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 (new therapeutic indication: non-small cell lung cancer, first-line, combination with pemetrexed and platinum-based chemotherapy)

of 6 February 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. For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h. 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 osimertinib (Tagrisso) was listed for the first time on 15 March 2016 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 28 June 2024, osimertinib 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 23 July 2024, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time 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 osimertinib with the new therapeutic indication

"Tagrisso is indicated in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations."

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The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 November 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 with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 is indicated in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

Therapeutic indication of the resolution (resolution of 06.02.2025):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations; first-line treatment

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

Appropriate comparator therapy for osimertinib in combination with pemetrexed and platinum-based chemotherapy:

- Afatinib (only for patients with the activating EGFR exon 19 deletion mutation)
  or
- Osimertinib

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 in combination with pemetrexed and platinum-based chemotherapy, afatinib, amivantamab, bevacizumab, cisplatin, dacomitinib, docetaxel, erlotinib, etoposide, gefitinib, gemcitabine, ifosfamide, lazertinib, mitomycin, nab-paclitaxel, osimertinib, paclitaxel, pembrolizumab, pemetrexed, ramucirumab, vindesine and vinorelbine are approved for the first-line treatment of EGFR-positive non-small cell lung cancer (NSCLC). The marketing authorisations are partly based on the use as monotherapy or in certain combination therapies. In addition, off-label use of carboplatin can be prescribed in this therapeutic indication.

On 2. Non-medicinal treatment is not considered. This does not affect the conduct of surgery or radiotherapy as palliative therapy options.

On 3. The following resolutions and guidelines of the G-BA are available for medicinal product treatment in the present therapeutic indication:

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

- Ramucirumab: resolution of 20.08.2020
- Dacomitinib: resolution of 17.10.2019
- Pembrolizumab: resolution of 19.09.2019
- Osimertinib: resolutions of 17.01.2019 and 15.09.2016
- Afatinib: resolution of 15.11.2015

Guidelines:

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

Carboplatin-containing medicinal products for advanced non-small cell lung cancer (NSCLC) - combination therapy

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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

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

It is assumed that no other molecularly stratified therapy (directed against ALK, BRAF, EGFR, exon-20, KRAS G12C, METex14, RET or ROS1) will be considered for patients at the time of therapy with osimertinib.

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

It is also assumed that there is neither an indication for definitive chemoradiotherapy nor for definitive local therapy.

According to the present guidelines, the therapy recommendations for patients with activating EGFR mutations are based on the specific EGFR mutation.

According to the current S3 guideline, patients with an exon 19 deletion should preferably be offered osimertinib based on the survival data. The joint statement of the Working Group for Internal Oncology of the German Cancer Society (AIO), the German Society of Haematology and Medical Oncology (DGHO) and the German Respiratory Society (DGP) in the present benefit assessment procedure (hereinafter: statement of the scientific-medical societies) recommends afatinib or dacomitinib in addition to osimertinib for patients with an exon 19 deletion. This mentions osimertinib as the preferred standard for "common mutations" due to its survival advantage over first-generation tyrosine kinase inhibitors (TKIs) and better tolerability than second-generation TKIs.

In the benefit assessment of osimertinib, a hint for a considerable additional benefit over gefitinib or erlotinib was identified for patients with locally advanced or metastatic NSCLC with an exon 19 deletion (resolution of 17 January 2019).

As a result of the benefit assessment of the active ingredient afatinib, a major additional benefit over cisplatin in combination with pemetrexed was identified for patients with locally advanced and/or metastatic NSCLC in the patient group with an exon 19 deletion (resolution of 5 November 2015).

In contrast, the G-BA did not identify any additional benefit of the active ingredient dacomitinib over the appropriate comparator therapy in the benefit assessment for patients with locally advanced or metastatic NSCLC with an exon 19 deletion (resolution of 17 October 2019).

With regard to the exon 21 (L858R) substitution mutation, the S3 guideline recommends selecting the therapy, depending on the efficacy and toxicity of the approved TKIs (afatinib, dacomitinib, erlotinib, gefitinib, osimertinib, erlotinib in combination with bevacizumab, erlotinib in combination with ramucirumab), based on the survival and/or efficacy data for L858R mutations.

