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 Osimertinib (reassessment after the deadline: non-small cell lung cancer, EGFR mutations, adjuvant treatment)

of 19 December 2024

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 pharmaceutical company submitted a dossier for the early benefit assessment for the active ingredient osimertinib (Tagrisso) to be assessed for the first time on 18 June 2021. For the resolution of 16 December 2021 made by the G-BA in this procedure, a limitation up to 1 July 2024 was pronounced.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Tagrisso recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO on 28 June 2024.

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

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 Osimertinib (Tagrisso) in accordance with the product information

Tagrisso as monotherapy is indicated for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations

Therapeutic indication of the resolution (resolution of 19 December 2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy

Appropriate comparator therapy for osimertinib as monotherapy:

Patient-individual therapy with selection of:

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

- 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 pemetrexed

taking into account the tumour stage and general condition.

b) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it

Appropriate comparator therapy for osimertinib 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 osimertinib, 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:

- Osimertinib (resolution of 16 December 2021)
- 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 health care provision.

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

The disease stage IB covered by the ADAURA study population pursuant to stage grouping according to UICC version 7.0 does not correspond to the current UICC version 8.0, which is also the basis for the currently valid guidelines. 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. The appropriate comparator therapy was determined for stages IB to IIIA according to the TNM tumour classification in the 8th edition of the UICC.

The approved therapeutic indication includes patients who are suitable 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 stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy

The recommendations in the present guidelines[2,3,4,5] on neoadjuvant 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. Patients with stage II NSCLC and an activating EGFR mutation (only exon 19 deletion, exon 21 L858R) should be offered adjuvant therapy with osimertinib for 3 years after complete resection and adjuvant chemotherapy. However, osimertinib itself is excluded as an appropriate comparator therapy with regard to the research question of the benefit assessment since the present case concerns the determination of the appropriate comparator therapy for osimertinib.

In the oral hearing as part of the benefit assessment procedure, 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 the standard therapy in the present therapeutic indication. However, combination therapy with paclitaxel has no significance in the adjuvant chemotherapy

[2] S3 guideline "Prevention, diagnosis, therapy and follow-up 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.

of NSCLC. Combination therapy with paclitaxel is not determined to be an appropriate comparator therapy for the present 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.

According to the available evidence, there is no indication for adjuvant chemotherapy in stage IB. For this stage, the monitoring wait-and-see approach is a suitable comparator therapy. The monitoring wait-and-see approach includes the follow-up examinations recommended according to the current state of medical knowledge.

Overall, it is therefore a heterogeneous patient population for which the choice of therapy depends on the individual tumour stage. Therefore, in addition to adjuvant chemotherapy, the monitoring wait-and-see approach can also be considered as a comparator therapy depending on the tumour size.

Overall, the appropriate comparator therapy is thus determined to be a patient-individual therapy with selection of the monitoring wait-and-see approach (only for patients in stage IB) and postoperative (adjuvant) systemic chemotherapy, taking into account the tumour stage and general condition.

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.

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

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.

<u>Cisplatin in combination with pemetrexed</u>

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.[6] Furthermore, the S3

[6] 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.

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 benefit assessment procedure, the clinical experts pointed out the significance of cisplatin in combination with pemetrexed in certain risk constellations and explained 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.

b) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it

The current S3 guideline recommends offering adjuvant therapy with osimertinib for 3 years after complete tumour resection and adjuvant chemotherapy to patients in tumour stages II and IIIA whose tumours have mutations of the epidermal growth factor receptor (EGFR) as a deletion in exon 19 or substitution mutation in exon 21 (L858R).

Osimertinib as monotherapy itself is excluded as an appropriate comparator therapy with regard to the research question of the benefit assessment since the present case concerns the determination of the appropriate comparator therapy for osimertinib as monotherapy.

In addition, 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 12.10.2023). The approved therapeutic indication has no restriction with regard to EGFR status. An additional benefit of pembrolizumab compared to the monitoring wait-and-see approach was not proven in the benefit assessment (resolution of 17.10.2024).

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 follow-up 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 stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy

was originally determined as follows:

Appropriate comparator therapy for osimertinib 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 stated above, the treatment option "cisplatin in combination with paclitaxel" is removed and the treatment option "cisplatin in combination with pemetrexed" is added to the postoperative (adjuvant) systemic chemotherapy.

