Gemeinsamer Bundesausschuss

Justification

to 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

Repotrectinib
(non-small cell lung cancer, ROS1-positive)

of 16 October 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,
7. number of study participants who participated in the clinical studies at study sites within the scope of SGB V, and total number of study participants.

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 decide 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient repotrectinib on 1 May 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 30 April 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 August 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 repotrectinib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. 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 repotrectinib.

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

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

2.1.1 Approved therapeutic indication of Repotrectinib (Augtyro) in accordance with the product information

AUGTYRO as monotherapy is indicated for the treatment of adult patients with ROS1-positive advanced non-small cell lung cancer (NSCLC).

Therapeutic indication of the resolution (resolution of 16.10.2025):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); no pretreatment with a ROS1 inhibitor

Appropriate comparator therapy for repotrectinib:

- Crizotinib

b1) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); pretreatment with a ROS1 inhibitor and with PD-L1 expression ≥ 50%

Appropriate comparator therapy for repotrectinib:

- Pembrolizumab as monotherapy

or

- atezolizumab as monotherapy

or

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

– nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1)

or

– pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients without ECOG-PS 0-1)

or

– atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG-PS 0-1)

or

– atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0-1)

or

– durvalumab in combination with tremelimumab and platinum-based chemotherapy (only for patients with ECOG-PS 0-1)

b2) <u>Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); pretreatment with a ROS1 inhibitor and with PD-L1 expression < 50%</u>

Appropriate comparator therapy for repotrectinib:

– pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients without ECOG-PS 0-1)

or

– Atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells)

or

– atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG-PS 0-1)

or

– atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0-1)

or

– nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1)

or

– durvalumab in combination with tremelimumab and platinum-based chemotherapy (only for patients with ECOG-PS 0-1)

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 (only for patients with ECOG-PS 2)

or

- carboplatin in combination with nab-paclitaxel (only for patients with ECOG-PS 2)

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

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

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

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

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

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

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

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

On 1. It is assumed in this therapeutic indication that no molecularly stratified therapy (directed against ALK, BRAF, EGFR, -Exon-20, KRAS G12C, METex14 or RET) will be considered for patients at the time of therapy with repotrectinib. Medicinal products with a corresponding marketing authorisation were therefore not considered. In addition, medicinal products for the treatment of NSCLC with exclusively squamous histology were not considered.

In terms of the authorisation status, cisplatin, docetaxel, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine, vinorelbine, erlotinib, nintedanib, atezolizumab, bevacizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, ramucirumab, tislelizumab and tremelimumab are generally available for the treatment of advanced or metastatic NSCLC. In addition, the protein kinase inhibitors crizotinib and entrectinib have been explicitly approved for the treatment of ROS1-positive advanced NSCLC.

On 2. For the present 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 (NSCLC, first-line; resolutions of 2 April 2020, 19 November 2021 and 20 March 2025)
- Ipilimumab (NSCLC, first-line; resolution of 3 June 2021)
- Nivolumab (NSCLC, first-line; resolution of 3 June 2021)
- Entrectinib (ROS1-positive NSCLC; resolution of 18 February 2021)
- Pembrolizumab (NSCLC, first-line; resolutions of 3 August 2017 and 19 September 2019)
- Durvalumab (NSCLC; resolutions of 4 April 2019 and 5 October 2023)
- Tremelimumab (NSCLC; resolution of 5 October 2023)
- Tislelizumab (NSCLC; resolution of 18 June 2025)
- Crizotinib (ROS1-positive NSCLC; resolution of 16 March 2017)

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 systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB

V (see “Information on Appropriate Comparator Therapy”). A written statement of the scientific-medical societies 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 guideline recommendations and the reality of care.

For the determination of the appropriate comparator therapy, It is assumed that no molecularly stratified therapy (directed against ALK, BRAF, EGFR, -Exon-20, KRAS G12C, METex14 or RET) will be considered for patients at the time of therapy with repotrectinib.

Since ROS1-positive, non-small cell lung cancer usually has a non-squamous histology, therapies that are explicitly indicated for squamous histology were not taken into account.

For the present therapeutic indication, it was generally assumed that there is neither an indication for definitive chemoradiotherapy nor for definitive local therapy.

The planned therapeutic indication for repotrectinib includes the treatment of ROS1-TKI-naïve patients and the treatment of patients who have been pretreated with a ROS1-TKI. Based on these two distinct treatment settings, the G-BA initially formed two sub-populations a and b, for which different appropriate comparator therapies were determined on the basis of the available evidence and the authorisation status of the medicinal products under consideration.

Patient group a) – no pretreatment with a ROS1 inhibitor

Relevant guidelines recommend crizotinib or entrectinib as first-line therapies for patients with ROS1-positive advanced NSCLC. Crizotinib and entrectinib are the only medicinal products explicitly approved for the treatment of ROS1-positive non-small cell lung cancer. However, the evidence for both active ingredients in the present treatment setting is limited and is based in each case on the results of non-comparator studies.

In the benefit assessments, no additional benefit of crizotinib and entrectinib (resolution of 16 March 2017 on crizotinib and resolution of 18 February 2021 on entrectinib) was identified for the treatment of non-pretreated patients with ROS1-positive advanced non-small cell lung cancer, as no comparator data were available in the overall assessment that enabled an assessment of the additional benefit of crizotinib or entrectinib compared to the appropriate comparator therapy. The period of validity of the resolution on entrectinib is limited until 31 December 2027, as an open-label, randomised controlled phase 3 study with crizotinib as a comparator was planned for entrectinib. The corresponding MO41552 study is ongoing. In particular against the background of these still pending comparator data, entrectinib is not determined as the appropriate comparator therapy for the present resolution.

For the other medicinal products generally approved in the therapeutic indication, the evidence regarding ROS1-positive NSCLC is limited and the corresponding treatment options are not recommended in the guidelines or are recommended less strongly.

Overall, a therapy with crizotinib is therefore determined as the appropriate comparator therapy for repotrectinib in the treatment of adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC), who have not yet been pretreated with a ROS1 inhibitor.

Patient group b) Pretreatment with a ROS1 inhibitor

According to the guidelines, further antineoplastic therapy is recommended for pretreated patients with ROS1-positive, metastatic, non-small cell lung cancer.

According to clinical experts in the written statement procedure, immunotherapies play a subordinate role in the treatment of ROS1-positive NSCLC.

