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
Sotorasib (lung cancer, non-small cell, KRAS G12C mutation, ≥ 1 prior therapy)

of 4 August 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 sotorasib 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 February 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 14 February 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 16 May 2022, 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 sotorasib 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 sotorasib.

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 Sotorasib (Lumykras) in accordance with the product information

LUMYKRAS as monotherapy is indicated for the treatment of adults with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy.

Therapeutic indication of the resolution (resolution of 4 August 2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with aPD-1/PD-L1 antibody as monotherapy

Appropriate comparator therapy for Sotorasib:

- 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) Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with cytotoxic chemotherapy

Appropriate comparator therapy for Sotorasib:

– 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)

c) Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with aPD-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 sotorasib:

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, nab-paclitaxel, paclitaxel, pemetrexed, vindesine, vinorelbine; afatinib, alectinib, amivantamab, brigatinib, capmatinib, ceritinib, crizotinib, dabrafenib, entrectinib, erlotinib, gefitinib, lorlatinib, nintedanib, Osimertinib, pralsetinib, selpercatinib, tepotinib, trametinib, atezolizumab, bevacizumab, durvalumab, nivolumab, pembrolizumab and ramucirumab.

Apart from sotorasib, there are currently no other approved medicinal therapies that are explicitly used in adults with a KRAS p.G12C mutation.

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, ceritinib, crizotinib, dabrafenib, durvalumab, entrectinib, lorlatinib, necitumumab, nintedanib, nivolumab, osimertinib, pembrolizumab, pralsetinib, ramucirumab, selpercatinib 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, METex14, RET or ROS1) will be considered for patients at the time of therapy with sotorasib. It should be noted that there is no higher quality evidence for the treatment of NSCLC related to the KRAS p.G12C mutation. So far, there are no other approved medicinal therapies besides sotorasib that are explicitly used in the presence of a KRAS p.G12C mutation according to the marketing authorisation. According to the scientific-medical societies involved and the European Public Assessment Report (EPAR), the treatment standards correspond to those of metastatic non-small cell lung cancer without specifically treatable oncogenic driver mutations.

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.

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

a) Following first-line therapy with aPD-1/PD-L1 antibody 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 drug (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, 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.

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 considerable 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 considerable 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 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.

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 aPD-1/PD-L1 antibody in combination with a platinum-containing chemotherapy or after sequential therapy with aPD-1/PD-L1 antibody 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 aPD-1/PD-L1 antibody therapy as part of first-line therapy or have received a platinum-containing chemotherapy and aPD-1/PD-L1 antibody 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 aPD-1/PD-L1 antibody 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 aPD-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). 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 mandate.

2.1.3 Extent and probability of the additional benefit

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

a) <u>Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with aPD-1/PD-L1 antibody as monotherapy</u>

An additional benefit is not proven.

b) <u>Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with cytotoxic chemotherapy</u>

An additional benefit is not proven.

c) <u>Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with a PD-1/PD-L1 antibody in combination with platinum-containing</u>

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

Study CodeBreak 100

For the assessment of the additional benefit of sotorasib, the pharmaceutical company presents results from the still ongoing open-label, uncontrolled, multicentre CodeBreak 100 phase I and II study. The study is being conducted in Asia, North America, Australia and Europe.

The study enrolled adult patients with locally advanced or metastatic solid tumours with molecularly diagnosed KRAS p.G12C mutation. Phase II of the CodeBreak 100 study is considered for the present benefit assessment. For this purpose, patients with NSCLC and KRAS p.G12C mutation who showed disease progression after therapy with aPD-1/PD-L1 antibody and/or platinum-containing combination chemotherapy and targeted therapy of oncogenic driver mutations were included. As further inclusion criteria, patients should also have received no more than 3 previous lines of therapy and have a general condition according to Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1.

The treatment with sotorasib was carried out according to the requirements in the product information. Treatment with study medication was continued until disease progression according to Response Evaluation Criteria In Solid Tumours (RECIST) criteria version 1.1 or disease progression without meeting RECIST criteria accompanied by deterioration of the patients' symptoms or general condition. Other reasons could also lead to therapy discontinuation. Under certain conditions, a therapy could be continued after disease progression.

