Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Selpercatinib (new therapeutic indication: first-line RET fusion-positive non-small cell lung cancer)

of 15 December 2022

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 trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient selpercatinib (Retsevmo) was listed for the first time on 15 March 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 21 June 2022, selpercatinib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 29 June 2022, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No.2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient selpercatinib with the new therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical

company about the approval for a new therapeutic indication): "Monotherapy for the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) not previously treated with an RET inhibitor".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 4 October 2022, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a decision on whether an additional benefit of selpercatinib 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 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) not previously treated with an RET inhibitor.

Therapeutic indication of the resolution (resolution of 15 December 2022):

This is an extension of the indication for selpercatinib as monotherapy for the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) in first-line not previously treated with an RET inhibitor.

The indication for the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy after platinum-containing chemotherapy and/or treatment with immunotherapy is the subject of the resolution on the benefit assessment of selpercatinib dated 2 September 2021.

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with an advanced RET fusion-positive non-small cell lung cancer (NSCLC) with PD-L1 expression ≥ 50% of tumour cells; first-line therapy

Appropriate comparator therapy:

- Pembrolizumab as monotherapy

b) Adults with an advanced RET fusion-positive non-small cell lung cancer (NSCLC) with PD-L1 expression < 50% of tumour cells; first-line therapy

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

- Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients without EGFR or ALK-positive tumour mutations and with non-squamous histology)

or

- Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for squamous histology)

or

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

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 as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the (G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

On 1. In terms of authorisation status, the active ingredients cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, nab-paclitaxel, paclitaxel, pemetrexed, vindesine, vinorelbine, afatinib, erlotinib, nintedanib, pralsetinib, atezolizumab, bevacizumab, cemiplimab, ipilimumab, nivolumab, pembrolizumab and ramucirumab are available for the treatment of advanced NSCLC.

At this time, it is assumed that no other molecularly stratified therapy (directed against ALK, BRAF, EGFR, exon-20, KRAS p.G12C, METex14, NTRK or ROS1) will be considered for patients at the time of therapy with selpercatinib. Medicinal products for the treatment of NSCLC with ALK translocations, METex14 skipping alteration, BRAF, EGFR, exon-20, KRAS p.G12C, NTRK or ROS1 mutations are therefore not considered.

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

On 3. For advanced NSCLC, resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V on the active ingredients afatinib, atezolizumab, cemiplimab, ipilimumab, nintedanib, nivolumab, pembrolizumab, ramucirumab and pralsetinib are available.

Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (off-label use): Carboplatin-containing medicinal products for advanced non-small cell lung cancer (NSCLC) – combination therapy

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

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

Among the approved active ingredients listed under 1., only certain active ingredients 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 this time, it is assumed that no other molecularly stratified therapy (directed against ALK, BRAF, EGFR, exon-20, KRAS p.G12C, METex14, NTRK or ROS1) will be considered for patients at the time of therapy with selpercatinib.

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

The present therapeutic indication includes first-line patients and those, whose disease has progressed after receiving prior therapy. In a previous benefit assessment procedure, the use of selpercatinib in patients after pretreatment with platinum-based chemotherapy and/or immunotherapy was already assessed (resolution of 21 September 2021). Due to the extension of the indication, only the first-line treatment in the indication area is considered in this assessment.

In first-line treatment of advanced NSCLC, based on the available evidence on treatment options, PD-L1 expression is differentiated into two sub-populations with a PD-L1 expression cut-off value of 50%.

a) *First-line therapy PD-L1 expression ≥ 50%*

Current guidelines recommend pembrolizumab monotherapy for first-line treatment of metastatic NSCLC when PD-L1 expression is ≥ 50%, regardless of histologic status. The corresponding benefit assessment showed an indication of a major additional benefit compared to platinum-based chemotherapy (resolution of 3 August 2017).

For non-squamous NSCLC, pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy was also subject to benefit assessment in the patient group with a PD-L1 expression of ≥ 50% (resolution of 19 September 2019). The data basis for this assessment was an adjusted indirect comparison versus pembrolizumab monotherapy. There was a benefit for overall survival but with relevant subgroup differences, which is why the extent of the additional benefit could not be quantified in relation to the entire sub-population of patients with PD-L1 expression ≥ 50%. In addition, an assessment of symptomatology and health-related quality of life was not possible. As a result, a non-quantifiable additional benefit was determined. For the present resolution, pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy is not determined to be an appropriate comparator therapy for the present patient group.