The statement of the scientific-medical societies recommends the active ingredients osimertinib or dacomitinib or another one of the approved TKIs for the treatment of an L858R mutation.

As already explained, this mentions osimertinib as the preferred standard for "common mutations" due to its survival advantage over first-generation tyrosine kinase inhibitors (TKIs) and better tolerability than second-generation TKIs.

In the benefit assessment of osimertinib, a hint for a considerable additional benefit over gefitinib or erlotinib was identified for patients with locally advanced or metastatic NSCLC with an L858R mutation (resolution of 17 January 2019).

In contrast, for patients with an L858R mutation, the benefit assessments of afatinib (resolution of 5 November 2015), dacomitinib (resolution of 17 October 2019) and ramucirumab in combination with erlotinib (resolution of 20 October 2020) each showed no additional benefit over the appropriate comparator therapy.

In summary, the G-BA considers it appropriate to determine osimertinib or afatinib as the appropriate comparator therapy on the basis of the underlying evidence, the statement of the scientific-medical societies and the results of the benefit assessment.

Afatinib is only indicated for patients with the activating EGFR exon 19 deletion mutation.

Amivantamab in combination with lazertinib is a new treatment option in the present therapeutic indication. The combination of active ingredients was only recently approved (marketing authorisation of amivantamab on 19.12.2024). Based on the generally accepted state of medical knowledge, amivantamab in combination with lazertinib is not determined to be an appropriate comparator therapy for the present resolution.

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

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

2.1.3 Extent and probability of the additional benefit

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

<u>Adults with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations; first-line treatment</u>

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company submits results of the ongoing, open-label FLAURA-2 RCT. The study was conducted in 153 study sites worldwide.

Adult patients with non-squamous, unresectable stage IIIB, IIIC and IV NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and have not yet received any prior therapy were enrolled in the study. Adjuvant or neoadjuvant therapies were permitted if they had been completed at least 12 months prior to recurrence. Pretreatment with an EGFR tyrosine kinase inhibitor (TKI) was generally excluded. Patients had to be in good general condition (World Health Organisation Performance Status [WHO-PS] ≤ 1).

557 patients were randomised in the study. 279 patients were in the osimertinib + chemotherapy arm and 278 patients in the osimertinib arm.

The primary endpoint of the FLAURA-2 study is progression-free survival (PFS). Other endpoints were collected in the categories of mortality, morbidity, health-related quality of life and side effects.

For the FLAURA-2 study, three data cut-offs are available so far:

- 1st data cut-off from 22.09.2021 (interim futility analysis)

- 2nd data cut-off from 03.04.2023 (pre-specified primary PFS analysis)

- 3rd data cut-off from 08.01.2024 (required by EMA to support the marketing authorisation procedure)

The pharmaceutical company does not conduct analyses on overall survival for the second data cut-off. In the dossier, only analyses of overall survival were conducted for the third data cut-off. The analyses presented by the pharmaceutical company from the non-pre-specified third data cut-off are incomplete, as only results on overall survival were presented and not

analyses on endpoints in the morbidity and side effects category. According to the information in the dossier, around 50% of patients were still being treated with the study medication at the second data cut-off and were therefore still being monitored for the endpoints in the side effects category. Although treatment with platinum-based chemotherapy took place at the start of treatment, uncertainties remain as to whether events in the endpoints of the side effects category occurred to a potentially relevant extent between the second and third data cut-offs. Therefore, the third data cut-off (data on overall survival) is only considered additionally for the present assessment.

On the subsequent therapies

In the FLAURA-2 study, continuation of study treatment after disease progression was possible if there was a clinical benefit according to the principal investigator's estimate, and no discontinuation criteria were met. In the study, around 85% of patients with disease progression were treated further with osimertinib. This continuation of treatment with osimertinib does not correspond to the recommendation in the product information for osimertinib.

