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 (reassessment after the deadline: lung cancer, non-small cell, KRAS G12C mutation, ≥ 1 prior therapy)

of 3 August 2023

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 pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient sotorasib (Lumykras) on 14 February 2022. For the resolution of 4 August 2022 made by the G-BA in this procedure, a limitation up to 1 July 2023 was pronounced. At the pharmaceutical company's request, this limitation was shortened until 1 February 2023 by the resolution of the G-BA of 5 January 2023.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Lumykras recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of

Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO on 31 January 2023. The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 May 2023 on the G-BA website (www.g-ba.de), therefore 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 3 August 2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

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

Appropriate comparator therapy for sotorasib 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 authorisation status, the active ingredients cisplatin, docetaxel, etoposide, ifosfamide, mitomycin, paclitaxel, pemetrexed, vindesine, vinorelbine, afatinib, erlotinib, nintedanib, atezolizumab, nivolumab, pembrolizumab and ramucirumab are available for the treatment of advanced NSCLC.

Medicinal products with an explicit marketing authorisation for the treatment of treatable mutations or for molecularly stratified therapy (directed against ALK, BRAF, EGFR, Exon-20, METex14, RET or ROS1) are not listed.

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

Medicinal products with an explicit marketing authorisation for the treatment of treatable mutations or for molecularly stratified therapy (directed against ALK, BRAF, EGFR, Exon-20, METex14, RET or ROS1) are not listed.

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 treatments 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 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. In the present procedure, patients with cytotoxic chemotherapy pretreatment (patient group b) and patients after first-line therapy with an anti-PD-1/PD-L1 in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 and platinum-containing chemotherapy (patient group c) are relevant.

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 immune checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab, partly only under certain conditions.

With docetaxel and pemetrexed, both as monotherapy, two established chemotherapeutic agents are available for second-line chemotherapy, although pemetrexed is 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 ≥ 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.

The appropriate comparator therapy determined here includes several therapeutic alternatives. In this context, individual therapeutic alternatives only represent a comparator therapy for the part of the patient population that has the patient and disease characteristics specified in brackets. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

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 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.

2.1.3 Extent and probability of the additional benefit

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

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

An additional benefit is not proven.

Justification:

For adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with cytotoxic chemotherapy, the pharmaceutical company does not submit data for the assessment of additional benefit. Therefore, an additional benefit is not proven.

c) Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with an anti-PD-1/PD-L1 in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 and platinum-containing chemotherapy

c1) Adults for whom docetaxel is the appropriate patient-individual therapy

Hint of a non-quantifiable additional benefit.

Justification:

For the proof of an additional benefit of sotorasib, the pharmaceutical company presents the still ongoing randomised, open-label and multicentre phase III CodeBreak 200 study comparing sotorasib versus docetaxel. The study has been conducted in 148 study sites in Asia, Australia, Europe and North and South America since 2020.

The study enrolled adult patients with locally advanced and unresectable or metastatic NSCLC with molecularly diagnosed KRAS G12C mutation. Patients had to have disease progression during or after at least 1 prior systemic therapy for advanced or unresectable stage of the disease. Prior therapy should include combined or sequential platinum-containing combination chemotherapy and an anti-PD-1/PD-L1. A total of 334 (96.8%) patients in the study received prior treatment with PD-1/PD-L1 inhibitor and platinum-containing chemotherapy (in combination or sequentially). For enrolment in the study, patients should have a general condition according to Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1, no relevant limitations in renal and liver function and no haematological limitations.

The total of 345 patients were randomised in a 1:1 ratio to either treatment with sotorasib (N = 171) or docetaxel (N = 174), stratified by number of prior lines of therapy in advanced stage of the disease (1 vs 2 vs > 2), descent (Asian vs non-Asian) and brain metastases at the time of randomisation (yes vs no).

