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 Lorlatinib (new therapeutic indication: non-small cell lung cancer, ALK+, first-line)

of 1 September 2022

Contents

1. Legal basis 2

2. Key points of the resolution 2

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy 3

2.1.1 Approved therapeutic indication of Lorlatinib (Lorviqua) in accordance with the product information 3

2.1.2 Appropriate comparator therapy 3

2.1.3 Extent and probability of the additional benefit 6

2.1.4 Summary of the assessment 9

2.2 Number of patients or demarcation of patient groups eligible for treatment 10

2.3 Requirements for a quality-assured application 10

2.4 Treatment costs 10

3. Bureaucratic costs calculation 12

4. Process sequence 13

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 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 lorlatinib (Lorviqua) was listed for the first time on 1 June 2019 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 27 January 2022, Lorviqua 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 24 February 2022, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval of 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 lorlatinib with the new therapeutic indication ("[...] is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor").

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 June 2022, 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 lorlatinib 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 lorlatinib.

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 Lorlatinib (Lorviqua) in accordance with the product information

Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

Therapeutic indication of the resolution (resolution of 01.09.2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor

Appropriate comparator therapy for lorlatinib as monotherapy:

– Alectinib

or

– Brigatinib

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

[1] General Methods, version 6.1 of 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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.

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

on 1. In the present therapeutic indication, the following active ingredients are generally available according to the authorisation status of the medicinal products: cytotoxic agents such as cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine and vinorelbine; protein kinase inhibitors such as alectinib, brigatinib, ceritinib, crizotinib, nintedanib, entrectinib and erlotinib as well as monoclonal antibodies such as atezolizumab, bevacizumab, nivolumab, durvalumab and ramucirumab.

Medicinal products with explicit marketing authorisation for the treatment of NSCLC with activating EGFR or BRAF V600 mutations and for the treatment of NSCLC with exclusively squamous histology were not included.

on 2. For the present therapeutic indication it is assumed that the patients have no indication for definitive local therapy. Therefore, a non-medicinal treatment cannot be considered in the present therapeutic indication.

on 3. For ALK-positive advanced NSCLC in first-line therapy, resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available for the active ingredients alectinib, brigatinib, ceritinib and crizotinib.

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 above, 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 health care.

Since ALK-positive non-small cell lung cancers are usually EGFR-negative and have a non-squamous histology, EGFR-specific therapy options as well as therapies explicitly indicated for squamous histology were not considered.

National and international guidelines for the treatment of patients with ALK-positive, non-small-cell lung cancer who have not yet received targeted therapy highly recommend therapy with ALK inhibitors. In this regard, medicinal products with the active ingredients alectinib, brigatinib, crizotinib and ceritinib are currently available in Germany.

The information in the international guidelines differs with regard to a therapy recommendation for a specific ALK inhibitor. The German S3 guidelines updated in 2018 generally recommend an ALK inhibitor in the first-line therapy for NSCLC patients with ALK translocations. In second-line therapy, the ALK inhibitor crizotinib is specifically recommended for ALK-positive NSCLC patients after standard platinum-based chemotherapy who did not receive an ALK inhibitor in the first line. The 2019 National Institute for Health and Care Excellence (NICE) guidelines list the ALK inhibitors ceritinib, alectinib and crizotinib as recommended ALK inhibitors in first-line therapy, which is also supported by the 2020 Italian Association of Medical Oncology (AIOM) guidelines. Here, however, first-line therapy with alectinib is given priority over first-line therapy with crizotinib or ceritinib. The 2017 National Cancer Control Programme Guideline Development Group (GDG) recommendations include the first-line ALK inhibitor crizotinib for patients with ALK-positive NSCLC. The American Society Of Clinical Oncology (ASCO) guidelines last updated in 2021 recommend alectinib and brigatinib as ALK inhibitors of choice in the first-line treatment of patients with ALK-positive NSCLC. Against the background of the recent marketing authorisation and introduction of several new treatment options into care, the recommendation of the ASCO guideline is considered particularly relevant due to its up-to-dateness.

The scientific-medical societies state that the standard of care for patients with ALK-positive, advanced NSCLC who have not previously been treated with an ALK inhibitor is therapy with alectinib or brigatinib. This assessment is based on survival data in first-line therapy with alectinib or brigatinib. First-line therapy with alectinib or brigatinib is also recommended in the 2021 ASCO guideline with a "strong" level of recommendation.

By resolution of 15 October 2020, the G-BA identified in the benefit assessment of brigatinib a hint for its considerable additional benefit over crizotinib for adult patients with ALK-positive advanced NSCLC who have not previously been treated with an ALK inhibitor and who have brain metastases. For patients who do not have brain metastases, a hint for a minor additional benefit over crizotinib was identified.

