Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Ramucirumab (New Therapeutic Indication: NSCLC, First- Line, EGFR Mutation, Combination with Erlotinib)

of 20 August 2020

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 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient ramucirumab (Cyramza®) was listed for the first time on 1 February 2015 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 23 January 2020, ramucirumab received the marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 14 February 2020, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient atezolizumab with the new therapeutic indication “Cyramza in combination with erlotinib is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations” in due time (i.e. at the latest within four

weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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 15 May 2020, 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 ramucirumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has assessed 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 ramucirumab.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at 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 ramucirumab (Cyramza®) in accordance with the product information

Cyramza in combination with erlotinib is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with metastatic NSCLC with the activating EGFR mutations L858R[2] or del 19[3]; first-line therapy:

Appropriate comparator therapy for ramucirumab in combination with erlotinib:

Afatinib or gefitinib or erlotinib or osimertinib

b) Adult patients with metastatic NSCLC with activating EGFR mutations other than L858R[2] or del 19[3]; first-line therapy:

Appropriate comparator therapy for ramucirumab in combination with erlotinib:

A patient-individual therapy depending on the activating EGFR mutation with selection of:

- Afatinib, gefitinib, erlotinib, osimertinib
- Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.
[2] Exon 21 substitution mutation
[3] Exon 19 deletion

- Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed; *cf* Annex VI to Section K of the Pharmaceuticals Directive)
- Carboplatin in combination with nab-paclitaxel

and

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

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to 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 applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee 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 addition to ramucirumab, cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine, vinorelbine, afatinib, dacomitinib, erlotinib, gefitinib, osimertinib, bevacizumab, and necitumumab are approved for the first-line treatment of EGFR-positive non-small cell lung cancer (NSCLC), whereby carboplatin is additionally prescribable in off-label use in the present therapeutic indication.

On 2. Non-medicinal treatment is not considered. The implementation of surgery or radiotherapy as a palliative therapy option remains unaffected.

On 3. The following resolutions and guidelines of the G-BA have been issued for medicinal therapies in the present therapeutic indication:

Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

Afatinib: Resolution of 5 November 2015

Osimertinib: Resolution of 15 September 2016

Necitumumab: Resolution of 15 September 2016

Osimertinib: Resolution of 17 January 2019

Dacomitinib: Resolution of 17 October 2019

Guidelines:

Carboplatin: Resolution of 18 October 2018 on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex VI – Off-label use Part A Item III: Carboplatin for advanced non-small cell lung carcinoma (NSCLC) – combination therapy

On 4. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines as well as systematic reviews of clinical studies.

a) Adult patients with metastatic NSCLC with the activating EGFR mutations L858R or del 19; first-line therapy:

In this case, it is assumed that the patients are in stage IV of the disease without indication for curative resection, radiation treatment, or radiochemotherapy.

The frequent activating EGFR mutations, exon 21 substitution mutation (L858R) and exon 19 deletion, comprise the majority of the present therapeutic indication with approx. 86% to 89%[4,5].

For patients with these activating EGFR mutations, current guidelines consistently recommend therapy with the tyrosine kinase inhibitors (TKI) erlotinib, gefitinib, afatinib, or osimertinib with no active ingredient being preferred. The use of tyrosine kinase inhibitors in patients with EGFR-positive NSCLC is based on the generally recognised state of medical knowledge, in particular because of the advantages in health-related quality of life, symptomatology, and certain side effects and has established itself in clinical treatment practice.

For afatinib, a significant survival benefit over cisplatin in combination with pemetrexed was found in the benefit assessment with resolution of 5 November 2015 in patients with the EGFR mutation exon 19 deletion. In contrast, for patients with the EGFR mutation exon 21 substitution (L858R) and other rare mutations, no additional benefit was derived by the G-BA.

