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, EGFR mutations, adjuvant treatment)

of 16 December 2021

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 reimbursable medicinal products with new active ingredients. This includes, in particular, the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company 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 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 forms 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 21 May 2021, 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, p. 7).

On 18 June 2021, 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 of the 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 (non-small cell lung cancer, EGFR mutations, adjuvant treatment).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 October 2021, 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 16 December 2021):

see approved therapeutic indication

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

a) 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 for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy.

Appropriate comparator therapy for Osimertinib as monotherapy:

- Monitoring wait-and-see approach (only for adult patients in stage IB)

or

- Systemic antineoplastic medicinal treatment according to doctor's instructions

b) 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 for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for these.

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:

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, in principle, 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 Federal Joint Committee has already determined the patient-relevant advantage 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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In addition to osimertinib, vinorelbine is an approved medicinal product for the adjuvant treatment of NSCLC.

on 2. For patients in stage IIIA, radiotherapy may be a treatment option in certain sub-stages on an individual basis. However, regular use of radiotherapy in stage IIIA is not recommended.

on 3. For the present therapeutic indication there are no resolutions or guidelines of the G-BA for medicinal applications or non-medicinal treatments.

on 4. The general state of medical knowledge, on which the finding of the G-BA is based, was illustrated by systematic research for guidelines as well as reviews of clinical studies in the present therapeutic indication.

For patients with stage II-IIIA NSCLC after complete resection, current guidelines recommend adjuvant cisplatin-containing chemotherapy, among other regimens. This is also in line with the statements of the scientific-medical societies on the question of appropriate comparator therapy. The recommendations are based on high-quality evidence from randomised studies showing a survival advantage for patients receiving cisplatin-containing chemotherapy.

With regard to stage IB, according to current guidelines, adjuvant chemotherapy should be indicated on an individual basis as the efficacy has not been conclusively clarified. Therefore, in addition to adjuvant chemotherapy at this stage, monitoring wait-and-see approach can also be considered as a comparator therapy.

The guidelines recommend cisplatin, carboplatin, vinorelbine, gemcitabine, docetaxel, paclitaxel, and pemetrexed as components for adjuvant chemotherapy, even for lower stages, but these are not approved in the present treatment setting or are approved only for advanced tumours. Thus, there is a discrepancy between medicinal therapies approved in the indication and those recommended by guidelines or used in care. The evidence suggests that cisplatin should be the primary treatment and that carboplatin should be reserved only for patients who are ineligible for cisplatin. Regarding the concomitant active ingredient, most evidence is available for vinorelbine, but gemcitabine, docetaxel, paclitaxel or pemetrexed are also equally recommended.

The patient population in the present therapeutic indication, especially within stage IIIA, is considered to be very heterogeneous. For patients with stage IIIA mediastinal N2 disease, a treatment strategy including postoperative radiotherapy or neoadjuvant (radio)chemotherapy may be considered on an individual basis according to the recommendations of the current guidelines.

As a result, the G-BA determines both systemic antineoplastic medicinal treatment according to doctor's instructions and the monitoring wait-and-see approach as an equally suitable appropriate comparator therapy for adult patients in stage IB. For adult patients in stages II and IIIA, systemic antineoplastic medicinal treatment according to doctor’s instructions is determined to be appropriate comparator therapy.

For patients with completely resected NSCLC or for patients who are ineligible for adjuvant chemotherapy, there is no marketing authorisation or recommendation for (further) medicinal or non-medicinal adjuvant treatment following adjuvant cisplatin-containing chemotherapy (and in individual cases, subsequent radiotherapy). Since patients in the therapeutic indication are considered disease-free, the recommendations of the current guidelines are limited to after-care with the aim of early diagnosis of recurrences. Therefore, the G-BA has determined the "Monitoring wait-and-see approach" as the appropriate comparator therapy for this patient group.

