Gemeinsamer Bundesausschuss

Justification

of 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 Selpercatinib (lung cancer, non-small cell, RET fusion-positive, after platinum-based chemotherapy and/or immunotherapy)

of 2 September 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 benefits,
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. Costs of therapy for the statutory health insurance,
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 relevant date for the first placing on the (German) market of the combination of active ingredient selpercatinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 March 2021. 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 12 March 2021.

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 15 June 2021, thus initiating the written statement procedure. In addition, an oral hearing was also held.

The G-BA came to a resolution on whether an additional benefit of selpercatinib 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, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. 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 selpercatinib.

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 selpercatinib (Retsevmo) in accordance with the product information

Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.

Therapeutic indication of the resolution (resolution from the 2 September 2021):

Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line therapy with an anti-PD-1/PD-L1 antibody as monotherapy

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

Appropriate comparator therapy:

- Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology))

or

- Carboplatin in combination with a third-generation cytostatic drug (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology)) cf. Annex VI to Section K of the Pharmaceuticals Directive

or

- Carboplatin in combination with nab-paclitaxel

or

- Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment)

b) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line cytotoxic chemotherapy

Appropriate comparator therapy:

- Docetaxel (only for patients with PD-L1 negative tumours)

or

- Pemetrexed (only for patients with PD-L1 negative tumours and except in cases of predominantly squamous histology)

or

- Nivolumab

or

- Pembrolizumab (only for patients with PD-L1 expressing tumours (TPS ≥ 1 %))

or

- Atezolizumab

or

- Docetaxel in combination with nintedanib (only for patients with PD-L1 negative tumours and adenocarcinoma histology)

c) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line therapy with an anti-PD-1/PD-L1 antibody in

combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy

Appropriate comparator therapy:

Patient-individual therapy taking into account prior therapy and histology; selecting afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib and vinorelbine.

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, principally, have a marketing authorisation for the therapeutic indication
2. If a non-medicinal treatment is considered 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 benefit shall be preferred.
4. The comparative therapy should be part of the appropriate therapy in the therapeutic indication according to the generally accepted state of medical knowledge.

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

on 1. In the present therapeutic indication, it is assumed that patients are not eligible for molecularly stratified therapy (directed against EGFR, ALK, BRAF or ROS1) at the time of therapy with selpercatinib.

In terms of authorisation status, the active ingredients generally available for the treatment of advanced non-small-cell lung cancer (NSCLC) without ALK translocation, EGFR, BRAF or ROS1 mutation are cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, nab-paclitaxel, paclitaxel, pemetrexed, vindesine, vinorelbine; Afatinib, erlotinib, nintedanib, atezolizumab, nivolumab, pembrolizumab and ramucirumab.

on 2. It is assumed that the patients have no indication for definitive local therapy for the present therapeutic indication. A non-medicinal treatment cannot be considered as a comparator therapy in this therapeutic indication.

on 3. Regarding treatments with medicinal products in the present therapeutic indication, the following resolutions and guidelines of the G-BA are available:

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

- Afatinib: Resolution of 20.10.2016
- Atezolizumab: Resolution of 16.03.2018
- Nintedanib: Resolution of 18.06.2015
- Nivolumab Resolutions of 04.02.2016 and 20.10.2016
- Pembrolizumab: Resolution of 02.02.2017
- Ramucirumab: Resolution of 01.09.2016

Section K of the Pharmaceuticals Directive, Annex VI - Off-label use, resolution of 18 October 2018: Carboplatin-containing medicinal products for advanced non-small cell lung cancer (NSCLC) - combination therapy

on 4. The general state of medical knowledge in the present therapeutic indication was represented by a systematic search for guidelines and reviews of clinical studies.

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

Among the approved active ingredients listed under 1.), only certain active ingredients 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 provision.

At present, no specific therapy recommendations depend on the presence of rearranged during transfection (RET) receptor tyrosine kinase fusion.

Furthermore, the available evidence does not indicate that any factors in NSCLC with RET fusion clearly argue against treatment with the previous or current standard therapies. Thus, for the appropriate comparator therapy, therapy options that are independent of RET fusion will be considered and thus eligible for the unselected patient population in this regard.

The present therapeutic indication includes patients whose disease has progressed after receiving anti-PD-1 or anti-PD-L1 immunotherapy and/or platinum-based combination chemotherapy. Thus, several lines of therapy are addressed in the appropriate comparator therapy as follows.

In second-line treatment, depending on the first-line therapy, a distinction is made between a) patients with anti-PD-1/PD-L1 antibody monotherapy pre-treatment, b)

patients with cytotoxic chemotherapy pre-treatment, and c) after first-line therapy with an anti-PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy as pre-treatment.

a) *After first-line therapy with an anti-PD-1/PD-L1 antibody as monotherapy*

In the guidelines, whose recommendations already include first-line therapy with immune checkpoint inhibitors, cytotoxic chemotherapy is recommended for this patient group in second-line therapy, with platinum-containing chemotherapy being given the highest priority overall, analogous to first-line therapy. In this regard, platinum-based (cisplatin or carboplatin) combination chemotherapy with a third-generation cytostatic (vinorelbine, gemcitabine, docetaxel, paclitaxel, or pemetrexed) represents the previous and current therapeutic standard. From the available evidence, it cannot be concluded that a combination is clearly inferior or superior in therapeutic benefit. In contrast to cisplatin, carboplatin is not approved for the treatment of NSCLC, but can be prescribed as an "off-label use" (see Annex VI to Section K of the Pharmaceuticals Directive), whereby the selection of the platinum component (carboplatin or cisplatin) in each case should be based on the different toxicity profile of both substances and existing comorbidities of the patients.