Osimertinib represents a relatively new treatment option in this indication. In the context of the benefit assessment, the G-BA found a hint for a considerable additional benefit for this active ingredient compared with gefitinib or erlotinib in patients with the EGFR mutations exon 21 substitution and exon 19 deletion in EGFR in first-line treatment (resolution of 17 January 2019). In their written statements on previous benefit assessments, clinical experts emphasised the importance of osimertinib in current care. The optimal timing for the use of osimertinib in the therapy sequence in the treatment of EGFR-positive NSCLC is the subject of ongoing discussions. Thus, osimertinib also has a high significance in the detection of acquired EGFR-TKI resistance as a result of an EGFR-T790M mutation (i.e. in second-line treatment after EGFR-TKI pre-treatment). Against this background, osimertinib is not considered as the only appropriate comparator therapy.

On 2 April 2019, the EGFR TKI dacomitinib was approved for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations. In its resolution of 17 October 2019, the G-BA did not find any additional benefit compared with gefitinib in the benefit assessment of dacomitinib in patients with exon 21 substitution mutation and exon 19 deletion in EGFR in first-line treatment.

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4 Gahr S, Stoehr R, Geissinger E, Ficker JH, Brueckl WM, Gschwendtner A et al. EGFR mutational status in a large series of Caucasian European NSCLC patients: data from daily practice. Br J Cancer 2013; 109(7): 1821-1828

5 Faehling, M., Schwenk, B., Kramberg, S., Eckert, R., Volckmar, A. L. et al. Oncogenic driver mutations, treatment, and EGFR-TKI resistance in a Caucasian population with non-small cell lung cancer: survival in clinical practice. Oncotarget 2017; 8(44): 77897-77914.

Dacomitinib is another treatment option that has been approved for this therapeutic indication and is still relatively new. The active ingredient is currently not considered an appropriate comparator therapy.

In summary, the tyrosine kinase inhibitors afatinib or erlotinib or gefitinib or osimertinib are equally suitable therapy options in the first-line treatment of NSCLC with the activating EGFR mutations L858R or del 19.

a) Adult patients with metastatic NSCLC with activating EGFR mutations other than L858R or del 19; first-line therapy:

In this case, it is assumed that the patients are in stage IV of the disease without indication for curative resection, radiation treatment, or radiochemotherapy.

Activating EGFR mutations other than L858R or del 19 account for a considerable proportion (11–14%) of the activating EGFR mutations covered by the present therapeutic indication [4,5].

The group of activating EGFR mutations other than L858R or del 19 is highly heterogeneous. However, there is limited evidence of the individual mutations included in this group. In general, the guidelines distinguish between mutations that are tyrosine kinase inhibitor (TKI)-sensitive and those that do not respond to TKI therapy. For TKI-sensitive mutations, current guidelines recommend TKI therapy with erlotinib, gefitinib, afatinib, or osimertinib in the sense of a molecularly stratified therapy in the present disease stage.

Osimertinib is also an approved treatment option for patients with activating EGFR mutations other than L858R or del 19. In the benefit assessment of osimertinib, the G-BA found no additional benefit for these patients (resolution of 17 January 2019: Patients with EGFR mutations other than L858R or del 19 (except for *de novo* T790M); resolution of 15 September 2016: patients with a *de novo* positive T790M mutation) because no suitable data on these patient groups were available in each case. Given the overall limited evidence of TKI in this patient group and considering that osimertinib is explicitly approved for the treatment of the T790M mutation, osimertinib is determined as an appropriate comparator therapy despite the result of the benefit assessment.

Furthermore, for patients with activating EGFR mutations other than L858R or del 19, dacomitinib is also available as another approved treatment option. However, it is still relatively new in this indication. In its resolution of 17 October 2019, in the context of the benefit assessment for dacomitinib in this patient group, the G-BA also found no additional benefit compared with the appropriate comparator therapy. Dacomitinib is currently not considered an appropriate comparator therapy.

