

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
Capmatinib (non-small cell lung cancer (NSCLC))

of 2 February 2023

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for 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 online 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 capmatinib 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 August 2022. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 12 August 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 November 2022 on the G-BA website (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 capmatinib 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, the statements submitted in the written statement and oral hearing procedure, and the addenda to the

benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods¹ was not used in the benefit assessment of capmatinib. 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 Capmatinib (Tabrecta) in accordance with the product information

Tabrecta as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

Therapeutic indication of the resolution (resolution of 02.02.2023):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

- a) Adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping after first-line therapy with an anti-PD-1/PD-L1 as monotherapy

Appropriate comparator therapy for capmatinib as monotherapy:

- Cisplatin 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))

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.

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

b) Adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping after first-line therapy with platinum-containing chemotherapy

Appropriate comparator therapy for capmatinib as monotherapy:

- 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, Tumour Proportion Score (TPS) $\geq 1\%$)
- or*
- Atezolizumab
- or*
- Docetaxel in combination with nintedanib (only for patients with PD-L1 negative tumours and adenocarcinoma histology)

c) Adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping after first-line therapy with a PD-1/PD-L1 antibody in combination with a platinum-based chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 and a platinum-containing chemotherapy

Appropriate comparator therapy for capmatinib as monotherapy:

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

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 the authorisation status, the following active ingredients are available for the treatment of advanced NSCLC: cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine, vinorelbine; alectinib, amivantamab, brigatinib, cemiplimab, ceritinib, crizotinib, dabrafenib, dacomitinib, erlotinib, gefitinib, lorlatinib, nintedanib, osimertinib, pralsetinib, sotorasib, selpercatinib, tepotinib, trametinib, atezolizumab, bevacizumab, durvalumab, nivolumab, pembrolizumab and ramucirumab.

Apart from tepotinib and capmatinib, there are currently no other medicinal treatments specifically approved for the treatment of NSCLC with alterations leading to METex14 skipping.

- 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, there are 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, alectinib, amivantamab, atezolizumab, brigatinib, cemiplimab, ceritinib, crizotinib, dabrafenib, dacomitinib, durvalumab, lorlatinib, necitumumab, nintedanib, nivolumab, osimertinib, pembrolizumab, ramucirumab, pralsetinib, sotorasib, selpercatinib, tepotinib and trametinib.

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 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 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 G12C, RET or ROS1) will be considered for patients at the time of therapy with capmatinib.

For the present therapeutic indication, it is also assumed that the patients are generally eligible for active antineoplastic therapy, which is why best supportive care is not considered as an appropriate comparator therapy in the present case.

It should be noted that there is no higher-quality evidence for the treatment of advanced NSCLC with alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping in relation to MET overexpression. So far, apart from tepotinib and capmatinib, there are no other medicinal treatments specifically approved for the treatment of NSCLC with alterations leading to METex14 skipping. No additional benefit was identified for the relatively new therapy option tepotinib in the benefit assessment (resolution of 1 September 2022). Data were not presented for any of the patient groups here compared to the appropriate comparator therapy. For the present resolution, tepotinib is not determined to be an appropriate comparator therapy.

Therefore, those therapy options that are applied independently of a MET alteration are basically considered for the present treatment setting.

In the second-line treatment, depending on the first-line therapy, a distinction is made between a) patients with an anti-PD-1/PD-L1 antibody monotherapy pretreatment, b) patients with cytotoxic chemotherapy pretreatment and c) after first-line therapy with an anti-PD-1/PD-L1 in combination with a platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 and a platinum-containing chemotherapy as pretreatment.

a) Following first-line therapy with an anti-PD-1/PD-L1 as monotherapy

In the guidelines, whose recommendations already include first-line therapy with immune checkpoint inhibitor (ICI), cytotoxic chemotherapy is also recommended for this patient group in the 2nd line, with platinum-containing chemotherapy being given the highest priority overall. 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; cf. Annex VI to Section K of the Pharmaceuticals Directive.

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

The question of the extent to which platinum-based combination chemotherapy should also be considered in patients with ECOG performance status 2 is not clearly answered in the present guidelines. In particular, 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, monotherapy 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.