The primary endpoint of the study was objective response rate. Other endpoints included overall survival and cancer-specific symptoms. In addition, endpoints of the categories health-related quality of life and side effects were collected.

In the CodeBreak 100 study, the following data cut-offs are available so far: 1st data cut-off from 01.09.2020 as prespecified primary analysis; 2nd data cut-off: 01.12.2020 as a requested data cut-off from the US regulatory authority, further data cut-offs from 15.03.2021 and 20.06.2021. For the benefit assessment, the pharmaceutical company submits the results of the 1st data cut-off for the endpoint categories of mortality, morbidity, health-related quality of life and side effects. In addition, it presents the results of the 2nd data cut-off for the endpoints of overall survival, progression-free survival and response.

In the written statement procedure, the pharmaceutical company submits data on the data cut-offs from 15.03.2021 and 20.06.2021.

CRISP KRAS G12C registry study

On the side of the appropriate comparator therapy, the pharmaceutical company uses the CRISP KRAS G12C registry study. This is based on the ongoing, open-label, non-interventional, prospective, clinical patient registry with over 150 German study sites. The registry includes adult patients predominantly with a pathological diagnosis of stage IV or stage IIIB NSCLC (if curative surgery or chemoradiotherapy is not possible) but also other stages of NSCLC as well as patients with small cell lung cancer. Patients must be included in the registry no later than

4 weeks after the start of first-line therapy. Inclusion in the register has been taking place since December 2015. Endpoints include overall survival, progression-free survival, response, and patient-reported data on health-related quality of life, depression, and physical and psychological well-being.

According to the pharmaceutical company, the CRISP KRAS G12C registry study enrolled patients with locally advanced or metastatic NSCLC who had been followed for at least 1 year as of the data cut-off from 30 June 2021, had a KRAS G12C mutation and an ECOG-PS 0 or 1, and were treated with second-line therapy (N = 62). For the descriptive comparison with the CodeBreak 100 study, the pharmaceutical company presents results for the endpoints of overall survival and progression-free survival.

As part of the written statement procedure, the pharmaceutical company submits updated evaluations of the *KRAS G12C* cohort of the CRISP registry.

Other databases

As part of the written statement procedure, the pharmaceutical company supplements evaluations of the Flatiron Health database as well as data on the *KRAS* G12C population of the RAStik study of the NGM registry.

Assessment

The evaluations presented by the pharmaceutical company are a descriptive comparison of individual arms from different studies without adjustment for potentially relevant effect modifiers or prognostic factors. Evaluations are only available for the patient-relevant endpoint of overall survival, so that it is not possible to weigh up the benefits and harms as part of the benefit assessment. Furthermore, the effects on the endpoint of overall survival are not large enough that they cannot arise exclusively by systematic risk of bias in the present data situation. The evidence submitted by the pharmaceutical company is assessed as being unsuitable for the benefit assessment.

In addition, in the dossier and also in the evaluations submitted as part of the written statement procedure, the pharmaceutical company refrains from a division into 3 patient groups with regard to prior therapy, as determined by the G-BA. The pharmaceutical company justifies this with the fact that > 80% of the patient population from the CodeBreak 100 study on the intervention side was assigned to patient group c) (after first-line therapy with aPD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with aPD-1/PD-L1 antibody and platinum-containing chemotherapy). On the comparator arm side, the pharmaceutical company does not split the patient population. Based on the information on previous therapies from the CRISP registry, the patient population on the comparison side, in contrast to the intervention side, cannot be assigned to patient group c). Thus, this patient population from the CRISP KRAS G12C registry study is unsuitable as a control group for the CodeBreak 100 study. The evaluations of the CRISP registry, the Flatiron Health database as well as the NGM registry submitted as part of the written statement procedure are also unsuitable for a comparison with the CodeBreak 100 study due to an unclear allocation to one of the patient groups defined by the G-BA.

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

In the present therapeutic indication, sotorasib may represent a relevant therapeutic option.

