ 47.71	€ 1.77	€ 1.73	€ 44.21
Cisplatin 100 mg	1 CIS	€ 76.59	€ 1.77	€ 3.10	€ 71.72
Docetaxel 160 mg	1 CIS	€ 515.78	€ 1.77	€ 23.94	€ 490.07
Gemcitabine 200 mg	1 PIF	€ 28.85	€ 1.77	€ 0.83	€ 26.25
Gemcitabine 1,000 mg	1 PIF	€ 102.35	€ 1.77	€ 10.62	€ 89.96
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							
Dexamethasone[13] 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[13,14]	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[13]	100 x 4 mg TAB	€ 79.54	€ 1.77	€ 5.40	€ 72.37	52.2	€ 75.55
Folic acid[15] 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[13] 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							
Cisplatin							
17.4 cycles of 21 days each							

[13] Fixed reimbursement rate

[14] 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.

[15] 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
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 105.54	€ 5.28	€ 4.26	€ 96.00	17.4	€ 167.04
Sodium chloride 0.9% infusion solution, 3 - 4.4 l/day	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	17.4	€ 104.66 – € 174.44
Paclitaxel							
17.4 cycles of 21 days each Carboplatin/ cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)							
Dexamethasone[13] 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/ cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)							
Dexamethasone[13] 2 x 4 mg	100 x 4 mg TAB	€ 79.54	€ 1.77	€ 5.40	€ 72.37	52.2	€ 75.55
Folic acid[15] 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[13] 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:

Adults with advanced NSCLC and with activating EGFR Exon 20 insertion mutations; first-line therapy

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

References:
Product information for 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.

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 3 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 28 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
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