For squamous NSCLC, the combination of pembrolizumab plus carboplatin and either paclitaxel or nab-paclitaxel is approved for first-line therapy. For patients with PD-L1 expression ≥ 50% of the tumour cells or a TPS ≥ 50%, no additional benefit over pembrolizumab monotherapy was identified by the G-BA in its resolution of 19 September 2019, as no suitable data were available for comparison with the appropriate comparator therapy. This combination therapy is therefore not considered an appropriate comparator therapy for the present patient population.

With the combination therapies of atezolizumab plus bevacizumab, paclitaxel and carboplatin, as well as atezolizumab plus nab-paclitaxel and carboplatin, two further treatment options are available for non-squamous NSCLC. In the corresponding benefit assessments, no additional benefit was identified for both combination therapies for patients with a PD-L1 expression ≥ 50% compared to the appropriate comparator therapy (in each case pembrolizumab monotherapy) (resolutions of 2 April 2020). Against the background of the previously mentioned alternative treatment options for

which an additional benefit could be found, the atezolizumab combination therapies are not determined to be appropriate comparator therapies for the present resolution.

Furthermore, the combination of nivolumab and ipilimumab and 2 cycles of platinum-based chemotherapy is available as another treatment option. The benefit assessment identified no additional benefit compared to pembrolizumab monotherapy for patients with PD-L1 expression ≥ 50% (resolutions of 3 June 2021). Nivolumab in combination with ipilimumab and platinum-based chemotherapy is not determined to be an appropriate comparator therapy for the present patient group, taking into account the results of the benefit assessment in relation to the treatment options mentioned above for the present resolution.

Furthermore, with atezolizumab as monotherapy and cemiplimab as monotherapy, further treatment options are available for patients with a PD-L1 expression ≥ 50%.

For atezolizumab as monotherapy, the G-BA determined in the benefit assessment procedure for patients with a PD-L1 expression ≥ 50% on the basis of an adjusted indirect comparison that an additional benefit is not proven (resolution of 19 November 2021). In the benefit assessment of cemiplimab as monotherapy, no additional benefit was identified in the resolution of 20 January 2022; no suitable data were available. The active ingredients are not determined to be appropriate comparator therapy for the present resolution.

For adults with advanced RET fusion-positive NSCLC, the still fairly new therapy option pralsetinib is available. No additional benefit was identified in the associated benefit assessment (resolution of 16 June 2022). For the present resolution, pralsetinib is not determined to be an appropriate comparator therapy.

Based on this data, the G-BA determined pembrolizumab as monotherapy as the sole appropriate comparator therapy for the first-line treatment of patients with a PD-L1 expression ≥ 50%.

b) *First-line therapy, PD-L1 expression < 50%*

For patients with a PD-L1 expression < 50%, platinum-based combination chemotherapy (cis- or carboplatin) with a third-generation cytostatic agent (vinorelbine, gemcitabine, docetaxel, paclitaxel, or pemetrexed) is a therapy standard according to the available evidence. However, no preference for a particular combination can be inferred from the evidence. In contrast to cisplatin, carboplatin is not approved for the treatment of NSCLC, but can be prescribed as "off-label use" for patients (see Annex VI to Section K of the Pharmaceuticals Directive), whereby the selection of the platinum component should be based on the different toxicity profile and existing comorbidities of the patients.

Nab-paclitaxel is approved in combination with carboplatin for the first-line treatment of NSCLC. In the guidelines, this combination is recommended in the present therapeutic indication, therefore the G-BA classifies nab-paclitaxel in combination with carboplatin as a further appropriate therapy option for patients with a PD-L1 expression of < 50%.