The treatment with sotorasib or docetaxel complied with the specifications of the product information with restrictions regarding a renewed intake of sotorasib after vomiting or regarding a permitted dose reduction of docetaxel to 55 mg/m^{2}body surface area and, if required, a second dose reduction to 37.5 mg/m^2 body surface area during the course of the study. Treatment with study medication continued until disease progression, intolerance of treatment, initiation of new anti-cancer therapy, withdrawal of consent, lost to follow-up or death. If certain criteria were met according to the principal investigator's assessment, further treatment with sotorasib or docetaxel was possible even after disease progression. Under certain conditions, e.g. the patients were not allowed to have started any other cancer therapy, a change of therapy from docetaxel to sotorasib was possible at the doctor's discretion.

The primary endpoint of the study was progression-free survival according to a blinded, independent central review. Other patient-relevant endpoints included overall survival and endpoints on symptomatology and health status. In addition, endpoints of the categories health-related quality of life and side effects were collected.

The pharmaceutical company presents results of the 1st data cut-off from 02.08.2022.

Implementation of the appropriate comparator therapy

The CodeBreak 200 study presented is a single-comparator study in which all patients in the comparator arm received docetaxel as monotherapy. Thus, the CodeBreak 200 study does not implement the appropriate comparator therapy, which provides for a patient-individual selection from several named treatment options. In the submitted dossier and in the context of the statement, the pharmaceutical company justifies the choice of docetaxel with advantages over the other options of the appropriate comparator therapy, in particular docetaxel in combination with ramucirumab or docetaxel in combination with nintedanib, and additionally cites the lack of global availability of individual therapy options.

Within the framework of the written statement procedure, the scientific-medical societies describe the therapy of pretreated NSCLC with docetaxel as a particularly relevant therapeutic alternative in view of the previous therapy for patients without contraindications. The other therapy options included in the appropriate comparator therapy play a particularly relevant therapeutic alternative. The other therapeutic alternative included in the appropriate comparator therapy also play a role.

Even taking into account the statements, the G-BA considers the CodeBreak 200 study as a whole to be a sufficiently suitable evidence base to make an assessment with regard to the sub-population of patients for whom docetaxel is the appropriate patient-individual therapy.

Consequently, a separate assessment is made for patients for whom docetaxel is the appropriate patient-individual therapy (patient group c1)) and patients for whom a therapy other than docetaxel is the appropriate patient-individual therapy (patient group c2)).

Extent and probability of the additional benefit

c1) Adults for whom docetaxel is the appropriate patient-individual therapy

Hint for a non-quantifiable additional benefit

Mortality

The endpoint of overall survival was defined in the CodeBreak 200 study as the time from the date of randomisation to death from any cause. There is no statistically significant difference between the treatment arms here.

With regard to overall survival, an additional benefit of sotorasib compared to docetaxel is therefore not proven.

Morbidity

Progression-free survival (PFS)

Progression-free survival (PFS) is defined in the study as the time from the date of randomisation until disease progression or death from any cause, whichever occurred first.

For the PFS, there is a statistically significant difference to the advantage of sotorasib compared to docetaxel.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component of mortality is already assessed via the endpoint of overall survival as an independent endpoint. The morbidity component is assessed according to RECIST criteria (version 1.1) and thus predominantly by means of imaging procedures. Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS. The overall statement on the extent of the additional benefit remains unaffected.

Progression of central nervous system (CNS) metastases

The endpoint of progression in the CNS is defined in the CodeBreak 200 study as the time from randomisation to radiological evidence of disease progression in the CNS (endpoint assessment only for patients who already had CNS disease at the time of enrolment in the study). The assessment is based solely on imaging procedures and does not take into account the symptomatology perceived by patients. Thus, the endpoint is not directly patient-relevant and is not presented. In addition, only patients who already had CNS disease at the time of enrolment in the study were included in the analysis. Patients without previous CNS disease or with first-time occurrence of CNS metastases were not included in the evaluation.

Cross-endpoint assessment of patient-reported endpoints (PRO) data:

With regard to the endpoints assessed in the CodeBreak 200 study using the EORTC QLQ-C30, EORTC QLQ-LC13, BPI-SF, FACT-G GP5, and PGI-C questionnaires, IQWiG noted in the addendum to the dossier assessment that there was a differential percentage of patients included in the evaluation between the treatment arms for all corresponding endpoints of > 15 percentage points each, which is why IQWiG assessed the data as unsuitable overall. For the present assessment, the results for the respective endpoints, in particular the effect estimator, the confidence interval and the percentage of patients included in the evaluation

in the treatment arms, are also taken into account in order to assess the extent to which these data are suitable or completely unsuitable for deriving statements on the additional benefit.