In the benefit assessment of alectinib for the first-line treatment of ALK-positive advanced NSCLC, a hint for a non-quantifiable additional benefit compared to crizotinib was identified (resolution of 21 June 2018).

In contrast, no additional benefit was identified for ceritinib in the benefit assessment compared to the appropriate comparator therapy crizotinib. No valid data were available for an assessment of additional benefit (resolution of 1 February 2018).

For crizotinib, a hint for a considerable additional benefit in the first-line treatment of patients with ALK-positive tumours was identified in a benefit assessment compared to platinum-based chemotherapy (resolution of 16 June 2016).

In the overall assessment of the available evidence, ALK-targeted therapy with alectinib or brigatinib is therefore determined to be the appropriate comparator therapy in the present therapeutic indication. Both treatment options are equally appropriate comparator therapies.

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

2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive, advanced non-small cell lung cancer (NSCLC) who have not previously been treated with an ALK inhibitor.

Justification:

In the absence of direct comparator studies of lorlatinib versus the appropriate comparator therapy, the pharmaceutical company uses an adjusted indirect comparison according to the method of Bucher et al. for the proof of an additional benefit. For the indirect comparison via the bridge comparator crizotinib, the pharmaceutical company includes the CROWN study on the lorlatinib side and the ALTLA-1L study on the brigatinib side.

CROWN study

The CROWN study is an open-label randomised controlled trial comparing lorlatinib with crizotinib.

The ongoing, multicentre, international study, which started in April 2017, enrolled adults with ALK-positive, untreated locally advanced or metastatic NSCLC. Patients should have a general condition, with an Eastern Cooperative Oncology Group Performance Status of 0 to 2. Patients with asymptomatic brain metastases were allowed to participate in the study. Only systemic prior therapies for the treatment of earlier stages were allowed as prior therapies, provided they had been completed 12 months prior to the time of enrolment in the study. Systemic prior therapies for the treatment of advanced or metastatic disease were not allowed.

The 296 patients enrolled in the study were randomised 1:1 into the lorlatinib arm (N=149) and crizotinib arm (N=147), stratified by presence of brain metastases at the start of the study (yes / no) and ancestry (Asian / non-Asian).

In both arms, treatment could be continued beyond disease progression if the patient continued to benefit from treatment at the discretion of the principal investigator. The product information of crizotinib has no information on whether treatment beyond disease progression is possible. According to the product information of lorlatinib, treatment should only be given until disease progression or unacceptable toxicity. No information is available on how many patients were treated with the study medication beyond disease progression.

In addition to the primary endpoint of progression-free survival (PFS), endpoints of the categories mortality, morbidity, health-related quality of life and adverse events were collected.

The study was conducted in 104 study sites in 23 countries in Europe, North and South America, and Asia-Pacific.

The pharmaceutical company presents evaluations for the 1st interim analysis (data cut-off from 20.03.2020).

ALTA-1L study

The completed ALTA-1L study is an open-label randomised controlled trial comparing brigatinib to crizotinib.

The multicentre, international study enrolled adults with ALK-positive, locally advanced, recurrent or metastatic NSCLC. Patients should have a general condition, with an Eastern Cooperative Oncology Group Performance Status of 0 to 2. Patients with asymptomatic brain metastases were allowed to participate in the study. A maximum of one systemic prior therapy for the treatment of advanced or metastatic disease was allowed as prior therapy. This excluded any prior therapy with a tyrosine kinase inhibitor. At the time of enrolment in the study, about 27% of the patients in the advanced or metastatic stage had received chemotherapy.

The 275 patients enrolled were randomised 1:1 into the brigatinib arm (N=137) and crizotinib arm (N=138), stratified by the presence of brain metastases at the start of the study (yes / no) and prior chemotherapy for the treatment of advanced or metastatic disease (yes / no).

Patients were treated until disease progression, initiation of new anti-neoplastic therapy, withdrawal of consent, unacceptable toxicity or end of the study. In the brigatinib arm, treatment could be continued beyond disease progression if, at the principal investigator's discretion, there was still clinical benefit. In the crizotinib arm, patients could receive brigatinib as subsequent therapy compliant with marketing authorisation after disease progression.

In addition to the primary endpoint PFS, endpoints of the categories mortality, morbidity, health-related quality of life and adverse events were collected.

The study was conducted in 92 study sites in 19 countries in Europe, North and South America, and Asia-Pacific.

The study commenced in May 2016 and was completed in January 2021.

The pharmaceutical company presents evaluations for the 2nd data cut-off for all endpoints and uses them for the adjusted indirect comparison. In addition, it presents evaluations for the 3rd data cut-off the for the endpoints of overall survival and PFS. The pharmaceutical company chooses the 2nd data cut-off for the adjusted indirect comparison and justifies this with a significantly longer follow-up period and the associated considerably higher significance.

