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 Pralsetinib (lung cancer, non-small cell, RET fusion+)

of 16 June 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 relevant date for the first placing on the (German) market of the active ingredient pralsetinib 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 December 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 14 December 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 March 2022 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of pralsetinib compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with

the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of pralsetinib.

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 Pralsetinib (Gavreto) in accordance with the product information

Gavreto is indicated as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.

Therapeutic indication of the resolution (resolution of 16.06.2022):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for pralsetinib:

- Pembrolizumab as monotherapy

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

Appropriate comparator therapy for pralsetinib:

- 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

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

- 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)

c) <u>Adults with RET fusion-positive advanced non-small cell lung cancer (NSCLC) after first-line therapy with a PD-1/PD-L1 antibody as monotherapy</u>

Appropriate comparator therapy for pralsetinib:

- 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)

d) <u>Adults with RET fusion-positive advanced non-small cell lung cancer (NSCLC) after first-line therapy with cytotoxic chemotherapy</u>

Appropriate comparator therapy for pralsetinib:

- 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, PD-L1 expression ≥ 1% of tumour cells)

or

- Atezolizumab

or

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

e) Adults with RET fusion-positive advanced non-small cell lung cancer (NSCLC); after first-line therapy with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy

Appropriate comparator therapy for pralsetinib:

Patient-individual therapy with selection of:

- Afatinib
- Pemetrexed
- Erlotinib
- Docetaxel
- Docetaxel in combination with ramucirumab
- Docetaxel in combination with nintedanib
- Vinorelbine

taking into account the previous therapy and histology.

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 cytostatic agents cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine and vinorelbine, the protein kinase inhibitors afatinib, erlotinib, nintedanib and selpercatinib, and the antibodies atezolizumab, cemiplimab, nivolumab, pembrolizumab and ramucirumab are available for the treatment of advanced NSCLC.

Medicinal products for the treatment of NSCLC with ALK translocations and EGFR, BRAF or ROS1 mutations were not considered here according to the therapeutic indication.

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 selpercatinib 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.

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. Thus, several lines of therapy are addressed in the appropriate comparator therapy.

<u>First-line therapy</u>

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 considerable 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. Based on these data, the combination therapy of pembrolizumab and platinum-containing chemotherapy is currently not considered 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 and 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 currently not considered to be appropriate comparator therapies, taking into account the current evidence.

Furthermore, the combination of nivolumab and ipilimumab and 2 cycles of platinum-based chemotherapy is still available as a fairly new treatment option in care. 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 currently determined to be an appropriate comparator therapy for the present patient group, taking into account the available evidence and the results of the benefit assessment in relation to the treatment options mentioned above.

Furthermore, with atezolizumab as monotherapy and cemiplimab as monotherapy, two new 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 therapeutic significance of these two options is not yet considered to be conclusively assessable. The active ingredients are currently not being considered as 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 therapy option (only in the case of non-squamour 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. Currently, the guidelines mentioned in the search and synopsis of evidence do not yet provide a clear recommendation for the use of the aforementioned combination therapy. However, it became clear from the statements of scientific-medical societies in recent benefit assessments in the present therapeutic indication that this combination has a relevant significance in care.

For the combination therapies of atezolizumab plus bevacizumab, paclitaxel and carboplatin and 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 currently not considered to be appropriate comparator therapies, taking into account the current evidence.

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 currently considered an appropriate comparator therapy.

Furthermore, nivolumab is available in combination with ipilimumab and 2 cycles of platinum-based chemotherapy. 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). However, as already explained, this combination is still a relatively new treatment option in the care, the therapeutic significance of which cannot yet be conclusively assessed. In relation to the results of the benefit assessment on the alternative treatment options mentioned above and taking into account the current evidence, the combination of nivolumab, ipilimumab and 2 cycles of platinum-based chemotherapy is currently not considered 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 therapy options mentioned.