The carboplatin combination with nab-paclitaxel is approved for the treatment of NSCLC and is also recommended in the guidelines.

For patients with reduced general condition, the toxicity profile of platinum-based combination chemotherapy must be weighed against the expected benefit, considering patient-individual criteria. Alternatively, for patients with ECOG performance status 2, monochemotherapy with gemcitabine or vinorelbine is considered appropriate for this patient group, in addition to platinum-based combination chemotherapy.

With regard to the approved therapeutic indications of pemetrexed, gemcitabine and nab-paclitaxel, the use of a PD-1/ PD-L1 inhibitor in the previous therapy is not interpreted as a line of therapy to be considered with regard to the marketing authorisation of the medicinal product.

b) After first-line therapy with cytotoxic chemotherapy

For patients in whom further antineoplastic therapy is indicated after first-line chemotherapy, several therapeutic options are available on the basis of the available evidence with the cytotoxic chemotherapeutic agents docetaxel and pemetrexed, in each case as monotherapy, docetaxel in combination with nintedanib, and the immune checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab, in some cases only under certain conditions.

With docetaxel and pemetrexed, both as monotherapy, two established chemotherapeutic agents are available for second-line chemotherapy, although pemetrexed is unsuitable in cases of predominantly squamous histology. For the combination of docetaxel and nintedanib, which is indicated for adenocarcinoma histology, an indication of a small additional benefit was identified in the benefit assessment compared with docetaxel monotherapy (resolution of 18 June 2015). In the guidelines, docetaxel combined with nintedanib is recommended alongside the other chemotherapy options, but is not regularly preferred. Based on the available evidence, docetaxel and pemetrexed, each as monotherapy, and docetaxel combined with nintedanib are considered therapeutically comparable, subject to tumour histology different side effect profiles.

For nivolumab for the treatment of patients after prior chemotherapy and squamous cell tumour histology, an indication of a considerable additional benefit was identified in the benefit assessment compared with docetaxel (resolution of 4 February 2016). For the treatment of patients after prior chemotherapy and non-squamous cell tumour histology, an indication of a considerable additional benefit was also identified for nivolumab in the benefit assessment compared with docetaxel (resolution of 20 October 2016).

For pembrolizumab and atezolizumab, used after prior chemotherapy, the benefit assessment also found an indication of a considerable additional benefit compared with docetaxel (pembrolizumab: the resolution of 2 February 2017, atezolizumab: the resolution of 16 March 2018). According to the marketing authorisation, in the present therapeutic indication, pembrolizumab is only indicated for patients with PD-L1 expressing tumours (TPS ≥ 1 %).

Nivolumab, pembrolizumab, and atezolizumab lead to a significant prolongation in overall survival compared with docetaxel and a significant reduction in side effects. Accordingly, guidelines regularly favour immune checkpoint inhibitors over cytotoxic chemotherapeutic agents. However, PD-L1 negative tumours are a fundamental exception. In these cases, the guidelines predominantly do not recommend a regular preference of immune checkpoint inhibitors over cytotoxic chemotherapy. Therefore, alternative cytotoxic chemotherapeutic agents are also determined to be appropriate comparator therapy to immune checkpoint inhibitors in PD-L1 negative tumours.

For ramucirumab in combination with docetaxel, no additional benefit was determined in the benefit assessment compared to docetaxel (resolution of 1 September 2016). Likewise, no additional benefit was identified in the benefit assessment of afatinib compared with docetaxel (resolution of 20 October 2016). Taking into account that, in the present therapeutic indication, benefit-assessed medicinal product treatments with an additional benefit are available, the treatment options ramucirumab in combination with docetaxel as well as afatinib, for which no additional benefit could be determined in each case, are not considered as an appropriate comparator therapy.

c) *After first-line therapy with an anti-PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy*

The present therapeutic indication may include patients who have either already received platinum-containing chemotherapy in combination with anti-PD-1/PD-L1 antibody therapy as part of first-line therapy or have received platinum-containing chemotherapy and anti-PD-1/PD-L1 antibody therapy sequentially in first- and second-line (regardless of which of the therapies was used first).

The former treatment setting of platinum-containing chemotherapy in combination with anti-PD-1/PD-L1 antibody therapy is a relatively new treatment option for advanced NSCLC. For the treatment situation after platinum-containing chemotherapy in combination with anti-PD-1/PD-L1 therapy as well as for the further treatment after sequential therapy with platinum-containing chemotherapy and anti-PD-1/PD-L1 antibody therapy in first and second line, there is no higher-quality evidence based on clinical studies.

According to the guidelines, patients in the present therapeutic indication are eligible for subsequent antineoplastic therapy, taking into account the previous therapy and tumour histology, with docetaxel, pemetrexed, docetaxel in combination with ramucirumab or nintedanib, erlotinib and afatinib being named as therapy options.

The recommendation of a further therapy with a (different) anti-PD-1/PD-L1 antibody does not emerge from the available evidence.

For the combination of docetaxel and nintedanib, which is indicated for adenocarcinoma histology, an indication of a small additional benefit was identified in the benefit assessment compared with docetaxel monotherapy (resolution of 18 June 2015).