In contrast, the activating exon 20 insertion mutation is not TKI-sensitive. For patients with the activating exon 20 insertion mutation, current guidelines recommend treatment analogous to EGFR wild-type patients. Accordingly, these patients are treated with a platinum-based combination chemotherapy with a third-generation cytostatic agent. In accordance with the Pharmaceuticals Directive (last revised: 18 October 2018): Annex VI – Off-label use Part A Item III: “Carboplatin for advanced non-small cell lung carcinoma (NSCLC) – combination therapy, carboplatin is prescribable, whereby the selection of the platinum component (carboplatin or cisplatin) should, in individual cases, be based on the different toxicity profile of the two substances as well as on the existing comorbidities.

Furthermore, nab-paclitaxel in combination with carboplatin is considered to be another appropriate therapy option for these patients.

For patients with reduced general condition, however, the toxicity profile of platinum-based combination chemotherapy must be weighed against the expected benefit, taking into account patient-individual criteria. As an alternative, patients with ECOG

performance status 2 may be considered for monochemotherapy with gemcitabine or vinorelbine, which is considered appropriate for this group of patients in addition to platinum-based combination chemotherapy.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of ramucirumab in combination with erlotinib is assessed as follows:

a) Adult patients with metastatic NSCLC with the activating EGFR mutations L858R or del 19; first-line therapy:

For the treatment of adult patients with first-line treatment of metastatic NSCLC with the activating EGFR mutations L858R or del 19, an additional benefit is not proven.

Justification:

To demonstrate the additional benefit of ramucirumab in combination with erlotinib in the first-line therapy of metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations, the pharmaceutical company presented the results of the RELAY study.

RELAY is a multi-centre, double-blind, randomised controlled study comparing ramucirumab in combination with erlotinib with erlotinib. The ongoing global study, which started in January 2016, includes adult patients without prior treatment for the metastatic stage of NSCLC with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1. In the presence of recurrent metastatic disease, (neo-)adjuvant therapy had to be completed at least 12 months before metastasis. In accordance with the inclusion criteria of the RELAY study, only patients with tumours with the EGFR mutation exon 21 substitution mutation (L858R) or exon 19 deletion (del 19) were included. The inclusion of patients with an additional known T790M mutation in exon 20 was not approved. Patients with CNS metastases were excluded from the RELAY study.

The 449 patients included were randomised into the intervention arm (ramucirumab + erlotinib; N = 224) and the comparison arm (placebo + erlotinib; N = 225) at a ratio of 1:1 with stratification by sex (male vs female), region (East Asia vs rest of the world), activating EGFR mutation (exon 19 deletion vs exon 21 substitution mutation), and EGFR test method (therascreen or cobas vs other PCR and sequence-based method).

Treatment with the study medication was to be continued until disease progression or discontinuation for other reasons (e.g. because of AE or patient decision).

RELAY is being conducted in 100 study centres in North America, Asia, and Europe. Predominantly Asian patients are examined; they represent approx. 3/4 of the study population.

The planned analysis for the primary endpoint progression-free survival (PFS) of 23 January 2019 from the RELAY study is currently available. This was planned after 270 events in the PFS endpoint and was performed after 280 PFS events. Results for all patient-relevant endpoints are available for this data cut-off. Only for the PFS endpoint was an additional interim analysis performed on 25 September 2019 at the request of the EMA. The final analysis on overall survival will be carried out when about 300 deaths occur. For the present benefit assessment, the data cut-off of 23 January 2019 is used.

Extent and probability of the additional benefit

Mortality

In the RELAY study, overall survival was defined as the time between randomisation and death regardless of the underlying cause of death.

For the overall survival endpoint, there was no statistically significant difference between ramucirumab in combination with erlotinib and erlotinib (HR: 0.83 [95% CI: 0.53; 1.30]; p = 0.421). In the RELAY study, median survival was not yet achieved because of the low number of events; final analyses on the overall survival endpoint are pending.

No additional benefit is identified for the overall survival endpoint.

Morbidity

Progression-free survival (PFS)

In the RELAY study, progression-free survival was the primary endpoint and defined in the study protocol/report as the time between randomisation and disease progression (determined using RECIST criteria version 1.1) or death regardless of the underlying cause.