Subsequent lines of therapy

In subsequent lines of therapy, depending on the first-line therapy, a distinction is made between c) patients with a PD-1/PD-L1 antibody monotherapy pretreatment, d) patients with cytotoxic chemotherapy pretreatment and e) after first-line therapy with a PD 1/PD-L1 antibody in combination with a platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and a platinum-containing chemotherapy as pretreatment.

c) Following first-line therapy with a 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 assigned the highest significance 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 therapy standard. It cannot be deduced from the available evidence that a combination is clearly inferior or superior in terms of therapeutic benefit. In contrast to cisplatin, carboplatin is not approved for the treatment of NSCLC, but can be prescribed as "off-label use" (see Annex VI to Section K of the Pharmaceuticals Directive), whereby the selection of the platinum component (carboplatin or cisplatin) should be based in the specific case on the different toxicity profile of the two substances and on the 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 a platinum-based combination chemotherapy must be weighed against the expected benefit, taking into account 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 prior therapy is not interpreted as

a line of therapy to be considered with regard to the marketing authorisation of the medicinal products.

For adults with advanced RET fusion-positive NSCLC, the still fairly new therapy option selpercatinib is also available. No additional benefit was proven in the associated benefit assessment (resolution of 2 September 2021). As the therapeutic significance cannot yet be conclusively assessed, selpercatinib is currently not considered as an appropriate comparator therapy.

In the overall assessment, the G-BA determined cisplatin in combination with a third-generation cytostatic, carboplatin in combination with a third-generation cytostatic, carboplatin in combination with nab-paclitaxel and monotherapy with gemcitabine or vinorelbine as equally appropriate comparator therapies for this patient group. The additional benefit can be demonstrated compared to one of the therapy options mentioned.

d) Following first-line therapy with cytotoxic chemotherapy

For patients for whom further antineoplastic therapy is indicated after first-line chemotherapy, several treatment 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, partly only under certain conditions.

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

For nivolumab for the treatment of patients after prior chemotherapy and squamous tumour histology, an indication of a considerable additional benefit was identified in the benefit assessment compared to docetaxel (resolution of 4 February 2016). For the treatment of patients after prior chemotherapy and non-squamous tumour histology, an indication of a considerable additional benefit was also identified for nivolumab in the benefit assessment compared to 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 to docetaxel (pembrolizumab: resolution of 2 February 2017, atezolizumab: resolution of 16 March 2018). According to the marketing authorisation for the present therapeutic indication, pembrolizumab is only indicated for patients with PD-L1 expressing tumours (TPS ≥ 1%).

Nivolumab, pembrolizumab and atezolizumab each lead to a significant prolongation in overall survival compared with docetaxel and also to a significant reduction in side effects. Accordingly, the guidelines regularly prefer 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, in PD-L1 negative tumours, alternative cytotoxic chemotherapeutic agents are also determined as an appropriate comparator therapy for the immune checkpoint inhibitors.

For ramucirumab in combination with docetaxel, no additional benefit was shown 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 to docetaxel (resolution of 20 October 2016). Taking into account that benefit-assessed medicinal therapies with an additional benefit are available in the present indication, 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.

For adults with advanced RET fusion-positive NSCLC, the still fairly new therapy option selpercatinib is also available. No additional benefit was proven in the associated benefit assessment (resolution of 2 September 2021). As the therapeutic significance cannot yet be conclusively assessed, selpercatinib is currently not considered as an appropriate comparator therapy.

In the overall assessment, the G-BA determined docetaxel, pemetrexed, nivolumab, pembrolizumab, atezolizumab and docetaxel in combination with nintedanib as equally appropriate comparator therapies for this patient group. The additional benefit can be demonstrated compared to one of the therapy options mentioned.

e) Following first-line therapy with a PD-1/PD-L1 antibody in combination with a platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and a platinum-containing chemotherapy

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

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

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

The recommendation of further therapy with a (different) 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 minor additional benefit was identified in the benefit assessment compared to docetaxel monotherapy (resolution of 18 June 2015).

For ramucirumab in combination with docetaxel, no additional benefit was shown in the benefit assessment compared to docetaxel (resolution of 1 September 2016). No additional benefit was identified for afatinib for the treatment of patients with squamous histology in the benefit assessment compared to docetaxel (resolution of 20 October 2016). With regard to the above-mentioned benefit assessments, however, it should be noted that they were based on the treatment setting of a second-line therapy after prior platinum-containing chemotherapy and thus, on an indication that deviated from the present treatment setting with regard to the prior therapy.

For adults with advanced RET fusion-positive NSCLC, the still fairly new therapy option selpercatinib is also available. No additional benefit was proven in the associated benefit assessment (resolution of 2 September 2021). As the therapeutic significance cannot yet be conclusively assessed, selpercatinib is currently not considered as an appropriate comparator therapy.

