Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Lorlatinib

of 22 November 2019

Contents

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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 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 shall pass a resolution 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 relevant date for the first placing on the market of the active ingredient lorlatinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 June 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 29 May 2019.

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 2 September 2019, 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 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. 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

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IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of lorlatinib.

In light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at 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) whose disease has progressed after:

- alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy;

or

- crizotinib and at least one other ALK-TKI.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for lorlatinib as monotherapy was determined as follows:

a) Patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy or crizotinib and at least one other ALK-TKI; for whom further antineoplastic systemic therapy is possible:

A patient-individual therapy taking into account the ALK inhibitors alectinib and ceritinib as well as combination or mono-chemotherapies

b) Patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy or crizotinib and at least one other ALK-TKI; for whom further antineoplastic systemic therapy is not possible:

Best-supportive-care

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 according to 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.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

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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 Federal Joint Committee 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. The protein kinase inhibitors alectinib, brigatinib, ceritinib, and crizotinib as well as the cytostatic drugs cisplatin, docetaxel, gemcitabin, ifosfamid, mitomycin, paclitaxel, nab-paclitaxel, permetrexed, vindesin, and vinorelbin are authorised for use in the present therapeutic indication, whereby in the present therapeutic indication, carboplatin may also be prescribed for off-label use.

On 2. A non-medicinal therapy is not considered.

On 3. The following resolutions and guidelines of the G-BA have been issued for medicinal therapies in the present therapeutic indication:

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

Alectinib: Resolution of 19 October 2017

Brigatinib: Resolution of 4 July 2019

Ceritinib: Resolution of 1 February 2018

Crizotinib: Resolution of 15 December 2016

Guidelines:

Carboplatin: Resolution of 18 October 2018 on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex VI – Off-label use Part A Item III: Carboplatin for advanced non-small cell lung carcinoma (NSCLC) – combination therapy

On 4. The guidelines and clinical trial reviews identified as part of the systematic research on the present therapeutic indication show an extremely limited body of evidence for the treatment of patients whose disease has progressed under second-generation ALK-TKI therapy or crizotinib and at least one other ALK inhibitor. In the guidelines of the German Cancer Society (DKG), German Cancer Aid, and Association of Scientific Medical Societies (AWMF), it is stated that ALK-positive patients after failure of approved ALK inhibitors should be treated with further ALK inhibitors in clinical studies or within the scope of compassionate use programmes. If this is not possible, they are treated with chemotherapy according to wild-type patients, although the evidence level of this recommendation is low. The National Comprehensive Cancer Network (NCCN) Guideline recommends local therapy, continuation of existing therapy, or chemotherapy after the progress of a second generation ALK-TKI depending on the type of progress (local/systemic and symptomatic/asymptomatic).

In view of the limited information available, a clinical expert from the Medicines Commission of the German Medical Profession (AkdÄ) was additionally consulted and asked about the current reality of care (last updated: August 2018). Accordingly to the current reality of care, patients with ALK-positive NSCLC after failure of a second-generation ALK-TKI are partly also treated with another second-generation ALK-TKI, if necessary, depending on a previously investigated resistance situation. Crizotinib is

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considered to be significantly less effective than second-generation ALK-TKI, which is why it is not considered in the present therapy situation. Furthermore, the clinical expert of AkdÄ explained that analogously to the guideline recommendations, patients are treated with chemotherapy analogous to the wild-type population in the reality of care unless inclusion in clinical studies or compassionate use programmes is possible. Here, platinum-based combination chemotherapy should be used. Only if this is not possible (e.g. contraindications, reduced general condition) would platinum-free monochemotherapy also be indicated. A further part of the patients are also treated exclusively in a symptom-oriented palliative manner (i.e. an active tumour-specific therapy is no longer carried out).

In addition, the written statements of the medical societies discussed the new options for therapy with the ALK inhibitor brigatinib as well as immunochemotherapy as therapy options in the present therapeutic indication. From the point of view of the G-BA, the therapeutic significance of these still relatively new therapies in the reality of care cannot yet be conclusively assessed, which is why they were not taken into account in the present determination of the appropriate comparator therapy.

Based on the national S3 guideline, the statements of the medical societies in the context of the present benefit assessment procedure, and taking into account the written statements of the clinical expert, the ALK inhibitors alectinib and ceritinib as well as a combination or monochemotherapy represent a suitable antineoplastic comparator therapy in the present therapeutic indication. However, a single comparator comparison would not fully reflect the health care reality.