For indirect comparison

A central prerequisite for an adjusted indirect comparison is the assumption of sufficient similarity between the studies.

In terms of the study design, the CROWN and ALTA-1L studies are similar, except with regard to the use of the bridge comparator crizotinib.

With regard to the similarity of the patient populations of the CROWN and ALTA-1L studies, the demographic and clinical characteristics are sufficiently comparable. However, differences exist in the allowed pretreatment between the two studies. For example, about 27% of the

patients in the ALTA-1L study had already received chemotherapy for treatment in the advanced or metastatic stage, which, in contrast, was not allowed in the CROWN study.

The patients in both studies received mainly ALK inhibitors as subsequent therapy. In the ALTA-1L study, more patients in the crizotinib arm were subsequently treated with brigatinib (53.3% vs CROWN 11.6%), as they were able to switch to brigatinib in the event of disease progression. Treatment switching was not allowed in the CROWN study. Another subsequent therapy in both studies was alectinib.

In summary, there are differences between the CROWN and ALTA-1L studies in the planned duration of follow-up and pretreatment of patients. Sufficient similarity for conducting an adjusted indirect comparison via the bridge comparator crizotinib is not fundamentally questioned despite the differences.

Extent and probability of the additional benefit

Mortality

In the indirect comparison, there was no statistically significant difference between lorlatinib and brigatinib for the endpoint of overall survival.

Morbidity, quality of life, side effects

The endpoints on morbidity, health-related quality of life and side effects were collected in the CROWN and ALTA-1L studies up to 28 and 30 days after the last administration of the study medication.

In the ALTA-1L study, patients in the crizotinib arm were able to switch to treatment with brigatinib in the intervention arm in the event of disease progression. After the switch, they continued to be followed for up to 30 days after the last administration of brigatinib. As 61 (44.2%) patients in the crizotinib arm had switched to treatment with brigatinib at the time of the 2nd data cut-off, a relevant percentage of patients continued to be observed under follow-up treatment with brigatinib and thus, beyond crizotinib treatment.

In the CROWN study, a change of therapy was not allowed. With the therapy discontinuation of crizotinib, the observation of the endpoints on morbidity, health-related quality of life and side effects for patients in the crizotinib arm ended.

Due to this difference in the operationalisation of the follow-up, the patients in the CROWN study were only observed during the (first) therapy with crizotinib and in the ALTA-1L study during the (first) therapy with crizotinib as well as during the subsequent therapy line with brigatinib.

As a result, there is insufficient similarity in the operationalisation of the endpoints on morbidity, health-related quality of life and side effects. Consequently, the results cannot be interpreted and the available data are not suitable for an adjusted indirect comparison.

Furthermore, there is a high risk of bias in the endpoints of morbidity, health-related quality of life and side effects. Thus, the requirements for certainty of results for the performance of an adjusted indirect comparison for these endpoints are not met. The high risk of bias is justified by the selective follow-up in the crizotinib arm in the ALTA-1L study described above and the lack of blinding in the subjective collection of the endpoints of morbidity, health-related quality of life and discontinuation due to AEs in both studies.

In summary, no usable data for an adjusted indirect comparison are available for the endpoints of morbidity, health-related quality of life and side effects.

Overall assessment / conclusion

For the assessment of the additional benefit of lorlatinib, an adjusted indirect comparison was presented for the endpoints of mortality, morbidity, health-related quality of life and side effects.

For the indirect comparison via the bridge comparator crizotinib, the pharmaceutical company includes the CROWN study on the lorlatinib side and the ALTLA-1L study on the brigatinib side.

Sufficient similarity to conduct an adjusted indirect comparison using the bridge comparator crizotinib is not fundamentally questioned despite the differences between the CROWN and ALTA-1L studies in the planned duration of follow-up and pretreatment of patients.

In the indirect comparison, there was no statistically significant difference between lorlatinib and brigatinib for the endpoint of overall survival. An additional benefit for overall survival is therefore not proven.

With regard to the endpoints of morbidity, health-related quality of life and side effects, there is no sufficient similarity in the operationalisation of these endpoints. Due to the difference in the operationalisation of the follow-up, the observation in the CROWN study only includes the (first) therapy with crizotinib, whereas the ALTA-1L study includes both the (first) therapy with crizotinib and the subsequent therapy line with brigatinib. The available data are therefore not suitable for an adjusted indirect comparison. An additional benefit for the endpoints of morbidity, health-related quality of life and side effects is thus not proven in each case.

Overall, an additional benefit of lorlatinib compared to brigatinib is therefore 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 lorlatinib.