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

Editorial change of the appropriate comparator therapy:

In the original version, the appropriate comparator therapy for patient group a) was worded as follows:

"For adults in stage IB:
- Monitoring wait-and-see approach

or

- systemic antineoplastic medicinal treatment according to doctor's instructions

For adults in stages II and IIIA:
- systemic antineoplastic medicinal treatment according to doctor's instructions"

In the present version of the appropriate comparator therapy, only a simplified presentation is made in this respect. This does not change the content and does not affect the present assessment.

2.1.3 Extent and probability of the additional benefit

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

a) 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 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 its 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) 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 for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for these.

   Indication of non-quantifiable additional benefit

Justification:

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

Adult patients with stage IB-IIIA NSCLC (UICC classification according to the 7th edition), whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations, were enrolled in the study after complete tumour resection.

Patients had to be in good general condition (World Health Organisation Performance Status [WHO-PS] ≤ 1). Patients with a WHO-PS > 1 were excluded from the study.

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

The patients were on average 62 years old and the percentage of female and male patients was comparable in both study arms. A WHO-PS of 0 was shown by 64% of the patients. At 68%, the greater percentage of patients were in stages II-IIIA, and 32% of patients were in stage IB.

An exon 19 deletion mutation was slightly more common in both study arms at 55% than an L858R mutation in exon 21 at 45%.

Prior adjuvant chemotherapy was received by approximately 75% of patients in stages II-IIIA and 26% in stage IB.

The study population was treated until recurrence, unacceptable toxicity, patient decision, or regular termination of study therapy after 3 years.

The primary endpoint of the study was disease-free survival. Patient-relevant secondary endpoints were mortality, morbidity, health-related quality of life, and adverse events (AEs).

For the benefit assessment, the data cut-off of 17 January 2020 is used (156 disease-free survival events in the sub-population of stage II-IIIA patients). This data cut-off was preferred to the planned primary analysis (247 disease-free survival events in the sub-population of stage II-IIIA patients), following the recommendation of an independent data monitoring committee.

Limitations of the ADAURA study

Uncertainties remain with regard to the transferability of the study results to the German health care context.

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.

Patients, whose disease stage was determined, based on the UICC classification according to the 7th edition, were enrolled in the ADAURA study. Based on the currently applicable UICC classification according to the 8th edition, differences in staging, especially for patients from previous stages IB and IIIA were observed. According to the statements by the clinical experts in the written statement procedure, the change in classification alters the basis for the recommendations for adjuvant therapy, especially for patients from the previous stages IB and IIIA. From the point of view of clinical experts, this results in a complex situation that makes transferability from clinical studies difficult.

The EMA marketing authorisation is based on the results of the ADAURA study. Patients were enrolled in the study based on the UICC classification according to the 7th edition. The present assessment of the results of the ADAURA study is also based on the UICC classification according to the 7th edition, which is why the information in the resolution on tumour stage in the patient groups is based on the UICC classification according to the 7th edition.

Taking into account the currently applicable UICC classification according to the 8th edition, on which current guideline recommendations are based, as well as the above statements by the clinical experts, the G-BA reserves the right to refer to the UICC classification according to the 8th edition in future assessments or to demand the presentation of differences in this respect in the dossier 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.

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

Overall, the number of events is low.

Morbidity

Recurrences

The endpoint is represented by recurrence rate and disease-free survival and includes the events local/regional recurrence, remote 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, remote 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 magnitude of the effect indicates a clinically significant improvement compared to the "Monitoring wait-and-see approach". The present data from the ADAURA study are based on a data cut-off that was preferred to the planned primary analysis (247 disease-free survival events in the sub-population of stage II-IIIA patients), following the recommendation of an independent data monitoring committee. In the view of the G-BA, the median observation period achieved (22.5 months in the intervention arm, 18.7 months in the comparator arm) is not considered sufficiently long to adequately reflect the high-risk period for disease recurrence after primary diagnosis. Thus, clinical experts in the written statement procedure also expressed the opinion that a longer observation period would be necessary in order to be able to assess the extent to which the effect is maintained in the long term and recurrences are prevented.