For ramucirumab in combination with docetaxel, no additional benefit was determined in the benefit assessment compared to docetaxel (resolution of 1 September 2016).

For afatinib for the treatment of patients with squamous cell histology, no additional benefit was determined in the benefit assessment compared with the appropriate comparator therapy docetaxel (resolution of 20 October 2016).

About the above-mentioned benefit assessments, however, it should be noted that they were based on the therapy situation of a second-line therapy after previous platinum-containing chemotherapy and thus on an indication that deviated from the present therapy situation concerning the previous therapy.

Overall, given the limited evidence for the present therapy situation, the G-BA determined as appropriate comparator therapy a patient-individual therapy taking into account the previous therapy and histology, selecting afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab and docetaxel in combination with nintedanib as well as vinorelbine.

The specific appropriate comparator therapy comprises a selection of different active ingredients and combinations of active ingredients that can be considered for the present therapeutic indication according to the authorisation status of the medicinal products and the recommendations in the guidelines.

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 selpercatinib is assessed as follows:

a) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line therapy with an anti-PD-1/PD-L1 antibody as monotherapy

An additional benefit is not proven.

b) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line cytotoxic chemotherapy

An additional benefit is not proven.

c) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line therapy with an anti-PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy

An additional benefit is not proven.

Justification:

Data basis:

In the dossier for the benefit assessment, the pharmaceutical company uses the results of the marketing authorisation study on selpercatinib. This is the LIBRETTO-001 study, which enrolled patients 12 years of age and older with locally advanced or metastatic solid tumours regardless of RET status or prior treatment.

LIBRETTO-001

The basket study LIBRETTO-001 is a 2 phase, non-controlled, prospective study that has been ongoing since May 2017. The maximum tolerated dose was determined in the already completed phase 1. The determined dose was applied in the still ongoing phase 2.

Phase 1 of the LIBRETTO-001 study

Phase 1 of the LIBRETTO-001 study evaluated dose escalation in patients 12 years of age and older with locally advanced or metastatic solid tumours regardless of RET status and prior treatment who had progressed on or were intolerant to prior standard therapies.

The presence of an alteration of the RET gene was not an inclusion criterion until after the minimum plasma concentration of selpercatinib, as defined by the study protocol, had been reached. Pre-treatment with specific active ingredients was allowed but not an inclusion criterion.

Phase 2 of the LIBRETTO-001 study

In phase 2 of the LIBRETTO-001 study, patients 12 years of age and older with locally advanced or metastatic solid tumours with a RET-alteration were enrolled into different cohorts. Cohort 1, which is relevant for the present therapeutic indication, included patients with advanced or metastatic solid tumours with RET fusion and progression under standard therapy or intolerance to standard therapy.

Treatment was started for all phase 2 patients, regardless of body weight, at 160 mg 2 times a day in cycles of 28 days. Treatment was continued until the occurrence of unacceptable toxicity or other event leading to treatment discontinuation (e.g., death). In case of progression, treatment could be continued in consultation with the pharmaceutical company if tolerability and clinical benefit were given.

The primary endpoint in phase 2 was the objective response rate. Patient-relevant secondary endpoints were assessed in the categories of overall survival, morbidity, health-related quality of life, and side effects.

The study was conducted in 84 study centres in Australia, Asia, Europe and North America.

For the benefit assessment in the present therapeutic indication, the pharmaceutical company draws the sub-population of patients with RET fusion-positive advanced NSCLC who require systemic therapy after platinum-based chemotherapy and/or treatment with immunotherapy. Here, the pharmaceutical company forms two subpopulations in the dossier: Patients with one prior therapy (second-line; n = 81 patients) and patients who received at least two prior therapies (third-line and higher lines; n = 169 patients).

In addition, the pharmaceutical company submits in its written statement evaluations for patients after cytotoxic chemotherapy (patient population b)) as well as evaluations for patients after sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy (patient population c)) of the LIBRETTO-001 study.

Comparative data

The marketing authorisation study LIBRETTO-001 is a uncontrolled study. Thus, this study does not include a comparator group to compare the results of treatment with selpercatinib.

For a comparison of selpercatinib, the pharmaceutical company identified Shen et al. (2020), Drilon et al. (2016), Mazieres et al. (2019), Guisier et al. (2020), and Hess et al. (2021) studies with no restrictions on prior therapies. Each of these studies was a single-arm retrospective data collection.

In the dossier, the pharmaceutical company first compares the results for the endpoints overall survival, progression-free survival and tumour response for the patient groups selected by it (second-line) and (third-line and higher lines) descriptively with those of the five studies in its study pool. To compare the patient-relevant endpoint overall survival, he uses only the Mazieres et al. (2019) study in a non-adjusted indirect comparison.

In its written statement, the pharmaceutical company submits data for patient population b) (patients who received first-line chemotherapy) from PD-1/ PD-L1-treated patients in the Mazieres et al. (2019) study versus data from the LIBRETTO-001 study in a non-adjusted indirect comparison.