As a result of the inclusion of this treatment option, it is also added that the general condition should also be taken into account for the patient-individual selection.

This change in the appropriate comparator therapy has no impact on the benefit assessment as the pharmaceutical company did not consider patient group a) in their dossier and therefore did not submit any data.

2.1.3 Extent and probability of the additional benefit

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

a) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy

   An additional benefit is not proven.

Justification:

No data are available to allow an assessment of the additional benefit. In their dossier, the pharmaceutical company does not consider patient population a) and accordingly does not present any data for the assessment of the additional benefit.

b) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it

Hint for a major additional benefit.

Justification:

For the benefit assessment on patient population b), the pharmaceutical company presented results from the completed, double-blind, randomised, placebo-controlled phase III ADAURA study. The study was conducted in 185 study sites across Australia, Asia, Europe, North America and South America.

Adult patients with stage IB-IIIA NSCLC whose tumours showed mutations of the EGFR as deletion in exon 19 or substitution mutation in exon 21 (L858R) were enrolled in the study after complete tumour resection. The staging at the start of the study was based on the classification of the 7th edition of the Union for International Cancer Control (UICC). The dossier also contains a classification according to the 8th edition of the UICCC. Pretreatment with platinum-based chemotherapy was permitted. Patients had to be in good general condition (World Health Organisation Performance Status [WHO-PS] ≤ 1).

In the study, 339 patients were randomised to treatment with osimertinib and 343 patients to treatment with placebo. This was performed stratified according to the stage of disease (IB vs II vs IIIA, classified according to the 7th edition of the UICC), EGFR mutational status (deletion in exon 19 vs substitution mutation in exon 21 [L858R]), and descent (Asian vs non-Asian).

Treatment with osimertinib was continued until relapse, unacceptable toxicity, patient decision, or regular termination of study treatment after 3 years. As of protocol amendment 4 of 02.07.2020, patients were allowed to switch to unblinded administration of osimertinib after a relapse and in the presence of an extensive (no longer curatively treatable) or metastatic stage.

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

3 data cut-offs are available for the ADAURA study:

- 1. data cut-off from 17.01.2020 (DFS interim analysis)
- 2. data cut-off from 11.04.2022 (final DFS analysis)
- 3. data cut-off from 27.01.2023 (pre-specified final analysis of overall survival)

For the benefit assessment, the results of the 3rd data cut-off from 27.01.2023 are used for the endpoint of overall survival. The results of the 2nd data cut-off from 11.04.2022 are used for all other relevant endpoints.

On the implementation of the time limit requirements

According to the justification of the resolution of 16 December 2021, the limitation was that further clinical data from the ADAURA study are expected, which may be relevant for the benefit assessment. For the new benefit assessment after the deadline, the pharmaceutical company must submit new results from the ADAURA study on overall survival and disease-free survival and all patient-relevant outcomes that are used to demonstrate the additional benefit.

In the process, subgroup analyses for patients with prior adjuvant platinum-based chemotherapy and without prior adjuvant platinum-based chemotherapy must be presented. Where possible, the detailed justification for this treatment decision against adjuvant platinum-based chemotherapy must also be provided for those patients not receiving such therapy.

In addition, differences between the staging used in the ADAURA study according to the 7th edition of the UICC and the currently applicable 8th edition of the UICC used in the current guidelines must be presented in the dossier for the new benefit assessment. This concerned in particular patients in stage IB and stage IIIA according to the 7th edition of the UICC.

For the reassessment after the deadline, the pharmaceutical company submitted the final results of the ADAURA study in the dossier. The time limit requirements are considered to have been implemented overall.

On the remaining limitations:

Subgroup of patients without prior adjuvant chemotherapy

It remains unclear whether the patient population of the ADAURA study can be completely assigned to patient group b) of the present benefit assessment, or whether 40% of patients enrolled in the study without prior adjuvant treatment also included a relevant percentage of patients who would have been eligible for adjuvant chemotherapy but did not receive it, thus assigning them to patient group a) and potentially undertreating them in the control arm. According to the pharmaceutical company, the principal investigator decided prior to randomisation whether the patients should receive adjuvant platinum-based chemotherapy. However, the criteria, based on which this decision was taken, are not sufficiently clear from the documents submitted. According to the current recommendations of the guidelines, adjuvant chemotherapy after complete tumour resection is recommended as a rule for patients in disease stages II and IIIA with a good general condition and without relevant comorbidities. Only patients in good general condition (WHO-PS 0-1) were enrolled in the ADAURA study.