Health-related quality of life

SF-36v2 – physical and mental component score

Quality of life was assessed using SF-36v2.

In the dossier, the pharmaceutical company presents not only evaluations based on mean differences for the physical and mental component score of the SF-36v2, but also responder analyses over the time to confirmed deterioration. According to the study design, the time to confirmed deterioration corresponds to the predefined operationalisation for the SF 36v2.

Censoring operations due to missing values for baseline or follow-up visits were only performed for a small percentage of patients in both study arms, based on the information provided.

The responder analyses over time to confirmed deterioration are therefore used for the present benefit assessment.

For the physical component score of the Sf-36v2, there is a statistically significant difference to the disadvantage of osimertinib compared to the "Monitoring wait-and-see approach", based on responder analysis over time to confirmed deterioration.

For the mental component score of the SF-36v2, there is no statistically significant difference between the study arms, based on the responder analysis over time to confirmed deterioration.

In the overall assessment of the results, there is a disadvantage of osimertinib compared to the "Monitoring wait-and-see approach" with regard to the health-related quality of life.

Side effects

In its dossier, the pharmaceutical company presents evaluations of the endpoints of side effects from the time of the first dose of study treatment until 28 days after the last dose.

Adverse events (AEs) in total

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

Serious AEs (SAE)

For the endpoint of SAE, no statistically significant difference was detected between the study arms.

Severe AEs (CTCAE grade ≥ 3), therapy discontinuation 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 (AEs)

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

Other specific AEs

For the specific AEs of gastrointestinal disorders (GI) (including diarrhoea, mouth ulcer, stomatitis), gastrointestinal disorders (severe AE), paronychia (AE) and decreased appetite (AE), there was a statistically significant difference to the disadvantage of osimertinib, compared to the "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, the present results do not show any statistically significant difference. Overall, the number of events is low.

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. The magnitude of the effect

indicates a clinically significant improvement compared to the "Monitoring wait-and-see approach". However, the results for this endpoint are not considered sufficient for a reliable quantification of the extent of improvement, especially against the background of the uncertainties described with regard to the ADAURA study and due to the available median observation period (22.5 months in the intervention arm, 18.7 months in the comparator arm).

For the health-related quality of life assessed by means of the SF-36v2, there was a statistically significant difference for the physical component score to the disadvantage of osimertinib, compared to the "Monitoring wait-and-see approach" and no statistically significant difference for the mental component score between the study arms. Thus, in the overall assessment of the results, there is a disadvantage of osimertinib compared to the "Monitoring wait-and-see approach" with regard to the health-related quality of life.

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 discontinuations due to AEs, and in detail for specific AEs, there are negative effects of osimertinib compared to "Monitoring wait-and-see approach".

In the overall assessment, the positive effect on recurrences is offset by relevant disadvantages in terms of health-related quality of life and side effects. The disadvantages in the category of side effects and health-related quality of life are weighted against the background of the present curative therapy claim and do not call into question the overall positive effect on recurrences. The magnitude of the effect on recurrences indicates a clinically significant improvement compared with the "Monitoring wait-and-see approach", but this cannot be quantified with certainty against the background of the uncertainties described.

Therefore, the overall assessment identifies an non-quantifiable additional benefit of osimertinib over the "Monitoring wait-and-see approach" as monotherapy for the adjuvant treatment of adults with stage IB-IIIA non-small cell lung cancer (NSCLC) with exon 19 deletion or exon 21 substitution (L858R) of epidermal growth factor receptor (EGFR) after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it.

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.

The risk of bias at the endpoint level for the results on the endpoints of overall survival and side effects is rated as low.

For the endpoint of recurrences, the overall magnitude of the measured effect suggests with a high degree of certainty an advantage for osimertinib over the monitoring wait-and-see approach.

For the endpoint of health-related quality of life, assessed by means of SF-36v2, the risk of bias is rated as high.

Overall, an indication is derived for the reliability of data of the additional benefit identified.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the present benefit assessment of osimertinib finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a paragraph 1 SGB V.

