Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Alectinib (new therapeutic indication: non-small cell lung cancer, ALK+, high risk of recurrence, adjuvant treatment)

of 16 January 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses 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 trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

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

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

2. Key points of the resolution

The active ingredient alectinib (Alecensa) was listed for the first time on 1 May 2017 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 6 June 2024, alectinib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 2 July 2024, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient alectinib with the new therapeutic indication "Alecensa as monotherapy is indicated as adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence" in due

time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 October 2024 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 alectinib 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, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has 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 alectinib.

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 Alectinib (Alecensa) in accordance with the product information

Alecensa as monotherapy is indicated as adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence.

Therapeutic indication of the resolution (resolution of 16 January 2025):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy

Appropriate comparator therapy for alectinib as monotherapy:

Patient-individual postoperative (adjuvant) systemic chemotherapy with selection of

- cisplatin in combination with vinorelbine

  and

- cisplatin in combination with pemetrexed

taking into account the general condition.

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

b) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection after prior adjuvant platinum-based chemotherapy or who are ineligible for this

Appropriate comparator therapy for alectinib as monotherapy:

- Monitoring wait-and-see approach

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. In addition to alectinib, medicinal products with the active ingredients pembrolizumab and vinorelbine are approved in the present therapeutic indication.

On 2. For patients with completely resected NSCLC, adjuvant cisplatin-based chemotherapy may be followed by radiotherapy in individual cases. However, this is not applied on a regular basis. The G-BA therefore expects for the present treatment setting that radiotherapy is eligible only in individual cases for a few patients and is therefore not included among the standard therapies in the therapeutic indication.

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

- Pembrolizumab (resolution of 17 October 2024)

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.

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

The recommendations in guidelines on adjuvant treatment options are made, depending on the respective tumour stage.

The determination of the appropriate comparator therapy is based on the currently valid TNM tumour classification in the 8th edition of the UICC.

There are changes to the stage classifications, particularly in stages IB and III, compared to the stage classification in the 7th edition of the UICC, on which the ALINA study was based.

When defining the high risk of recurrence following complete tumour resection, the product information for alectinib is based on the patient population enrolled in the ALINA study (stages IB T ≥ 4 cm to IIIA after the 7th edition of the UICC).

According to the stage classification in the 8th edition of the UICC, only patients with a tumour size of exactly 4 cm with regard to stage IB are enrolled in the ALINA study. In this regard, the clinical experts stated during the written statement procedure that patients in resectable stages IIA to IIIB (8th edition of the UICC) are classified as patients at high risk of recurrence and subgrouping of patients in stage IB is obsolete.

The appropriate comparator therapy was determined for stages IIB to IIIA according to the 8th edition of the UICC.

The approved therapeutic indication includes patients who are eligible for adjuvant platinum-based chemotherapy and have not yet received it, as well as patients who have already received previous adjuvant platinum-based chemotherapy or who are ineligible for it. To determine the appropriate comparator therapy, a distinction is therefore made between patients who are suitable for adjuvant platinum-based chemotherapy (patient group a) or who have received prior adjuvant platinum-based chemotherapy or who are ineligible for it (patient group b).

a) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy

The recommendations in the present guidelines[2,3,4,5] on adjuvant therapy options are made, depending on the respective tumour stage.

The S3 guideline recommends offering adjuvant cisplatin-containing chemotherapy to patients who have undergone R0 resection and systematic lymph node dissection in stages II or IIIA. The guidelines list the active ingredients cisplatin, vinorelbine, gemcitabine, docetaxel, paclitaxel and pemetrexed as components for adjuvant cisplatin-containing chemotherapy also for lower stages of the disease.

As part of the benefit assessment procedure on the adjuvant treatment of NSCLC[6], clinical experts stated that adjuvant chemotherapy with cisplatin in combination with vinorelbine and, in certain risk constellations, chemotherapy with cisplatin in combination with pemetrexed is a standard therapy in the adjuvant treatment of NSCLC.

However, a combination therapy with paclitaxel has no significance in the adjuvant chemotherapy of NSCLC. The combination therapy with paclitaxel is not determined to be an appropriate comparator therapy for this resolution.

For adjuvant cisplatin-containing chemotherapy, cisplatin in combination with vinorelbine and cisplatin in combination with pemetrexed are therefore determined as appropriate comparator therapies in the context of a patient-individual treatment decision, taking into account the general condition based on the tolerability of the active ingredients vinorelbine and pemetrexed.

Of the aforementioned treatment options, only vinorelbine in combination with platinum-based chemotherapy is approved for the present indication.