Overall, in view of the limited evidence for the present treatment setting, the G-BA determined a patient-individual therapy as the appropriate comparator therapy, taking into account the prior therapy and histology, selecting afatinib, pemetrexed, erlotinib, docetaxel, ramucirumab in combination with docetaxel and nintedanib in combination with docetaxel 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 pralsetinib is assessed as follows:

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

An additional benefit is not proven.

c) Adults with RET fusion-positive advanced non-small cell lung cancer (NSCLC) after first-line therapy with a PD-1/PD-L1 antibody as monotherapy

An additional benefit is not proven.

d) Adults with RET fusion-positive advanced non-small cell lung cancer (NSCLC) after first-line therapy with cytotoxic chemotherapy

An additional benefit is not proven.

e) Adults with RET fusion-positive advanced non-small cell lung cancer (NSCLC); after first-line therapy with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy

An additional benefit is not proven.

Justification:

Data basis

ARROW study

For the proof of additional benefit of pralsetinib for the treatment of adults with rearranged-during-transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC), who have not previously been treated with an RET inhibitor, the pharmaceutical company has submitted the results of the ARROW study.

ARROW is an ongoing, international, multicentre, single-arm, open-label, phase I/II study.

Adults with an RET fusion-positive NSCLC, medullary thyroid cancer (MTC) or other RET-altered solid tumours were enrolled in the study.

Depending on the type of pretreatment (none, platinum-based or specific pretreatment), origin of the patients (China or rest of the world) and type of tumour (NSCLC, MTC or other), there are 9 cohorts in the ARROW study, 3 of which include patients with NSCLC:

- Patients with platinum-based pretreatment
- Patients without platinum-based pretreatment
- Patients from China with platinum-based pretreatment

In phase I of the ARROW study, the dose of pralsetinib was escalated, and in phase II, study participants received 400 mg pralsetinib once daily every 4 weeks.

In addition to the co-primary endpoints of objective response rate and assessment of safety and tolerability, endpoints in the categories of mortality, morbidity and health-related quality of life were collected.

About further comparisons submitted

The ARROW study is a single-arm study. Thus, this study does not include a comparator group which allows comparison of the results of treatment with pralsetinib.

For a comparison of pralsetinib versus a comparator therapy, evaluations based on patient-individual data from the IMpower132 study were submitted by the pharmaceutical company. A search for further studies for the appropriate comparator therapy was not conducted.

The IMpower132 study is an international, multicentre, open-label, phase III study that has enrolled adult patients with stage IV non-squamous NSCLC and ECOG PS 0 and 1, who have not received prior treatment for their metastatic disease. No testing for RET fusion was done. Patients received 4 or 6 cycles of carboplatin or cisplatin plus pemetrexed in the control arm or in combination with atezolizumab in the verum arm, as decided by the principal investigators.

The pharmaceutical company presents an indirect comparison of the ARROW study with a cohort (pemetrexed plus cisplatin/carboplatin) from the IMpower132 study using propensity score analyses. However, the analyses are only conducted for the endpoints of overall survival and progression-free survival and the results are only presented additionally by the pharmaceutical company in the dossier. Results for the endpoints of symptomatology, health-

related quality of life and side effects are only presented for the ARROW study. Furthermore, the methodology of the analysis was not sufficiently documented by the pharmaceutical company.

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

and

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

Assessment

The results of the ARROW study presented alone are not suitable for assessing the additional benefit of pralsetinib as they do not allow a comparison with the appropriate comparator therapy.

The comparison presented is not suitable for making any statements on the additional benefit. The methodology of the applied propensity score analyses was not sufficiently documented by the pharmaceutical company. Furthermore, the pharmaceutical company presents results exclusively for the endpoints of overall survival and progression-free survival from the ARROW and IMpower132 studies. Results for the endpoints of symptomatology, health-related quality of life and side effects are only presented for the ARROW study. The results presented for the comparison of the ARROW and IMpower132 studies are thus incomplete. A search for further studies for the comparator therapy was not conducted. Thus, the study pool on the part of the appropriate comparator therapy is potentially incomplete. Furthermore, the observed effects for an indirect comparison without a bridge comparator are not of a magnitude that they could not arise solely due to a systematic bias caused by confounding variables.

Overall, there are therefore no suitable data for the assessment of the additional benefit of pralsetinib compared to the appropriate comparator therapy. Therefore, an additional benefit is not proven.