In contrast, according to the statement of the scientific-medical societies, continuing treatment with osimertinib beyond progression in imaging corresponds to the reality of care. This delays a switch to increased burden of therapy in many clinically asymptomatic patients until clinical progression.

The current German S3 guideline provides for a subsequent therapy according to clinical progression and thus at the doctor's discretion. In this regard, the S3 guideline states that oligoprogressions are relatively common in patients with NSCLC with EGFR mutations, which can be treated with local therapies, primarily radiotherapy or surgery. In several retrospective studies, such use of ablative procedures while continuing the previous molecularly targeted systemic therapy has led to a median delay of about 5-10 months in changing the systemic therapy and should always be reviewed prior to a change in the systemic therapy.

Based on the information on subsequent therapies, it is also striking that a relevant percentage of patients received an EGFR-TKI as subsequent therapy, which does not correspond to the guideline recommendations.

Extent and probability of the additional benefit

Mortality

The overall survival was operationalised in the FLAURA-2 study as the time from randomisation to death from any cause.

For the endpoint of overall survival, there was no statistically significant difference between the treatment groups.

The data of the 3rd data cut-off show a positive effect of osimertinib in combination with pemetrexed and platinum-based chemotherapy compared to osimertinib.

With regard to the subsequent therapies used (see above), there is uncertainty in the assessment of the effect.

Morbidity

Progression-free survival (PFS)

Progression-free survival was operationalised in the FLAURA-2 study as the time from randomisation or from the first study treatment dose for the safety run-in to objective disease progression or death from any cause. The endpoint was assessed by the principal investigators using the RECIST criteria version 1.1.

For the PFS endpoint, there was a statistically significant advantage for osimertinib in combination with pemetrexed and platinum-based chemotherapy compared to osimertinib.

The present PFS endpoint is a composite endpoint consisting of endpoints from the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" is collected according to RECIST criteria and thus predominantly by means of imaging procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS.

The available data on morbidity and health-related quality of life are used to interpret the PFS results. These results are potentially relevant in the present case because radiologically disease progression may be associated to effects on morbidity and/or quality of life.

The prolonged PFS with osimertinib in combination with pemetrexed and platinum-based chemotherapy was not associated with an advantage in terms of morbidity or quality of life in the FLAURA-2 study.

In summary, the available data do not indicate that the statistically significant prolonged time of progression-free survival with osimertinib in combination with pemetrexed and platinum-based chemotherapy – radiologically determined disease progression according to RECIST criteria – is associated with an improvement in morbidity or health-related quality of life.

The results on the PFS endpoint are not used for the present assessment.

CNS metastases

41% of patients in the FLAURA-2 study had CNS metastases. The statements of the scientific-medical societies state that the difference in PFS in favour of the chemotherapy arm in the subgroup analyses is most evident in patients with CNS metastases. In view of the higher rate of side effects caused by chemotherapy, the scientific-medical societies consider osimertinib in combination with chemotherapy primarily indicated in patients with CNS metastases.

The subgroup feature "CNS metastases at baseline" was predefined for the PFS endpoint. The present subgroup analyses show no statistically significant effect modifications by the characteristic "CNS metastases at baseline" for the other endpoints. Only the subgroup analyses of the symptom scales of the EORTC QLQ-LC13 show a corresponding effect modification for the individual endpoint "cough".

Symptomatology (EORTC QLQ-C30, EORTC QLQ-LC13 and PGIS)

Symptomatology was assessed in the FLAURA-2 study using the symptom scales of the EORTC QLQ-C30, EORTC QLQ-LC13 and PGIS questionnaires. The mean differences are used for the evaluation of the benefit assessment.