The patient population in the present therapeutic indication, especially within stage IIIA, is considered to be very heterogeneous. After R0 resection, patients with affected mediastinal lymph node in stages IIIA1 and IIIA2 have the therapy option of postoperative mediastinal irradiation in addition to adjuvant chemotherapy. The current guidelines recommend individually checking the indication, but not routinely. Due to the unclear data basis, adjuvant chemotherapy with subsequent radiotherapy is not defined as an appropriate comparator therapy.

[2] S3 guideline "Prevention, diagnosis, therapy and after-care of lung cancer", version 2.1, December 2022.
[3] Daly ME et al., 2022. Management of Stage III Non-Small-Cell Lung Cancer: ASCO Guideline.
[4] National Institute for Health and Care Excellence (NICE), 2019. Lung cancer: diagnosis and management.
[5] Pisters K et al., 2022. Adjuvant systemic therapy and adjuvant radiation therapy for stage I-IIIA completely resected non-small-cell lung cancer: ASCO Guideline Rapid Recommendation Update.
[6] Osimertinib, resolution of 19 December 2024; alectinib, resolution of 16 January 2025

On the determination of an off-label use of medicinal products as the appropriate comparator therapy:

Only the active ingredient vinorelbine in combination with platinum-based chemotherapy is approved for the systemic adjuvant treatment of patients with NSCLC, who have not yet received platinum-based chemotherapy for adjuvant treatment.

Cisplatin in combination with pemetrexed

The S3 guideline recommends adjuvant chemotherapy, which should be administered with a cisplatin-containing combination in patients in stage II and in good general condition. With regard to the active ingredients for the combination with cisplatin, the S3 guideline states that the greatest evidence is available for the combination of cisplatin and vinorelbine. It is also stated that the combination of cisplatin and pemetrexed showed similar overall survival with better tolerability (less severe febrile neutropenia, neutropenia and anaemia) compared to cisplatin in combination with vinorelbine in a randomised study involving 804 patients.[7] Furthermore, the S3 guideline states that incompatibilities between cisplatin and vinorelbine led to a significant dose reduction of this combination.

In the oral hearing as part of the present benefit assessment procedure on ALK-positive NSCLC, the clinical experts showed the significance of cisplatin in combination with pemetrexed and pointed out that cisplatin in combination with pemetrexed is part of the therapy standard.

It is thus established that the off-label use of the active ingredients cisplatin and pemetrexed in combination therapy consisting of cisplatin and pemetrexed is generally preferable to the previously approved medicinal products for a relevant patient group in the therapeutic indication according to the generally recognised state of medical knowledge in accordance with Section 6, paragraph 2, sentence 2, number 3 AM-NutzenV.

[7] Kenmotsu H, Yamamoto N, Yamanaka T, Yoshiya K, Takahashi T, Ueno T, et al. Randomised phase III study of pemetrexed/cisplatin (Pem/Cis) versus vinorelbine /cisplatin (Vnr/Cis) for completely resected stage II-IIIA non-squamous non-small-cell lung cancer (Ns-NSCLC): The JIPANG study. Journal of Clinical Oncology. 2019;37:8501.

b) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection after prior adjuvant platinum-based chemotherapy or who are ineligible for this

The immune checkpoint inhibitor pembrolizumab is available as monotherapy for further adjuvant treatment of patients with completely resected NSCLC and after platinum-based chemotherapy. Pembrolizumab was only recently approved for this indication (marketing authorisation on 12 October 2023). The approved therapeutic indication has no restriction with regard to ALK status. An additional benefit of pembrolizumab compared to the monitoring wait-and-see approach was not proven in the benefit assessment (resolution of 17 January 2024).

According to the S3 guideline, patients with completely resected NSCLC in stages II or IIIA should be offered adjuvant treatment with pembrolizumab after prior adjuvant platinum-based chemotherapy. However, the recommendation is restricted to patients without EGFR or ALK alteration.

Based on the generally accepted state of medical knowledge, pembrolizumab is not determined to be an appropriate comparator therapy for the present patient group.

In the overall assessment and taking into account the existing treatment setting, according to which the patients are subject to corresponding after-care examinations in the medical care after complete tumour resection , the G-BA determined "monitoring wait-and-see approach" as an appropriate comparator therapy.