Due to the uncertainties in the allocation of the total patient population of the ADAURA study to patient population b), it is unclear to what extent treatment according to the appropriate comparator therapy for patient population a) rather than monitoring wait-and-see approach would have been indicated for a percentage of patients as treatment in the comparator arm.

Staging according to the currently applicable 8th edition of the UICC classification

In addition, the pharmaceutical company stated in the dossier how the staging of the patients is performed in accordance with the currently applicable 8th edition of the UICC classification.

Shifts within stages IIA and IIB are particularly evident here. In the higher stages IA, II and IIIA, there are no relevant changes in the percentages of patients. However, according to the new staging in accordance with the 8th edition of the UICC classification, 3.8% of patients in the total population were in a stage which is outside of the therapeutic indication to be assessed or for which no information was available. Nevertheless, the pharmaceutical company included these patients in the analyses they presented in the ADAURA study. Due to the small percentage of patients outside of the therapeutic indication to be assessed, this has no consequences for the benefit assessment.

Extent and probability of the additional benefit

Mortality

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

For the endpoint of overall survival, there was a statistically significant difference to the advantage of osimertinib versus the monitoring wait-and-see approach. The median survival time was not reached in either treatment group at the present data cut-off (final analysis of overall survival), which must be viewed against the background of the present early treatment setting in the course of the disease. During interpretation of the effect, it should be taken into account that a relevant percentage of patients with relapse in the comparator arm of the ADAURA study is to be assumed to have received inadequate subsequent therapy with an EGFR tyrosine kinase inhibitor. In view of the size of the effect, the advantage of osimertinib in the overall survival endpoint is not questioned, although its extent cannot be quantified with certainty.

Morbidity

Recurrences

The endpoint is represented by recurrence rate and disease-free survival and includes the events local/regional recurrence, distant recurrence with CNS recurrences, and death from any cause.

The recurrence rate is defined as the percentage of patients who suffer disease recurrence or die after complete tumour resection up to the present data cut-off. An event is the first occurrence of locoregional recurrence, distant recurrence, or death.

Disease-free survival is defined as the time from randomisation to disease recurrence or death (from any cause in the absence of recurrence).

Both endpoints (recurrence rates and disease-free survival) showed a statistically significant difference to the advantage of osimertinib, the extent of which is assessed as major improvement.

Quality of life

SF-36v2 – physical and mental component summary scores

Quality of life was assessed using SF-36v2.

In the dossier, the pharmaceutical company presented evaluations of the time to first deterioration of the physical component summary (PCS) score and mental component summary (MCS) score. Confirmation was not necessary during the subsequent visit. A

decrease by ≥ 9.423 points (PCS) or ≥ 9.618 points (MCS) was considered a deterioration. This corresponds to a deterioration by ≥ 15% of the scale range in each case. Accordingly, the responder analyses of the time to first deterioration can be used to derive the additional benefit.

For the endpoints of physical component summary (PCS) score and mental component summary (MCS) score, there was no statistically significant difference between the treatment arms in the evaluation of the time to first deterioration.

With regard to health-related quality of life, there were therefore neither positive nor negative effects of osimertinib compared to the monitoring wait-and-see approach.

Side effects

Total adverse events (AE) (presented additionally)

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

Serious AEs (SAEs)

For the endpoint of SAEs, there is no statistically significant difference between the treatment arms.

Severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs

For the endpoints of severe AEs and discontinuation due to AEs, there was a statistically significant difference to the disadvantage of osimertinib, compared to the monitoring wait-and-see approach.

Specific AEs

Skin and subcutaneous tissue disorders (SOC, AEs)

For the endpoint of skin and subcutaneous tissue disorders (SOC, AEs), there was a statistically significant difference to the disadvantage of osimertinib, compared to the monitoring wait-and-see approach.

ILD and pneumonitis (PTs, SAEs) and cardiac events (severe AEs)

For the endpoints of ILD and pneumonitis (PTs, SAEs) and cardiac events (severe AEs), there was no statistically significant difference between the treatment arms.