According to the available guidelines, on the other hand, those therapy options that are recommended in first-line therapy for non-pretreated patients without treatable tumour mutations (platinum-containing chemotherapy or chemoimmunotherapy) may also be considered here. The guidelines do not recommend renewed therapy with crizotinib after first-line failure and there is no marketing authorisation for therapy with another TKI in the second line, such as entrectinib.

On this basis, the G-BA consider (chemo)immunotherapies and chemotherapies to be appropriate comparator therapies in accordance with the recommendations for first-line treatment in wild-type patients.

Based on the available evidence on therapy options depending on PD-L1 expression, it is also differentiated into two sub-populations with a cut-off value of PD-L1 expression of 50% of tumour cells (TC):

Patient group b1) - Pretreatment with a ROS1 inhibitor and with PD-L1 expression ≥ 50%

For first-line treatment of metastatic NSCLC with PD-L1 expression in ≥ 50% of tumour cells, the present guidelines recommend monotherapy with the immune checkpoint inhibitors (ICI) atezolizumab, cemiplimab and pembrolizumab, regardless of histological status. However, cemiplimab is not approved for ROS1 aberrations present and is therefore not considered for the patients with ROS1-positive NSCLC covered by the therapeutic indication.

Furthermore, the present guidelines consider the combination therapies of an ICI and a platinum-containing chemotherapy as an alternative to ICI monotherapies, especially for patients with burden of remission due to burdensome symptomatology, high tumour burden or rapid tumour growth. In terms of therapy selection, a distinction is made between patients with a reduced general condition (ECOG performance status (PS) 2) and patients with a good general condition (ECOG-PS 0-1). The present guidelines refer to the limited data basis available for the treatment of patients with ECOG-PS 2. Accordingly, the present guidelines recommend combination therapies consisting of an ICI and chemotherapy for patients with ECOG-PS 0-1.

For patients with non-squamous NSCLC, pembrolizumab can be used in combination with pemetrexed and platinum-containing chemotherapy, atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, or atezolizumab in combination with nab-paclitaxel and carboplatin as well as tislelizumab in combination with pemetrexed and platinum-containing chemotherapy.

The combination therapy of nivolumab and ipilimumab and two cycles of platinum-based chemotherapy as well as durvalumab in combination with tremelimumab and platinum-based chemotherapy is also available as a histology-independent treatment option.

The active ingredient tislelizumab is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved. Based on the generally accepted state of medical knowledge, tislelizumab in combination with pemetrexed and platinum-containing chemotherapy is not identified to be an appropriate comparator therapy for the present resolution.

In summary, based on the available body of evidence, the G-BA consider it appropriate to determine ICI as monotherapies and as combination therapy with platinum-containing chemotherapy as appropriate comparator therapies. The combination therapies of ICI and chemotherapies should only be used for patients with an ECOG-PS of 0 and 1 in accordance with the guideline recommendations.

b2) Pretreatment with a ROS1 inhibitor and with PD-L1 expression < 50%

For first-line treatment of metastatic NSCLC with PD-L1 expression in < 50% of the tumour cells, the present guidelines also make the therapy recommendations depending on ECOG-PS and tumour histology.

For patients with an ECOG-PS of 0-1, the present guidelines recommend the combination therapies of the ICIs atezolizumab, nivolumab or pembrolizumab and chemotherapy, depending on the tumour histology.

For patients with non-squamous NSCLC, pembrolizumab can be used in combination with pemetrexed and platinum-containing chemotherapy, atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, or atezolizumab in combination with nab-paclitaxel and carboplatin.

The combination therapy of nivolumab and ipilimumab and two cycles of platinum-based chemotherapy, atezolizumab as monotherapy as well as durvalumab in combination with tremelimumab and platinum-based chemotherapy is available as a histology-independent treatment option.

For patients with an ECOG-PS 2, chemotherapy can also be a relevant therapy option according to the present guidelines.

The choice of the platinum active ingredient among the corresponding platinum-containing chemotherapies is primarily based on the specific toxicity expected, with cisplatin having a higher toxicity. Taking into account the relevance of toxicity, particularly for patients with a reduced general condition (ECOG-PS 2), the G-BA considers it appropriate to designate carboplatin alone as the platinum active ingredient for patients with an ECOG-PS 2, thereby determining carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) as the appropriate comparator therapy. The combination of carboplatin and nab-paclitaxel is also recommended and determined to be an appropriate comparator therapy for patients with an ECOG-PS 2. In contrast to cisplatin, carboplatin is not approved for the treatment of NSCLC, but can be prescribed for patients as "off-label use" (see Annex VI to Section K of the Pharmaceuticals Directive).

In summary, based on the available body of evidence, the G-BA consider it appropriate to determine atezolizumab as monotherapy as well as the combination therapies of ICI and platinum-containing chemotherapy as appropriate comparator therapies. The combination therapies of ICI and platinum-containing chemotherapy should only be used for patients with an ECOG-PS 0 and 1 in accordance with the guideline recommendations. In contrast, the combination chemotherapies of carboplatin with a third-generation cytostatic or carboplatin with nab-paclitaxel were only determined as appropriate comparator therapy for patients with ECOG-PS 2.

For patient group b2), it should be noted that the appropriate comparator therapy determined here comprises several therapy options. In this context, the therapy options only represent a comparator therapy for the part of the patient population that has the patient and disease characteristics specified in brackets. The therapeutic

alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics. The sole comparison with a therapy option that only represents a comparator therapy for part of the patient population is generally insufficient to demonstrate the additional benefit for the total population.

Overall, the marketing authorisation and dosage specifications in the product information of the active ingredients must be considered and deviations must be justified separately.

In addition, with regard to the appropriate comparator therapies for patient groups b1 and b2, it is pointed out that the results should be presented as the main analysis, summarising the respective patient groups, in the benefit assessment dossier, if suitable data are available from direct comparator studies that can be used to demonstrate an additional benefit in two patient groups separately according to PD-L1 expression status. In this case, complete subgroup analyses with the characteristics of the summarised patient groups should be presented.

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.

Change in the appropriate comparator therapy

Compared to the originally determined appropriate comparator therapy, this is supplemented in the present resolution by the alternative treatment option "durvalumab in combination with tremelimumab and platinum-based chemotherapy" in patient groups b1) and b2) and the monotherapies with gemcitabine or vinorelbine are deleted from patient group b2). According to current evidence, immunochemotherapies should be offered for first-line treatment of metastatic NSCLC for patients with a good general condition (ECOG-PS 0-1), regardless of histological status and regardless of PD-L1 status. For patients with NSCLC, regardless of the occurring histology, durvalumab in combination with tremelimumab and platinum-based chemotherapy is also clearly mentioned. Monotherapy with gemcitabine or vinorelbine no longer corresponds to the standard in this therapeutic indication. For this reason, the G-BA considers it appropriate to change the appropriate comparator therapy for the present resolution, thus adapting it to the current state of medical knowledge.