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 sotorasib 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 sotorasib to the EMA for review, which may be relevant for the assessment of the additional benefit of the medicinal product pursuant to Section 35a SGB V. The limitation enables the timely inclusion of the evidence to be provided to the regulatory authority with regard to safety and efficacy in the benefit assessment of the medicinal product according to Section 35a SGB V.

Regarding the evidence to be provided, the EMA requires that the results of the phase III CodeBreak200 study be submitted to confirm the efficacy and safety of sotorasib in the treatment of adult patients with KRAS-G12C-positive, advanced NSCLC compared to the treatment with docetaxel. The study report is expected on 31 March 2023.

The patient population of the CodeBreak 200 study includes pretreated patients with metastatic NSCLC. Thus, clinical efficacy and safety data from the CodeBreak 200 study are expected to be relevant for the assessment of the medicinal product's benefit in the second or third-line therapy. Against this background, it is justified to limit in time the resolution regarding patient groups b) and c) until further scientific evidence is available for the assessment of the additional benefit of sotorasib. The limitation enables the expected results from the CodeBreak 200 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 1 July 2023 to be appropriate.

Conditions of the limitation:

For the new benefit assessment in patient groups b) and c) after expiry of the deadline, the results from the clinical study report of the CodeBreak 200 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 sotorasib 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 sotorasib 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 sotorasib 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 Lumykras with the active ingredient sotorasib.

This medicinal product was approved under special conditions.

The active ingredient sotorasib is approved for the treatment of adults with advanced non-small cell lung cancer (NSCLC) with a KRAS G12C mutation who have experienced disease progression after at least one prior systemic therapy.

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

a) 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.

b) Adults after first-line therapy with a cytotoxic chemotherapy

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

c) Adults 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.

   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 CodeBreak 100 study for the treatment with sotorasib. On the side of the appropriate comparator therapy, the pharmaceutical company uses the CRISP KRAS G12C registry study as well as evaluations from other registries.

The evaluations presented by the pharmaceutical company are a descriptive comparison of individual arms from different studies without adjustment for potentially relevant effect modifiers or prognostic factors. Only evaluations for the endpoint of overall survival are available.

Overall, the data presented are unsuitable for the assessment of the additional benefit, which is why an additional benefit of sotorasib compared to the appropriate comparator therapy is not proven.

In the present therapeutic indication, sotorasib may represent a relevant therapeutic option.

The resolution is limited for patient groups b) and c) until 1 July 2023. Clinical efficacy and safety data are expected from the CodeBreak 200 study.

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 KRAS mutation is 11 to 14% (2,442 to 5,306 patients).

5. Of these, as first-line treatment

5a. 14.3% (349 to 759 patients) received monotherapy with aPD-1/PD-L1 antibody,

5b. 10.7% (261 to 568 patients) received chemotherapy or

5c. 75% (1,831 to 3,979 patients) received aPD-1/PD-L1 antibody in combination with platinum-containing chemotherapy.

6. In relation to step number 4, 38.7% to 45.9% of patients received second-line treatment (635 to 1,379 patients). Of these, as first-line treatment

6a. 91 to 197 patients received monotherapy with aPD-1/PD-L1 antibody (patient population a),

6b. 68 to 148 patients received chemotherapy (patient population b) and

6c. 476 to 1,035 patients received monotherapy with aPD-1/PD-L1 antibody and platinum-containing chemotherapy.

7. Taking into account a percentage of SHI-insured patients of 88.3%, step 6a-c results in 561 to 1,218 patients after prior therapy with aPD-1/PD-L1 antibody and/or chemotherapy, of which

7a. 80 to 174 patients with aPD-1/PD-L1 antibody as first-line treatment (patient population a),

7b. 60 to 130 patients with chemotherapy as first-line treatment (patient population b) and

7c. 420 to 914 patients with a PD-1/PD-L1 antibody 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 Lumykras (active ingredient: sotorasib) at the following publicly accessible link (last access: 20 May 2022):

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

Treatment with sotorasib 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.