Mazieres et al. (2019)

The Mazieres et al. study is based on the international patient registry IMMUNOTARGET (24 centres in 10 countries). It includes 551 patients with lung cancer and various oncogenic driver mutations, including 16 patients with RET fusion. Patients received an anti-PD-1/PD-L1 antibody as monotherapy in any line of therapy. Several lines of therapy were allowed as pre-treatment. However, it is not clear from the publication which therapies were previously administered. The primary endpoint of the study was progression-free survival depending on the driver mutation. Secondary endpoints included overall survival.

a) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line therapy with an anti-PD-1/PD-L1 antibody as monotherapy

Evaluation:

For patient population a), the pharmaceutical company presents the results from the marketing authorisation study LIBRETTO-001. In its dossier, the pharmaceutical company divides the patients from the LIBRETTO-001 study with RET fusion-positive advanced NSCLC who require systemic therapy after platinum-based chemotherapy and/or treatment with immunotherapy only according to the number of previous therapies. Here he distinguishes patients with one prior therapy from those who have received at least two prior therapies. Deviating from this, the G-BA differentiated the patients according to the type of their first-line therapy (anti-PD-1/PD-L1 antibody as monotherapy vs cytotoxic chemotherapy vs anti-PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after

sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy).

The results from the LIBRETTO-001 study alone are not suitable for assessing the additional benefit of selpercatinib, as they do not allow for a comparison with the appropriate comparator therapy.

In the dossier, the pharmaceutical company initially compares the endpoints' overall survival, progression-free survival and tumour response descriptively with those of the five studies in its patient group (second-line). He uses the Mazieres et al. (2019) study to compare the patient-relevant endpoint overall survival in a non-adjusted indirect comparison.

Notwithstanding that the patient population formed by the pharmaceutical company (number of previous therapies) does not correspond to the patient population formed by the G-BA (type of first-line therapy), this is a comparison of individual arms from different studies. Thus, the results are subject to uncertainty due to the lack of randomisation, so that an additional benefit can only be derived if the effects are sufficiently large. For the indirect comparison presented, the observed effects are not large enough to be due to systematic bias alone.

In its written statement, the pharmaceutical company presents results from the LIBRETTO-001 study for patients who received first-line cytotoxic chemotherapy (patient population b) and again draws a non-adjusted comparison versus the Mazieres et al. (2019) study. Results of the LIBRETTO-001 study for patients after first-line therapy with an anti-PD-1/PD-L1 antibody (patient population a) are not presented in the written statement of the pharmaceutical company. Thus, no suitable data are available for assessing the additional benefit compared with the appropriate comparator therapy for patient population a).

Conclusion:

Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of selpercatinib as monotherapy in adult patients with RET fusion-positive advanced NSCLC in whom systemic therapy is indicated after first-line therapy with an anti-PD-1/PD-L1 antibody is not proven.

In some cases, selpercatinib may represent a relevant therapeutic option in the present therapeutic indication.

b) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line cytotoxic chemotherapy

Evaluation:

For patient population b), the pharmaceutical company also presents the results from the marketing authorisation study LIBRETTO-001. In its dossier, the pharmaceutical company divides the patients from the LIBRETTO-001 study with RET fusion-positive advanced NSCLC who require systemic therapy after platinum-based chemotherapy and/or treatment with immunotherapy only as already described, according to the number of previous therapies.

The results from the LIBRETTO-001 study alone are not suitable for assessing the additional benefit of selpercatinib, as they do not allow for a comparison with the appropriate comparator therapy.

In the dossier, the pharmaceutical company initially compares the endpoints' overall survival, progression-free survival and tumour response descriptively with those of the five studies in its patient group (second-line). He uses the Mazieres et al. (2019) study to compare the patient-relevant endpoint overall survival in a non-adjusted indirect comparison.

In addition, in its written statement, the pharmaceutical company presents results for patients who received first-line cytotoxic chemotherapy from the LIBRETTO study versus data from anti-PD-1/PD-L1 antibody-treated patients from the Mazieres et al. (2019) study in a non-adjusted indirect comparison for the endpoints of overall survival, progression-free survival, and tumour response.

The indirect comparisons on the patient-relevant endpoint of overall survival presented in the dossier and the written submission involve a comparison of individual arms from different studies. Thus, the results are subject to uncertainty due to the lack of randomisation, so that an additional benefit can only be derived if the effects are sufficiently large. For the indirect comparisons presented, the observed effects are not large enough for them not to be due solely to systematic bias. Notwithstanding the above, the indirect comparisons presented are not suitable for the assessment of additional benefit as the patients from the LIBRETTO-001 and Mazieres et al. (2019) studies are not comparable in terms of their lines of therapy.

Conclusion:

Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy. Therefore, an additional benefit of selpercatinib as monotherapy in adult patients with RET fusion-positive advanced NSCLC in whom systemic therapy is indicated after first-line chemotherapy is not proven.

In some cases, selpercatinib may represent a relevant therapeutic option in the present therapeutic indication.

c) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line therapy with an anti-PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy

Evaluation:

For patient population c), the pharmaceutical company also presents the results from the marketing authorisation study LIBRETTO-001.

In its dossier, the pharmaceutical company divides the patients from the LIBRETTO-001 study with RET fusion-positive advanced NSCLC who require systemic therapy after platinum-based chemotherapy and/or treatment with immunotherapy according to the number of previous

therapies, as already described. Here, the pharmaceutical company forms two subpopulations in the dossier: Patients with one previous therapy (second-line) and patients who have received at least two prior therapies (third-line and higher lines). The pharmaceutical company uses the latter sub-population for patient population c) determined by the G-BA and first compares the results descriptively with those of the five studies of its study pool for the endpoints overall survival, progression-free survival and tumour response. For the patient-relevant endpoint of overall survival, he uses the Mazieres et al. (2019) study in a non-adjusted indirect comparison.