The present assessment of the additional benefit of repotrectinib remains unaffected by this change in the appropriate comparator therapy.

2.1.3 Extent and probability of the additional benefit

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

a) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); no pretreatment with a ROS1 inhibitor

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company presented the results of the ongoing, single-arm, pivotal TRIDENT-1 study. The efficacy, safety and pharmacokinetics of repotrectinib are investigated in this phase II study. Adults and adolescents 12 years of age and older were enrolled and divided into 6 different cohorts based on their tumour entity (NSCLC or another solid tumour), the gene fusion present (ROS1 or NTRK1-3) and their pretreatment (with or without tyrosine kinase inhibitor, chemotherapy and immunotherapy).

The results of patients with ROS1-positive advanced NSCLC with and without pretreatment (cohorts 1-4) are relevant for this benefit assessment.

In the study, treatment with repotrectinib was carried out without any relevant deviations from the product information.

The primary endpoint in phase 2 of the study was the objective response rate. Secondary endpoints are collected in the categories of mortality, morbidity, health-related quality of life and side effects.

In the dossier, the pharmaceutical company presented data on the label-enabling data cut-off from October 2023.

In addition, the pharmaceutical company presented results of a Matching-Adjusted Indirect Comparison (MAIC) analysis without a bridge comparator based on the TRIDENT-1 study and pooled data of individual arms from five clinical studies (PROFILE 1001, OO-1201, cohort A of METROS, EUCROSS and ROS1 population in AcSé) versus crizotinib for the endpoints of overall survival, tumour response and progression-free survival for patients without TKI pretreatment.

Assessment

As the TRIDENT-1 study is a single-arm study, it does not allow an assessment of the additional benefit of repotrectinib compared with the appropriate comparator therapy and is therefore unsuitable for the benefit assessment of repotrectinib.

MAIC analyses using aggregated data in the comparator arm are generally considered inappropriate in the context of the benefit assessment.

An additional benefit is therefore not proven for the treatment of adults with ROS1-positive advanced or metastatic NSCLC without TKI pretreatment.

b1) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); pretreatment with a ROS1 inhibitor and with PD-L1 expression ≥ 50%

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company only presented the results of the ongoing, single-arm, pivotal phase II TRIDENT-1 study on adults with ROS1-positive, advanced or metastatic NSCLC and pretreatment with a ROS1 inhibitor, without further information on the percentages of patients with PD-L1 expression ≥ 50% or < 50%.

There is no comparison with the appropriate comparator therapy for the assessment of the additional benefit. Therefore, an additional benefit is not proven.

b2) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); pretreatment with a ROS1 inhibitor and with PD-L1 expression < 50%

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company only presented the results of the ongoing, single-arm, pivotal phase II TRIDENT-1 study on adults with ROS1-positive, advanced or metastatic NSCLC and pretreatment with a ROS1 inhibitor, without further information on the percentages of patients with PD-L1 expression ≥ 50% or < 50%.

There is no comparison with the appropriate comparator therapy for the assessment of the additional benefit. Therefore, an additional benefit is not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the findings made in the resolution on the patient population a) "Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); no pretreatment with a ROS1 inhibitor" of the benefit assessment of repotrectinib has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. According to this, the G-BA can 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.

In view of the fact that comparator data on the efficacy and safety of repotrectinib compared to crizotinib based on the randomised, controlled phase III TRIDENT-III study (NCT06140836) for adults with ROS1-positive NSCLC without pretreatment with a ROS1 inhibitor are expected, which may be relevant for the assessment of the benefit of the medicinal product, limiting the resolution (in time) until further scientific findings are available for the assessment of the additional benefit of repotrectinib is justified. The time limit allows the expected results from the TRIDENT-III study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V. According to statements made by the pharmaceutical company in the written statement procedure, the first data are expected at the end of 2026.

For this purpose, the G-BA considers a limitation for the resolution until 1 July 2027 to be appropriate.

Conditions of the limitation

The results from the TRIDENT-3 study on overall survival and all other patient-relevant endpoints used to demonstrate an additional benefit are to be presented for the new benefit assessment of repotrectinib for the treatment of adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC) and without pretreatment with a ROS1 inhibitor after expiry of the deadline.

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, No. 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, No. 6 VerfO, the procedure for the benefit assessment of the medicinal product repotrectinib recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of repotrectinib in relation to the appropriate

comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

The possibility that a benefit assessment for the medicinal product repotrectinib can be carried out at an earlier point in time due to other reasons (cf. Chapter 5 Section 1, paragraph 2, nos. 2 to 4 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

This assessment concerns the benefit assessment for the active ingredient repotrectinib. The therapeutic indication assessed here is as follows:

"AUGTYRO as monotherapy is indicated for the treatment of adult patients with ROS1-positive advanced non-small cell lung cancer (NSCLC)."

In the therapeutic indication to be considered, 3 patient groups were distinguished:

a) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); no pretreatment with a ROS1 inhibitor

Crizotinib was determined as the appropriate comparator therapy.

b1) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); pretreatment with a ROS1 inhibitor and with PD-L1 expression ≥ 50%

The appropriate comparator therapy includes various immune checkpoint inhibitors, both as monotherapy and in combination with platinum-based chemotherapy.

b2) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); pretreatment with a ROS1 inhibitor and with PD-L1 expression < 50%

The appropriate comparator therapy includes various platinum-based chemotherapies, partly in combination with an immune checkpoint inhibitor, as well as an immune checkpoint inhibitor as monotherapy.

On a)

The pharmaceutical company presented data from the single-arm TRIDENT-1 study for the benefit assessment. Furthermore, the pharmaceutical company presented the result of a Matching-Adjusted Indirect Comparison (MAIC) analysis.

The TRIDENT-1 study is unsuitable for the benefit assessment as it does not allow a comparison with the appropriate comparator therapy.

MAIC analyses using aggregated data in the comparator arm are generally considered inappropriate in the context of the benefit assessment.

There are therefore no appropriate data for the benefit assessment.

An additional benefit of repotrectinib is therefore not proven for the treatment of adults with advanced or metastatic NSCLC without pretreatment with a ROS1 inhibitor.