Testing KRAS G12C mutation

The presence of a KRAS G12C mutation must be confirmed by a validated test prior to start of therapy.

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 July 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				
Sotorasib	1 x daily	365	1	365
Appropriate comparator therapy				
a) Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with a PD-1/PD-L1 antibody as monotherapy				
Cisplatin in combination with a third-generation cytostatic drug (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)				
Cisplatin	1 x per 21-day cycle	17.4	1	17.4

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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 drug (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[2]				
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

[2] 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
b) Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with cytotoxic chemotherapy				
Docetaxel (only for patients with PD-L1 negative tumours)				
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed[3]				
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[4]				
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[5]				
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
c) Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation 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				
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				

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

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

[5] 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
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
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)[6]

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

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Sotorasib	960 mg	960 mg	8 x 120 mg	365	2,920 x 120 mg
Appropriate comparator therapy					
a) Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with a PD-1/PD-L1 antibody as monotherapy					
Cisplatin in combination with a third-generation cytostatic drug (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

[6] 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
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	47.5mg - 57mg	1 x 50 mg - 1 x 50 mg + 1 x 10 mg	34.8	34.8 x 50 mg - 34.8 x 50 mg + 34.8 x 10 mg
Carboplatin in combination with a third-generation cytostatic drug (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)					
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
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	47.5mg - 57mg	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[2]					
Gemcitabine	1,000 mg/ m² = 1,900 mg	1,900 mg	1 x 2,000 mg	39	39 x 2,000 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Vinorelbine[2]	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
b) Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with cytotoxic chemotherapy					
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[3]					
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[4]					
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
Docetaxel in combination with nintedanib[5]					
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
c) Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation 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					
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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Pemetrexed					
Pemetrexed	500 mg/m² = 950 mg	950 mg	1 x 1,000 mg	17.4	17.4 x 1,000 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[5]					
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					
Sotorasib 120 mg	240 FCT	€ 10,547.41	€ 1.77	€ 599.07	€ 9,946.57
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[7]	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	€ 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	€ 3,035.99	€ 1.77	€ 170.10	€ 2,864.12
Pemetrexed 1,000 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					

LAUER-TAXE® last revised: 15 July 2022

<u>Costs for additionally required SHI services:</u>

Only costs directly related to the use of the medicinal product are taken into account. If there

[7] Fixed reimbursement rate

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: sotorasib							
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[7], 50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08	€ 2.34	17.4	€ 40.74

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
Dimetindene IV 1 ml/ 10 kg, 5 x 4 mg SFI	€ 18.86	€ 1.77	€ 1.77	€ 15.32	€ 6.13	17.4	€ 106.63
Cimetidine 300 mg IV, 10 CIS x 200 mg	€ 19.77	€ 1.77	€ 0.40	€ 17.60	€ 3.52	17.4	61.25
Pemetrexed							
Dexamethasone [7,8]2 x 4 mg, 100 TAB	€ 79.50	€ 1.77	€ 5.40	€ 72.33	€ 1.45	52.2	€ 75.69
Folic acid 350 – 1,000 µg/day, 100 TAB	€ 16.70	€ 0.84	€ 2.41	€ 13.45	€ 0.14 - € 0.27	365	€ 49.09 - € 98.19
Vitamin B12[7] 1,000 µg/day, every 3 cycles, 10 SFI	€ 7.40	€ 0.37	€ 0.33	€ 6.70	€ 0.67	5.8	€ 3.89
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

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

ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 23 March 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 February 2022, the pharmaceutical company submitted a dossier for the benefit assessment of sotorasib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 15 February 2022 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 sotorasib.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 May 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 16 May 2022. The deadline for submitting written statements was 7 June 2022.

The oral hearing was held on 27 June 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 26 July 2022, and the proposed resolution was approved.

At its session on 4 August 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 March 2021	Determination of the appropriate comparator therapy
Working group Section 35a	22 June 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 June 2022	Conduct of the oral hearing
Working group Section 35a	5 July 2022 19 July 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	26 July 2022	Concluding discussion of the draft resolution
Plenum	4 August 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 August 2022

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

Prof. Hecken