The present results on overall survival and recurrences are based on the early data cut-off of 17 January 2020 of the ADAURA study (after 156 disease-free survival events in the sub-population of stage II-IIIA patients). This data cut-off for primary evaluation was originally planned after 247 disease-free survival events in the sub-population of stage II-IIIA patients.

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

For this purpose, the G-BA considers a limitation for the resolution until 1 July 2024 to be appropriate.

Conditions of the limitation:

For the new benefit assessment after the deadline, new results from the ADAURA study on overall survival and disease-free survival are to be presented in the dossier. In addition, the results on all other patient-relevant endpoints that are used for the proof of an additional benefit must be presented.

Subgroup analyses for patients with and without prior adjuvant platinum-based chemotherapy will be presented. Where possible, the detailed rationale for the treatment decision against adjuvant platinum-based chemotherapy should 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 concerns, in particular patients in stage IB and stage IIIA according to the 7th edition of the UICC.

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

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of the medicinal product osimertinib recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of osimertinib in comparison with the appropriate comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). If the assessment is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

This does not affect the possibility of carrying out a benefit assessment for the medicinal product osimertinib at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, nos. 2 – 4 VerfO).

2.1.5 Summary of the assessment

The present assessment is the benefit assessment of osimertinib for the treatment 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, after complete tumour resection.

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

a) 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 for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy.

b) 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 for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for these.

Patient group a)

The appropriate comparator therapy was determined as follows:

- Monitoring wait-and-see approach (only for adult patients in stage IB)

or

- Systemic antineoplastic medicinal treatment according to doctor's instructions

The pharmaceutical company did not submit any data to prove the additional benefit. Therefore, an additional benefit is not proven.

Patient group b)

The appropriate comparator therapy was determined as follows:

- Monitoring wait-and-see approach

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, the present results do not show any statistically significant difference.

In the endpoints of "recurrence rate" and "disease-free survival", there is a clinically and statistically significant difference to the advantage of osimertinib.

For the health-related quality of life, the overall results show a disadvantage of osimertinib compared to the "monitoring wait-and-see approach".

For the side effects, there are negative effects of osimertinib compared to the "monitoring wait-and-see approach" with regard to the endpoints of severe AEs (CTCAE grade≥ 3), therapy discontinuations due to AEs, and in detail for the specific AEs.

The disadvantages in the categories of side effects and health-related quality of life do not call into question the overall positive effect on recurrences. However, the extent of the effect on recurrences cannot be quantified with certainty, particularly in view of the relevant limitations of the ADAURA study and the insufficiently long observation period. It is unclear whether the patient population of the ADAURA study can be completely assigned to patient group b) of the present benefit assessment, or whether a relevant percentage of patients, who would have been eligible for adjuvant chemotherapy but did not receive it, were also enrolled in the study.

In the overall assessment, a non-quantifiable additional benefit is identified for osimertinib compared to the "Monitoring wait-and-see approach".

The reliability of data of the additional benefit identified is classified in the "indication" category.

The period of validity of the present resolution is limited to 1 July 2024. For the new benefit assessment after the deadline, among others, current results from the ADAURA study on overall survival and disease-free survival are to be presented in the dossier.

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).

In order to allow consistent consideration of patient numbers, taking into account the resolutions made on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication of non-small cell lung cancer, the incidence of 62,380 patients forecast by the Robert Koch Institute for 2020 is used for the present calculation.

This is lower than the number of 64,922 patients used by the pharmaceutical company.

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

1. The percentage of patients with NSCLC is 80.3 - 82% (50,091 - 51,152).
2. The percentage of patients with NSCLC is subdivided by the pharmaceutical company by stage: IB (5.58%), IIA (2.18%), IIB (7.81%) and IIIA (12.31%). This results in a range of 13,965 - 14,261. Uncertainties exist due to the different staging according to the UICC 7th and 8th editions.