With regard to patient group a), the period of validity of the resolution is limited until 1 July 2027 due to the expected results from the phase III TRIDENT-3 study. The TRIDENT-3 study is an RCT comparing repotrectinib with crizotinib.

On b1)

The pharmaceutical company presented data from the single-arm TRIDENT-1 study for the benefit assessment, the data being unsuitable for the benefit assessment as they do not allow

a comparison with the appropriate comparator therapy. No suitable data are thus available to allow an assessment of the additional benefit. An additional benefit is therefore not proven.

On b2)

The pharmaceutical company presented data from the single-arm TRIDENT-1 study for the benefit assessment, the data being unsuitable for the benefit assessment as they do not allow a comparison with the appropriate comparator therapy. No suitable data are thus available to allow an assessment of the additional benefit. An additional benefit is therefore 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).

For the number of German patients with lung cancer, the projected incidence for 2024 (59,851 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] (44,050 to 50,035 patients).
2. Of these, 46.63% of patients are in stage IV at initial diagnosis[4]. Of the remaining 53.37% 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 34,073 to 38,703.
3. 1.5% to 3.7% (661 to 1,851 patients) had ROS1-positive advanced NSCLC[7].
4. Of these, 67.19% (444 to 1,244 patients) received first-line therapy and 32.81% (217 to 607 patients) were eligible for second-line therapy[8].
5. In 28.9% (63 to 176 patients), PD-L1 expression was ≥ 50% and in 71.1% (154 to 432 patients) < 50%[9].
6. Taking into account 87.28% of SHI-insured patients, there are 388 to 1,086 patients in first-line therapy and 55 to 153 patients with PD-L1 expression ≥ 50% and 135 to 377 patients with PD-L1 expression < 50% in second-line therapy, depending on the PD-L1 status.

Due to uncertainties regarding the data basis in the target population in Germany, both an overestimation and an underestimation of patient numbers are possible.

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 Augtyro (active ingredient: repotrectinib) at the following publicly accessible link (last access: 7 October 2025):

[2] Robert Koch Institute, Society of Epidemiological Cancer Registries in Germany. Cancer in Germany for 2019/2020. 2024
[3] Benefit assessment procedure D-655 selpercatinib
[4] Benefit assessment procedure D-923 tremelimumab
[5] 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
[6] Benefit assessment procedure D-935 cemiplimab
[7] Benefit assessment procedure D-558 entrectinib
[8] German Cancer Society. Evaluation of key figures 2022; annual report of the certified lung cancer study sites; audit year 2021 / year of key figures 2020 [online]. 2022. URL https://www.krebsgesellschaft.de/jahresberichte.html?file=files/dkg/deutschekrebsgesellschaft/content/pdf/Zertifizierung/Jahresberichte%20mit%20DOI%20und%20ISBN/Lungenkrebszentren/qualitaetsindikatoren_lungenkrebs_2022-A1_220601.pdf&cid=105102
[9] Benefit assessment procedure D-705 cemiplimab

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

Treatment with repotrectinib 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 other specialist groups participating in the Oncology Agreement.

A validated test is required for the selection of patients with ROS1-positive NSCLC. A ROS1-positive status must be confirmed prior to initiation of therapy with repotrectinib.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

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: 15 August 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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.

For carboplatin, a cycle duration of 3 weeks is used. 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 the use of carboplatin in combination with nab-paclitaxel, a dosage of 500 mg/m² BSA is also used, according to the product information.

For nivolumab, the recommended dose is 360 mg every 3 weeks in combination with 1 mg/kg BW (body weight) ipilimumab every 6 weeks and platinum-based chemotherapy every 3 weeks, whereby treatment with 360 mg nivolumab intravenously every 3 weeks in combination with 1 mg/kg ipilimumab intravenously every 6 weeks continues after 2 cycles of chemotherapy.

According to the product information for cisplatin, the typical dosage in the case of combination therapy for the treatment of non-small cell lung cancer is 80 mg/m² BSA, which is used for the combination with vinorelbine.

According to the product information of the concomitant active ingredient, the single dose of cisplatin in combination with gemcitabine is 75 – 100 mg/m² BSA, in combination with docetaxel or pemetrexed 75 mg/m² BSA and in combination with paclitaxel 80 mg/m² BSA.

The two pembrolizumab doses of 200 mg every 3 weeks or 400 mg every 6 weeks recommended according to the product information are listed in the cost representation.

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.

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

Durvalumab is administered in combination with tremelimumab and platinum-based chemotherapy every 3 weeks for 4 cycles, followed by durvalumab monotherapy and histology-based maintenance treatment with pemetrexed every 4 weeks including a fifth dose of tremelimumab in week 16.

Treatment period:

a) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); no pretreatment with a ROS1 inhibitor

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Repotrectinib	Day 1 – 14: 1 x daily From day 15: Continuously, 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
Crizotinib	Continuously, 2 x daily	365.0	1	365.0

b1) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); pretreatment with a ROS1 inhibitor and with PD-L1 expression ≥ 50%

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Repotrectinib	Day 1 – 14: 1 x daily From day 15: Continuously, 2 x daily	365.0	1	365.0
Appropriate comparator therapy				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Pembrolizumab as monotherapy				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
atezolizumab as monotherapy				
Atezolizumab	1 x per 21-day cycle	17.4	1	17.4
Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1)				
Nivolumab	1 x per 21-day cycle	17.4	1	17.4
Ipilimumab	1 x per 42-day cycle	8.7	1	8.7
Carboplatin	1 x per 21-day cycle	2	1	2.0
Cisplatin	1 x per 21-day cycle	2	1	2.0
Docetaxel	1 x per 21-day cycle	2	1	2.0
Gemcitabine	2 x per 21-day cycle	2	2	4.0
Nab-paclitaxel	3 x per 21-day cycle	2	3	6.0
Paclitaxel	1 x per 21-day cycle	2	1	2.0
Pemetrexed	1 x per 21-day cycle	2	1	2.0
Vinorelbine	2 x per 21-day cycle	2	2	4.0
Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients without ECOG-PS 0-1)				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Pemetrexed	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
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG-PS 0-1)				
Induction therapy				
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
Paclitaxel	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
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
Atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0-1)				
Induction therapy				
Atezolizumab	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
Nab-paclitaxel	3 x per 21-day cycle	4 – 6	3	12.0 – 18.0
Maintenance treatment				
Atezolizumab	1 x per 21-day cycle	11.4 – 13.4	1	11.4 – 13.4
Durvalumab in combination with tremelimumab and platinum-based chemotherapy (only for patients with ECOG-PS 0-1)				
Durvalumab	1 x per 21-day cycle	4	1	4.0
Tremelimumab	1 x per 21-day cycle	4	1	4.0
Carboplatin	1 x per 21-day cycle	4	1	4.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cisplatin	1 x per 21-day cycle	4	1	4.0
Docetaxel	1 x per 21-day cycle	4	1	4.0
Gemcitabine	2 x per 21-day cycle	4	2	8.0
Nab-paclitaxel	3 x per 21-day cycle	4	3	12.0
Paclitaxel	1 x per 21-day cycle	4	1	4.0
Pemetrexed	1 x per 21-day cycle	4	1	4.0
Vinorelbine	2 x per 21-day cycle	4	2	8.0
Antibody maintenance treatment and histology-based maintenance treatment with pemetrexed				
Durvalumab	1 x per 28-day cycle	10	1	10.0
Tremelimumab	1 x in week 16	1	1	1.0
Pemetrexed	1 x per 28-day cycle	10	1	10.0