Symptomatology

In the endpoint category of morbidity, the CodeBreak 200 study recorded symptomatology using the EORTC QLQ-C30 and LC-13 questionnaires, the endpoints of worst pain and impairment due to pain using BPI-SF items 3 and 9a-g, respectively, and the endpoint of therapy burden using the single item GP5 from the FACT-G questionnaire.

Health status

In the CodeBreak 200 study, health status was assessed both with the PGI-C questionnaire (change in physical condition via the symptoms of cough, chest pain and shortness of breath) and via the EQ-5D visual analogue scale *(VAS*). With regard to the evaluations of the VAS of the EQ-5D, a statistically significant difference to the advantage of sotorasib over docetaxel is shown for the endpoint of health status.

Symptomatology

As a result of the above assessment of the data, the present assessment assumes an overall positive effect of sotorasib on symptomatology compared to docetaxel. This assessment is supported by the consistent and, in some cases, very significant effects on several endpoints on symptomatology as well as the statistically significant difference to the advantage of sotorasib in the endpoint of health status (EQ-5D VAS). Notwithstanding the fact that the differential percentage of > 15 percentage points per se results in a high risk of bias and a resulting large uncertainty, an overall advantage can thus be derived for sotorasib with regard to symptomatology.

Conclusion on morbidity endpoints:

In the overall analysis of the results, an advantage of sotorasib can be determined with regard to morbidity, the extent of which cannot be quantified.

Health-related quality of life

The health-related quality of life of the patients in the CodeBreak 200 study is assessed using the functional scales of the EORTC QLQ-C30 questionnaire. As a result of the above assessment of the data, the large uncertainty predominates based on a weighing of the extent of the differential percentage of patients included in the treatment arms in the evaluation and the magnitude of the effects on the quality of life endpoints. Therefore, an effect on the overall quality of life cannot be assumed with sufficient certainty. The result is that the data are not assessable.

Side effects

Adverse events (AEs) in total

In the CodeBreak 200 study, AEs occurred in both treatment arms in almost all study participants. The results were only presented additionally.

Serious AEs (SAEs), severe AEs and discontinuation due to AEs

There is no statistically significant difference between the treatment arms for each of the endpoints of SAEs, severe AEs and discontinuation due to AEs.

Specific AEs

Interstitial lung disease (severe AE)

There was no statistically significant differences between the treatment arms for the specific AE of interstitial lung disease.

Liver disorders (severe AEs)

For the specific AE of liver disorders (severe AEs), there is a statistically significant difference to the disadvantage of sotorasib versus docetaxel.

Other specific AEs

For the specific AEs of stomatitis (AE), peripheral oedema (AE), peripheral neuropathy (AE), alopecia (AE), blood and lymphatic system disorders (AE), fatigue (AE), fever (AE) and infections and infestations (AE), there was a statistically significant difference to the advantage of sotorasib versus docetaxel.

For the specific AE of chest pain (AE) and diarrhoea (AE), there was a statistically significant difference to the disadvantage of sotorasib versus docetaxel.

For the AEs of fever (AE) and infections and infestations (AE), there is an effect modification by the age characteristic in each case. With regard to the AE of fever, there was a statistically significant difference for patients < 65 years of age to the advantage of sotorasib, whereas for patients ≥ 65 years of age there was no statistically significant difference between the treatment arms. With regard to the AE of infections and infestations (AE), there was a statistically significant difference for patients ≥ 65 years of age to the advantage of sotorasib, whereas for patients < 65 years of age there was no statistically significant difference between the treatment arms.

This effect modification is not evident in other endpoints. Overall, the significance of the available subgroup results is considered insufficient for the assessment of the additional benefit.

Patient-reported Outcome - Common Terminology Criteria for Adverse Events (PRO-CTCAE)

In the CodeBreak 200 study, side effects were also recorded with the PRO-CTCAE instrument. However, it is not clear from the available documents on what basis the events were selected from the PRO-CTCAE system. More detailed information on the procedure was not provided by the pharmaceutical company. It is also not possible to tell whether the side effects of sotorasib and docetaxel are adequately shown. Overall, the results of the PRO-CTCAE cannot be used.