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 treatment options mentioned.

b) Following first-line therapy with cytotoxic chemotherapy

For patients with NSCLC 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 ICIs 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 unsuitable 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 and corresponding therapy recommendations in the guidelines, 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 adults after prior chemotherapy and squamous tumour histology, an indication of a major additional benefit was identified in the benefit assessment compared to docetaxel (resolution of 4 February 2016). For nivolumab for the treatment of adults after prior chemotherapy and non-squamous tumour histology, an indication of a major additional benefit was also identified 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 major 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 \geq 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 treatments 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.

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 treatment options mentioned.

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

The treatment setting addressed in the present case may include patients who have either already received a platinum-containing chemotherapy in combination with an

anti-PD-1/PD-L1 therapy as part of first-line therapy or have received a platinum-containing chemotherapy and an anti-PD-1/PD-L1 therapy sequentially in the first and second line of therapy (regardless of which of the therapies was administered first).

For the first-mentioned option of platinum-containing chemotherapy in combination with an anti-PD-1/PD-L1 therapy, it is true that this is a fairly new treatment option for advanced and metastatic NSCLC. For both the treatment setting after platinum-containing chemotherapy in combination with an anti-PD-1/PD-L1 therapy and for further treatment after sequential therapy with a platinum-containing chemotherapy and an anti-PD-1/PD-L1 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) anti-PD-1/ PD-L1 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). The benefit assessment showed no additional benefit for afatinib for the treatment of adults with squamous cell histology compared to the appropriate comparator therapy 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.

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, docetaxel in combination with ramucirumab and docetaxel in combination with nintedanib as well as vinorelbine.

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

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

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 capmatinib is assessed as follows:

- a) Adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping after first-line therapy with an anti-PD-1/PD-L1 as monotherapy

An additional benefit is not proven.

- b) Adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping after first-line therapy with platinum-containing chemotherapy

An additional benefit is not proven.

Adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping after first-line therapy with a PD-1/PD-L1 antibody in combination with a platinum-based chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 and a platinum-containing chemotherapy

An additional benefit is not proven.

Justification:

Data basis:

GEOMETRY mono-1 study

The pharmaceutical company presents results from the still ongoing open-label, uncontrolled, multicentre phase II cohort study GEOMETRY mono-1 for the proof of additional benefit of capmatinib for the treatment of adults with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with platinum-based chemotherapy and/or immunotherapy.

The study has been conducted since June 2015 in a total of 152 study sites in Europe, Asia and North, Central and South America

The study included a total of 373 adult patients with advanced (stage IIIB or IV) NSCLC with METex14 skipping mutation or MET amplification in the first or higher line of therapy. At the start of the study, patients had to be in good general condition - corresponding to an Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) of 0 or 1 - and tumours had to have wild-type epidermal growth factor receptor (EGFR) status (for exon 19 deletions and exon 21 L858R substitution mutations) and negative anaplastic lymphoma kinase (ALK) translocation status.

Patients with symptomatic central nervous system (CNS) metastases who were neurologically unstable or who received an increasing dose of steroids for CNS symptoms in the 2 weeks prior to the start of the study were excluded.

The patients were divided into a total of 7 cohorts according to the present MET alteration and depending on possible previous therapies (no, 1 or 2 antitumour therapy(s)) in the advanced stage of the disease; of these 7 cohorts, 2 were divided into subcohorts a and b.

The objective response rate, assessed by a blinded independent review committee (BRIC), is the primary endpoint of the study. Overall survival, morbidity, health-related quality of life and adverse events are further patient-relevant endpoints (AEs).

RECAP study

The RECAP study is a comparison of individual arms from different studies, consisting of patient-individual data on capmatinib from the GEOMETRY mono-1 prospective cohort study and patient-individual data from the National Network Genomic Medicine Lung Cancer (nNGM) database for mapping the appropriate comparator therapy.

Patients in the first and second line were included in the study; however, only the patient population in the second line is relevant for the present benefit assessment.

A study protocol as well as a statistical analysis plan were written by the pharmaceutical company, but there is no entry in a study register.

The following endpoints were collected from different studies in this comparison of individual arms: Overall survival, progression-free survival (PFS), overall response rate, time to progression in central nervous system (CNS), time to discontinuation of therapy due to adverse events (AEs), unplanned or prolonged hospitalisation, unplanned or prolonged hospitalisation or death. Due to the lack of suitable register data, the information on side effects cannot be assessed from the perspective of the pharmaceutical company.

The pharmaceutical company submits the results of data cut-off 8 dated 30.08.2021 from the GEOMETRY mono-1 study for 81 patients from cohort 4 and a subset from cohort 6 (patients with METex14 skipping mutation in the second or higher lines of therapy) on the intervention side.