b2) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); pretreatment with a ROS1 inhibitor and with PD-L1 expression < 50%

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Repotrectinib	Day 1 – 14: 1 x daily From day 15: Continuously, 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients without ECOG-PS 0-1)				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x per 42-day cycle	8.7	1	8.7
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells)				
Atezolizumab	1 x per 21-day cycle	17.4	1	17.4
Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG-PS 0-1)				
Induction therapy				
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
Paclitaxel	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
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
Atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0-1)				
Induction therapy				
Atezolizumab	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
Nab-paclitaxel	3 x per 21-day cycle	4 – 6	3	12.0 – 18.0
Maintenance treatment				
Atezolizumab	1 x per 21-day cycle	11.4 – 13.4	1	11.4 – 13.4

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1)				
Nivolumab	1 x per 21-day cycle	17.4	1	17.4
Ipilimumab	1 x per 42-day cycle	8.7	1	8.7
Carboplatin	1 x per 21-day cycle	2	1	2.0
Cisplatin	1 x per 21-day cycle	2	1	2.0
Docetaxel	1 x per 21-day cycle	2	1	2.0
Gemcitabine	2 x per 21-day cycle	2	2	4.0
Nab-paclitaxel	3 x per 21-day cycle	2	3	6.0
Paclitaxel	1 x per 21-day cycle	2	1	2.0
Pemetrexed	1 x per 21-day cycle	2	1	2.0
Vinorelbine	2 x per 21-day cycle	2	2	4.0
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 (only for patients with ECOG-PS 2)				
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 (only for patients with ECOG-PS 2)				
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
Nab-paclitaxel	3 x per 21-day cycle	17.4	3	52.2
Durvalumab in combination with tremelimumab and platinum-based chemotherapy (only for patients with ECOG-PS 0-1)				
Durvalumab	1 x per 21-day cycle	4	1	4.0
Tremelimumab	1 x per 21-day cycle	4	1	4.0
Carboplatin	1 x per 21-day cycle	4	1	4.0
Cisplatin	1 x per 21-day cycle	4	1	4.0
Docetaxel	1 x per 21-day cycle	4	1	4.0
Gemcitabine	2 x per 21-day cycle	4	2	8.0
Nab-paclitaxel	3 x per 21-day cycle	4	3	12.0
Paclitaxel	1 x per 21-day cycle	4	1	4.0
Pemetrexed	1 x per 21-day cycle	4	1	4.0
Vinorelbine	2 x per 21-day cycle	4	2	8.0
Antibody maintenance treatment and histology-based maintenance treatment with pemetrexed				
Durvalumab	1 x per 28-day cycle	10	1	10.0
Tremelimumab	1 x in week 16	1	1	1.0
Pemetrexed	1 x per 28-day cycle	10	1	10.0

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body

weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[10].

a) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); no pretreatment with a ROS1 inhibitor

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					
Repotrectinib	160 mg	Day 1 – 14: 160 mg From day 15: 320 mg	Day 1 – 14: 1 x 160 mg From day 15: 2 x 160 mg	365.0	716 x 160 mg
Appropriate comparator therapy					
Crizotinib	250 mg	500 mg	2 x 250 mg	365.0	730 x 250 mg

b1) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); pretreatment with a ROS1 inhibitor and with PD-L1 expression ≥ 50%

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					
Repotrectinib	160 mg	Day 1 – 14: 160 mg From day 15: 320 mg	Day 1 – 14: 1 x 160 mg From day 15: 2 x 160 mg	365.0	716 x 160 mg
Appropriate comparator therapy					
Pembrolizumab as monotherapy					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
atezolizumab as monotherapy					
Atezolizumab	1,875 mg	1,875 mg	1 x 1,875 mg	17.4	17.4 x 1,875 mg