Lorviqua was approved under conditional authorisation.

The therapeutic indication assessed here is as follows: "as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) who have not been previously treated with an ALK inhibitor".

Treatment with alectinib or brigatinib was determined as the appropriate comparator therapy.

The pharmaceutical company presents an adjusted indirect comparison via the bridge comparator crizotinib with the CROWN study on the lorlatinib side and the ALTLA-1L study on the brigatinib side.

In the indirect comparison, there was no statistically significant difference for the endpoint of overall survival. An additional benefit is not proven.

With regard to the endpoints of morbidity, health-related quality of life and side effects, there is no sufficient similarity in the operationalisation of these endpoints. Due to the difference in the operationalisation of the follow-up, the observation in the CROWN study only includes the (first) therapy with crizotinib, whereas the ALTA-1L study includes both the (first) therapy with crizotinib and the subsequent therapy line with brigatinib. The available data are therefore not suitable for an adjusted indirect comparison. An additional benefit is therefore not proven in each case.

Overall, an additional benefit of lorlatinib compared to brigatinib 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 projected incidence for 2021 (60,333 patients) is used as the basis for the calculations.

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% (44,405 to 50,439 patients).

2. Of these, 51.8 to 61.6% of patients are in stage IIIB and IV at initial diagnosis (23,002 to 31,070 patients). The number of patients in stage I and IIA who have progressed to stage IV in 2021 is 5,866 to 8,364 patients. The total number of patients in tumour stage IIIB and IV is 28,868 to 39,434.

3. First-line therapy is given in 76.9 to 96.1% of cases (22,200 - 37,896 patients).

4. The percentage of patients with ALK mutation is 2 to 3.9% (444 to 1,478 patients).

5. Taking into account SHI-insured percentage of patients of 88.3%, this results in 392 to 1,305 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 Lorviqua (active ingredient: lorlatinib) at the following publicly accessible link (last access: 6 May 2022):

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

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

ALK evidence

Evidence of ALK-positive NSCLC is required for patient selection for treatment with lorlatinib, as a proven benefit is identified only for these patients. Testing for ALK-positive NSCLC should be carried out by laboratories that have proven expertise in the technology used. Improper test performance can lead to unreliable test results.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2022).

According to the product information of brigatinib (last revised: 01/2022), the dosage in the 1st week is 1 x daily 90 mg, from the 2nd week onwards 1 x daily 180 mg.

Alectinib is administered in accordance with the product information (last revised: 06/ 2022) with a maximum daily dose of 1,200 mg - divided into 2 doses of 4 capsules of 150 mg each.

Treatment period:

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 is patient-individual 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.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Lorlatinib	1 x daily	365	1	365
Appropriate comparator therapy				
Alectinib or brigatinib				
Alectinib	2 x daily	365	1	365
Brigatinib	1 x daily	365	1	365

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 comorbidities) 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					
Lorlatinib	100 mg	100 mg	1 x 100 mg	365	365 x 100 mg
Appropriate comparator therapy					
Alectinib or brigatinib					
Alectinib	600 mg	1,200 mg	8 x 150 mg	365	2,920 x 150 mg
Brigatinib	Day 1 - 7: 90 mg From day 8: 180 mg	90 – 180 mg	1 x 90 mg – 1 x 180 mg	365	7 x 90 mg + 358 x 180 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

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					
Lorlatinib 100 mg	30 FCT	€ 5,409.56	€ 1.77	€ 305.65	€ 5,102.14
Appropriate comparator therapy					
Alectinib 150 mg	224 HC	€ 5,976.87	€ 1.77	€ 338.05	€ 5,637.05
Brigatinib starter pack 90 mg + 180 mg	28 FCT	€ 5,911.92	€ 1.77	€ 334.34	€ 5,575.81
Brigatinib 180 mg	28 FCT	€ 5,911.92	€ 1.77	€ 334.34	€ 5,575.81
Abbreviations: FCT = film-coated tablets; HC = hard capsules					

LAUER-TAXE® last revised: 15 August 2022

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 22 June 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 24 February 2022, the pharmaceutical company submitted a dossier for the benefit assessment of lorlatinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 25 February 2022 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 lorlatinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 May 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 June 2022. The deadline for submitting written statements was 22 June 2022.

The oral hearing was held on 11 July 2022.

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 23 August 2022, and the proposed resolution was approved.

At its session on 1 September 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	22 June 2022	Determination of the appropriate comparator therapy
Working group Section 35a	5 July 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 July 2022	Conduct of the oral hearing,
Working group Section 35a	19 July 2022 2 August 2022 16 August 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	23 August 2022	Concluding discussion of the draft resolution
Plenum	1 September 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 September 2022

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

Prof. Hecken