In the benefit assessment, a hint for a non-quantifiable additional benefit was identified for pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (resolution of 19 September 2019) for patients with non-squamous NSCLC and a PD-L1 expression of < 50% compared with pemetrexed in combination with platinum-containing chemotherapy. For the present determination of the appropriate comparator therapy, it is taken into account that a meta-analysis of

two randomised controlled trials forms the data basis for this sub-population. Overall, the G-BA also considers this therapy option to be another appropriate comparator therapy (only in the case of non-squamous histology) for patients with a PD-L1 expression < 50%.

For pembrolizumab in combination with carboplatin and (nab-)paclitaxel, a hint of considerable additional benefit for squamous NSCLC in patients with PD-L1 expression < 50% was declared by resolution dated 19 September 2019. On this data basis, the G-BA also determines pembrolizumab in combination with carboplatin and (nab-)paclitaxel to be another appropriate comparator therapy.

For the combination therapies of atezolizumab plus bevacizumab, paclitaxel and carboplatin as well as atezolizumab plus nab-paclitaxel and carboplatin in non-squamous NSCLC, no additional benefit was identified in the respective benefit assessments for patients with PD-L1 expression < 50% (TPS) compared to the appropriate comparator therapy (resolutions of 2 April 2020). Against the background of the previously mentioned alternative treatment options for which an additional benefit could be found, the atezolizumab combination therapies are not determined to be appropriate comparator therapies for the present resolution.

For atezolizumab as monotherapy, no data were available for the benefit assessment procedure for patients with PD-L1 expression < 50% (TPS), so that the additional benefit is not proven (resolution of 19 November 2021). Atezolizumab is not determined to be an appropriate comparator therapy for this resolution.

Furthermore, nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is available. In the benefit assessment, an indication of a minor additional benefit compared to the appropriate comparator therapy (platinum-based chemotherapy) was found for patients with a PD-L1 expression < 50% (resolutions of 3 June 2021). In relation to the results of the benefit assessment on the alternative treatment options indicated above, the combination of nivolumab, ipilimumab and 2 cycles of platinum-based chemotherapy is not determined to be an appropriate comparator therapy for the present resolution.

There are no clear recommendations in the guidelines for patients with a deteriorated general condition (ECOG performance status (PS) 2). Taking into account patient-individual criteria, it should be weighed here against the background of the toxicity profile of a platinum-based combination chemotherapy versus the expected benefit. In this regard, monotherapy with gemcitabine or vinorelbine is considered appropriate as an alternative to combination chemotherapy for patients with ECOG-PS 2.

For adults with advanced RET fusion-positive NSCLC, the still fairly new therapy option pralsetinib is available. No additional benefit was identified in the associated benefit assessment (resolution of 16 June 2022). For the present resolution, pralsetinib is not determined to be an appropriate comparator therapy.

In the overall assessment, the G-BA determines cisplatin in combination with a third-generation cytostatic agent, carboplatin in combination with a third-generation cytostatic agent, carboplatin in combination with nab-paclitaxel, pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy, pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel, and a monotherapy with gemcitabine or vinorelbine as equally appropriate comparator therapies for patients with a PD-L1 expression < 50%. The additional benefit can be demonstrated compared to one of the treatment options mentioned.

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

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

2.1.3 Extent and probability of the additional benefit

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

a) Adults with an advanced RET fusion-positive non-small cell lung cancer (NSCLC) with PD-L1 expression ≥ 50% of tumour cells; first-line therapy

An additional benefit is not proven.

b) Adults with an advanced RET fusion-positive non-small cell lung cancer (NSCLC) with PD-L1 expression < 50% of tumour cells; first-line therapy

An additional benefit is not proven.

Justification:

a) Adults with an advanced RET fusion-positive non-small cell lung cancer (NSCLC) with PD-L1 expression ≥ 50% of tumour cells; first-line therapy

and

b) Adults with an advanced RET fusion-positive non-small cell lung cancer (NSCLC) with PD-L1 expression < 50% of tumour cells; first-line therapy

Data basis:

In the dossier for the benefit assessment, the pharmaceutical company submits the results of the approval study on selpercatinib. This is the LIBRETTO-001 study, in which patients aged 12 years and older with locally advanced or metastatic solid tumours were enrolled, regardless of RET status and pretreatment.