Notwithstanding that the sub-population used by the pharmaceutical company (third-line and higher lines) is not suitable for the assessment of additional benefit for patient population c), this is a comparison of individual arms from different studies. Thus, the results are subject to uncertainty due to the lack of randomisation, so that an additional benefit can only be derived if the effects are sufficiently large. For the indirect comparison presented, the observed effects are not large enough to be due to systematic bias alone.

In its written statement, the pharmaceutical company also submits evaluations on the endpoint categories mortality, morbidity and side effects for patients after sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy of the LIBRETTO-001 study. However, data on the subpopulation of patients after first-line therapy with an anti-PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy are not available.

The results from the LIBRETTO-001 study alone are not suitable for assessing the additional benefit of selpercatinib, as they do not allow for a comparison with the appropriate comparator therapy.

Conclusion:

Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy. Therefore, an additional benefit of selpercatinib as monotherapy in adult patients with RET fusion-positive advanced NSCLC in whom systemic therapy is indicated after first-line therapy with an anti-PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy is not proven.

In some cases, selpercatinib may represent a relevant therapeutic option in the present therapeutic indication.

2.1.4 Summary of the assessment

The benefit assessment is carried out for the new medicinal product Retsevmo with the active ingredient selpercatinib.

This medicinal product was approved under special conditions.

Retsevmo is approved as monotherapy for the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

In the therapeutic indication being studied, three patient populations were differentiated:

a) Adults with advanced RET fusion-positive lung cancer NSCLC, for whom systemic therapy is indicated; after first-line therapy with an anti-PD-1/PD-L1 antibody as monotherapy

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

– Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology))

or

– Carboplatin in combination with a third-generation cytostatic drug (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology)) cf. Annex VI to Section K of the Pharmaceuticals Directive

or

– Carboplatin in combination with nab-paclitaxel

or

– Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment)

For the benefit assessment, the pharmaceutical company submitted the results from the marketing authorisation study LIBRETTO-001 for the treatment with selpercatinib. This is a non-controlled study and therefore does not include a comparison group.

Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of selpercatinib as monotherapy in adults with RET fusion-positive advanced NSCLC in whom systemic therapy is indicated after a first-line therapy with an anti-PD-1/PD-L1 antibody is not proven.

In some cases, selpercatinib may represent a relevant therapeutic option in the present therapeutic indication.

b) Adults with RET fusion-positive advanced NSCLC for whom systemic therapy is indicated; after first-line therapy with cytotoxic chemotherapy

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

– Docetaxel (only for patients with PD-L1 negative tumours)

or

– Pemetrexed (only for patients with PD-L1 negative tumours and except in cases of predominantly squamous histology)

or

– Nivolumab

or

– Pembrolizumab (only for patients with PD-L1 expressing tumours (TPS ≥ 1 %))

or

– Atezolizumab

or

– Docetaxel in combination with nintedanib (only for patients with PD-L1 negative tumours and adenocarcinoma histology)

For the benefit assessment, the pharmaceutical company submitted the results from the marketing authorisation study LIBRETTO-001 for the treatment with selpercatinib. This is a non-controlled study and therefore does not include a comparison group. Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of selpercatinib as monotherapy in adults with RET fusion-positive advanced NSCLC in whom systemic therapy is indicated after first-line therapy with cytotoxic chemotherapy is not proven.

In some cases, selpercatinib may represent a relevant therapeutic option in the present therapeutic indication.

c) Adults with RET fusion-positive advanced NSCLC for whom systemic therapy is indicated; after first-line therapy with an anti-PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy

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

Patient-individual therapy taking into account prior therapy and histology; selecting afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib and vinorelbine.

For the benefit assessment, the pharmaceutical company submitted the results from the marketing authorisation study LIBRETTO-001 for the treatment with selpercatinib. This is a non-controlled study and therefore does not include a comparison group. Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy. Therefore, an additional benefit of selpercatinib as monotherapy in adults with RET fusion-positive NSCLC in whom systemic therapy is indicated after first-line therapy with an anti-PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy is not proven.

In some cases, selpercatinib may represent a relevant therapeutic option in the present therapeutic indication.

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 projected incidence for 2021 (60,333 patients) is used to calculate the number of German patients with lung cancer.

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

1. The percentage of lung cancer patients with NSCLC ranges from 73.6% to 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 stages I and IIA patients who will progress to stage IV in 2021 is 5,866 to 8,364 patients. The total number of patients with 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 to 37,896 patients).

4. The percentage of patients with RET fusion range from 0.6% to 0.9% (133 to 341 patients).

5. Of these, as first-line treatment,

5a. 11.0% to 16.9% (15 to 58 patients) received monotherapy with an anti-PD-1/PD-L1 antibody,

5b. 48.3% to 57.5% (64 to 194 patients) received chemotherapy or

5c. 31.5% to 33.4% (42 to 114 patients) received an anti-PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy.

In total, the percentage of patients who received one of the above therapy options in first-line is 98.6% to 100% (131 to 341 patients) related to step number 4. Of these

6. 38.7% to 45.9% of patients received second-line treatment (51 to 157 patients). Of these, as first-line treatment,

6a. 6 to 26 patients received monotherapy with an anti-PD-1/PD-L1 antibody (patient population a),

6b. 25 to 90 patients received chemotherapy (patient population b) and

6c. 16 to 52 patients received monotherapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy (sub-population c1).