The present therapeutic indication also includes patients for whom treatment with the therapies recommended so far and used in practice is not indicated because of the risk profile, the pharmacological properties of the active ingredient (e.g. overcoming the blood-brain barrier), or the existence of resistances. This also applies to patients for whom combination or monochemotherapy or treatment with the ALK-TKI alectinib or ceritinib is out of the question because of a reduced general condition. According to the current state of medical knowledge, there is no specific standard therapy for this group of patients. The patient-individual treatment is intended to alleviate symptoms and improve quality of life without prolonging survival as a primary therapeutic goal (best supportive care).

The present determination of the appropriate comparator therapy was also endorsed in the context of the written statements of the medical societies in the present benefit assessment procedure.

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

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2.1.3 Extent and probability of the additional benefit

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

a) Patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy or crizotinib and at least one other ALK-TKI; for whom further antineoplastic systemic therapy is possible:

An additional benefit is not proven

b) Patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy or crizotinib and at least one other ALK-TKI; for whom further antineoplastic systemic therapy is not possible:

An additional benefit is not proven.

Justification:

To demonstrate the additional benefit, the pharmaceutical company used data from the international, multi-centre, open Phase I/II pivotal study B7461001. This is a single-arm study evaluating the efficacy and safety of lorlatinib in adult patients with advanced ALK-positive or ROS1-positive NSCLC. In the study, six patient cohorts were distinguished depending on the driver mutation and its pre-treatment. For the benefit assessment, the pharmaceutical company presents three cohorts in the dossier.

In the dossier, the pharmaceutical company shall not present any results from directly comparative studies or studies suitable for an adjusted indirect comparison. Based on this data basis, it is not possible to derive an additional benefit for the two patient populations.

The additional benefit for loratinib in the treatment of patients with ALK-positive advanced NSCLC whose disease has progressed after alectinib or ceritinib as the first ALK-TKI therapy or crizotinib and at least one other ALK-TKI; for whom further antineoplastic systemic therapy is possible or for whom further antineoplastic systemic therapy is not possible is thus not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Lorviqua with the active ingredient lorlatinib.

Lorlatinib received a conditional market authorisation.

The therapeutic indication assessed here is as follows: Lorviqua as monotherapy is indicated for the treatment of adult patients with ALK-positive, advanced NSCLC whose disease has progressed after: alectinib or ceritinib as the first ALK-TKI therapy; or crizotinib and at least one other ALK-TKI.

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

a) Patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy or crizotinib and at least one other ALK-TKI; for whom further antineoplastic systemic therapy is possible

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and

b) Patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy or crizotinib and at least one other ALK-TKI; for whom further antineoplastic systemic therapy is not possible

The appropriate comparator therapy was determined by the G-BA as follows:

Patient group a)

A patient-individual therapy taking into account the ALK inhibitors alectinib and ceritinib as well as combination or mono-chemotherapies

Patient group b)

Best-supportive-care

The pharmaceutical company uses data from the single-arm B7461001 pivotal study to prove the additional benefit. For the assessment of the additional benefit of loratinib, the dossier of the pharmaceutical company does not include any direct comparative studies or studies for an adjusted indirect comparison with the appropriate comparator therapy.

The additional benefit cannot be assessed based on the evidence provided. Thus, an additional benefit is not proven.

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

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

The calculation of the pharmaceutical company in the dossier on the number of patients in the sub-populations is subject to uncertainties because these are mainly based on therapies with cytostatic drugs before ALK-TKIs were introduced into the care system.

Overall, the sources and derivation in this dossier are not assessed to be better than the sources and derivation of patient numbers in the resolution on alectinib. For the purposes of this resolution, the information on patients provided in the resolution on the benefit assessment of alectinib of 19 October 2017, which is based on the following derivation, is therefore used:

1. The proportion of lung cancer patients with NSCLC is approx. 80.3–82%.
   (64,802–112,265 patients)
2. Of these, 61.6–66.1% are stage IIIB/IV patients.
   (39,918 – 74,207 patients)
3. The proportion of patients with ALK-positive tumours is 2–7%.
   (798–5,194 patients)
4. The proportion of patients with second-line crizotinib therapy is 29%.
   (231–1,506 patients)
5. 86.8% of the German population is covered by SHI.
   (201–1,307 patients)
6. For 80.9% of patients, further systemic therapy is possible

   (approx. 160–1,060 patients)

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7. For 19.1% of patients, no further systemic therapy is possible

(approx. 40–250 patients)

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: 8 October 2019):
https://www.ema.europa.eu/documents/product-information/lorviqua-epar-product-information_de.pdf

Treatment with lorlatinib should be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and pneumology, specialists in pulmonary medicine, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with non-small cell lung carcinoma.