On the comparator side, the pharmaceutical company takes data for 21 adult patients (ECOG-PS ≤ 1 , EGFR wild-type and ALK-negative, no symptomatic CNS metastases) with locally advanced or metastatic NSCLC with METex14 skipping mutation from retrospective patient records from the nNGM database for his main analysis. The diagnosis of these patients who have already received 1 prior therapy with a PD-1 or PD-L1 antibody, cytotoxic chemotherapy or a PD-1 or PD-L1 antibody in combination with platinum-containing chemotherapy in the advanced stage of the disease was made at one of the participating nNGM study sites between 2018 and 2020.

Comparison of individual arms from different studies

In the dossier, the pharmaceutical company presents comparisons of individual arms from different studies exclusively for patients in second-line therapy. No comparative data were presented for third- and higher-line therapy(s). According to the designated patient populations, the pharmaceutical company makes a subdivision of the second-line treatment and furthermore combines these patients in a pool population.

For this pool population 1, the pharmaceutical company carries out a propensity score procedure and submits comparisons of individual arms from different studies for the endpoints mentioned above. In addition, the pharmaceutical company submits comparisons of the individual arms from the two sources without adjustment by means of propensity score procedures for the endpoints mentioned for the sub-populations.

In order to reflect the German reality of care and to take into account a larger number of patients (n = 46), the pharmaceutical company also submits a pre-specified sensitivity analysis "Capmatinib vs Standard of Care (SoC)" of the RECAP study. Through this, the pharmaceutical

company says it includes all therapies administered in the nNGM sites, taking into account previous therapies according to the patient populations.

For the endpoint CNS progression

The endpoint CNS progression was reoperationalised for the RECAP study as it was not prespecified in the GEOMETRY mono-1 study. The endpoint was operationalised as the time from treatment initiation to the first radiologically documented evidence of brain metastases.

For the sub-population of patients who received first-line cytotoxic chemotherapy, a statistically significant difference between treatment arms was shown in the comparison of individual arms from different studies without a bridge comparator submitted by the pharmaceutical company. Only patients without brain metastases at the start of the study were included in this evaluation.

In the intervention arm, the endpoint CNS progression in the GEOMETRY-mono-1 study was only collected up to disease progression confirmed by BIRC. Based on the study protocol of the RECAP study and the Kaplan-Meier curves on PFS and CNS progression submitted by the pharmaceutical company, it can be assumed that events for the endpoint CNS progression were recorded in the comparator arm over the entire observation period - even after progression of the disease outside the CNS.

According to the study protocol of the GEOMETRY mono-1 study (intervention arm), further brain scans were only performed at the start of the study in patients without brain metastases if there were symptoms suggestive of brain metastases. Based on these current recommendations, it can be assumed that also on the side of the comparison arm (nNGM sites), a brain scan was only performed in patients with symptoms suggestive of brain metastases.

However, only patients who did not have brain metastases at the beginning of the study were included in the evaluation. However, symptom-related progression, which takes into account symptomatology perceived by patients, is in principle also relevant for this endpoint in patients with brain metastases at the start of the study.

Due to the specifications in the GEOMETRY mono-1 study, patients with brain metastases in the intervention arm are also excluded. On the other hand, it cannot be ruled out that patients with asymptomatic brain metastases who were not detected before the start of treatment were also included in the evaluation. In everyday care - and thus also in the nNGM sites - a brain scan is not regularly performed at the beginning of treatment.

In addition, the assessment of CNS progression is based exclusively on imaging procedures and does not take into account any symptomatology perceived by patients, which means that this operationalisation of the endpoint (related to patients with known brain metastases) is not directly relevant to patients.

In summary, the results for the endpoint CNS progression, regardless of its patient relevance, are not interpretable in the present case.

Assessment

For the benefit assessment of capmatinib, the results from the still ongoing, open-label, non-controlled phase II cohort study GEOMETRY mono-1 are available. The descriptive analysis of the results from the GEOMETRY mono-1 study conducted by the pharmaceutical company are

not suitable on their own for the assessment of the additional benefit of capmatinib compared to the appropriate comparator therapy, as they do not allow a comparison with the appropriate comparator therapy.