LIBRETTO-001

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

The study was conducted in 84 study sites in 16 countries in Europe, North America, and Asia-Pacific.

Phase 1 of the LIBRETTO-001 study

Phase 1 of the LIBRETTO-001 study investigated dose escalation in patients 12 years of age and older with locally advanced or metastatic solid tumours, regardless of RET status and pretreatment, who showed disease progression or were intolerant to previous standard

therapies. The presence of an alteration of the RET gene was only an inclusion criterion after the minimum plasma concentration of selpercatinib specified in the study protocol had been reached. Pretreatment with certain 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 aged 12 years and older with locally advanced or metastatic solid tumours with RET alteration were enrolled into different cohorts. Cohort 2, which is relevant for the present therapeutic indication, included patients with advanced or metastatic solid tumours with RET fusion without prior standard therapy.

Treatment was started for all patients in phase 2, regardless of body weight, with 160 mg 2 times a day in cycles of 28 days. Treatment was continued until the occurrence of unacceptable toxicity or another event leading to therapy discontinuation (e.g. death). In the event of disease progression, the 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.

For the benefit assessment in the present therapeutic indication, the pharmaceutical company uses the sub-population of patients with advanced RET fusion-positive NSCLC who have not yet received first-line therapy.

Comparator data

The LIBRETTO-001 approval study is an uncontrolled study. Thus, this study does not include a comparator group which allows comparison of the results of treatment with selpercatinib. For a comparison of selpercatinib, the pharmaceutical company included the Gautschi 2017, Lee 2020, Shen 2020 (all three with intervention chemotherapy [different regimens]) and Bhandari 2021 studies (intervention: Programmed Cell Death 1 [PD-1] / Programmed Cell Death-Ligand 1 [PD-L1] antibody in combination with platinum-based chemotherapy). These studies are all retrospective data collections, whereby in the three studies presented with chemotherapy intervention, neither information on the treatment or observation duration nor on the PD-L1 expression of the tumour cells is available. In the dossier, the pharmaceutical company first descriptively compares the results of the data cut-off 4 (15.06.2021) for the endpoints of overall survival, progression-free survival (PFS) and tumour response with those of the four studies in its study pool for the patient group it has selected (first-line). Based on the descriptive comparison, the pharmaceutical company additionally calculates approximate relative risks with 95% confidence intervals and p values for the endpoint of tumour response.

Kaplan-Meier curves were available from the Shen 2020 study for the endpoints of overall survival and PFS, which were used for time-to-event analyses. Based on these data, the pharmaceutical company presents both non-weighted comparisons and matching adjusted indirect comparison (MAIC) analyses.

Gautschi 2017 (chemotherapy)

In the Gautschi 2017 study, which was conducted in a total of 29 study sites in Europe, Asia and the United States, 165 patients with RET fusion-positive NSCLC identified between June

2015 and April 2016 were enrolled. Patients could have received 1 or more prior therapy/ therapies consisting of an RET inhibitor or systemic chemotherapy. The pharmaceutical company is considering 84 of these patients for the comparison of overall survival and PFS who received platinum-based chemotherapy in the first-line, predominantly in combination with pemetrexed (66 of the 84 patients).

Lee 2020 (chemotherapy)

In the Lee 2020 study, 59 patients with RET fusion-positive NSCLC who were treated at Samsung Medical Center in Seoul, South Korea, between January 2006 and January 2018 were enrolled. The patients could have already received one or more prior therapies, but no further information is available. For the comparison of tumour response, the pharmaceutical company is considering 36 patients who received pemetrexed-based chemotherapy in the first-line.

Shen 2020 (chemotherapy)

In the Shen 2020 study, 62 adult patients with RET fusion-positive NSCLC (50 of whom with an advanced stage of the disease), who were identified in 10 hospitals in China between 2011 and 2018 and could have received prior therapy but for whom no further information is available, were enrolled. For the comparison, the pharmaceutical company uses 38 patients who received platinum-based chemotherapy with or without pemetrexed or pemetrexed as monotherapy in the first-line and for whom data on overall survival and PFS were available. Only assumptions can be made about the duration of observation on the basis of the Kaplan-Meier curve available here.