3. The percentage of patients after tumour resection, subdivided by stage: IB (76.09%), IIA (74.25%), IIB (71.12%) and IIIA (50.08%), results in a range of 8,798 - 8,984. After complete tumour resection, subdivided by stage: IB - IIB (98.04%) and IIIA (90.0%), results in a total range of 8,377 - 8,555. After deducting a 30-day lethality, the percentage is 98.35% (8,239 - 8,414). The underlying percentages are subject to uncertainties only with regard to NSCLC and transferability to patients with NSCLC in stages IB to IIIA.
4. The percentage of patients with EGFR mutation ranges from 10.3 to 14.1% (849 - 1,186).
5. The percentage of patients with activating EGFR mutations L858R or exon 19 deletion is 85.6 - 88.7% (727 - 1,052).
6. Taking into account a percentage of patients insured by the SHI of 88.3%, this results in: 642 - 929 patients.

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

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Tagrisso (active ingredient: osimertinib) at the following publicly accessible link (last access: 22 September 2021):
https://www.ema.europa.eu/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 contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 December 2021).

The basis for the cost information is the dosage for treatment with osimertinib recommended in the product information for Tagrisso® (last revised: May 2021).

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration varies from patient to patient and/or is shorter on average.

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	1	365
Appropriate comparator therapy				
a) 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 for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy.				
Monitoring wait-and-see approach (only for adult patients in stage IB)	incalculable			
Systemic antineoplastic medicinal treatment according to doctor's instructions[a]	different from patient to patient			
b) 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 for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for these.				
Monitoring wait-and-see approach	incalculable			

[a] All medicinal therapies that represent a suitable comparator for the present benefit assessment in the context of a therapy according to doctor's instructions are not approved in the present therapeutic indication, which is why no costs are presented for these medicinal products. These are cisplatin, carboplatin, vinorelbine, gemcitabine, docetaxel, paclitaxel and pemetrexed.

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed:					
Osimertinib	80 mg	80 mg	1 x 80 mg	365	365 x 80 mg
Appropriate comparator therapy					
a) 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 for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy.					
Monitoring wait-and-see approach (only for adult patients in stage IB)	incalculable				
Systemic antineoplastic medicinal treatment according to doctor's instructions[a]	different from patient to patient				
b) 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 for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for these.					
Monitoring wait-and-see approach	incalculable				

[a] All medicinal therapies that represent a suitable comparator for the present benefit assessment in the context of therapy according to a doctor's instructions are not approved in the present therapeutic indication, which is why no costs are presented for these medicinal products. These are cisplatin, carboplatin, vinorelbine, gemcitabine, docetaxel, paclitaxel and pemetrexed.

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 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.

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	€ 6,155.92	€ 1.77	€ 348.29	€ 5,805.86
Appropriate comparator therapy					
a) 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 for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy.					
Monitoring wait-and-see approach (only for adult patients in stage IB)	incalculable				
Systemic antineoplastic medicinal treatment according to doctor's instructions[a]	different from patient to patient				
b) 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 for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for these.					
Monitoring wait-and-see approach	incalculable				

[a] All medicinal therapies that represent a suitable comparator for the present benefit assessment in the context of therapy according to a doctor's instructions are not approved in the present therapeutic indication, which is why no costs are presented for these medicinal products. These are cisplatin, carboplatin, vinorelbine, gemcitabine, docetaxel, paclitaxel and pemetrexed.

Abbreviations: FCT = Film-coated tablets

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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.

Because there are no 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, no costs for

additionally required SHI services had to be taken into account.

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.

On 18 June 2021 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 2 VerfO.

By letter dated 22 June 2021 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 September 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 01 October 2021. The deadline for submitting written statements was 22 October 2021.

The oral hearing was held on 8 November 2021.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 December 2021, and the proposed resolution was approved.

At its session on 16 December 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	6 October 2020	Determination of the appropriate comparator therapy
Working group Section 35a	3 November 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	8 November 2021	Conduct of the oral hearing
Working group Section 35a	17 November 2021 1 December 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	7 December 2021	Concluding discussion of the draft resolution
Plenum	16 December 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 December 2021

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

Prof. Hecken