Pralsetinib may represent a relevant treatment option in specific cases in the present therapeutic indication.

c) Adults with RET fusion-positive advanced non-small cell lung cancer (NSCLC) after first-line therapy with a PD-1/PD-L1 antibody as monotherapy

and

d) Adults with RET fusion-positive advanced non-small cell lung cancer (NSCLC) after first-line therapy with cytotoxic chemotherapy

and

e) Adults with RET fusion-positive advanced non-small cell lung cancer (NSCLC); after first-line therapy with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy

Assessment

In the dossier, the pharmaceutical company considers patients with RET fusion-positive advanced NSCLC who have received a platinum-based chemotherapy and/or treatment with

immune checkpoint inhibitors in the first line of therapy altogether. In deviation from this, the G-BA differentiated the patients into 3 patient groups according to the type of their first-line therapy: PD-1 / PD-L1 antibody as monotherapy vs cytotoxic chemotherapy vs PD-1 / PD-L1 antibody in combination with a platinum-containing chemotherapy or after sequential therapy with a PD-1 / PD-L1 antibody and a platinum-containing chemotherapy.

The results of the ARROW study presented alone are not suitable for assessing the additional benefit of pralsetinib as they do not allow a comparison with the appropriate comparator therapy.

The comparison presented is not suitable for making any statements on the additional benefit. The methodology of the applied propensity score analyses was not sufficiently documented by the pharmaceutical company. Furthermore, the pharmaceutical company presents results exclusively for the endpoints of overall survival and progression-free survival from the ARROW and IMpower132 studies. Results for the endpoints of symptomatology, health-related quality of life and side effects are only presented for the ARROW study. The results presented for the comparison of the ARROW and IMpower132 studies are thus incomplete. A search for further studies for the comparator therapy was not conducted. Thus, the study pool on the part of the appropriate comparator therapy is potentially incomplete. Furthermore, the observed effects for an indirect comparison without a bridge comparator are not of a magnitude that they could not arise solely due to a systematic bias caused by confounding variables.

Overall, there are therefore no suitable data for the assessment of the additional benefit of pralsetinib compared to the appropriate comparator therapy. Therefore, an additional benefit is not proven.

Pralsetinib may represent a relevant treatment option in specific cases in the present therapeutic indication.

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 pralsetinib 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 pralsetinib, which may be relevant for the assessment of the additional benefit of the medicinal product pursuant to Section 35a SGB V, to the EMA for review. 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 AcceleRET-Lung (BLU-667-2303) study be submitted to confirm the efficacy and safety of pralsetinib in the treatment of adult patients with RET fusion-positive advanced NSCLC. The final clinical study report is expected on 31 December 2026.

The patient population of the AcceleRET-Lung study includes 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 AcceleRET-Lung study are expected to be relevant for the assessment of the medicinal product's benefit in the first-line therapy. Against this background, it is justified to limit in time the resolution regarding patient groups a and b until further scientific evidence is available for the assessment of the additional benefit of pralsetinib. The limitation enables the expected results from the AcceleRET-Lung 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 2027 to be appropriate.

Conditions of the limitation:

For the new benefit assessment in patient groups a and b (first-line therapy) after expiry of the deadline, the results from the final clinical study report of the AcceleRET-Lung study on overall survival as well as on all other patient-relevant endpoints used for the proof 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 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of the medicinal product pralsetinib 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 pralsetinib in comparison with the appropriate comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). If the assessment is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

The possibility that a benefit assessment for the medicinal product pralsetinib 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 Gavreto with the active ingredient pralsetinib.

This medicinal product was approved under special conditions.

The active ingredient pralsetinib is approved for the treatment of adult patients with rearranged-during-transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) who have not been previously treated with an RET inhibitor.

In the therapeutic indication under consideration, 5 patient groups were distinguished and the appropriate comparator therapy was determined as follows (abbreviated version):

a) Adults with a PD-L1 expression ≥ 50% of tumour cells in first-line therapy

   The immune checkpoint inhibitor pembrolizumab was determined as the appropriate comparator therapy.

b) Adults with a PD-L1 expression < 50% of tumour cells in first-line therapy

   The appropriate comparator therapy includes platinum-based (cisplatin/ carboplatin) chemotherapy, which can also be combined with an immune checkpoint inhibitor (pembrolizumab). For adults with an ECOG performance status of 2, monochemotherapy may be considered as an alternative.