Bhandari 2021 (PD-1/ PD-L1 antibody in combination with platinum-based chemotherapy)

In the Bhandari 2021 study, which is based on the Flatiron Health-Foundation Medicine Clinico-Genomic Database (CGDB) and the Guardant Health Database (GHD), data from a total of 69 patients with RET fusion-positive advanced NSCLC were analysed. For its comparisons, the pharmaceutical company exclusively considers 12 patients from the CGDB who received carboplatin, pemetrexed and pembrolizumab in the first-line. However, no data are available on the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutational status, nor on the histology of the tumours in these patients. In addition, information on PD-L1 expression is available for 45% of the 69 patients (divided into ≥ 1% and < 1% of the tumour cells).

Methodology of the comparison of individual arms of different studies

For the endpoints of overall survival, PFS and tumour response, the pharmaceutical company presents comparisons of individual arms or MAIC analyses without a bridge comparator. In the comparisons of individual arms submitted by the pharmaceutical company, results from different studies are compared without adjustment for potentially relevant effect modifiers or prognostic factors. These are subject to inherent uncertainty due to the lack of randomisation.

The MAIC analyses presented are unsuitable for the benefit assessment. In the case of non-randomised comparisons without a bridge comparator, only those procedures that are carried out using individual patient data, in contrast to MAIC analysis, are generally useful for

confounder adjustment. In contrast, the MAIC analysis accounts for confounding based on aggregate data. Moreover, there are no effects for the only patient-relevant endpoint of overall survival for which it can be safely excluded in the present setting of a comparison of individual arms from different studies that they do not result solely from a systematic risk of bias due to confounding variables.

Overall assessment

The results of the single-arm LIBRETTO-001 study presented alone are unsuitable for assessing the additional benefit of selpercatinib as they do not allow a comparison with the appropriate comparator therapy.

In the dossier, the pharmaceutical company first descriptively compares the results of the data cut-off 4 (15.06.2021) for its first-line sub-population on the endpoints of overall survival, progression-free survival and tumour response with those of the four studies in its study pool and then performs unsuitable MAIC analyses without a bridge comparator.

Furthermore, in the comparisons of individual arms from different studies submitted by the pharmaceutical company, there is no subdivision according to PD-L1 expression. It is therefore not possible to verify whether the patients in the studies on the comparator side received a therapy in accordance with the specifications for the appropriate comparator therapy.

Regardless of the implementation of the appropriate comparator therapy in the comparator studies, the comparisons conducted by the pharmaceutical company are unsuitable for the assessment of the additional benefit of selpercatinib.

Overall, the data presented are unsuitable 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 advanced RET fusion-positive NSCLC in the first-line is not proven.

2.1.4 Limitation of the period of validity of the resolution

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

The pharmaceutical company is obliged to submit further clinical data on the safety and efficacy of selpercatinib to the EMA for review, which may be relevant for the assessment of the additional benefit of the medicinal product pursuant to Section 35a SGB V. The limitation enables the timely inclusion of the evidence to be provided to the regulatory authority with regard to safety and efficacy in the benefit assessment of the medicinal product according to Section 35a SGB V.

Regarding the evidence to be provided, the EMA requires that the results of the phase III LIBRETTO-431 study (J2G-MC-JZJC) be submitted to confirm the efficacy and safety of selpercatinib in the treatment of adult patients with advanced RET fusion-positive NSCLC compared to the treatment with platinum-based and pemetrexed therapy with or without pembrolizumab. The final clinical study report is expected on 31 December 2024.

The patient population of the LIBRETTO-431 study includes, among others, patients with metastatic NSCLC who have not yet received systemic therapy to treat the metastatic disease (first-line therapy). Thus, clinical efficacy and safety data from the LIBRETTO-431 study that are relevant for the assessment of the medicinal product's benefit in the first-line therapy are expected. Against this background, it is justified to limit in time the resolution for both patient groups until further scientific evidence is available for the assessment of the additional benefit of selpercatinib. The limitation enables the expected results from the LIBRETTO-431 study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V.

For this purpose, the G-BA considers a limitation for the resolution until 31 December 2025 to be appropriate.