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

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

Change of the appropriate comparator therapy:

The appropriate comparator therapy for

a) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy

was originally determined as follows:

Appropriate comparator therapy for alectinib as monotherapy:

Patient-individual therapy with selection of:

- monitoring wait-and-see approach (only for patients in stage IB)
  and
- postoperative (adjuvant) systemic chemotherapy with selection of
  - cisplatin in combination with vinorelbine
    and
  - cisplatin in combination with paclitaxel (only for extensive-stage patients)

taking into account the tumour stage.

Taking into account the statements of clinical experts in the present benefit assessment procedure and for the reasons mentioned above, the monitoring wait-and-see approach is removed for patients in stage IB. For postoperative (adjuvant) systemic chemotherapies, the

treatment option "Cisplatin in combination with paclitaxel" is removed and the treatment option "Cisplatin in combination with pemetrexed" is added.

As a result of the change in treatment options, the general condition of the patient should be taken into account for the patient-individual selection.

This change in the appropriate comparator therapy leads to the conclusion that the results of the ALINA study submitted by the pharmaceutical company in the dossier can be used for the present assessment. The results of the ALINA study were analysed by IQWiG in the addendum to the dossier assessment. In addition, these were the subject of the statements, which is why the change in the appropriate comparator therapy does not necessitate a renewed conduct of the benefit assessment procedure.

2.1.3 Extent and probability of the additional benefit

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

a) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy

Hint for a major additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company presented the results of the ongoing, open-label, randomised, controlled phase III ALINA study. The study is being conducted in 113 study sites across Australia, Asia, Europe and North America.

Adult patients with completely resected, histologically confirmed stage IB (tumour size ≥ 4 cm) to IIIA NSCLC, who were found to have ALK-positive disease, were enrolled in the study. The staging at the start of the study was based on the classification of the 7th edition of the UICC.

The dossier also contains a classification according to the 8th edition of the UICCC. Patients also had to be eligible for platinum-based chemotherapy in accordance with local marketing authorisation or guidelines, and be in good general condition (ECOG performance status ≤ 1).

Overall, 130 patients were randomly assigned to treatment with alectinib and 127 patients to treatment with platinum-based chemotherapy. The allocation was stratified according to the stage of the disease (IB [tumour ≥ 4 cm] vs II vs IIIA, classified according to the 7th edition of the UICC) and descent (Asian vs non-Asian).

Treatment with alectinib was continued for 24 months or until recurrence, unacceptable toxicity, the patient's decision on therapy discontinuation, or until death. In the comparator arm, the principal investigator could choose between the therapies: cisplatin in combination with vinorelbine, cisplatin in combination with gemcitabine and cisplatin in combination with pemetrexed. Should treatment with cisplatin result in unacceptable toxicity, cisplatin could be replaced by carboplatin in the regimens mentioned.

The primary endpoint of the ALINA study is disease-free survival. Patient-relevant secondary endpoints are overall survival, endpoints on morbidity and health-related quality of life, and adverse events.

The pharmaceutical company submits the results of the ALINA study at the data cut-off from 26 June 2023. This is the pre-specified data cut-off for disease-free survival. The benefit assessment is based on this data cut-off.

Limitations of the ALINA study

Selection of the different therapy options in the comparator arm

For the implementation of patient-individual therapy in a direct comparator study, it is expected that investigators will have a choice of several treatment options that will allow a patient-individual treatment decision to be made, taking into account the criteria mentioned. However, the available information on the ALINA study does not provide any information on selection criteria for the various therapy options in the comparator arm.

Use of therapy options that are not included in the appropriate comparator therapy

In the ALINA study, 13 of the patients treated in the control arm switched from a therapy with cisplatin to carboplatin and one patient received carboplatin from the start of treatment. Of these, 12 subjects (9%) received carboplatin in combination with pemetrexed and two (2%) received carboplatin in combination with vinorelbine. One patient (1%) received cisplatin in combination with gemcitabine. Vinorelbine or pemetrexed in combination with carboplatin and the active ingredient gemcitabine are not included in the appropriate comparator therapy.

Extent and probability of the additional benefit

Mortality

The overall survival is operationalised in the ALINA study as the time from randomisation to death from any cause or end of study.

For the endpoint of overall survival, there was no statistically significant difference between the treatment arms. Only a few events occurred at the time of the data cut-off (pre-specified analysis for disease-free survival).

Morbidity

Recurrences

The endpoint is represented by recurrence rate and disease-free survival, and includes the events of local recurrence, regional recurrence, distant recurrence, new primary NSCLC and death from any cause.

The recurrence rate is defined as the percentage of patients who suffer a recurrence, a new primary NSCLC or die after complete tumour resection up to the present data cut-off. The first qualifying event is deemed to be an event.