Other specific AEs

For each of the specific AEs of gastrointestinal disorders (SOC, AEs, including: diarrhoea [PT, AEs], mouth ulcer [PT, AEs], stomatitis [PT, AEs]), paronychia (PT, AEs), loss of appetite (PT, AEs), gastrointestinal disorders (SOC, severe AEs) and examinations (SOC, severe AEs), there was a statistically significant difference to the disadvantage of osimertinib compared to monitoring wait-and-see approach.

In summary, a disadvantage of osimertinib treatment can be identified due to several negative effects in severe AEs (CTCAE grade ≥ 3), therapy discontinuations due to AEs, and in detail, specific AEs.

Overall assessment/ conclusion

For the endpoint categories of mortality, morbidity, health-related quality of life and side effects, results of the ADAURA study are available for the benefit assessment of osimertinib as monotherapy for adjuvant treatment after complete tumour resection of adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC), whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations, compared to the monitoring wait-and-see approach.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of osimertinib versus the monitoring wait-and-see approach. The median survival time was not reached in either treatment group at the present data cut-off (final analysis of overall survival), which must be viewed against the background of the present early treatment setting in the course of the disease. During interpretation of the effect, it should be taken into account that a relevant percentage of patients with relapse in the comparator arm of the ADAURA study is to be assumed to have received inadequate subsequent therapy with an EGFR tyrosine kinase inhibitor. In view of the size of the effect, the advantage of osimertinib in the overall survival endpoint is not questioned, although its extent cannot be quantified with certainty.

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 osimertinib, which is rated as major improvement.

For the endpoints of health-related quality of life, there were no statistically significant differences between the treatment arms.

For the side effects, there was no statistically significant difference between the study arms concerning the endpoint of serious AEs. For the endpoints of severe AEs (CTCAE grade≥ 3), therapy discontinuation due to AEs, and in detail for specific AEs, there were negative effects of osimertinib compared to the monitoring wait-and-see approach, which is why a disadvantage of the treatment with osimertinib is to be identified overall.

In the overall analysis, the positive effects on the endpoints of recurrences and overall survival are offset by the negative effects on the endpoints of side effects. The disadvantage in terms of side effects is weighted against the background of the curative therapy claim and does not call into question the extent of the improvement in the overall assessment.

In the overall assessment, a major additional benefit of osimertinib over the monitoring wait-and-see approach is identified.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, double-blind, placebo-controlled phase III ADAURA study.

For the results on the endpoint of overall survival, it should be taken into account that a relevant percentage of patients with relapse in the comparator arm of the ADAURA study is

to be assumed to have received inadequate subsequent therapy with an EGFR tyrosine kinase inhibitor, which results in uncertainty.

For the endpoint of recurrences, an overall high reliability of data is assumed, taking into account the size of the effect.

The results on health-related quality of life are based on a high risk of bias. An overall high reliability of data is assumed for the results on side effects.

Overall, the reliability of data of the additional benefit identified is limited to a relevant extent due to uncertainties regarding the allocation of the total patient population of the ADAURA study to patient group b). In this respect, it remains unclear to what extent a relevant percentage of patients, for whom adjuvant chemotherapy would have been suitable and who would therefore be assigned to patient group a), were enrolled in the study.

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

2.1.4 Summary of the assessment

The present assessment is a benefit reassessment after the deadline for a therapeutic indication for the active ingredient osimertinib.

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

a) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy

b) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it

Patient population a)

The appropriate comparator therapy was determined to be a patient-individual therapy with selection of monitoring wait-and-see approach (only for patients in stage IB) and postoperative (adjuvant) chemotherapy with selection of cisplatin in combination with vinorelbine or pemetrexed, taking into account the tumour stage and general condition.

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

Patient population b)

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

For the assessment of the additional benefit of osimertinib, the pharmaceutical company presents results from the randomised, double-blind, placebo-controlled phase III ADAURA

study on the endpoint categories of mortality, morbidity, health-related quality of life and side effects compared to the monitoring wait-and-see approach.

For the endpoint of overall survival, there was a statistically significant advantage of osimertinib compared to the monitoring wait-and-see approach. Median survival time was not reached in either treatment group. Uncertainties arise due to inadequate subsequent therapies in the comparator arm.

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 osimertinib.

For health-related quality of life, there was no statistically significant difference between the treatment arms.