Conditions of the limitation

For the new benefit assessment of selpercatinib in the first-line after expiry of the deadline, the results from the final clinical study report of the LIBRETTO-431 study on overall survival as well as on all other patient-relevant endpoints used for the evidence of additional benefit are to be submitted in the dossier.

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

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, No. 6 VerfO, the procedure for the benefit assessment of the medicinal product selpercatinib recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of selpercatinib in relation to the appropriate comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 8, number 5 VerfO). If the assessment is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

The possibility that a benefit assessment for the medicinal product selpercatinib can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1, paragraph 2, nos. 2 – 4 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Retsevmo with the active ingredient selpercatinib.

This medicine has been given 'conditional approval' in the following therapeutic indication.

Retsevmo as monotherapy is indicated for the treatment of adults with:

– advanced RET fusion-positive non-small cell lung cancer (NSCLC) not previously treated with an RET inhibitor.

The assessment refers exclusively to the first-line treatment of RET fusion-positive NSCLC, whereby 2 patient groups were distinguished:

a) Adults with an advanced RET fusion-positive non-small cell lung cancer (NSCLC) with PD-L1 expression ≥ 50% of tumour cells; first-line therapy

and

b) Adults with an advanced RET fusion-positive non-small cell lung cancer (NSCLC) with PD-L1 expression < 50% of tumour cells; first-line therapy

About patient group a)

Pembrolizumab was determined to be the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company submitted the results from the ongoing, prospective LIBRETTO-001 basket study for the treatment with selpercatinib. This is an uncontrolled study and therefore, does not include a comparator group.

Overall, the data presented are unsuitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of selpercatinib as monotherapy in adults with advanced RET fusion-positive NSCLC with a PD-L1 expression ≥ 50% of tumour cells in first-line therapy is not proven.

About patient group b)

The appropriate comparator therapy includes platinum-based (cisplatin/ carboplatin) chemotherapy, which may also be combined with an immune checkpoint inhibitor (pembrolizumab) with or without pemetrexed, paclitaxel or nab-paclitaxel. For adults with an ECOG performance status of 2, monochemotherapy may be considered as an alternative.

For the benefit assessment, the pharmaceutical company submitted the results from the ongoing, prospective LIBRETTO-001 basket study for the treatment with selpercatinib. This is an uncontrolled study and therefore, does not include a comparator group.

Overall, the data presented are unsuitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of selpercatinib as monotherapy in adults with advanced RET fusion-positive NSCLC with a PD-L1 expression < 50% of tumour cells in first-line therapy is not proven.

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

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

For the number of German patients with lung cancer, the projected incidence for 2021 (60,333 patients) is used as the basis for the calculations.

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

1. The percentage of lung cancer patients with NSCLC is between 73.6 and 83.6% (44,405 to 50,483 patients).
2. Of these, 51.8 to 61.6% of patients are in stage IIIB and IV at initial diagnosis (23,001 to 31,070 patients). The number of patients in stage I and IIA who have progressed to stage IV in 2021 is 5,866 to 8,364. The total number of patients in tumour stage IIIB and IV is 28,867 to 39,434.
3. First-line therapy is given in 76.9 to 96.1% of cases (22,199 - 37,896 patients).
4. The percentage of patients with RET fusion is 0.6 to 0.9% (133 to 341 patients).
5. The percentage of patients with PD-L1 expression ≥ 50% of tumour cells is 25.9 to 28.9% (35 to 99 patients) and PD-L1 expression < 50% of tumour cells is 71.1 to 74.1% (95 to 253 patients).
6. Considering 88.3% of patients are insured by the SHI, there are 114 to 310 patients in the first-line therapy (PD-L1 expression ≥ 50%): 30 to 87 patients; PD-L1 expression < 50%: 84 to 223 patients)

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

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Retsevmo (active ingredient: selpercatinib) at the following publicly accessible link (last access: 6 December 2022):

https://www.ema.europa.eu/en/documents/product-information/retsevmo-epar-product-information_en.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 other doctors from specialist groups participating in the Oncology Agreement.

This medicine has been given 'conditional approval'. 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.

RET testing

The selection of patients for treatment of advanced RET fusion-positive NSCLC should be based on a validated test method.