With the RECAP study, the pharmaceutical company additionally presents a comparison of individual arms from different studies, in which patient-individual data on capmatinib from the prospective cohort study GEOMETRY mono-1 and patient-individual data from the database of the National Network Genomic Medicine Lung Cancer (nNGM) on the appropriate comparator therapy are compared.

The comparisons based on the pooled population 1 are, irrespective of the selection of the confounders named by the pharmaceutical company and the propensity score method used, not suitable to consider the study population according to the presently determined appropriate comparator therapy. The sensitivity analyses presented are also not suitable for a comparison of capmatinib with the appropriate comparator therapy, as 54% of the patients included in the sensitivity analysis did not receive a treatment corresponding to the appropriate comparator therapy.

Overall, the comparisons of individual arms from different studies presented by the pharmaceutical company show no statistically significant effects in the individual endpoints, except for the endpoint CNS progression for the pharmaceutical company's sub-population d (patient group b). However, due to the systematically shortened observation period in the intervention arm, the results for the endpoint CNS progression are not suitable for a comparison of individual arms.

There are therefore no data for the assessment of the additional benefit of capmatinib compared to the appropriate comparator therapy. Therefore, an additional benefit is not proven for all 3 patient groups.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Tabrecta with the active ingredient capmatinib.

The active ingredient capmatinib is approved for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping who require systemic therapy after platinum-based chemotherapy and/or treatment with immunotherapy.

In the therapeutic indication under consideration, 3 patient groups were distinguished and the appropriate comparator therapy was determined as follows (abbreviated version):

- a) Adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping after first-line therapy with an anti-PD-1/PD-L1 as monotherapy

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

- b) Adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping after first-line therapy with platinum-containing chemotherapy

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

Adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping after first-line therapy with a PD-1/PD-L1 antibody in combination with a platinum-based chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 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 presented the results from the non-controlled study GEOMETRY mono-1 as well as comparisons of individual arms from different studies within the framework of the RECAP study. As both studies are not suitable for comparison with the appropriate comparator therapy, an additional benefit of capmatinib compared to the appropriate comparator 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).

In order to allow consistent consideration of patient numbers, taking into account the resolutions made on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication of lung cancer, the incidence of 59,700 patients forecast by the Robert Koch Institute for 2022 is used for the present calculation².

This is higher than the number of 58,368 patients used by the pharmaceutical company.

For the number of German patients with lung cancer, the projected incidence for 2022 (59 700 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 proportion of lung cancer patients with NSCLC is between 73.6 and 83,6 %³ (43,939 bis 49,909 patients).
2. Of these, 51.8 to 61.6% of patients are in stage IIIB and IV at initial diagnosis (22,761 to 30,744 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 28,627 to 39,108.
3. First-line therapy is given in 76.9 to 96.1% of cases (22,014 - 37,583 patients).

² Robert Koch Institute, Society of Epidemiological Cancer Registries in Germany. Cancer in Germany for 2017/2018. 2021

³ Benefit assessment procedure D-828 atezolizumab; <https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/849/>

4. The proportion of patients with alterations leading to METex14 skipping is 2.7%⁴ (594 to 1,015 patients).
5. Of these, as first-line treatment
 - 5a. 14.3% (85 to 145 patients) received monotherapy with an anti-PD-1/PD-L1,
 - 5b. 10.7% (64 to 109 patients) received chemotherapy or
 - 5c. 75% (446 to 761 patients) received an anti-PD-1/PD-L1 in combination with platinum-containing chemotherapy.
6. Taking into account a proportion of SHI-insured patients of 88.3%, step 5a-c results in 525 to 896 patients after prior therapy with an anti-PD-1/PD-L1 and/or chemotherapy, of which
 - 6a. 75 to 128 patients with an anti-PD-1/PD-L1 as first-line treatment (patient population a),
 - 6b. 56 to 95 patients with chemotherapy as first-line treatment (patient population b) and
 - 6c. 394 to 672 patients with an anti-PD-1/PD-L1 and platinum-containing chemotherapy as first-line treatment

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 Tabrecta (active ingredient: capmatinib) at the following publicly accessible link (last access: 10 January 2023):

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

Treatment with capmatinib 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.

METex14 skipping test

Prior to treatment with capmatinib, the presence of alterations leading to METex14 skipping must be confirmed by 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 January 2023).