7. The proportion of patients receiving third-line therapy was 30.0% to 40.0% (15 to 63 patients; sub-population c2).

8. Taking into account a percentage of patients insured by the SHI of 88.3 %, steps 6a-c and 7 results in 5 to 138 patients after previous therapy with an anti-PD-1/PD-L1 antibody and/or chemotherapy, of which

8a. 5 to 23 patients with an anti-PD-1 / PD-L1 antibody as first-line treatment (patient population a),

8b. 22 to 79 patients with chemotherapy as first-line treatment (patient population b) and

8c. 14 to 46 patients with an anti-PD-1 / PD-L1 antibody and platinum-containing chemotherapy as first-line treatment (sub-population c1) and 14 to 55 patients with at least

two prior systemic therapies (subpopulation c2). In total, the number of patients after first-line therapy with an anti-PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy is 28 to 101 patients (patient population c).

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 Retsevmo (active ingredient: selpercatinib) at the following publicly accessible link (last access: 29 July 2021):

https://www.ema.europa.eu/en/documents/product-information/retsevmo-epar-product-information_de.pdf

Treatment with selpercatinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of patients with non-small cell lung 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.

This medicinal product has been authorised under a so-called "conditional approval" scheme. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency (EMA) will assess new information on this medicinal product at least annually and update the product information for healthcare professionals as necessary.

RET testing

A validated test should confirm the presence of RET gene fusion prior to initiation of treatment with selpercatinib.

2.4 Treatment costs

The treatment costs are based on the product information as well as the information in the LAUER-TAXE® (last revised: 15 August 2021).

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

Cisplatin is dosed differently depending on the combination preparation. According to the product information of the combination preparations, the single dose of cisplatin in combination with vinorelbine or gemcitabine is 75 - 100 mg/m², in combination with docetaxel and pemetrexed 75 mg/m² and in combination with paclitaxel 80 mg/m².

For carboplatin, a cycle duration of 3 weeks is used. For the use of carboplatin in the off-label indication "combination therapy for advanced NSCLC", Annex VI of the Pharmaceuticals Directive specifies the following dosage: up to 500 mg/m² or AUC 6.0. For the use of carboplatin in combination with nab-paclitaxel, a dosage of 500 mg/m² 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 (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.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Selpercatinib	continuously, 2 times a day	365	1	365
Appropriate comparator therapy				
a) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line therapy with an anti-PD-1/PD-L1 antibody as monotherapy				
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology))				
Cisplatin	1 x per 21 day cycle	17.4 cycles	1	17.4
Docetaxel	1 x per 21 day cycle	17.4 cycles	1	17.4
Gemcitabine	2 x per 21 day cycle	17.4 cycles	2	34.8
Paclitaxel	1 x per 21 day cycle	17.4 cycles	1	17.4
Pemetrexed	1 x per 21 day cycle	17.4 cycles	1	17.4
Vinorelbine	2 x per 21 day cycle	17.4 cycles	2	34.8

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Carboplatin in combination with a third-generation cytostatic drug (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology)) cf. Annex VI to Section K of the Pharmaceuticals Directive				
Carboplatin	1 x per 21 day cycle	17.4 cycles	1	17.4
Docetaxel	1 x per 21 day cycle	17.4 cycles	1	17.4
Gemcitabine	2 x per 21 day cycle	17.4 cycles	2	34.8
Paclitaxel	1 x per 21 day cycle	17.4 cycles	1	17.4
Pemetrexed	1 x per 21 day cycle	17.4 cycles	1	17.4
Vinorelbine	1 x per 21 day cycle	17.4 cycles	2	34.8
Carboplatin in combination with nab-paclitaxel				
Carboplatin	1 x per 21 day cycle	17.4 cycles	1	17.4
Nab-paclitaxel	3 x per 21 day cycle	17.4 cycles	3	52.2
Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment)				
Gemcitabine	on day 1, 8 and 15 of 28 day cycle	13 cycles	3	39
Vinorelbine	1 x every 7 days	52.1 cycles	1	52.1
b) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line cytotoxic chemotherapy				
Docetaxel	1 x per 21 day cycle	17.4 cycles	1	17.4
Pemetrexed[2]	1 x per 21 day cycle	17.4 cycles	1	17.4

[2] only for patients with PD-L1 negative tumours and except in cases of predominantly squamous histology

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Nivolumab	1 x per 14 day cycle	26.1 cycles	1	26.1
Pembrolizumab[3]	1 x per 21 day cycle	17.4 cycles	1	17.4
	or			
	1 x per 42 day cycle	8.7 cycles	1	8.7
Atezolizumab	1 x per 21 day cycle	17.4 cycles	1	17.4
Docetaxel in combination with nintedanib[4]				
Docetaxel	1 x per 21 day cycle	17.4 cycles	1	17.4
Nintedanib	2 x a day on days 2-21 of an 21 day cycle	17.4 cycles	20	348
c) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line therapy with an anti-PD-1/PD-L1antibody in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy				
Afatinib	1 x daily	365 days	1	365
Pemetrexed	1 x per 21 day cycle	17.4 cycles	1	17.4
Erlotinib	1 x daily	365 days	1	365
Vinorelbine	1 x every 7 days	52.1 cycles	1	52.1
Docetaxel	1 x per 21 day cycle	17.4 cycles	1	17.4
Docetaxel in combination with ramucirumab				
Docetaxel	1 x per 21 day cycle	17.4 cycles	1	17.4
Ramucirumab	1 x per 21 day cycle	17.4 cycles	1	17.4
Docetaxel in combination with nintedanib				

[3] only for patients with PD-L1 expressing tumours (TPS ≥ 1)
[4] only for patients with PD-L1 negative tumours and adenocarcinoma histology

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Docetaxel	1 x per 21 day cycle	17.4 cycles	1	17.4
Nintedanib	2 x a day on days 2-21 of an 21 day cycle	17.4 cycles	20	348

Consumption:

For the cost representation only the doses 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.