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 November 2022).

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Selpercatinib	2 x daily	365	1	365
Appropriate comparator therapy				
Patient population a)				
Pembrolizumab as monotherapy				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Patient population b)				
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[2])				
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Vinorelbine	2 x per 21-day cycle	17.4	2	34.8
Gemcitabine	2 x per 21-day cycle	17.4	2	34.8
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4

[2] except in the case of predominantly squamous histology

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[2])				
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Vinorelbine	2 x per 21-day cycle	17.4	2	34.8
Gemcitabine	2 x per 21-day cycle	17.4	2	34.8
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Carboplatin in combination with nab-paclitaxel				
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
nab-paclitaxel	3 x per 21-day cycle	17.4	3	52.2
Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy[3]				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel[4]				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4

[3] Only for patients without EGFR or ALK-positive tumour mutations and with non-squamous histology

[4] only for squamous histology

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	or			
	1 x per 42-day cycle	8.7	1	8.7
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
nab-paclitaxel	3 x per 21-day cycle	17.4	3	52.2
Monotherapy with gemcitabine or vinorelbine[5]				
Gemcitabine	3 x per 28-day cycle	13.0	3	39
Vinorelbine	1 x every 7 days	52.1	1	52.1

Consumption:

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

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

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.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements 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)[6].

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

[5] only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment
[6] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

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 (area under the curve). For the use of carboplatin in combination with nab-paclitaxel, a dosage of AUC 6.0 is also used, according to the product information.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Selpercatinib	160 mg	320 mg	4 x 80 mg	365	1,460 x 80 mg
Appropriate comparator therapy					
Patient population a)					
Pembrolizumab as monotherapy					
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
Patient population b)					
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[2])					
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
	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
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
Gemcitabine	1,250 mg/m² = 2,375 mg	2,375 mg	1 x 2,000 mg + 2 x 200 mg	34.8	34.8 x 2,000 mg + 69.6 x 200 mg
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 mg + 1 x 150 mg	17.4	34.8 x 100 mg + 17.4 x 150 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[2])					
Carboplatin	500 mg/m² = 950 mg	950 mg	2 x 450 mg + 1 x 50 mg	17.4	34.8 x 450 mg + 17.4 x 50 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
Gemcitabine	1,250 mg/m² = 2,375 mg	2,375 mg	1 x 2,000 mg + 2 x 200 mg	34.8	34.8 x 2,000 mg + 69.6 x 200 mg
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 mg + 1 x 150 mg	17.4	34.8 x 100 mg + 17.4 x 150 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg
Carboplatin in combination with nab-paclitaxel					
Carboplatin	500 mg/m² = 950 mg	950 mg	2 x 450 mg + 1 x 50 mg	17.4	34.8 x 450 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
Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy[2]					
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
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
Carboplatin	500 mg/m² = 950 mg	950 mg	2 x 450 mg + 1 x 50 mg	17.4	34.8 x 450 mg + 17.4 x 50 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	1 x 1,000 mg	17.4	17.4 x 1,000 mg
Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel[3]					
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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Carboplatin	500 mg/m² = 950 mg	950 mg	2 x 450 mg + 1 x 50 mg	17.4	34.8 x 450 mg + 17.4 x 50 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 mg + 1 x 150 mg	17.4	34.8 x 100 mg + 17.4 x 150 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[4]					
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/mg² = 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

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Selpercatinib 80 mg	112 HC	€ 4,119.95	€ 1.77	€ 232.00	€ 3,886.18
Appropriate comparator therapy					
Carboplatin 450 mg	1 CIS	€ 228.21	€ 1.77	€ 10.29	€ 216.15
Carboplatin 50 mg	1 CIS	€ 34.63	€ 1.77	€ 1.11	€ 31.75
Cisplatin 100 mg	1 CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
Cisplatin 50 mg	1 CIS	€ 47.67	€ 1.77	€ 1.73	€ 44.17
Cisplatin 10 mg	1 CIS	€ 17.49	€ 1.77	€ 0.30	€ 15.42
Docetaxel 80 mg	1 CIS	€ 415.86	€ 1.77	€ 19.20	€ 394.89
Gemcitabine 200 mg	1 CIS	€ 28.81	€ 1.77	€ 0.83	€ 26.21