⁴ Benefit assessment procedure D-781 tepotinib; www.g-ba.de/bewertungsverfahren/nutzenbewertung/807/

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				
Capmatinib	Continuously, 2 x daily	365	1	365
Appropriate comparator therapy				
Patient population a)				
<i>Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)⁵</i>				
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
<i>Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)⁵</i>				
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
<i>Carboplatin in combination with nab-paclitaxel</i>				
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
<i>Monotherapy with gemcitabine or vinorelbine⁶</i>				
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 b)				

⁵ except in the case of predominantly squamous histology

⁶ 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
<i>Docetaxel (only for patients with PD-L1 negative tumours)</i>				
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
<i>Pemetrexed⁷</i>				
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
<i>Nivolumab</i>				
Nivolumab	1 x per 14-day cycle	26.1	1	26.1
<i>Pembrolizumab⁸</i>				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
<i>Atezolizumab</i>				
Atezolizumab	1 x per 21-day cycle	17.4	1	17.4
<i>Docetaxel in combination with nintedanib⁹</i>				
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 c)				
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				
<i>Afatinib</i>				
Afatinib	1 x daily	365	1	365
<i>Pemetrexed</i>				
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
<i>Erlotinib</i>				
Erlotinib	1 x daily	365	1	365
<i>Docetaxel</i>				
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
<i>Docetaxel in combination with ramucirumab</i>				
Docetaxel	1 x per 21-day cycle	17.4	1	17.4

⁷ only for patients with PD-L1 negative tumours and except in the case of predominantly squamous cell histology

⁸ only for patients with PD-L1 expressing tumours, Tumour Proportion Score (TPS) ≥ 1%

⁹ 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
<i>Docetaxel in combination with nintedanib⁹</i>				
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
<i>Vinorelbine</i>				
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 varies from patient to patient 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)¹⁰.

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.

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.

¹⁰ 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					
Capmatinib	400 mg	800 mg	4 x 200 mg	365	1460 x 200 mg
Appropriate comparator therapy					
Patient population a)					
<i>Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)⁵</i>					
Cisplatin	75 mg/m ² = 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/m ² = 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/m ² = 190 mg	190 mg	2 x 100 mg	17.4	34.8 x 100 mg
Docetaxel	75 mg/m ² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 mg
Gemcitabine	1,250 mg/m ² = 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/m ² = 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/m ² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Vinorelbine	25 mg/m ² = 47.5 mg - 30 mg/m ² = 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
<i>Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)⁵</i>					
Carboplatin	500 mg/m ² = 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/m ² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 mg
Gemcitabine	1,250 mg/m ² = 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/m ² = 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/m ² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Vinorelbine	25 mg/m ² = 47.5 mg - 30 mg/m ² = 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
<i>Carboplatin in combination with nab-paclitaxel</i>					
Carboplatin	500 mg/m ² = 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/m ² = 190 mg	190 mg	2 x 100 mg	52.2	104.4 x 100 mg
<i>Monotherapy with gemcitabine or vinorelbine⁶</i>					
Gemcitabine	1,000 mg/m ² = 1,900 mg	1,900 mg	1 x 2,000 mg	39	39 x 2,000 mg
Vinorelbine	25 mg/m ² = 47.5 mg - 30 mg/mg ² = 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 b)					
<i>Docetaxel (only for patients with PD-L1 negative tumours)</i>					
Docetaxel	75 mg/m ² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 mg
<i>Pemetrexed⁴</i>					
Pemetrexed	500 mg/m ² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
<i>Nivolumab</i>					
Nivolumab	240 mg	240 mg	2 x 120 mg	26.1	52.2 x 120 mg
<i>Pembrolizumab⁵</i>					
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
<i>Atezolizumab</i>					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Atezolizumab	1,200 mg	1,200 mg	1 x 1,200 mg	17.4	17.4 x 1,200 mg
<i>Docetaxel in combination with nintedanib⁹</i>					
Docetaxel	75 mg/m ² = 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 c)					
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.					
<i>Afatinib</i>					
Afatinib	40 mg	40 mg	1 x 40 mg	365	365 x 40 mg
<i>Pemetrexed</i>					
Pemetrexed	500 mg/m ² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
<i>Erlotinib</i>					
Erlotinib	150 mg	150 mg	1 x 150 mg	365	365 x 150 mg
<i>Docetaxel</i>					
Docetaxel	75 mg/m ² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 mg
<i>Docetaxel in combination with ramucirumab</i>					
Docetaxel	75 mg/m ² = 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
<i>Docetaxel in combination with nintedanib⁹</i>					
Docetaxel	75 mg/m ² = 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
<i>Vinorelbine</i>					
Vinorelbine	25 mg/m ² = 47.5 mg - 30 mg/m ² = 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.