Disease-free survival is defined as the time from randomisation until recurrence, new primary NSCLC or death, whichever occurs first.

The pharmaceutical company submitted both analyses according to the principal investigators' assessment and supplementary analyses according to the Blinded Independent Central Review (BICR).

Between the evaluations, particularly in the control arm, there are differences between the principal investigators' and BICR's assessments as to whether recurrences occurred during the course of the study. According to the principal investigators' assessment, 11 (22%) more recurrences were found in the comparator arm, which shows a clear imbalance in recurrences between the principal investigators' and BICR's assessments for the control arm.

The principal investigators' assessment was based on radiological and (if available) pathological data as well as the clinical status. For the BICR, the information provided by the pharmaceutical company only indicates that the assessment was based on radiological and other data. According to the European Public Assessment Report, this is a retrospective BICR, which is why it is assumed that the principal investigators' assessment was significant for the decision on therapy discontinuation (and thus, determined the end of the imaging investigations) and that the assessment of the BICR was consequently not taken into account for this decision. In the event that the BICR subsequently came to the different assessment that there was no recurrence, it is assumed accordingly that the BICR subsequently had no further scans to determine a recurrence (according to the BICR).

In principle, a BICR analysis is methodologically superior to an assessment by the principal investigators. In this case, however, the BCIR analysis has the limitations described above, which is why the BICR analyses are only presented additionally.

Based on the principle of the principal investigators' assessment, both endpoints (recurrence rates and disease-free survival) showed a statistically significant difference to the advantage of alectinib, the extent of which is assessed as major improvement.

It should be noted that the present evaluations are based on a median duration of observation of approx. 28 months (intervention arm 30.0 months, control arm 23.5 months). A median

duration of observation of approx. 28 months is considered insufficient in the present treatment setting to adequately reflect the high-risk period for the recurrence.

Health status (EQ-5D VAS)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. Health status should be assessed every 3 weeks until week 12 and then every 12 weeks until recurrence, death, withdrawal of consent or week 96, according to the study protocol.

The pharmaceutical company submitted both responder evaluations for deterioration at week 12 and analyses using a mixed linear model with repeated measurements (MMRM) for the change at week 12.

The MMRM analysis of the change at week 12 is used for this benefit assessment as there were clear differences in the return rates between the treatment arms.

There was no statistically significant difference between the treatment arms.

It should be noted that the available evaluations of health status only allow statements to be made about a single early point in time during treatment. Patients in the control arm were treated with platinum-based chemotherapy for 4 cycles of 21 days each. In this respect, the analyses at week 12 represent a time of high burden, particularly in the control arm. Although the health status was assessed up to week 96, no evaluations are available for the entire survey period. It is therefore not possible to make statements about longer-term effects on the health status on the basis of the data.

Quality of life

SF-36v2 – physical and mental component summary scores

Health-related quality of life was assessed using the Sf-36v2 questionnaire. The questionnaire should be collected every 3 weeks until week 12 and then every 12 weeks until recurrence, death, withdrawal of consent or week 96, according to the study protocol.

The pharmaceutical company submitted both responder analyses on deterioration at week 12 and evaluations using MMRM on the change at week 12.

A decrease by ≥ 9.4 points for the physical component summary (PCS) score and ≥ 9.6 points for the mental component summary (MCS) score was considered a deterioration. Accordingly, the responder analyses of the deterioration at week 12 can be used to derive the additional benefit.

The evaluation of the deterioration at week 12 showed no statistically significant difference between the treatment arms for the PCS. In contrast, there was a statistically significant difference to the advantage of alectinib over platinum-based chemotherapy for the MCS.

It should be noted that the available evaluations of health-related quality of life only allow statements to be made about a single early point in time during treatment. Patients in the comparator arm were treated with platinum-based chemotherapy for 4 cycles of 21 days each. In this respect, the analyses at week 12 represent a time of high burden, particularly in the comparator arm. Although the health status was assessed up to week 96, no evaluations are available for the entire survey period.

It is therefore not possible to make statements about longer-term effects on the health-related quality of life on the basis of the data.

Side effects

Side effects were assessed in both treatment groups up to 28 days after the last dose of study medication. Due to the different durations of observation in the treatment groups, the median duration of observation for the endpoint category of side effects differs significantly in both treatment groups (24.8 months in the intervention arm vs 3.7 months in the control arm). Therefore, the hazard ratio reflects only the first 4 months.

Adverse events (AEs) in total

In the ALINA study, AEs occurred in both study arms in almost all patients. The results were only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3)

For the endpoint of SAEs and severe AEs (CTCAE grade ≥ 3), there was a statistically significant difference for each endpoint to the advantage of alectinib compared to platinum-based chemotherapy.