In the overall assessment of the results on side effects, neither an advantage nor a disadvantage for treatment with sotorasib compared to docetaxel can be found.

<u>Overall assessment/ conclusion</u>

For the assessment of the additional benefit of sotorasib in adults with advanced NSCLC with KRAS p.G12C mutation after first-line therapy with an anti-PD 1/PD-L1 in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD 1/PD-L1 and platinum-containing chemotherapy, results on mortality, morbidity, health-related quality of life and side effects are available from the open-label, randomised, controlled phase III CodeBreak 200 study.

In the CodeBreak 200 study, sotorasib was compared to docetaxel.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment arms.

With regard to the endpoints of symptomatology and health status, which were assessed in the CodeBreak 200 study by means of the EORTC QLQ-C30, EORTC QLQ-LC13, BPI-SF, FACT-G GP5, and PGI-C questionnaires, there are uncertainties resulting from the differential percentage of patients of > 15 percentage points included in the evaluations between the treatment arms. With regard to the evaluations of the EQ-5D VAS, there is a statistically significant difference for the endpoint of health status to the advantage of sotorasib over docetaxel. In the overall analysis of the results, an advantage of sotorasib can be determined with regard to morbidity, the extent of which cannot be quantified.

No assessable data are available for the endpoint category of health-related quality of life assessed using the functional scales of the EORTC QLQ-C30 questionnaire.

In the overall assessment of the results on side effects, neither an advantage nor a disadvantage for treatment with sotorasib compared to docetaxel can be found.

In the overall assessment, therefore, a non-quantifiable additional benefit over docetaxel is identified for sotorasib as monotherapy for the treatment of adults with advanced NSCLC with KRAS p.G12C mutation after first-line therapy with an anti-PD-1/PD-L1 in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 and platinum-containing chemotherapy for which docetaxel is the appropriate patient-individual therapy.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the randomised, open-label phase III CodeBreak 200 study.

The risk of bias across endpoints at the study level is rated as generally low for the CodeBreak 200 study. However, there are uncertainties regarding the implementation of the criteria specified in the context of the appropriate comparator therapy for the treatment decision for the use of docetaxel as an appropriate patient-individual therapeutic alternative.

The risk of bias of the results for the endpoint of overall survival is rated as high. This is justified by the high percentage of patients who switch from the docetaxel arm to the sotorasib arm during the course of the study and due to the unclear percentage of censoring at the start of the study.

At the endpoint level of the endpoint category of side effects and for the endpoint of health status, the risk of bias is classified as high due to the differential percentages of patients included in the evaluations between the treatment arms.

For the endpoints of health status, discontinuation due to AEs, non-severe and non-serious specific AEs, the lack of blinding additionally contributes to the high risk of bias of the results.

Overall, a hint is derived for the reliability of data of the additional benefit identified.

c2) Adults for whom a therapy other than docetaxel is the appropriate patient-individual therapy

An additional benefit is not proven.

Justification

For the sub-population of adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with an anti-PD-1/PD-L1 in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 and platinum-containing chemotherapy and for whom a therapy other than docetaxel is the appropriate patient-individual therapy, no statements on the additional benefit can be made taking into account the CodeBreak 200 study. Since only results with a comparison to docetaxel were presented for the benefit assessment, no usable data are available overall. An additional benefit of sotorasib is therefore not proven for sub-population c2).

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient sotorasib due to the expiry of the limitation of the resolution of 4 August 2022. The assessment relates exclusively to the use of sotorasib as monotherapy for the treatment of adults with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation who have been diagnosed with progression after at least one prior systemic therapy, in the following patient population:

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

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

No data are available to allow an assessment of the additional benefit. An additional benefit is therefore not proven.

c) Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with an anti-PD-1/PD-L1 in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 and platinum-containing chemotherapy

The appropriate comparator therapy comprises patient-individual therapy with a choice of afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib and vinorelbine, taking into account prior therapy and histology.