c) Adults after first-line therapy with a PD-1/PD-L1 antibody as monotherapy

The appropriate comparator therapy includes platinum-based (cisplatin/ carboplatin) chemotherapy. For adults with an ECOG performance status of 2, monochemotherapy may be considered as an alternative.

d) Adults after first-line therapy with cytotoxic chemotherapy

The appropriate comparator therapy includes different chemotherapies without platinum (cisplatin/ carboplatin) as well as treatment with an immune checkpoint inhibitor as monotherapy.

e) Adults after first-line therapy with a PD-1/PD-L1 antibody in combination with a platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and a platinum-containing chemotherapy

The appropriate comparator therapy includes several active ingredients as monotherapy as well as in combination therapies, which are available for a patient-individual treatment decision, taking into account prior therapy and histology.

For the benefit assessment, the pharmaceutical company submitted the results from the ARROW study for the treatment with pralsetinib. This is a non-controlled study that does not include a comparator group and therefore does not allow a comparison with the appropriate comparator therapy.

Furthermore, the pharmaceutical company presents an indirect comparison of the ARROW study with a cohort (pemetrexed plus cis-/carboplatin) from the IMpower132 study. This comparator therapy corresponds to the appropriate comparator therapy for patient group b only. The comparison of individual arms from different studies is not suitable for making statements on the additional benefit. Only overall survival and progression-free survival were compared and the results were only presented additionally in the dossier. The results presented are thus incomplete.

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 pralsetinib is not proven.

Pralsetinib may represent a relevant treatment option in specific cases in the present therapeutic indication.

The resolution is limited in time for patient groups a and b until 31 December 2027.

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

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

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

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

1. The percentage of lung cancer patients with NSCLC is between 73.6% and 83.6% (44,405 to 50,439 patients).

2. Of these, 51.8 to 61.6% of patients are in stage IIIB and IV at initial diagnosis (23,002 to 31,070 patients). The number of patients in stage I and IIA who have progressed to stage IV in

2021 is 5,866 to 8,364 patients. The total number of patients in tumour stage IIIB and IV is 28,868 to 39,434.

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

4. The percentage of patients with 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. Related to step 4, of these, as first-line treatment,

6a. 11.0 to 16.9% (15 to 58 patients) received monotherapy with a PD-1 / PD-L1 antibody,

6b. 48.3 to 57.5% (64 to 194 patients) received chemotherapy or

6c. 31.5 to 33.4% (42 to 114 patients) received a PD-1 / PD-L1 antibody in combination with platinum-containing chemotherapy.

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

7. 38.7 to 45.9% of patients received second-line treatment (51 to 157 patients). Of these, as first-line treatment,

7a. 6 to 26 patients received monotherapy with a PD-1 / PD-L1 antibody (patient population c),

7b. 25 to 90 patients received chemotherapy (patient population d) and

7c. 16 to 52 patients received monotherapy with a PD-1 / PD-L1 antibody and platinum-containing chemotherapy (sub-population e1).

8. The percentage of patients receiving third-line therapy is 30.0 to 40.0% (15 to 63 patients; sub-population e2).

9. Taking into account a percentage of patients insured by the SHI of 88.3%, step 5 in the first-line therapy results in

9a. 30 to 87 patients with a PD-L1 expression ≥ 50% of the tumour cells (patient population a) and

9b. 84 to 223 patients with a PD-L1 expression < 50% of tumour cells (patient population b).

Taking into account a percentage of SHI-insured patients of 88.3%, steps 7a-c and 8 result in 5 to 138 patients after prior therapy with a PD-1 / PD-L1 antibody and/or chemotherapy, of which

9c. 5 to 23 patients with a PD-1 / PD-L1 antibody as first-line treatment (patient population c),

9d. 22 to 79 patients with chemotherapy as first-line treatment (patient population d) and

9e. 14 to 46 patients with a PD-1 / PD-L1 antibody and platinum-containing chemotherapy as first-line treatment (sub-population e1) and 14 to 55 patients with at least two previous systemic therapies (sub-population e2). In total, the number of patients after first-line therapy with a PD-1/PD-L1 antibody in combination with a platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and a platinum-containing chemotherapy is 28 to 101 patients (patient population e).