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
Gemcitabine 2,000 mg	1 CIS	€ 194.20	€ 1.77	€ 8.68	€ 183.75
nab-paclitaxel 100 mg	1 PIS	€ 429.33	€ 1.77	€ 52.91	€ 374.65
Paclitaxel 100 mg	1 CIS	€ 304.03	€ 1.77	€ 13.89	€ 288.37
Paclitaxel 150 mg	1 CIS	€ 450.83	€ 1.77	€ 20.86	€ 428.20
Pembrolizumab 100 mg	1 CIS	€ 3,035.99	€ 1.77	€ 170.10	€ 2,864.12
Pemetrexed 1,000 mg	1 CIS	€ 2,239.34	€ 1.77	€ 106.80	€ 2,130.54
Vinorelbine 10 mg	1 CIS	€ 38.87	€ 1.77	€ 1.31	€ 35.79
Vinorelbine 50 mg	1 CIS	€ 152.61	€ 1.77	€ 6.71	€ 144.13
Abbreviations: HC = hard capsules, CIS = concentrate for the preparation of an infusion solution, PIS = powder for the preparation of an infusion suspension					

LAUER-TAXE® last revised: 15 November 2022

Costs for additionally required SHI services:

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

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

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I to 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.

In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.

Type of service	Cost/pack (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Cost/ service	Treatment days/ year	Cost/ patient/ year
Medicinal product to be assessed: selpercatinib							
Not applicable							
Appropriate comparator therapy							

Type of service	Cost/pack (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Cost/ service	Treatment days/ year	Cost/ patient/ year
Cisplatin							
Mannitol 10% infusion solution, 37.5 g/day, 10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	€ 9.11	17.4	€ 158.51
Sodium chloride 0.9% infusion solution, 3 - 4.4 l/day, 10 x 500 ml INF/ 10 x 1,000 ml INF	€ 22.72 € 34.68	€ 1.14 € 1.73	€ 0.69 € 1.08	€ 20.89 € 31.87	€ 9.56 - € 14.84	17.4 17.4	€ 166.36 - € 258.16
Paclitaxel							
Dexamethasone 20 mg[7], 50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08	€ 2.34	17.4	€ 40.74
Dimetindene IV 1 ml/ 10 kg, 5 x 4 mg SFI	€ 23.67	€ 1.77	€ 5.58	€ 16.32	€ 6.53	17.4	€ 113.59
Cimetidine 300 mg IV, 10 CIS x 200 mg	€ 19.77	€ 1.77	€ 0.40	€ 17.60	€ 3.52	17.4	€ 61.25
Pemetrexed							
Dexamethasone 2 x 4 mg[7], 100 TAB	€ 79.50	€ 1.77	€ 5.40	€ 72.33	€ 1.45	52.2	€ 75.51
Folic acid 350 – 1,000 µg/day, 100 TAB	€ 16.89	€ 0.84	€ 2.52	€ 13.53	€ 0.14 - € 0.27	365	€ 49.39 - € 98.77
Vitamin B12[7] 1,000 µg/day, every 3 cycles, 10 SFI	€ 7.40	€ 0.37	€ 0.33	€ 6.70	€ 0.67	5.8	€ 3.89

[7] Fixed reimbursement rate

Type of service	Cost/pack (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Cost/ service	Treatment days/ year	Cost/ patient/ year
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 € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Selpercatinib

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal

product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 07 December 2021, 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 24 May 2022.

On 29 June 2022, 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 2 VerfO.

By letter dated 29 June 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 28 September 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 4 October 2022. The deadline for submitting written statements was 25 October 2022.

The oral hearing was held on 7 November 2022.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 6 December 2022, and the proposed resolution was approved.

At its session on 15 December 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 December 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	24 May 2022	New determination of the appropriate comparator therapy
Working group Section 35a	1 November 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 November 2022	Conduct of the oral hearing
Working group Section 35a	15 November 2022 29 November 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	6 December 2022	Concluding discussion of the draft resolution
Plenum	15 December 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 December 2022

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

Prof. Hecken