This medicinal product was authorised under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

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 October 2019).

The cost estimate is based on the dosage recommended in the product information for Lorviqua® (last revised: August 2019) for treatment with lorlatinib.

According to the product information (Cisplatin Accord (last updated: April/2015)), the dosage of cisplatin varies depending on the combination partner. According to the product information of the combination partners, the single dose of cisplatin in combination with vinorelbine or gemcitabine is 75–100 mg/m^2, in combination with docetaxel or pemetrexed, 75 mg/m^2, and in combination with paclitaxel, 80 mg/m^2.

Carboplatin is based on a cycle duration of 3 weeks. For the use of carboplatin in the off-label indication “combination therapy for advanced NSCLC”, the dosage specified in Annex VI of the Pharmaceuticals Directive is up to 500 mg/m² or AUC 6.0 (Area Under the Curve). For the use of carboplatin in combination with nab-paclitaxel, the dosage of AUC 6.0 is also used according to the product information.

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 is patient-individual and/or is shorter on average.

Treatment duration:

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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 × daily	365	1	365
Appropriate comparator therapy				
a) Patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy or crizotinib and at least one other ALK-TKI; for whom further antineoplastic systemic therapy is possible:				
a patient-individual therapy taking into account the ALK inhibitors alectinib and ceritinib as well as combination or mono-chemotherapies				
Alectinib	2 × daily	365	1	365
Ceritinib	1 × daily	365	1	365
Cisplatin or carboplatin in combination with a third generation cytostatic agent				
Cisplatin	1 × per 21-day cycle	17 cycles	1	17
Carboplatin	1 × per 21-day cycle	17 cycles	1	17
+ vinorelbine	2 × per 21-day cycle	17 cycles	2	34
+ gemcitabine	2 × per 21-day cycle	17 cycles	2	34
+ docetaxel	1 × per 21-day cycle	17 cycles	1	17
+ paclitaxel	1 × per 21-day cycle	17 cycles	1	17
+ pemetrexed	1 × per 21-day cycle	17 cycles	1	17
Carboplatin in combination with nab-paclitaxel				
Carboplatin	1 × per 21-day cycle	17 cycles	1	17
+ nab-paclitaxel	3 × per 21-day cycle	17 cycles	3	51
Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment)				

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Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Gemcitabine	3 × per 28-day cycle	13 cycles	3	39
Vinorelbine	1 × per 7-day cycle	52 cycles	1	52
b) Patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy or crizotinib and at least one other ALK-TKI; for whom further antineoplastic systemic therapy is not possible:				
Best-supportive-care	different for each individual patient			

Usage and consumption:

The body surface calculated using the Du Bois formula using an average body weight of 77.0 kg and an average body height of 1.72 m (according to the 2017 microcensus) = 1.90 m² (calculated to 2 decimal places). Differences between women and men were not to be considered because of the therapeutic indication.[2]

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption by potency
Medicinal product to be assessed					
Lorlatinib	100 mg	100 mg	1 × 100 mg	365	365 × 100 mg
Appropriate comparator therapy					
a) Patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy or crizotinib and at least one other ALK-TKI; for whom further antineoplastic systemic therapy is possible:					
a patient-individual therapy taking into account the ALK inhibitors alectinib and ceritinib as well as combination or mono-chemotherapies					
Alectinib	600 mg	1,200 mg	8 × 150 mg	365	2920 × 150 mg
Ceritinib	450 mg	450 mg	3 × 150 mg	365	1,095 × 150 mg

[2] Statistisches Bundesamt [German Federal Office for statistics]. Microcensus: Fragen zur Gesundheit; Körpermaße der Bevölkerung 2017 [Questions about health; body measurements of the 2017 population] [online]. 2 August 2018 [Accessed: 26 September 2019]. URL: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