Therapy discontinuation due to AEs (of all active ingredient components in the comparator arm)

Information on the therapy discontinuation of at least one active ingredient component is not available. For the endpoint of therapy discontinuation due to AEs (all active ingredient components in the comparator arm), there was a statistically significant difference to the advantage of alectinib over platinum-based chemotherapy.

However, the subgroup analysis showed an effect modification due to the age characteristic. For patients < 65 years of age, there was a statistically significant difference to the advantage of alectinib over platinum-based chemotherapy, while for patients ≥ 65 years of age, there was no statistically significant difference between the treatment groups.

In the overall analysis of the present results, the significance of the present subgroup result for the age characteristic is considered insufficient overall and not used for the assessment of the additional benefit.

Specific AEs

Malaise (AE), loss of appetite (AE) and haematopoietic cytopenias (severe AE)

For the specific AEs of malaise (AE), loss of appetite (AE) and haematopoietic cytopenias (severe AE), there was a statistically significant difference to the advantage of alectinib compared to platinum-based chemotherapy.

Gastrointestinal disorders (AE)

For the endpoint, there was a statistically significant difference to the advantage of alectinib compared to platinum-based chemotherapy.

However, the subgroup analysis showed an effect modification due to the age characteristic. For patients < 65 years of age, there was a statistically significant difference to the advantage of alectinib over platinum-based chemotherapy, while for patients ≥ 65 years of age, there was no statistically significant difference between the treatment groups.

In the overall analysis of the present results, the significance of the present subgroup result for the age characteristic is considered insufficient overall and not used for the assessment of the additional benefit.

Hepatotoxicity (severe AE) and elevated creatine phosphokinase level in the blood (severe AE)

For the specific AEs of hepatotoxicity (severe AE) and elevated creatine phosphokinase level in the blood (severe AE), there was a statistically significant difference to the disadvantage of alectinib compared to platinum-based chemotherapy.

Myalgia (severe AE) and ILD/ pneumonitis (SAE)

There was no statistically significant difference between the treatment arms for the endpoints of myalgia (severe AE) and ILD/ pneumonitis (SAE).

Overall, there were advantages of alectinib for serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs. In detail, both advantages and disadvantages of treatment with alectinib compared to platinum-based chemotherapy can be identified for the specific AEs. However, due to the short observation period in the control arm, comparative statements can only be derived for the first approximately 4 months of therapy based on the time-to-event analyses duration of observation. No statements on longer-term side effects can be made on the basis of the data.

Overall assessment

For the benefit assessment of alectinib as monotherapy for adjuvant treatment following complete tumour resection in adult patients with ALK-positive NSCLC at high risk of recurrence, results of the ALINA study are available for the endpoint categories of mortality, morbidity, health-related quality of life and side effects compared with platinum-based chemotherapy.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment arms.

The avoidance of recurrences is an essential therapeutic goal in the present curative treatment setting. Both endpoints of recurrence rate and disease-free survival showed a statistically significant difference to the advantage of alectinib, which is rated as major improvement.

For the health status (assessed using EQ-5D VAS), there was no statistically significant difference between the treatment arms.

It is not possible to make statements about longer-term effects on the health-related quality of life on the basis of the data. In the evaluations of the deterioration at week 12 (assessed using SF 36), there was a statistically significant difference to the advantage for alectinib for the mental component summary (MCS) score. For the physical component summary (PCS) score, there was no statistically significant difference between the treatment arms.

Only comparative statements for the period of the first 4 months of treatment or so can be derived on the basis of the time-to-event analyses for the side effects due to the short duration of observation in the comparator arm. There were statistically significant advantages of alectinib in serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs. In detail, both advantages and disadvantages of treatment with alectinib compared to platinum-based chemotherapy can be identified for the specific AEs.

In the overall analysis, there were advantages of alectinib with regard to the endpoints of recurrences and serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs.

In the overall assessment, a major additional benefit of alectinib over platinum-based chemotherapy is identified.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the ongoing, randomised, controlled, open-label phase III ALINA study. Overall, the risk of bias at the study level is rated as low. However, the available information on the ALINA study does not provide any information on selection criteria for the various therapy options in the comparator arm.

The risk of bias of the results for the endpoint of overall survival is rated as low.

Due to the open study design and the resulting lack of blinding in the case of subjective endpoint assessment, the endpoints on morbidity and health-related quality of life are classified as highly biased.