The evaluations did not show any statistically significant difference between the treatment arms for each of the endpoints of pain, dyspnoea, insomnia and diarrhoea. (EORTC QLQ-C30*)*

For the endpoints of fatigue, nausea and vomiting, appetite loss and constipation, there was a statistically significant difference, the relevance of which cannot be confirmed by considering the standardised mean difference. (EORTC QLQ-C30*)*

For the endpoint of cough there was a statistically significant difference whose relevance cannot be confirmed by considering the standardised mean difference. However, patients with CNS metastases at baseline showed a hint for an advantage of the therapy with osimertinib in combination with pemetrexed and platinum-based chemotherapy over osimertinib. (EORTC QLQ-LC13)

For the endpoints of haemoptysis, dysphagia, pain (arm/ shoulder), pain (other body parts), pain (chest), dyspnoea, peripheral neuropathy and alopecia, the evaluations based on the mean difference did not show any statistically significant difference between the treatment arms in each case. (EORTC QLQ-LC13)

For the endpoint of pain (other body parts), there was an effect modification due to the age characteristic. Patients < 65 years of age showed a hint for a disadvantage of the therapy with osimertinib in combination with pemetrexed and platinum-based chemotherapy over osimertinib. (EORTC QLQ-LC13)

For the endpoint of sore mouth, there was a statistically significant difference whose relevance cannot be confirmed by considering the standardised mean difference. (EORTC QLQ-LC13)

For the endpoints of haemoptysis, dysphagia, pain (arm/ shoulder), pain (other body parts), pain (chest), dyspnoea, peripheral neuropathy and alopecia, the evaluations based on the mean difference did not show any statistically significant difference between the treatment arms in each case. (PGIS)

Health status (assessed by EQ-5D VAS)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. The mean differences are used for the evaluation of the benefit assessment.

There was no statistically significant difference between the treatment arms.

Quality of life

EORTC-QLQ-30

Quality of life is assessed in the FLAURA-2 study using the functional scale of the EORTC QLQ-C30 questionnaire. The mean differences between the treatment arms are used for the benefit assessment.

There was no significant difference between the treatment arms for the endpoints of role functioning and emotional functioning.

For the endpoints of physical functioning, cognitive functioning, social functioning and global health status, there was a statistically significant difference whose relevance cannot be confirmed by considering the standardised mean difference.

The overall analysis of the results on health-related quality of life showed no advantages of osimertinib in combination with pemetrexed and platinum-based chemotherapy compared to osimertinib as monotherapy.

Side effects

Serious adverse events

For the SAE endpoint, there was a statistically significant difference to the disadvantage of osimertinib in combination with pemetrexed and platinum-based chemotherapy for patients < 65 years of age. For patients ≥ 65 years, there was no significant difference between the treatment arms.

Severe adverse events (CTCAE grade ≥ 3)

For the endpoint of severe AEs (CTCAE grade ≥ 3), there was a statistically significant difference to the disadvantage of osimertinib + pemetrexed + platinum-based chemotherapy compared to osimertinib.

Therapy discontinuation due to adverse events

For the endpoint of therapy discontinuation due to AEs, there was a statistically significant difference to the disadvantage of osimertinib in combination with pemetrexed and platinum-based chemotherapy compared to osimertinib.

PRO-CTCAE

No appropriate data are available in the dossier for the PRO-CTCAE endpoint.

Specific adverse events

Skin and subcutaneous tissue disorders (AEs), ILD and pneumonitis (severe AEs)

There was no statistically significant difference between the treatment arms for the endpoints of skin and subcutaneous tissue disorders (AEs), ILD and pneumonitis (severe AEs).

Cardiac effects (severe AEs)

For the endpoint of cardiac effects (severe AEs), there was a statistically significant difference to the disadvantage of osimertinib in combination with pemetrexed and platinum-based chemotherapy compared to osimertinib.

Other specific AEs

There was a statistically significant difference to the disadvantage of osimertinib in combination with pemetrexed and platinum-based chemotherapy compared to osimertinib for each of the endpoints of loss of appetite (AEs), general disorders and administration site conditions (severe AEs), blood and lymphatic system disorders (SAEs), gastrointestinal disorders (severe AEs) and investigations (SAEs).

Overall assessment

For the assessment of the additional benefit of osimertinib in combination with pemetrexed and platinum-based chemotherapy for adults with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 substitution mutations, results for mortality, morbidity, health-related quality of life and side effects are available from the randomised, controlled, multicentre FLAURA-2 study. FLAURA-2 study compared osimertinib in combination with pemetrexed and platinum-based chemotherapy with osimertinib. The assessment is based on the 2nd data cut-off from 3 April 2023 (primary PFS data cut-off).