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1)					
Nivolumab	360 mg	360 mg	3 x 120 mg	17.4	52.2 x 120 mg
Ipilimumab	1 mg/kg = 77.7 mg	77.7 mg	2 x 50 mg	8.7	17.4 x 50 mg
Carboplatin	500 mg/m² = 955 mg	955 mg	2 x 450 mg + 2 x 50 mg	2.0	4 x 450 mg + 4 x 50 mg
Cisplatin	75 mg/m² = 143.3 mg	143.3 mg	1 x 50 mg + 1 x 100 mg	2.0	2 x 50 mg + 2 x 100 mg
	80 mg/m² = 152.8 mg	152.8 mg	1 x 10 mg + 1 x 50 mg + 1 x 100 mg	2.0	2 x 10 mg + 2 x 50 mg + 2 x 100 mg
	100 mg/m² = 191 mg	191 mg	2 x 100 mg	2.0	4 x 100 mg
Docetaxel	75 mg/m² = 143.3 mg	143.3 mg	1 x 160 mg	2.0	2 x 160 mg
Gemcitabine	1,250 mg/m² = 2,387.5 mg	2,387.5 mg	2 x 200 mg + 2 x 1,000 mg	4.0	8 x 200 mg + 8 x 1,000 mg
Nab-paclitaxel	100 mg/m² = 191 mg	191 mg	2 x 100 mg	6.0	12 x 100 mg
Paclitaxel	175 mg/m² = 334.3 mg	334.3 mg	2 x 100 mg + 1 x 150 mg	2.0	4 x 100 mg + 2 x 150 mg
Pemetrexed	500 mg/m² = 955 mg	955 mg	1 x 1,000 mg	2.0	2 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	4.0	4 x 50 mg – 4 x 50 mg + 4 x 10 mg
Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients without ECOG-PS 0-1)					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
Pemetrexed	500 mg/m² = 955 mg	955 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg
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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Cisplatin	75 mg/m^2 = 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
Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG-PS 0-1)					
Induction therapy					
Atezolizumab	1,875 mg	1,875 mg	1 x 1,875 mg	4 – 6	4 x 1,875 mg – 6 x 1,875 mg
Bevacizumab	7.5 mg/kg = 582.8 mg	582.8 mg	1 x 400 mg + 2 x 100 mg	4 – 6	4 x 400 mg + 8 x 100 mg – 6 x 400 mg + 12 x 100 mg
	or				
	15 mg/kg = 1,165.5 mg	1,165.5 mg	3 x 400 mg	4 – 6	12 x 400 mg – 18 x 400 mg
Paclitaxel	175 mg/m^2 = 334.3 mg	334.3 mg	1 x 150 mg + 2 x 100 mg	4 – 6	4 x 150 mg + 8 x 100 mg – 6 x 150 mg + 12 x 100 mg
Carboplatin	500 mg/m^2 = 955 mg	955 mg	2 x 450 mg + 2 x 50 mg	4 – 6	8 x 450 mg + 8 x 50 mg – 12 x 450 mg + 12 x 50 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	582.8 mg	1 x 400 mg + 2 x 100 mg	11.4 – 13.4	11.4 x 400 mg + 22.8 x 100 mg – 13.4 x 400 mg + 26.8 x 100 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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0-1)					
Induction therapy					
Atezolizumab	1,875 mg	1,875 mg	1 x 1,875 mg	4 – 6	4 x 1,875 mg – 6 x 1,875 mg
Carboplatin	500 mg/m² = 955 mg	955 mg	2 x 450 mg + 2 x 50 mg	4 – 6	8 x 450 mg + 8 x 50 mg – 12 x 450 mg + 12 x 50 mg
Nab-paclitaxel	100 mg/m² = 191 mg	191 mg	2 x 100 mg	12 – 18	24 x 100 mg – 36 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
Durvalumab in combination with tremelimumab and platinum-based chemotherapy (only for patients with ECOG-PS 0-1)					
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	4.0	12 x 500 mg
Tremelimumab	75 mg	75 mg	3 x 25 mg	4.0	12 x 25 mg
Carboplatin	500 mg/m² = 955 mg	955 mg	2 x 450 mg + 2 x 50 mg	4.0	8 x 450 mg + 8 x 50 mg
Cisplatin	75 mg/m² = 143.3 mg	143.3 mg	1 x 50 mg + 1 x 100 mg	4.0	4 x 50 mg + 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	4.0	4 x 10 mg + 4 x 50 mg + 4 x 100 mg
	100 mg/m² = 191 mg	191 mg	2 x 100 mg	4.0	8 x 100 mg
Docetaxel	75 mg/m² = 143.3 mg	143.3 mg	1 x 160 mg	4.0	4 x 160 mg
Gemcitabine	1,250 mg/m² = 2,387.5 mg	2,387.5 mg	2 x 200 mg + 2 x 1,000 mg	8.0	16 x 200 mg + 16 x 1,000 mg
Nab-paclitaxel	100 mg/m² = 191 mg	191 mg	2 x 100 mg	12.0	24 x 100 mg
Paclitaxel	175 mg/m²	334.3 mg	2 x 100 mg +	4.0	8 x 100 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
	= 334.3 mg		1 x 150 mg		4 x 150 mg
Pemetrexed	500 mg/m² = 955 mg	955 mg	1 x 1,000 mg	4.0	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	8.0	8 x 50 mg – 8 x 50 mg + 8 x 10 mg
Antibody maintenance treatment and histology-based maintenance treatment with pemetrexed					
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	10.0	30 x 500 mg
Tremelimumab	75 mg	75 mg	3 x 25 mg	1.0	3 x 25 mg
Pemetrexed	500 mg/m² = 955 mg	955 mg	1 x 1,000 mg	10.0	10 x 1,000 mg

b2) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); pretreatment with a ROS1 inhibitor and with PD-L1 expression < 50%

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					
Repotrectinib	160 mg	Day 1 – 14: 160 mg From day 15: 320 mg	Day 1 – 14: 1 x 160 mg From day 15: 2 x 160 mg	365.0	716 x 160 mg
Appropriate comparator therapy					
Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients without ECOG-PS 0-1)					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
Pemetrexed	500 mg/m² = 955 mg	955 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg
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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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
Atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells)					
Atezolizumab	1,875 mg	1,875 mg	1 x 1,875 mg	17.4	17.4 x 1,875 mg
Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG-PS 0-1)					
Induction therapy					
Atezolizumab	1,875 mg	1,875 mg	1 x 1,875 mg	4 – 6	4 x 1,875 mg – 6 x 1,875 mg
Bevacizumab	7.5 mg/kg = 582.8 mg	582.8 mg	1 x 400 mg + 2 x 100 mg	4 – 6	4 x 400 mg + 8 x 100 mg – 6 x 400 mg + 12 x 100 mg
	or				
	15 mg/kg = 1,165.5 mg	1,165.5 mg	3 x 400 mg	4 – 6	12 x 400 mg – 18 x 400 mg
Paclitaxel	175 mg/m² = 334.3 mg	334.3 mg	1 x 150 mg + 2 x 100 mg	4 – 6	4 x 150 mg + 8 x 100 mg – 6 x 150 mg + 12 x 100 mg
Carboplatin	500 mg/m² = 955 mg	955 mg	2 x 450 mg + 2 x 50 mg	4 – 6	8 x 450 mg + 8 x 50 mg – 12 x 450 mg + 12 x 50 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	582.8 mg	1 x 400 mg + 2 x 100 mg	11.4 – 13.4	11.4 x 400 mg + 22.8 x 100 mg – 13.4 x 400 mg + 26.8 x 100 mg
	or				