For the benefit assessment, the pharmaceutical company presents data from the randomised, controlled, open-label phase III CodeBreak 200 study comparing sotorasib versus docetaxel.

Due to the lack of comparison with other treatment options, the CodeBreak200 study only allows statements to be made on the additional benefit of sotorasib in those patients for whom docetaxel is the most appropriate patient-individual therapy. Based on the available evidence, the G-BA therefore considers it appropriate to form two patient groups according to their patient-individual suitability for docetaxel:

c1) Adults for whom docetaxel is the appropriate patient-individual therapy

and

c2) Adults for whom a therapy other than docetaxel is the appropriate patient-individual therapy

on c1)

Results on mortality, morbidity, health-related quality of life and side effects are available from the CodeBreak 200 study.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment arms.

Uncertainties exist with regard to the endpoints of symptomatology and health status. In the overall analysis of the results, an advantage of sotorasib can be determined with regard to morbidity, the extent of which cannot be quantified.

No assessable data are available for the endpoint category of health-related quality of life.

In the overall assessment of the results on side effects, neither an advantage nor a disadvantage of treatment with sotorasib can be found.

In the overall assessment, therefore, a non-quantifiable additional benefit over docetaxel is identified for sotorasib for the sub-population of adults with pretreated locally advanced and unresectable or metastatic NSCLC with KRAS G12C mutation, for whom docetaxel is the appropriate patient-individual therapy.

Overall, a hint is derived for the reliability of data of the additional benefit identified.

on c2)

For the sub-population of adults with pretreated locally advanced and unresectable or metastatic NSCLC with KRAS G12C mutation, for whom a therapy other than docetaxel is the appropriate patient-individual therapy, no statements on the additional benefit can be made on the basis of the CodeBreak 200 study, as no usable data are available. An additional benefit of sotorasib is therefore not proven for sub-population c2).

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 ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of sotorasib (resolution of 4 August 2022)[2].

Here, the incidence of 59,700 patients forecast by the Robert Koch Institute for 2022 is used as an updated basis for the calculations[3].

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: 5 June 2023):

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 approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency EMA 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 2023).

Treatment period:

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

[2] Benefit assessment procedure D-787 https://www.g-ba.de/downloads/40-268-8725/2022-08-04_AM-RL-XII_Sotorasib_D-787_TrG.pdf

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

the "number of treatments/ patient/ year", time intervals between individual treatments and the maximum treatment duration, if specified in the product information.

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	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
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[4]				
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[5]				
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 14-day cycle	26.1	1	26.1
	or			
	1 x per 21-day cycle	17.4	1	17.4
	or			

[4] only for patients with PD-L1 negative tumours and except in the case of predominantly squamous cell histology
[5] only for patients with PD-L1 expressing tumours, PD-L1 expression ≥ 1% of tumour cells

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x per 28-day cycle	13.0	1	13.0
Docetaxel in combination with nintedanib[6]				
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	348.0
c) Adults with advanced non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation after first-line therapy with an anti-PD-1/PD-L1 in combination with platinum-containing chemotherapy or after sequential therapy with an anti-PD-1/PD-L1 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	Continuously, 1 x daily	365.0	1	365.0
Pemetrexed				
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Erlotinib				
Erlotinib	Continuously, 1 x daily	365.0	1	365.0
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[6]				
Docetaxel	1 x per 21-day cycle	17.4	1	17.4

[6] 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
Nintedanib	2 x on day 2-21 of a 21-day cycle	17.4	20	348.0
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.

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)[7].

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	365.0	2,920 x 120 mg
Appropriate comparator therapy					
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	1 x 160 mg	17.4	17.4 x 160 mg
Pemetrexed					
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Nivolumab					
Nivolumab	240 mg	240 mg	2 x 120 mg	26.1	52.2 x 120 mg
Pembrolizumab					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg

[7] 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
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
Atezolizumab					
Atezolizumab	840 mg	840 mg	1 x 840 mg	26.1	26.1 x 840 mg
	or				
	1,200 mg	1,200 mg	1 x 1,200 mg	17.4	17.4 x 1,200 mg
	or				
	1,680 mg	1,680 mg	2 x 840 mg	13.0	26 x 840 mg
Docetaxel in combination with nintedanib					
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Nintedanib	200 mg	400 mg	4 x 100 mg	348.0	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 an anti-PD-1/PD-L1 in					
Patient-individual therapy, taking into account prior 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	365.0	365 x 40 mg
Pemetrexed					
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Erlotinib					
Erlotinib	150 mg	150 mg	1 x 150 mg	365.0	365 x 150 mg
Docetaxel					
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Docetaxel in combination with ramucirumab					
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Ramucirumab	10 mg/kg = 770 mg	770 mg	1 x 500 mg + 3 x 100 mg	17.4	17.4 x 500 mg +

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					52.2 x 100 mg
Docetaxel in combination with nintedanib					
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Nintedanib	200 mg	400 mg	4 x 100 mg	348.0	1,392 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	€ 4,820.84	€ 2.00	€ 466.34	€ 4,352.50
Appropriate comparator therapy					
Atezolizumab 1,200 mg	1 CIS	€ 4,319.46	€ 2.00	€ 417.25	€ 3,900.21
Atezolizumab 840 mg	1 CIS	€ 3,040.90	€ 2.00	€ 292.07	€ 2,746.83
Afatinib 40 mg	28 FCT	€ 2,515.23	€ 2.00	€ 240.61	€ 2,272.62
Docetaxel 160 mg	1 CIS	€ 515.75	€ 2.00	€ 23.94	€ 489.81
Erlotinib 150 mg[8]	30 FCT	€ 880.24	€ 2.00	€ 68.73	€ 809.51
Nintedanib 100 mg	120 SC	€ 2,761.26	€ 2.00	€ 110.29	€ 2,648.97

[8] 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
Nivolumab 120 mg	1 CIS	€ 1,546.93	€ 2.00	€ 145.81	€ 1,399.12
Pembrolizumab 100 mg	1 CIS	€ 2,974.79	€ 2.00	€ 285.60	€ 2,687.19
Pemetrexed 500 mg	1 CIS	€ 572.64	€ 2.00	€ 26.64	€ 544.00
Ramucirumab 500 mg	1 CIS	€ 2,141.31	€ 2.00	€ 204.00	€ 1,935.31
Ramucirumab 100 mg	1 CIS	€ 441.14	€ 2.00	€ 40.80	€ 398.34
Vinorelbine 10 mg	10 CIS	€ 293.98	€ 2.00	€ 13.42	€ 278.56
Vinorelbine 50 mg	10 CIS	€ 1,424.53	€ 2.00	€ 67.07	€ 1,355.46
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 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 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed: Sotorasib							
Not applicable							
Appropriate comparator therapy:							
Pemetrexed							

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Dexamethasone[8,9] (2 x 4 mg P.O.)	100 TAB 4 mg each	€ 79.50	€ 2.00	€ 5.40	€ 72.10	52.2	€ 75.27
Folic acid (350 – 1,000 µg/day, p.o.)	100 TAB 400 µg each	€ 16.89	€ 0.84	€ 2.13	€ 13.92	365.0	€ 50.81 - € 101.62
Vitamin B12[8] (1,000 µg/day, every 3 cycles, IM)	10 AMP 1000 µg each	€ 7.40	€ 0.37	€ 0.32	€ 6.71	5.8	€ 3.89
Abbreviations: TAB = tablets; AMP = ampoules							

Other SHI services:

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

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an 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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

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

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 Sotorasib

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

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

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

3. Bureaucratic costs calculation

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

4. Process sequence

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

On 31 January 2023, 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 5 VerfO.

By letter dated 31 January 2023 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 25 April 2023, and the written statement procedure was initiated with publication on the G-BA website on 2 May 2023. The deadline for submitting statements was 23 May 2023.

The oral hearing was held on 5 June 2023.

By letter dated 6 June 2023, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 7 July 2023.

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 25 July 2023, and the proposed resolution was approved.

At its session on 3 August 2023, 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	30 May 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	5 June 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	13 June 2023 5 July 2023 19 July 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	25 July 2023	Concluding discussion of the draft resolution
Plenum	3 August 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 August 2023

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

Prof. Hecken