For the endpoint of overall survival, there was no statistically significant difference between the treatment groups. The data of the 3rd data cut-off show a positive effect of osimertinib in combination with pemetrexed and platinum-based chemotherapy compared to osimertinib.

With regard to symptomatology (assessed using the EORTC QLQ-C30, EORTC QLQ-LC13 and PGIS), there were a few positive and negative effects and mostly no statistically significant differences. Overall, there is no relevant difference. The data on health status (collected using EQ-5D VAS) also show no relevant difference.

For health-related quality of life (assessed using the EORTC QLQ-C30), there was no relevant difference overall.

For the endpoint category of side effects, there were significant disadvantages in the severe AEs, serious AEs, therapy discontinuation due to AEs, and in detail, specific AEs.

In a weighted decision, with additional consideration of the positive effect on overall survival in the 3rd data cut-off, the G-BA concludes that an additional benefit of osimertinib in combination with pemetrexed and platinum-based chemotherapy for the treatment of adults with advanced NSCLC, whose tumours have EGFR exon 19 deletions or exon 21 substitution mutations, compared to monotherapy with osimertinib is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient osimertinib:

Tagrisso is indicated in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

The appropriate comparator therapy comprises treatment with afatinib (only for patients with the activating EGFR exon 19 deletion mutation) or osimertinib.

For the benefit assessment, the pharmaceutical company submits results of the open-label FLAURA-2 RCT. Adult patients with non-squamous, unresectable stage IIIB, IIIC and IV NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and have not yet received any prior therapy were enrolled in the study.

557 patients were randomised in the study. 279 patients were in the osimertinib + chemotherapy arm and 278 patients in the osimertinib arm.

For the endpoint of overall survival, there was no statistically significant difference between the treatment groups. The data from the third data cut-off show a positive effect of osimertinib in combination with pemetrexed and platinum-based chemotherapy compared to osimertinib. The third data cut-off was required by the EMA. Only data on overall survival which are considered additionally for the present assessment were presented for this data cut-off.

With regard to symptomatology (assessed using the EORTC QLQ-C30, EORTC QLQ-LC13 and PGIS), there were a few positive and negative effects and mostly no statistically significant differences. Overall, there is no relevant difference. The data on health status (collected using EQ-5D VAS) also show no relevant difference.

For health-related quality of life (assessed using the EORTC QLQ-C30), there was no relevant difference overall.

For the endpoint category of side effects, there were significant disadvantages in the severe AEs, serious AEs, therapy discontinuation due to AEs, and in detail, specific AEs.

In a weighted decision with additional consideration of the positive effect on overall survival in the third data cut-off, the G-BA concludes that an additional benefit of osimertinib in combination with pemetrexed and platinum-based chemotherapy for the treatment of adults with advanced NSCLC, whose tumours have EGFR exon 19 deletions or exon 21 substitution mutations, compared to monotherapy with osimertinib 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).

For the number of German patients with lung cancer, the incidence for 2020 (56,690 patients)[2] is used as the basis for the calculations. The current publications lack projected data. This is why later developments cannot be presented here.

The following calculation steps are used to narrow down this patient group to the target population:

1. The percentage of lung cancer patients with NSCLC is between 73.6% and 83.6%[3] (41,723 to 47,392 patients).
2. Of these, 46.63% of patients are in stage IV at initial diagnosis[4]. Of the remaining 53.37% of patients who are in stage I-IIIB, 37.7% will progress to stage IV in 2022[5]. The percentage of patients in stage IIIB/IIIC is 4.5% to 6.1%[6]. The total number of patients is 32,273 to 36,658.
3. First-line therapy is given in 76.9% to 96.1%[3] of cases (24,818 - 35,228 patients).
4. 63.1% to 78.6% of patients with stage IIIB/IV[7]NSCLC (15,660 to 27,689 patients) had non-squamous histology.
5. The suitability for a platinum-based therapy exists in 70%-90% of patients (10,962 to 24,920 patients).
6. The percentage of patients with EGFR mutation is 10.3% to 14.1% (1,129 to 3,513 patients).[8]
7. The percentage of patients with activating EGFR L858R mutations or exon 19 deletion is 85.6%-88.7% (966 to 3,116 patients). [8]
8. Taking into account the percentage of SHI-insured patients of 87.28%, there are 843 to 2,720 patients in the first-line therapy.