For the endpoint of recurrences, the overall magnitude of the measured effect suggests with a high degree of certainty an advantage of alectinib over platinum-based chemotherapy. However, uncertainties remain, as the median duration of observation in the ALINA study is only approx. 28 months. A median duration of observation of approx. 28 months is considered insufficient in the present treatment setting to adequately reflect the high-risk period for the recurrence. Furthermore, additional uncertainties arise due to the clear imbalance in recurrences between the principal investigators' assessment and the BICR assessment for the control arm.

Both the results on health status and health-related quality of life are based on analyses at week 12 in the course of the study. These therefore only allow statements to be made about a single early point in time during treatment and represent a point in time with high burden, particularly in the control arm. It is therefore not possible to make statements about longer-term effects on the health status and health-related quality of life on the basis of the data, as a result of which further uncertainties remain.

For the results on side effects, uncertainties result from the short observation period in the control arm. As a result, only comparative statements for the period of the first 4 months of therapy or so can be derived on the basis of the time-to-event analyses. No statements on longer-term side effects can be made on the basis of the data.

Overall, a hint is derived for the reliability of data of the additional benefit identified.

b) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection after prior adjuvant platinum-based chemotherapy or who are ineligible for this

An additional benefit is not proven.

Justification:

No data are available to allow an assessment of the additional benefit.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient alectinib. The therapeutic indication assessed here is as follows:

"Alecensa as monotherapy is indicated as adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence."

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

a) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy

and

b) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection after prior adjuvant platinum-based chemotherapy or who are ineligible for this

Patient population a)

A patient-individual postoperative (adjuvant) systemic chemotherapy with a choice of cisplatin in combination with vinorelbine and cisplatin in combination with pemetrexed was determined as the appropriate comparator therapy, taking into account the general condition.

The results from the phase III ALINA study on the endpoint categories of mortality, morbidity, health-related quality of life and side effects compared to platinum-based chemotherapy are available for the assessment.

However, there were no statistically significant differences between the treatment arms for the overall survival.

Considering the present curative therapeutic approach, the avoidance of recurrences represents a significant therapeutic goal. The results for the endpoints of recurrence rate and disease-free survival showed a statistically significant advantage of alectinib.

It is not possible to make statements about longer-term effects on the health-related quality of life. There was a statistically significant difference to the advantage of alectinib for the mental component summary (MCS) score at week 12.

In terms of side effects, there were statistically significant advantages of alectinib for serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs. In detail, advantages and disadvantages of alectinib can be identified for specific AEs.

A major additional benefit of alectinib over platinum-based chemotherapy is identified as a result.

Uncertainties arise due to the lack of information on selection criteria for the various therapy options in the comparator arm and due to the lack of blinding. For the endpoint of recurrences, the overall magnitude of the measured effect suggests with a high degree of certainty an advantage of alectinib, but uncertainties remain as the median duration of observation of approx. 28 months does not adequately represent the period with high risk of recurrence. The results on health status and quality of life are based on analyses at week 12. For the side effects, comparative statements can only be derived for the period of the first approximately 4 months of therapy. Uncertainties therefore remain, as it is not possible to make any statements about longer-term effects.

The reliability of data is therefore classified in the "hint" category.

Patient population b)

The monitoring wait-and-see approach was determined as the appropriate comparator therapy.

For patient population b), the pharmaceutical company did not submit any data to prove the additional benefit. Therefore, an additional benefit is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on information provided by the pharmaceutical company in the dossier on the benefit assessment.

This information is subject to uncertainties, which result primarily from the following aspects:

In the publication (Kraywinkel et al. (2018)) on the classification of tumour stages according to the UICC used by the pharmaceutical company to calculate the percentage of patients at high risk of recurrence, it was only possible to classify the tumour stages in around 80% of NSCLC cases. The percentage values per stage might have been different if information had been available for those cases with unknown UICC stage. Furthermore, the pharmaceutical company defines the patient group at high risk of recurrence based on tumour stages IB (tumours ≥ 4 cm) to IIIA according to the 7th edition of the UICC, and is guided by section 5.1 of the product information for alectinib. The now 8th edition of the UICC has resulted in some changes to the stage classifications and the percentage values for the individual stages.

There are uncertainties with regard to the percentage of patients with anatomical lung resection, as the percentage values used refer to all primary cases of lung cancer without limitation to NSCLC.