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Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption by potency
Cisplatin or carboplatin in combination with a third generation cytostatic agent					
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 × 100 mg + 1 × 50 mg	17	17 × 100 mg + 17 × 50 mg
	80 mg/m² = 152 mg	152 mg	1 × 100 mg + 1 × 50 mg + 1 × 10 mg	17	17 × 100 mg + 17 × 50 mg + 17 × 10 mg
	100 mg/m² = 190 mg	190 mg	2 × 100 mg	17	34 × 100 mg
Carboplatin	500 mg/m² = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	17	17 × 600 mg + 17 × 450 mg
+ vinorelbine	25 mg/m² = 47.5 mg	47.5 mg	1 × 50 mg	34	34 × 50 mg
	30 mg/m² = 57 mg	57 mg	1 × 50 mg + 1 × 10 mg	34	34 × 50 mg + 34 × 10 mg
+ gemcitabine	1,250 mg/m² = 2,375 mg	2,375 mg	1 × 2,000 mg + 2 × 200 mg	34	34 × 2,000 mg + 68 × 200 mg
+ docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 × 160 mg	17	17 × 160 mg
+ paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 × 100 mg + 1 × 150 mg	17	34 × 100 mg + 17 × 150 mg
+ pemetrexed	500 mg/m² = 950 mg	950 mg	2 × 500 mg	17	34 × 500 mg
Carboplatin in combination with nab-paclitaxel					
Carboplatin	500 mg/m² = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	17	17 × 600 mg + 17 × 450 mg
+ nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 × 100 mg	51	102 × 100 mg
Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment)					
Gemcitabine	1000 mg/m² = 1900 mg	1900 mg	1 × 2,000 mg	39	39 × 2,000 mg

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Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption by potency
Vinorelbine	25 mg/m² = 47.5 mg	47.5 mg	1 × 50 mg	52	52 × 50 mg
	30 mg/m² = 57 mg	57 mg	1 × 50 mg + 1 × 10 mg	52	52 × 50 mg + 52 × 10 mg
b) Patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy or crizotinib and at least one other ALK-TKI; for whom further antineoplastic systemic therapy is not possible:					
Best-supportive-care	different for each individual patient				

Costs:

Costs of the medicinal product:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail 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.

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Lorlatinib	30 FCT	€ 7,815.40	€ 1.77	€ 443.07	€ 7,370.56
Appropriate comparator therapy					
Alectinib	224 HC	€ 5,976.57	€ 1.77	€ 338.05	€ 5,636.75
Carboplatin 600 mg	1 IFC	€ 300.51	€ 1.77	€ 13.74	€ 285.00
Carboplatin 450 mg	1 IFC	€ 227.91	€ 1.77	€ 10.29	€ 215.85
Ceritinib	90 HC	€ 5,504.20	€ 1.77	€ 0.00	€ 5,502.43
Cisplatin 100 mg	1 IFC	€ 76.26	€ 1.77	€ 3.10	€ 71.39
Cisplatin 50 mg	1 IFC	€ 47.37	€ 1.77	€ 1.73	€ 43.87
Cisplatin 10 mg	1 IFC	€ 17.20	€ 1.77	€ 0.30	€ 15.13
Docetaxel 160 mg	1 IFC	€ 1,397.30	€ 1.77	€ 175.44	€ 1,220.09
Gemcitabine 2,000 mg	1 IFC	€ 193.90	€ 1.77	€ 8.68	€ 183.45

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Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Gemcitabine 200 mg	1 IFC	€ 28.51	€ 1.77	€ 0.83	€ 25.91
nab-paclitaxel	1 PIS	€ 429.03	€ 1.77	€ 23.15	€ 404.11
Paclitaxel 100 mg	1 IFC	€ 360.21	€ 1.77	€ 16.57	€ 341.87
Paclitaxel 150 mg	1 IFC	€ 535.25	€ 1.77	€ 24.88	€ 508.60
Pemetrexed	1 PIS	€ 2,533.24	€ 1.77	€ 558.64	€ 1,972.83
Vinorelbine 50 mg	10 IFC	€ 1,424.23	€ 1.77	€ 67.07	€ 1,355.39
Vinorelbine 10 mg	10 IFC	€ 293.68	€ 1.77	€ 13.42	€ 278.49
Abbreviations: FCT = film-coated tablets; IFC = concentrate for the preparation of an infusion solution; HC = hard capsules; PISC = powder for the preparation of an infusion solution concentrate; PIS = powder for the preparation of an infusion suspension					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 October 2019

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 standard expenditure in the course of the treatment are not shown.