For dosages depending on body weight or body surface, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m, average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[5].

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient / year	Average annual consumption by potency
Medicinal product to be assessed					
Selpercatinib	160 mg	320 mg	4 x 80 mg	365	1460 x 80 mg
Appropriate comparator therapy					
a) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line therapy with an anti-PD-1/PD-L1 antibody as monotherapy					
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology))					
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 100 mg + 1 x 50 mg	17.4	17.4 x 100 mg + 17.4 x 50 mg

[5]Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient / year	Average annual consumption by potency
	80 mg/m²= 152 mg	152 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	17.4	17.4 x 100 mg + 17.4 x 50 mg + 17.4 x 10 mg
	100 mg/m² = 190 mg	190 mg	2 x 100 mg	17.4	34.8 x 100 mg
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Gemcitabine	1 250 mg/m² =2375 mg	2 375 mg	1 x 2 000 mg x 2 x 200 mg	34.8	34.8 x 2 000 mg + 69.6 x 200 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 + 1 x 150 mg	17.4	17.4 x 150 mg + 34.8 x 100 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Vinorelbine	25 mg/m² = 47.5 mg - 30 mg/m² = 57 mg	47.5 mg - 57 mg	1 x 50 mg- 1 x 50 mg + 1 x 10 mg	34.8	34.8 x 50 mg- 34.8 x 50 mg + 34.8 x 10 mg
Carboplatin in combination with a third-generation cytostatic drug (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology)) cf. Annex VI to Section K of the Pharmaceuticals Directive					
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 2 x 150 mg + 1 x 50 mg	17.4	17.4 x 600 mg + 34.8 x 150 mg + 17.4 x 50 mg
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Gemcitabine	1 250 mg/m² =2375 mg	2375 mg	1 x 2 000 mg x 2 x 200 mg	34.8	34.8 x 2 000 mg + 69.6 x 200 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 + 1 x 150 mg	17.4	17.4 x 150 mg + 34.8 x 100 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Vinorelbine	25 mg/m² = 47.5 mg -	47.5 mg -	1 x 50 mg-	34.8	34.8 x 50 mg-

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient / year	Average annual consumption by potency
	30 mg/m² = 57 mg	57 mg	1 x 50 mg + 1 x 10 mg		34.8 x 50 mg + 34.8 x 10 mg
Carboplatin in combination with nab-paclitaxel					
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 2 x 150 mg + 1 x 50 mg	17.4	17.4 x 600 mg + 34.8 x 150 mg + 17.4 x 50 mg
nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 x 100 mg	52.2	104.4 x 100 mg
Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment)					
Gemcitabine	1,000 mg/m² = 1,900 mg	1,900 mg	1 x 2,000 mg	39	39 x 2,000 mg
Vinorelbine	25 mg/m² = 47.5 mg - 30 mg/m² = 57 mg	47.5 mg - 57 mg	1 x 50 mg- 1 x 50 mg + 1 x 10 mg	52.1	52.1 x 50 mg- 52.1 x 50 mg + 52.1 x 10 mg
b) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line cytotoxic chemotherapy					
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Nivolumab	240 mg	240 mg	2 x 100 mg + 1 x 40 mg	26.1	52.2 x 100 mg + 26.1 x 40 mg
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
Atezolizumab	1 200 mg	1 200 mg	1 x 1,200 mg	17.4	17.4 x 1,200 mg
Docetaxel in combination with nintedanib					
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Nintedanib	200 mg	400 mg	4 x 100 mg	348	1,392 x 100 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient / year	Average annual consumption by potency
c) Adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) for whom systemic therapy is indicated; after first-line therapy with an anti-PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 antibody and platinum-containing chemotherapy					
Afatinib	40 mg	40 mg	1 x 40 mg	365	365 x 40 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Erlotinib	150 mg	150 mg	1 x 150 mg	365	365 x 150 mg
Vinorelbine	25 mg/m² = 47.5 mg - 30 mg/m² = 57 mg	47.5 mg - 57 mg	1 x 50 mg- 1 x 50 mg + 1 x 10 mg	52.1	52.1 x 50 mg- 52.1 x 50 mg + 52.1 x 10 mg
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Docetaxel in combination with ramucirumab					
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Ramucirumab	10 mg/kg = 770 mg	770 mg	1 x 500 mg + 3 x 100 mg	17.4	17. 4 x 500 mg + 52.2 x 100 mg
Docetaxel in combination with nintedanib					
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Nintedanib	200 mg	400 mg	4 x 100 mg	348	1392 x 100 mg

Costs:

Costs of the medicinal products:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 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. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. Having determined the

number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

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					
Selpercatinib	60 HC	€ 7,380.94	€ 1.77	€ 418.25	€ 6,960.92
Appropriate comparator therapy					
Atezolizumab 1,200 mg	1 CIS	€ 4,128.95	€ 1.77	€ 232.53	€ 3,894.65
Afatinib 40 mg	28 FCT	€ 2,514.99	€ 1.77	€ 140.35	€ 2,372.87
Carboplatin 50 mg	1 CIS	€ 34.38	€ 1.77	€ 1.11	€ 31.50
Carboplatin 150 mg	1 CIS	€ 82.79	€ 1.77	€ 3.40	€ 77.62
Carboplatin 600 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Cisplatin 10 mg	1 CIS	€ 17.26	€ 1.77	€ 0.30	€ 15.19
Cisplatin 50 mg	50 CIS	€ 47.43	€ 1.77	€ 1.73	€ 43.93
Cisplatin 100 mg	1 CIS	€ 76.31	€ 1.77	€ 3.10	€ 71.44
Docetaxel 160 mg	1 CIS	€ 1,397.36	€ 1.77	€ 175.44	€ 1,220.15
Erlotinib 150 mg	30 FCT	€ 754.46	€ 1.77	€ 35.28	€ 717.41
Gemcitabine 200 mg	1 CIS	€ 28.57	€ 1.77	€ 0.83	€ 25.97
Gemcitabine 2000 mg	21 CIS	€ 193.96	€ 1.77	€ 8.68	€ 183.51
nab-paclitaxel 100 mg	1 PIS	€ 429.09	€ 1.77	€ 52.91	€ 374.41
Nintedanib 100 mg	120 SC	€ 2,761.03	€ 1.77	€ 0.00	€ 2,759.26
Nivolumab 100 mg	1 CIS	€ 1,344.24	€ 1.77	€ 73.81	€ 1,268.66
Nivolumab 40 mg	1 CIS	€ 544.32	€ 1.77	€ 29.53	€ 513.02
Paclitaxel 100 mg	1 CIS	€ 303.80	€ 1.77	€ 13.89	€ 288.14
Paclitaxel 150 mg	1 CIS	€ 450.59	€ 1.77	€ 20.86	€ 427.96
Pembrolizumab 100 mg	1 CIS	€ 3,037.06	€ 1.77	€ 170.17	€ 2,865.12
Pemetrexed 500 mg	1 PIC	€ 601.47	€ 1.77	€ 28.02	€ 571.68
Ramucirumab 500 mg	1 CIS	€ 2,141.07	€ 1.77	€ 119.00	€ 2,020.30
Ramucirumab 100 mg	1 CIS	€ 440.91	€ 1.77	€ 23.80	€ 415.34
Vinorelbine 10 mg	1 CIS	€ 41.39	€ 1.77	€ 3.84	€ 35.78
Vinorelbine 50 mg	1 CIS	€ 156.44	€ 1.77	€ 18.40	€ 136.27
Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; PIC = powder for the preparation of an infusion solution concentrate; PIS = powder for the preparation of an infusion suspension; SC = soft capsules					

LAUER-TAXE® last revised: 18.08.2021

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

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed							
Selpercatinib							
-							
Appropriate comparator therapy							
Cisplatin							
In clinical practice, an appropriate antiemetic treatment is established before and/or after the administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Mannitol 10% Inf. Solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	17.4	€ 158.51
Sodium chloride 0.9% Inf. Solution, 3 - 4.4 l/day	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58	17.4	€ 170.07 -
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		€ 263.11

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Paclitaxel							
Dexamethasone 20 mg[6]	50 TAB	€ 118.61	€ 1.77	€ 0.00	€ 116.84	17.4	€ 81.32
Dimetindene i.v. 1 mg/10 kg	5 x 4 mg SFI	€ 18.62	€ 1.77	€ 1.92	€ 14.93	17.4	€ 103.91
Cimetidine 300 mg i.v. [6]	10 CIS x 200 mg	€ 21.55	€ 1.77	€ 0.00	€ 19.78	17.4	€ 68.83
Pemetrexed							
Dexamethasone[6] 2 x 4 mg	100 TAB 4 mg	€ 79.27	€ 1.77	€ 5.40	€ 72.10	52.2	€ 75.27
Folic acid: 350 - 1,000 µg/day	100 x 400 µg TAB	€ 16.21	€ 0.81	€ 2.36	€ 13.04	365	€ 47.60 - € 95.19
Vitamin B12[6] 1,000 µg/day, every 3 cycles	10 x 1,000 µg SFI	€ 7.40	€ 0.37	€ 0.33	€ 6.70	5.8	€ 3.89
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; INF = infusion solution; TAB = tablets							

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe)(Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an

[6]Fixed reimbursement rate

approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy sales price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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 26 May 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 9 February 2021.

On 12 March 2021, the pharmaceutical company submitted a dossier for the benefit assessment of selpercatinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 12 March 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 selpercatinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 June 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 June 2021. The deadline for submitting written statements was 6 July 2021.

The oral hearing was held on 26 July 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 the 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 were discussed at the session of the subcommittee on 24 August 2021, and the proposed resolution was approved.

At its session on 2 September 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	26.05.2020	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	09.02.2021	New implementation of the appropriate comparator therapy
Working group Section 35a	13.07.2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	26.07.2021	Conduct of the oral hearing
Working group Section 35a	04.08.2021; 18.08.2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal product	24.08.2021	Concluding consultation of the draft resolution
Plenum	02.09.2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 September 2021

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

Prof. Hecken