There are uncertainties regarding the percentage of patients with ALK-positive NSCLC, as the percentage values also include stages that are not covered by the definition of high risk of recurrence described above. It is also unclear whether the underlying publications by Blackhall et al. (2014) and Chaft et al. (2018) included patients who had an R0 resection or whether patients who did not undergo complete tumour resection were also included in the calculation. In addition, the publications used are based on a limited data basis.

As part of the written statement procedure, the pharmaceutical company submitted further explanations on the calculation of the number of patients in the SHI target population, in which it derived corresponding percentages and numbers for both patient populations. This information is subject to relevant uncertainties, which is why it is not used as the basis for the present assessment. The significant uncertainties arise from the following aspects:

With regard to the definition of patients, who are eligible or ineligible for platinum-based chemotherapy, it should be noted that the ECOG-PS of 0 or 1 is not the only significant factor in clinical practice in the decision in favour of or against adjuvant platinum-based chemotherapy, but that other criteria can also be taken into account in this decision. The exclusive consideration of the criterion of an ECOG-PS of 0 or 1 for the suitability of platinum-based chemotherapy against the background of other criteria to be taken into account leads to uncertainty. Furthermore, the pharmaceutical company's approach does not take into account that the patient population b includes not only those patients who are ineligible for platinum-based chemotherapy, but also those who have previously received platinum-based chemotherapy. Some of the patients from patient population a would fall into the group of patient population b after receiving adjuvant platinum-based chemotherapy.

With regard to the sources used to determine the percentage ranges for patient groups a and b, it should be noted that each of these has a very small data basis. The publication by Schmid et al. (2022) also included patients who are not covered by the present therapeutic indication (e.g. stages IA or IIIB). The publication shows that 40% of patients were in stage I and 50% of patients were in stage III. In addition, there was no information on ECOG-PS at the time of diagnosis for 15 of the 48 patients (approx. 31%). The calculated percentage of those with an ECOG-PS 0 or 1 would possibly be different if information on those cases with an unknown

ECOG-PS was available. Furthermore, the publication does not exclusively include patients who have already undergone resection, meaning that the transferability of the percentage value to the patient numbers stated in the originally submitted dossier is only guaranteed to a limited extent.

The evaluation based on the Flatiron eNSCLC EDM database, which the pharmaceutical company uses for the upper limit, may also have included patients with stages that are not covered by the present therapeutic indication (e.g. stage IIIB). No information on ECOG-PS is available for 12 of the 27 patients included (approx. 44%). This also creates uncertainty, as the percentage value determined by the pharmaceutical company may also be different if information on those cases with an unknown ECOG-PS was available.

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 Alecensa (active ingredient: alectinib) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 18 December 2024):

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

Treatment with alectinib 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 carcinoma, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and other doctors from specialist groups participating in the Oncology Agreement.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 December 2024).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916).[8]

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

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

The cost representation for the therapy option cisplatin in combination with vinorelbine is based on the S3 guideline and the source referenced therein[2,9].

In the present therapeutic indication, pemetrexed has not been granted marketing authorisation as a component of the therapy option cisplatin in combination with pemetrexed determined to be the appropriate comparator therapy. The cost representation is based on the study by Kenmotsu et al.[10]

Treatment period:

a) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Alectinib	Continuously, 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
Patient-individual postoperative (adjuvant) systemic chemotherapy with selection of				
o cisplatin in combination with vinorelbine				
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Vinorelbine	2 x per 21-day cycle	17.4	2	34.8
o Cisplatin in combination with pemetrexed[10]				
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4

[9] Randomised Phase III Study of Cisplatin With Pemetrexed and Cisplatin With Vinorelbine for Completely Resected Nonsquamous Non–Small-Cell Lung Cancer: The JIPANG Study Protocol. Yamamoto, Nobuyuki et al. Clinical Lung Cancer, Volume 19, Issue 1.

[10] Kenmotsu H, Yamamoto N, Yamanaka T, Yoshiya K, Takahashi T, Ueno T, et al. Randomised phase III study of pemetrexed/cisplatin (Pem/Cis) versus vinorelbine /cisplatin (Vnr/Cis) for completely resected stage II-IIIA non-squamous non-small-cell lung cancer (Ns-NSCLC): The JIPANG study. Journal of Clinical Oncology. 2019;37:8501. URL: https://doi.org/10.1200/JCO.2019.37.15_suppl.8501

b) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection after prior adjuvant platinum-based chemotherapy or who are ineligible for this

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Alectinib	Continuously, 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
Monitoring wait-and-see approach				
Monitoring wait-and-see approach	Not calculable			