Non-prescription medicinal products are subject to the regulations on the prescribability of non-prescription medicinal products (OTC medicinal products) at the expense of statutory health insurance. These medicinal products are not subject to the current medicinal product price regulation but rather, in accordance with Section 129, paragraph 5a of the German Social Code, Book V, (SGB V) when a non-prescription medicinal product is sold and invoiced in accordance with Section 300 SGB V, for the insured person, a pharmaceutical selling price in the amount of the selling price of the pharmaceutical company – plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the 31 December 2003 version – shall apply.

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Cost per package	Costs after deduction of statutory rebates[3]	Costs per service[4]	Treatment days per year	Cost per patient per year
Cisplatin				
Anti-emetic treatment				
In clinical practice, appropriate anti-emetic treatment is established before and/or after cisplatin administration. The product information of cisplatin does not contain any concrete information on this, which is why the necessary costs cannot be quantified.				
Forced diuresis with mannitol 10% infusion solution, 37.5 g/day				
10 × 500 ml: € 106.22	€ 91.10 (€ 5.31; € 9.81)	€ 9.11	17	€ 154.87
Hydration: sodium chloride 0.9% infusion solution, 3–4.4 l/day				
10 × 1,000 ml: € 35.47 10 × 500 ml: € 22.72	€ 32.58 (€ 1.77; € 1.12) € 20.89 (€ 1.14; € 0.69)	€ 9.77–15.12	17	€ 166.16–257.06
Pemetrexed				
Pre-medication: Dexamethasone 2 × 4 mg/day, oral				
100 × 4 mg: € 79.21 (FB)	€ 72.04 (€ 1.77; € 5.40)	€ 1.44	51	€ 73.48
Folic acid: 350 – 1,000 µg/day[5], oral				
100 × 400 µg: € 15.55	€ 12.63 (€ 0.78; € 2.14)	€ 0.13 – 0.25	365	€ 46.10 – 92.20
Vitamin B12: 1,000 µg/day, i.m.				
10 × 1,000 µg: € 7.40 (FB)	€ 6.70 (€ 0.37; € 0.32)	€ 0.70	6	€ 4.03
Paclitaxel				
Pre-medication: Dexamethasone 2 × 20 mg/day, oral				
20 × 20 mg: € 53.75 (FB)	€ 51.98 (€ 1.77; €0.00)	€ 5.20	17	€ 88.37
Antihistamine: Dimetindene 1 mg per 10 kg BW, i.v.				
5 × 4 mg: € 18.56	€ 14.82 (€1.77; € 1.97)	€ 5.93[6]	17	€ 100.78
Ranitidine: 50 mg/day, i.v.				
5 × 50 mg: € 15.02	€ 13.06 (€1.77; € 0.19)	€ 2.61	17	€ 44.40

3 Section 130 SGB V and Section 130a SGB V

4 Proportionate costs of costs per package for consumption per treatment day

5 The cost of folic acid is calculated on the basis of the single dose of 400 µg of the non-divisible tablets available for cost calculation, based on a dose range of 400–800 µg per day, even if a dose range of 350–1000 µg is specified in the product information.

6 For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average height: 1.72 m, average body weight: 77 kg).
Source: German Federal Office For Statistics, Wiesbaden 2018:
https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

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Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy retail price publicly accessible in the directory services in accordance with Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic products of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy retail price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for production and is only an approximation of the treatment costs. This presentation does not take into account, for example, the discounts on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 21 August 2018.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 2 April 2019.

On 29 May 2019, 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 1, sentence 2 VerfO.

By letter dated 29 May 2019 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 29 August 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 2 September 2019. The deadline for submitting written statements was 23 September 2019.

The oral hearing was held on 7 October 2019.

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.

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The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 29 October 2019, and the proposed resolution was approved.

At its session on 22 November 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	21 August 2018	Determination of the appropriate comparator therapy
Working group Section 35a	2 April 2019	Adjustment of the AWG according to positive opinion Confirmation of the appropriate comparator therapy
Working group Section 35a	2 October 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 October 2019	Conduct of the oral hearing
Working group Section 35a	15 October 2019 22 October 2019	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	29 October 2019	Concluding discussion of the proposed resolution
Plenum	22 November 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 22 November 2019

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

Prof Hecken

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