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

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

[4] Benefit assessment according to Section 35a SGB V, A23-29 | A23-31, durvalumab and tremelimumab, 29.06.2023

[5] Tumour Registry Munich ICD-10 C34: Non-small cell. BC Survival [online]. 2022. URL: https://www.tumorregister-muenchen.de/facts/surv/sC34N_G-ICD-10-C34-Nicht-kleinzell.-BC-Survival.pdf; 37.7% (for the longest possible observation period of 15 years)

[6] Benefit assessment according to Section 35a SGB V, A23-37, cemiplimab, 28.04.2023

[7] Benefit assessment according to Section 35a SGB V, A19-84, atezolizumab, 02.04.2020

[8] Benefit assessment according to Section 35a SGB V, A21-86, osimertinib, 29.09.2021

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: 4 October 2024):

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

Treatment with osimertinib may only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of patients with non-small cell lung cancer, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and doctors from other specialist groups participating in the Oncology Agreement.

If the use of osimertinib is considered, EGFR mutational status must be determined using a validated assay.

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 January 2025).

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).[9]

The treatment regimens used in the FLAURA-2 approval study will be used for osimertinib in combination with pemetrexed and platinum-based chemotherapy.

The dosage according to the target AUC of carboplatin is calculated using the Calvert formula and the estimation of renal function with the Cockcroft-Gault equation using the average height (women: 166 cm, men: 179 cm), the average weight (women 69.2 kg, men 85.8 kg) and the average age of women and men in Germany in 2021 (women: 46 years, men: 43.4 years) [10] and the mean standard serum creatinine concentration (women: 0.75 mg/dl, men: 0.9 mg/dl)[11].

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

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

[11] DocCheck Flexikon – Serum creatinine, URL: https://flexikon.doccheck.com/de/Serumkreatinin [last access: 06.01.2025]

The mean value (AUC 5 = 700.7 mg) formed from these doses for women (AUC 5 = 637 mg) and men (AUC 5 = 764.5 mg) was used as the basis for calculating the cost of carboplatin.

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

Treatment period:

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 in combination with pemetrexed and platinum-based chemotherapy				
Osimertinib + pemetrexed + cisplatin				
Osimertinib	Continuously, 1 x daily	365.0	1	365.0
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Cisplatin	1 x per 21-day cycle	4	1	4
Osimertinib + pemetrexed + carboplatin				
Osimertinib	Continuously, 1 x daily	365.0	1	365.0
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Carboplatin	1 x per 21-day cycle	4	1	4
Appropriate comparator therapy				
Afatinib (only for patients with the activating EGFR exon 19 deletion mutation)				
Afatinib	Continuously, 1 x daily	365.0	1	365.0
Osimertinib as monotherapy				
Osimertinib	Continuously, 1 x daily	365.0	1	365.0

Consumption:

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

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 in combination with pemetrexed and platinum-based chemotherapy					
Osimertinib + pemetrexed + cisplatin					
Osimertinib	80 mg	80 mg	1 x 80 mg	365.0	365 x 80 mg
Pemetrexed	500 mg/m^2 BSA = 955 mg	955 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg
Cisplatin	75 mg/m^2 BSA = 143.3 mg	143.3 mg	1 x 50 mg + 1 x 100 mg	4	1 x 50 mg + 1 x 100 mg
Osimertinib + pemetrexed + carboplatin					
Osimertinib	80 mg	80 mg	1 x 80 mg	365.0	365 x 80 mg
Pemetrexed	500 mg/m^2 BSA = 955 mg	955 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg
Carboplatin	AUC 5 = 700.7 mg	700.7 mg	1 x 600 mg + 1 x 150 mg	4	4 x 600 mg + 4 x 150 mg
Appropriate comparator therapy					
Afatinib (only for patients with the activating EGFR exon 19 deletion mutation)					
Afatinib	40 mg	40 mg	1 x 40 mg	365.0	365 x 40 mg
Osimertinib as monotherapy					
Osimertinib	80 mg	80 mg	1 x 80 mg	365.0	365 x 80 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with 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
Carboplatin 600 mg	1 CIS	€ 300.84	€ 2.00	€ 13.74	€ 285.10
Carboplatin 150 mg	1 CIS	€ 83.06	€ 2.00	€ 3.40	€ 77.66
Cisplatin 100 mg	1 CIS	€ 76.59	€ 2.00	€ 3.10	€ 71.49
Cisplatin 50 mg	1 CIS	€ 47.71	€ 2.00	€ 1.73	€ 43.98
Pemetrexed 1,000 mg	1 CIS	€ 1,124.81	€ 2.00	€ 52.84	€ 1,069.97
Appropriate comparator therapy					
Osimertinib 80 mg	30 FCT	€ 5,760.15	€ 2.00	€ 325.67	€ 5,432.48
Afatinib 40 mg	28 FCT	€ 2,515.27	€ 2.00	€ 140.35	€ 2,372.92
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 January 2025

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed:							
Osimertinib in combination with pemetrexed and platinum-based chemotherapy							
Osimertinib + pemetrexed + cisplatin							
Pemetrexed (17.4 cycles)							
Dexamethasone 2 x 4 mg[12]	100 x 4 mg TAB	€ 79.54	€ 2.00	€ 5.40	€ 72.14	52.2	€ 75.31
Folic acid 350 – 1,000 µg/day[13]	100 x 400 µg TAB	€ 17.60	€ 0.88	€ 2.12	€ 14.60	365.0	€ 53.29 - € 106.58
Vitamin B12 1,000 µg/day, every 3 cycles[12]	10 x 1,000 µg AMP	€ 8.19	€ 0.41	€ 0.37	€ 7.41	6.8	€ 5.04
Cisplatin (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	4	€ 96.00
Sodium chloride 0.9% Inf. Sol., 3 - 4.4 l/day	10 x 500 ml INF	€ 13.28	€ 0.66	€ 0.96	€ 11.66	4	€ 34.98 -
	10 x 1000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05		€ 40.10
Osimertinib + pemetrexed + carboplatin							
Pemetrexed (17.4 cycles)							
Dexamethasone 2 x 4 mg[12]	100 x 4 mg TAB	€ 79.54	€ 2.00	€ 5.40	€ 72.14	52.2	€ 75.31
Folic acid 350 – 1,000 µg/day[13]	100 x 400 µg TAB	€ 17.60	€ 0.88	€ 2.12	€ 14.60	365.0	€ 53.29 - € 106.58

[12] Fixed reimbursement rate

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

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Vitamin B12 1,000 µg/day, every 3 cycles[12]	10 x 1,000 µg AMP	€ 8.19	€ 0.41	€ 0.37	€ 7.41	6.8	€ 5.04

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:

Adults with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations; first-line treatment

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.
References:
Product information on osimertinib (Tagrisso); product information on Tagrisso 40 mg film-coated tablets Tagrisso 80 mg film-coated tablets; last revised: June 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 23 May 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. Working group 35a newly determined the appropriate comparator therapy at its session on 2 July 2024.

On 23 July 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 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 30 July 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 29 October 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2024. The deadline for submitting statements was 22 November 2024.

The oral hearing was held on 9 December 2024.

By letter dated 10 December 2024, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 7 January 2025.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 28 January 2025, and the proposed draft resolution was approved.

At its session on 6 February 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 May 2023	Determination of the appropriate comparator therapy
Working group Section 35a	2 July 2024	New determination of the appropriate comparator therapy
Working group Section 35a	3 December 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 December 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	17 December 2024 14 January 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	28 January 2025	Concluding discussion of the draft resolution
Plenum	6 February 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 6 February 2025

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

Prof. Hecken