For the side effects, there was no statistically significant difference with regard to the endpoint of serious AEs. There was a disadvantage of osimertinib for the endpoints of severe AEs, therapy discontinuation due to AEs and in detail for the specific AEs.

In the overall analysis, the positive effects on the endpoints of recurrences and overall survival are offset by the negative effects on the endpoints of side effects. The disadvantage in terms of side effects is weighted against the background of the curative therapy claim and does not call into question the extent of the improvement in the overall assessment.

A major additional benefit of osimertinib over the monitoring wait-and-see approach is identified as a result.

Uncertainties arise for the endpoint of overall survival due to inadequate subsequent therapies in the comparator arm and the allocation of the total patient population to patient group b) overall. The reliability of data is therefore classified in the "hint" category.

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 pharmaceutical company's approach of basing the resolution on the patient numbers from the previous resolution of 16 December 2021 is comprehensible. However, it should be noted that the information on the SHI target population should still be regarded as uncertain. The pharmaceutical company's assumption that all patients who are eligible for adjuvant chemotherapy will also receive it and the resulting allocation of the total SHI target population to patient population b) is however incomprehensible. This is because, according to the product information, osimertinib can be administered regardless of whether chemotherapy is an option for patients in this therapeutic indication, meaning that osimertinib can also be considered as a therapy option for patient population a). The SHI target population shown therefore includes patients from patient populations a) and b) and is shown as a whole.

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 Tagrisso (active ingredient: osimertinib) at the following publicly accessible link (last access: 30 August 2024):

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

Treatment with osimertinib 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: 1 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).[7]

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.

The cost representation for the therapy option cisplatin in combination with vinorelbine is based on the S3 guideline and the source referenced therein[8][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

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

[8] S3 guideline "Prevention, diagnosis, therapy and follow-up of lung cancer", version 2.1, December 2022.

[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.

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 stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and 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				
Osimertinib	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Patient-individual therapy with selection of:				
- monitoring wait-and-see approach (only for patients in stage IB)				
Monitoring wait-and-see approach	Not calculable			
and				
- 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
and				
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

[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 stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Osimertinib	Continuously, 1 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 stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and 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					
Osimertinib	80 mg	80 mg	1 x 80 mg	365.0	365 x 80 mg
Appropriate comparator therapy					
Patient-individual therapy with selection of:					
- monitoring wait-and-see approach (only for patients in stage IB)					
Monitoring wait-and-see approach	Not calculable				
and					
- postoperative (adjuvant) systemic chemotherapy with selection of					
o cisplatin in combination with vinorelbine					
Cisplatin	80 mg/m^2 BSA = 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/m² BSA = 47.8 mg - 30 mg/m² BSA = 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
and					
o Cisplatin in combination with pemetrexed[10]					
Cisplatin	75 mg/m² 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
Pemetrexed	500 mg/m² BSA = 955 mg	955 mg	2 x 500 mg	17.4	34.8 x 500 mg

b) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it

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					
Osimertinib	80 mg	80 mg	1 x 80 mg	365.0	365 x 80 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					
Osimertinib 80 mg	30 FCT	€ 5,760.15	€ 2.00	€ 325.67	€ 5,432.48
Appropriate comparator therapy					
a) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and 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 500 mg	1 CIS	€ 567.62	€ 2.00	€ 26.40	€ 539.22
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 stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it					
Monitoring wait-and-see approach	Not calculable				
Abbreviations: FCT = film-coated tablets; 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 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.

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. Solution, 3 - 4.4 l/day	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	17.4	€ 104.66 - € 174.44
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 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 stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and 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.

b) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it

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.

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 6 October 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 7 August 2024.

On 28 June 2024 the pharmaceutical company submitted a dossier for the benefit assessment of osimertinib to the G-BA in due time in accordance with Chapter 5 Section 1, paragraph 2, number 7 VerfO.

By letter dated 28 June 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 osimertinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 September 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 October 2024. The deadline for submitting statements was 22 October 2024.

The oral hearing was held on 11 November 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 10 December 2024, and the proposed draft resolution was approved.

At its session on 19 December 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	6 October 2020	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	7 August 2024	New determination of the appropriate comparator therapy
Working group Section 35a	4 November 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 November 2024	Conduct of the oral hearing
Working group Section 35a	19 November 2024 3 December 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	10 December 2024	Concluding discussion of the draft resolution
Plenum	19 December 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 December 2024

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

Prof. Hecken