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	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
Atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0-1)					
Induction therapy					
Atezolizumab	1,875 mg	1,875 mg	1 x 1,875 mg	4 – 6	4 x 1,875 mg – 6 x 1,875 mg
Carboplatin	500 mg/m^2 = 955 mg	955 mg	2 x 450 mg + 2 x 50 mg	4 – 6	8 x 450 mg + 8 x 50 mg – 12 x 450 mg + 12 x 50 mg
Nab-paclitaxel	100 mg/m^2 = 191 mg	191 mg	2 x 100 mg	12 – 18	24 x 100 mg – 36 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
Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1)					
Nivolumab	360 mg	360 mg	3 x 120 mg	17.4	52.2 x 120 mg
Ipilimumab	1 mg/kg = 77.7 mg	77.7 mg	2 x 50 mg	8.7	17.4 x 50 mg
Carboplatin	500 mg/m^2 = 955 mg	955 mg	2 x 450 mg + 2 x 50 mg	2.0	4 x 450 mg + 4 x 50 mg
Cisplatin	75 mg/m^2 = 143.3 mg	143.3 mg	1 x 50 mg + 1 x 100 mg	2.0	2 x 50 mg + 2 x 100 mg
	80 mg/m^2 = 152.8 mg	152.8 mg	1 x 10 mg + 1 x 50 mg + 1 x 100 mg	2.0	2 x 10 mg + 2 x 50 mg + 2 x 100 mg
	100 mg/m^2 = 191 mg	191 mg	2 x 100 mg	2.0	4 x 100 mg
Docetaxel	75 mg/m^2 = 143.3 mg	143.3 mg	1 x 160 mg	2.0	2 x 160 mg
Gemcitabine	1,250 mg/m^2 =	2,387.5 mg	2 x 200 mg + 2 x 1,000 mg	4.0	8 x 200 mg + 8 x 1,000 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
	2,387.5 mg				
Nab-paclitaxel	100 mg/m² = 191 mg	191 mg	2 x 100 mg	6.0	12 x 100 mg
Paclitaxel	175 mg/m² = 334.3 mg	334.3 mg	2 x 100 mg + 1 x 150 mg	2.0	4 x 100 mg + 2 x 150 mg
Pemetrexed	500 mg/m² = 955 mg	955 mg	1 x 1,000 mg	2.0	2 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	4.0	4 x 50 mg – 4 x 50 mg + 4 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 (only for patients with ECOG-PS 2)					
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
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
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
Docetaxel	75 mg/m² = 143.3 mg	143.3 mg	1 x 160 mg	17.4	17.4 x 160 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
Carboplatin in combination with nab-paclitaxel (only for patients with ECOG-PS 2)					
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
Durvalumab in combination with tremelimumab and platinum-based chemotherapy (only for patients with ECOG-PS 0-1)					
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	4.0	12 x 500 mg
Tremelimumab	75 mg	75 mg	3 x 25 mg	4.0	12 x 25 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
Carboplatin	500 mg/m² = 955 mg	955 mg	2 x 450 mg + 2 x 50 mg	4.0	8 x 450 mg + 8 x 50 mg
Cisplatin	75 mg/m² = 143.3 mg	143.3 mg	1 x 50 mg + 1 x 100 mg	4.0	4 x 50 mg + 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	4.0	4 x 10 mg + 4 x 50 mg + 4 x 100 mg
	100 mg/m² = 191 mg	191 mg	2 x 100 mg	4.0	8 x 100 mg
Docetaxel	75 mg/m² = 143.3 mg	143.3 mg	1 x 160 mg	4.0	4 x 160 mg
Gemcitabine	1,250 mg/m² = 2,387.5 mg	2,387.5 mg	2 x 200 mg + 2 x 1,000 mg	8.0	16 x 200 mg + 16 x 1,000 mg
Nab-paclitaxel	100 mg/m² = 191 mg	191 mg	2 x 100 mg	12.0	24 x 100 mg
Paclitaxel	175 mg/m² = 334.3 mg	334.3 mg	2 x 100 mg + 1 x 150 mg	4.0	8 x 100 mg + 4 x 150 mg
Pemetrexed	500 mg/m² = 955 mg	955 mg	1 x 1,000 mg	4.0	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	8.0	8 x 50 mg – 8 x 50 mg + 8 x 10 mg
Antibody maintenance treatment and histology-based maintenance treatment with pemetrexed					
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	10.0	30 x 500 mg
Tremelimumab	75 mg	75 mg	3 x 25 mg	1.0	3 x 25 mg
Pemetrexed	500 mg/m² = 955 mg	955 mg	1 x 1,000 mg	10.0	10 x 1,000 mg

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Repotrectinib 160 mg	60 HC	€ 10,226.34	€ 1.77	€ 580.74	€ 9,643.83
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
Bevacizumab 100 mg	1 CIS	€ 176.43	€ 1.77	€ 9.14	€ 165.52
Carboplatin 50 mg	1 CIS	€ 34.66	€ 1.77	€ 1.11	€ 31.78
Carboplatin 450 mg	1 CIS	€ 228.24	€ 1.77	€ 10.29	€ 216.18
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
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
Crizotinib 250 mg	60 HC	€ 5,426.22	€ 1.77	€ 0.00	€ 5,424.45
Docetaxel 160 mg	1 CIS	€ 515.78	€ 1.77	€ 23.94	€ 490.07
Durvalumab 500 mg	1 CIS	€ 2,105.19	€ 1.77	€ 116.94	€ 1,986.48
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
Ipilimumab 50 mg	1 CIS	€ 3,489.23	€ 1.77	€ 195.98	€ 3,291.48
Nivolumab 120 mg	1 CIS	€ 1,539.71	€ 1.77	€ 84.64	€ 1,453.30
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
Pembrolizumab 100 mg	2 CIS	€ 4,962.26	€ 1.77	€ 280.10	€ 4,680.39
Pemetrexed 1,000 mg	1 CIS	€ 1,124.81	€ 1.77	€ 52.84	€ 1,070.20
Tremelimumab 25 mg	1 CIS	€ 1,779.95	€ 1.77	€ 98.36	€ 1,679.82
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: HC = hard capsules; 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
Appropriate comparator therapy							
Pemetrexed							
2 cycles Nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1)							
Dexamethasone 2 x 4 mg[11]	20 x 4 mg TAB	€ 24.61	€ 1.77	€ 1.05	€ 21.79	6	€ 21.79
Folic acid[12] 350 – 1,000 µg/day	50 x 400 µg TAB	€ 10.40	€ 0.53	€ 1.24	€ 8.63	49	€ 8.63 – € 14.74
	100 x 400 µg TAB	€ 17.60	€ 0.88	€ 1.98	€ 14.74		
Vitamin B12[11] 1,000 µg/day, every 3 cycles	5 x 1,000 µg ILO	€ 4.95	€ 0.25	€ 0.22	€ 4.48	1	€ 4.48
4 cycles of 21 days each Durvalumab in combination with tremelimumab and platinum-based chemotherapy (only for patients with ECOG-PS 0-1)							
Dexamethasone 2 x 4 mg[11]	100 x 4 mg TAB	€ 79.54	€ 1.77	€ 5.40	€ 72.37	12.0	€ 17.37