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					
Capmatinib 200 mg	120 FCT	€ 10,540.69	€ 1.77	€ 1,026.33	€ 9,512.59
Appropriate comparator therapy					
Atezolizumab 1,200 mg	1 CIS	€ 4,319.46	€ 1.77	€ 417.25	€ 3,900.44
Afatinib 40 mg	28 FCT	€ 2,515.23	€ 1.77	€ 240.61	€ 2,272.85
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 ¹¹	30 FCT	€ 880.24	€ 1.77	€ 68.73	€ 809.74
Gemcitabine 200 mg	1 CIS	€ 28.81	€ 1.77	€ 0.83	€ 26.21
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
Nintedanib 100 mg	120 SC	€ 2,761.26	€ 1.77	€ 110.29	€ 2,649.20
Nivolumab 120 mg	1 CIS	€ 1,546.93	€ 1.77	€ 145.81	€ 1,399.35
Paclitaxel 100 mg	1 CIS	€ 289.43	€ 1.77	€ 13.20	€ 274.46
Paclitaxel 150 mg	1 CIS	€ 428.94	€ 1.77	€ 19.82	€ 407.35
Pembrolizumab 100 mg	1 CIS	€ 2,974.79	€ 1.77	€ 285.60	€ 2,687.42
Pemetrexed 500 mg	1 PCI	€ 1,124.90	€ 1.77	€ 52.85	€ 1070.28
Ramucirumab 100 mg	1 CIS	€ 441.14	€ 1.77	€ 40.80	€ 398.57
Ramucirumab 500 mg	1 CIS	€ 2,141.31	€ 1.77	€ 204.00	€ 1,935.54
Vinorelbine 10 mg	1 CIS	€ 41.63	€ 1.77	€ 3.84	€ 36.02
Vinorelbine 50 mg	1 CIS	€ 156.68	€ 1.77	€ 18.40	€ 136.51
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					

¹¹ Fixed reimbursement rate

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
suspension; PCI = powder for a concentrate for the preparation of a solution for infusion; SC = soft capsules					

LAUER-TAXE® last revised: 15 January 2023

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 of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5a SGB 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 capmatinib							
Not applicable							
Appropriate comparator therapy							
<i>Cisplatin</i>							
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
	€ 22.72	€ 1.14	€ 0.69	€ 20.89	€ 15.12	17.4	€ 263.11

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
Sodium chloride 0.9% Inf. Solution, 3 - 4.4 l/day, 10 x 500 ml INF/ 10 x 1,000 ml INF	€ 35.74	€ 1.77	€ 1.12	€ 32.58	€ 9.77	17.4	- € 170.07
<i>Paclitaxel</i>							
Dexamethasone 20 mg ¹¹ , 50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08	€ 4.68	17.4	€ 40.74
Dimetindene IV 1 ml/ 10 kg, 5 x 4 mg SFI	€ 23.67	€ 1.77	€ 5.81	€ 16.09	€ 6.44	17.4	€ 111.99
Cimetidine 300 mg IV, 10 CIS x 200 mg	€ 19.77	€ 1.77	€ 0.40	€ 17.60	€ 3.52	17.4	€ 61.25
<i>Pemetrexed</i>							
Dexamethasone 2 x 4 mg ^{11, 12} , 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	€ 49.38 - € 98.77
Vitamin B12 ¹¹ 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.

¹² To reduce the frequency and severity of skin reactions, a corticosteroid must be given the day before and the day after pemetrexed administration.

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 Capmatinib

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.

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 27 August 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 06 September 2022.

On 12 August 2022, the pharmaceutical company submitted a dossier for the benefit assessment of capmatinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 12 August 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 capmatinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 November 2022, and the written statement procedure was initiated with publication on the G-BA website on 15 November 2022. The deadline for submitting written statements was 06 December 2022.

The oral hearing was held on 19 December 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 24 January 2023, and the proposed resolution was approved.

At its session on 2 February 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	27 August 2019	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	6 September 2022	New implementation of the appropriate comparator therapy
Working group Section 35a	13 December 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	19 December 2022	Conduct of the oral hearing
Working group Section 35a	3 January 2023 17 January 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	24 January 2023	Concluding discussion of the draft resolution
Plenum	2 February 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 February 2023

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

Prof. Hecken