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 Gavreto (active ingredient: pralsetinib) at the following publicly accessible link (last access: 4 April 2022):
https://www.ema.europa.eu/en/documents/product-information/gavreto-epar-product-information_en.pdf

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

RET testing

The selection of patients for treatment of RET fusion-positive advanced 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: 1 June 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				
Pralsetinib	1 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)				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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
Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)				
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[2]				
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[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
Carboplatin	1 x per 21-day cycle	17.4	1	17.4

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

[3] only for squamous histology

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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[4]				
Gemcitabine	on day 1, 8 and 15 of a 28-day cycle	13.0	3	39
Vinorelbine	1 x every 7 days	52.1	1	52.1
Patient population c)				
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)				
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Gemcitabine	2 x per 21-day cycle	17.4	2	34.8
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Vinorelbine	2 x per 21-day cycle	17.4	2	34.8
Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)				
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Gemcitabine	2 x per 21-day cycle	17.4	2	34.8
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Vinorelbine	2 x per 21-day cycle	17.4	2	34.8
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
Monotherapy with gemcitabine or vinorelbine				
Gemcitabine	on day 1, 8 and 15 of a 28-day cycle	13.0	3	39
Vinorelbine	1 x every 7 days	52.1	1	52.1
Patient population d)				

[4] only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Docetaxel (only for patients with PD-L1 negative tumours)				
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed[5]				
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Nivolumab				
Nivolumab	1 x per 14-day cycle	26.1	1	26.1
Pembrolizumab[6]				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Atezolizumab				
Atezolizumab	1 x per 21-day cycle	17.4	1	17.4
Docetaxel in combination with nintedanib[7]				
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Nintedanib	2 x on day 2-21 of a 21-day cycle	17.4	20	348
Patient population e)				
Patient-individual therapy, taking into account previous therapy and histology with selection of afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib and vinorelbine				
Afatinib				
Afatinib	1 x daily	365	1	365
Pemetrexed				
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Erlotinib				
Erlotinib	1 x daily	365	1	365
Docetaxel				
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Docetaxel in combination with ramucirumab				
Docetaxel	1 x per 21-day cycle	17.4	1	17.4

[5] only for patients with PD-L1 negative tumours and except in the case of predominantly squamous cell histology

[6] only for patients with PD-L1 expressing tumours, PD-L1 expression ≥ 1% of tumour cells

[7] 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)	Treatment days/ patient/ year
Ramucirumab	1 x per 21-day cycle	17.4	1	17.4
Docetaxel in combination with nintedanib				
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Nintedanib	2 x on day 2-21 of a 21-day cycle	17.4	20	348
Vinorelbine				
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 comorbidities) 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 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)[8]

Cisplatin is dosed differently, depending on the concomitant medicinal product. 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.

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.

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

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					
Pralsetinib	400 mg	400 mg	4 x 100 mg	365	1,460 x 100 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)					
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 1000 mg	17.4	17.4 x 1000 mg
Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)					
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 -	47.5 mg - 57 mg	1 x 50 mg - 1 x 50 mg +	34.8	34.8 x 50 mg - 34.8 x 50 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
	30 mg/m² = 57 mg		1 x 10 mg		34.8 x 10 mg
Gemcitabine	1,250 mg/m² = 2,375 mg	2375 mg	1 x 2000 mg + 2 x 200 mg	34.8	34.8 x 2000 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 1000 mg	17.4	17.4 x 1000 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 1000 mg	17.4	17.4 x 1000 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
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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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
Patient population c)					
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)					
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
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 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
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	1 x 1000 mg	17.4	17.4 x 1000 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 (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)					
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
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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	1 x 1000 mg	17.4	17.4 x 1000 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 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
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[4]	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
Patient population d)					
Docetaxel (only for patients with PD-L1 negative tumours)					
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 mg
Pemetrexed[5]					
Pemetrexed	500 mg/m² = 950 mg	950 mg	1 x 1000 mg	17.4	17.4 x 1000 mg
Nivolumab					
Nivolumab	240 mg	240 mg	2 x 120 mg	26.1	52.2 x 120 mg
Pembrolizumab[6]					
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					
Atezolizumab	1,200 mg	1,200 mg	1 x 1,200 mg	17.4	17.4 x 1,200 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
Docetaxel in combination with nintedanib[7]					
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 mg
Nintedanib	200 mg	400 mg	4 x 100 mg	348	1,392 x 100 mg
Patient population e)					
Patient-individual therapy, taking into account previous therapy and histology with selection of afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib and vinorelbine					
Afatinib					
Afatinib	40 mg	40 mg	1 x 40 mg	365	365 x 40 mg
Pemetrexed					
Pemetrexed	500 mg/m² = 950 mg	950 mg	1 x 1000 mg	17.4	17.4 x 1000 mg
Erlotinib					
Erlotinib	150 mg	150 mg	1 x 150 mg	365	365 x 150 mg
Docetaxel					
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 mg
Docetaxel in combination with ramucirumab,					
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 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	2 x 80 mg	17.4	34.8 x 80 mg
Nintedanib	200 mg	400 mg	4 x 100 mg	348	1392 x 100 mg
Vinorelbine					
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