[11] Fixed reimbursement rate

[12] 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
Folic acid[12] 350 – 1,000 µg/day	100 x 400 µg TAB	€ 17.60	€ 0.88	€ 1.98	€ 14.74	84.0	€ 12.38 – € 24.76
Vitamin B12[11] 1,000 µg/day, every 3 cycles	10 x 1,000 µg AMP	€ 8.19	€ 0.41	€ 0.37	€ 7.41	2.0	€ 1.48
10 cycles of 28 days each (Antibody maintenance treatment and histology-based maintenance treatment with pemetrexed)							
Dexamethasone 2 x 4 mg[11]	100 x 4 mg TAB	€ 79.54	€ 1.77	€ 5.40	€ 72.37	30.0	€ 43.42
Folic acid[12] 350 – 1,000 µg/day	100 x 400 µg TAB	€ 17.60	€ 0.88	€ 1.98	€ 14.74	281.0	€ 41.42 – € 82.84
Vitamin B12[11] 1,000 µg/day, every 3 cycles	10 x 1,000 µg AMP	€ 8.19	€ 0.41	€ 0.37	€ 7.41	3.0	€ 2.22
17.4 cycles Pembrolizumab + pemetrexed + platinum-containing chemotherapy and 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 (only for patients with ECOG-PS 2)							
Dexamethasone[11] 2 x 4 mg	100 x 4 mg TAB	€ 79.54	€ 1.77	€ 5.40	€ 72.37	52.2	€ 75.55
Folic acid[12] 350 – 1,000 µg/day	100 x 400 µg TAB	€ 17.60	€ 0.88	€ 1.98	€ 14.74	365	€ 53.80 – € 107.60
Vitamin B12[11] 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
Paclitaxel							
2 cycles Nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1)							
Dexamethasone[11] 2 x 20 mg PO	10 x 20 mg TAB	€ 32.42	€ 1.77	€ 0.00	€ 30.65	2	€ 30.65
Dimetindene IV 1 mg/10 kg BW = 7.8 mg	5 x 4 mg SFI	€ 26.24	€ 1.77	€ 6.92	€ 17.55	2	€ 17.55
Cimetidine 300 mg IV	10 x 200 mg AMP	€ 22.56	€ 1.77	€ 1.42	€ 19.37	2	€ 19.37
4 cycles Durvalumab in combination with tremelimumab and platinum-based chemotherapy (only for patients with ECOG-PS 0-1)							

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
Dexamethasone[11] 2 x 20 mg PO	10 x 20 mg TAB	€ 32.42	€ 1.77	€ 0.00	€ 30.65	4	€ 30.65
Dimetindene IV 1 mg/10 kg BW = 7.8 mg	5 x 4 mg SFI	€ 26.24	€ 1.77	€ 6.92	€ 17.55	4	€ 35.10
Cimetidine 300 mg IV	10 x 200 mg AMP	€ 22.56	€ 1.77	€ 1.42	€ 19.37	4	€ 19.37
4 – 6 cycles Atezolizumab + bevacizumab + paclitaxel + carboplatin (only for patients with ECOG-PS 0-1)							
Dexamethasone[11] 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	€ 30.65 – € 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
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 (only for patients with ECOG-PS 2)							
Dexamethasone[11] 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
Cisplatin							
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.							
Hydration and forced diuresis 2 cycles (Nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy)							
Mannitol 10% Inf. sol., 37.5 g/day	10 x 500 ml INF	€ 105.54	€ 5.28	€ 4.26	€ 96.00	2	€ 96.00

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
Sodium chloride 0.9% inf. sol., 3 - 4.4 l/day	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	2	€ 20.05
Hydration and forced diuresis 4 cycles Durvalumab in combination with tremelimumab and platinum-based chemotherapy (only for patients with ECOG-PS 0-1)							
Mannitol 10% Inf. sol., 37.5 g/day	10 x 500 ml INF	€ 105.54	€ 5.28	€ 4.26	€ 96.00	4	€ 96.00
Sodium chloride 0.9% Inf. sol., 3 - 4.4 l/day	10 x 500 ml INF	€ 13.28	€ 0.66	€ 0.96	€ 11.66	4	€ 34.98
	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	4	€ 40.10
Hydration and forced diuresis 17.4 cycles (Pembrolizumab + pemetrexed + platinum-containing chemotherapy)							
Mannitol 10% Inf. sol., 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% Inf. sol., 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
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 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 ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); no pretreatment with a ROS1 inhibitor

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

b1) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); pretreatment with a ROS1 inhibitor and with PD-L1 expression ≥ 50%

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

b2) Adults with ROS1-positive, advanced or metastatic non-small cell lung cancer (NSCLC); pretreatment with a ROS1 inhibitor and with PD-L1 expression < 50%

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

2.6 Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product repotrectinib (Augtyro) is a medicinal product placed on the market from 1 January 2025. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV. Approval studies include all studies submitted to the regulatory authority in the authorisation dossier for the assessment of the clinical efficacy and safety of the medicinal product in the therapeutic indication to be assessed.

No information was provided on the number of study participants involved in the clinical studies of the medicinal product in the therapeutic indication under assessment, which were conducted or commissioned by the pharmaceutical company at study sites within the scope of SGB V and/or on the total number of study participants.

Due to the absence of information, it is therefore not possible to determine that the percentage of study participants reached or exceeded the relevance threshold of at least 5 per cent.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant extent within the scope of SGB V.

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

On 30 April 2025, the pharmaceutical company submitted a dossier for the benefit assessment of repotrectinib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 30 April 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 repotrectinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 July 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 August 2025. The deadline for submitting statements was 22 July 2025.

The oral hearing was held on 8 September 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 7 October 2025, and the proposed draft resolution was approved.

At their session on 16 October 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	13 April 2023	Determination of the appropriate comparator therapy
Working group Section 35a	3 September 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	8 September 2025	Conduct of the oral hearing, if applicable: commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	17 September 2025; 1 October 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	7 October 2025	Concluding discussion of the draft resolution
Plenum	16 October 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 October 2025

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

Prof. Hecken