Consumption:

a) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy

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					
Alectinib	600 mg	1,200 mg	8 x 150 mg	365.0	2,920 x 150 mg
Appropriate comparator therapy					
Patient-individual postoperative (adjuvant) systemic chemotherapy with selection of					
o cisplatin in combination with vinorelbine					
Cisplatin	80 mg/m^2 = 152.8 mg	152.8 mg	1 x 10 mg + 1 x 50 mg + 1 x 100 mg	17.4	17.4 x 10 mg + 17.4 x 50 mg + 17.4 x 100 mg
Vinorelbine	25 mg/m^2 = 47.8 mg - 30 mg/m^2 = 57.3 mg	47.8 mg - 57.3 mg	1 x 50 mg - 1 x 10 mg + 1 x 50 mg	34.8	34.8 x 50 mg - 34.8 x 10 mg + 34.8 x 50 mg
o cisplatin in combination with pemetrexed[10]					
Cisplatin	75 mg/m^2 BSA = 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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Pemetrexed	500 mg/m² BSA = 955 mg	955 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg

b) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection after prior adjuvant platinum-based chemotherapy or who are ineligible for this

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					
Alectinib	600 mg	1,200 mg	8 x 150 mg	365.0	2,920 x 150 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach					
Monitoring wait-and-see approach	Not calculable				

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 Sections 130 and 130 a 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					
Alectinib 150 mg	224 HC	€ 5,976.91	€ 2.00	€ 338.05	€ 5,636.86
Appropriate comparator therapy					
a) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy					
Monitoring wait-and-see approach (only for patients in stage IB)	Not calculable				
Cisplatin 10 mg	1 CIS	€ 17.53	€ 2.00	€ 0.30	€ 15.23
Cisplatin 50 mg	1 CIS	€ 47.71	€ 2.00	€ 1.73	€ 43.98
Cisplatin 100 mg	1 CIS	€ 76.59	€ 2.00	€ 3.10	€ 71.49
Pemetrexed 1,000 mg	1 CIS	€ 1,124.81	€ 2.00	€ 52.84	€ 1,069.97
Vinorelbine 50 mg	1 CIS	€ 152.64	€ 2.00	€ 6.71	€ 143.93
Vinorelbine 10 mg	1 CIS	€ 38.90	€ 2.00	€ 1.31	€ 35.59
b) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection after prior adjuvant platinum-based chemotherapy or who are ineligible for this					
Monitoring wait-and-see approach	Not calculable				
Abbreviations: HC = hard capsules; CIS = concentrate for the preparation of an infusion solution					

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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 5a SGB V, when a non-prescription medicinal product is dispensed invoiced according Section 300, a medicinal product sale price applies to the insured person in the amount of the sale price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the valid version of 31 December 2003.

As the appropriate comparator therapy in the present case was exceptionally determined as the off-label use of medicinal products in the therapy option cisplatin in combination with pemetrexed, no statement can be made as to whether there are regular differences in the necessary use of medical treatment or in the prescription of other services when using the medicinal product to be assessed compared with the appropriate comparator therapy according to the product information. Therefore, no costs for additionally required SHI services are taken into account here for the therapy options mentioned above.

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:							
Cisplatin in combination with vinorelbine							
Cisplatin 17.4 cycles							
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							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 105.54	€ 5.28	€ 4.26	€ 96.00	17.4	€ 167.04
Sodium chloride 0.9% Inf. Sol., 3 - 4.4 l/day	10 x 1000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	17.4	€ 104.66 - € 174.44
Abbreviations: INF = infusion solution							

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not

take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates 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 has 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 has 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 has 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 ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy

   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.

References:
Product information for alectinib (Alecensa); Alecensa; last revised: October 2024

b) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection after prior adjuvant platinum-based chemotherapy or who are ineligible for this

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.

References:
Product information for alectinib (Alecensa); Alecensa; last revised: October 2024

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 its session on 11 June 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 2 July 2024, the pharmaceutical company submitted a dossier for the benefit assessment of alectinib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 4 July 2024 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 alectinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 October 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 October 2024. The deadline for submitting statements was 5 November 2024.

The oral hearing was held on 25 November 2024.

By letter dated 26 November 2024, the IQWiG was commissioned with a supplementary assessment. The addenda prepared by IQWiG was submitted to the G-BA on 13 December 2024.

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 January 2025, and the proposed draft resolution was approved.

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

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 June 2024	Determination of the appropriate comparator therapy
Working group Section 35a	19 November 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	25 November 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	3 December 2024 17 December 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	7 January 2025	Concluding discussion of the draft resolution
Plenum	16 January 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 January 2025

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

Prof. Hecken