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					
Pralsetinib 100 mg	120 HC	€ 10,108.36	€ 1.77	€ 574.00	€ 9,532.59
Appropriate comparator therapy					
Atezolizumab 1,200 mg	1 CIS	€ 4,151.65	€ 1.77	€ 233.81	€ 3,916.07
Afatinib 40 mg	28 FCT	€ 2,515.23	€ 1.77	€ 140.35	€ 2,373.11
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
Erlotinib 150 mg[9]	30 FCT	€ 880.24	€ 1.77	€ 68.73	€ 809.74
Gemcitabine 200 mg	1 CIS	€ 28.81	€ 1.77	€ 0.83	€ 26.21
Gemcitabine 2000 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
Nintedanib 100 mg	120 SC	€ 2,761.26	€ 1.77	€ 0.00	€ 2,759.49
Nivolumab 120 mg	1 CIS	€ 1,546.93	€ 1.77	€ 85.05	€ 1,460.11
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	€ 3,037.30	€ 1.77	€ 170.17	€ 2,865.36
Pemetrexed 1000 mg	1 CIS	€ 2,239.34	€ 1.77	€ 106.80	€ 2,130.77
Ramucirumab 500 mg	1 CIS	€ 2,141.31	€ 1.77	€ 119.00	€ 2,020.54
Ramucirumab 100 mg	1 CIS	€ 441.14	€ 1.77	€ 23.80	€ 415.57
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: FCT = film-coated tablets, HC = hard capsules, CIS = concentrate for the preparation of an infusion solution, PIS = powder for the preparation of an infusion suspension; SC = soft capsules					

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[9] Fixed reimbursement rate

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: pralsetinib							
Not applicable							
Appropriate comparator therapy							
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	€ 1.14	€ 0.69	€ 20.89	€ 15.12	17.4	€ 263.11 -
	€ 35.47	€ 1.77	€ 1.12	€ 32.58	€ 9.77	17.4	€ 170.07
Paclitaxel							
Dexamethasone 20 mg[9], 50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08	€ 2.34	17.4	€ 40.74
Dimetindene IV	€ 18.86	€ 1.77	€ 1.90	€ 15.19	€ 6.08	17.4	€ 105.72

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
1 ml/ 10 kg, 5 x 4 mg SFI							
Cimetidine 300 mg IV, 10 CIS x 200 mg [6]	€ 19.77	€ 1.77	€ 0.00	€ 18.00	€ 3.60	17.4	€ 62.64
Pemetrexed							
Dexamethasone[10] 2 x 4 mg, 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	€ 16.70	€ 0.84	€ 2.58	€ 13.28	€ 0.13 - € 0.27	365	€ 48.47 - € 96.94
Vitamin B12[6] 1,000 µg/day, every 3 cycles, 10 SFI	€ 7.40	€ 0.37	€ 0.33	€ 6.70	€ 0.67	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 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.

[10] To reduce the frequency and severity of skin reactions, a corticosteroid must be given the day before and the day after pemetrexed administration.

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 7 January 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

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 7 December 2021.

On 14 December 2021, the pharmaceutical company submitted a dossier for the benefit assessment of pralsetinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 14 December 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 pralsetinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 March 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 15 March 2022. The deadline for submitting written statements was 5 April 2022.

The oral hearing was held on 25 April 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 8 June 2022, and the draft resolution was approved.

At its session on 16 June 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 January 2020	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	7 December 2021	New determination of the appropriate comparator therapy
Working group Section 35a	21 April 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	25 April 2022	Conduct of the oral hearing
Working group Section 35a	4 May 2022 18 May 2022 1 June 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	8 June 2022	Concluding discussion of the draft resolution
Plenum	16 June 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 June 2022

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

Prof. Hecken