In the intervention arm, there was a statistically significant increase in median PFS of 7.0 months compared with the control arm (median of 19.4 vs 12.4 months; HR: 0.59 [95% CI: 0.46; 0.76]; p < 0.0001).

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” was surveyed as an independent endpoint using the endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively using imaging procedures (radiologically determined disease progression according to the RECIST criteria). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint.

For the interpretation of the PFS results, the data available on morbidity and health-related quality of life are used. Data on morbidity and health-related quality of life are potentially relevant in this respect, especially when, as in the present case, a radiologically determined disease progression is associated with effects on morbidity and/or quality of life.
Overall, the data from the RELAY study show no statistically significant difference between the intervention arm and control arm in terms of symptomatology and health status. Data on health-related quality of life were not surveyed in the RELAY study. Accordingly, prolonged PFS under ramucirumab plus erlotinib was not associated with an advantage in terms of morbidity or quality of life.

In summary, the data available do not suggest that the statistically significant prolongation of progression-free survival under ramucirumab plus erlotinib – radiologically determined disease progression according to the RECIST criteria – is associated with an improvement in morbidity or health-related quality of life.

The results on the progression-free survival endpoint are not used in this assessment.

Time to diagnosis of CNS metastases

In the RELAY study, the time to diagnosis of CNS metastases was surveyed as an explorative endpoint. It was defined as the time from randomisation to the radiological detection of CNS metastases.

Because the prognosis of patients in the present therapeutic indication is significantly worsened by the first occurrence of CNS metastases in conjunction with newly occurring symptomatology, the endpoint “time to diagnosis of CNS metastases” has clinical relevance for the present patient population. This is also due to the limited therapy options.
Accordingly, the prevention of the development of brain metastases is given relevant importance. This view was also supported by clinical experts during the commenting procedure on the present benefit assessment.

In the RELAY study, a statistically significant effect in favour of ramucirumab in combination with erlotinib compared with erlotinib was found on the basis of time-to-event analysis. However, there are significant uncertainties in the interpretation of this effect. These are explained below.

Firstly, it must be taken into account that the evaluation in question is based on very small numbers of events. There were thus two events (0.9%) in the intervention arm and eight events (3.6%) in the comparator arm.
On the other hand, there is insufficient information on the extent to which the survey of the endpoint was symptom-based and which criteria formed the basis of the survey. According to the information available in the study protocol, a survey was to be carried out by radiological examination if it was clinically indicated. As part of the written statement procedure on the present benefit assessment, the pharmaceutical company explained that the endpoint was surveyed by the doctor on suspicion and that symptomatic cases were to be assumed.
Furthermore, the G-BA has no information on whether the RECIST or RANO criteria, which are specific to the evaluation of brain metastases in comparison with the RECIST criteria, were used for the survey.

Against the background of the relevant uncertainties regarding the interpretation and reliability of data, no additional benefit is derived for the endpoint “time to diagnosis of CNS metastases” based on the data available.

Symptomatology

In the RELAY study, symptomatology was assessed using the LCSS ASBI (Lung Cancer Symptom Scale Average Symptom Burden Index) questionnaire.

The survey was conducted regularly during treatment (bi-weekly from the second treatment cycle) and 30 days after the end of treatment.

For the benefit assessment, the pharmaceutical company presented in the dossier responder analyses for the time until initial deterioration and continuous evaluations (analyses of mean differences). The time to first deterioration was defined as an increase of the score by at least 15 mm compared with baseline.

No statistically significant differences between the study arms were found in either analysis variant.

Health status (EQ-5D visual analogue scale)

The general health status was assessed using the visual analogue scale of the EQ-5D. The survey was conducted regularly during treatment (bi-weekly from the second treatment cycle) and 30 days after the end of treatment.

For the benefit assessment, the pharmaceutical company presented responder analyses for the time to first deterioration by ≥ 7 or 10 points of the VAS score compared with baseline as well as continuous evaluations (analyses of mean differences).

In the dossier assessment of the IQWiG, the analyses of mean differences were used. The responder analyses were also presented in the annex to the dossier assessment. There are

no comments on the decision-making process regarding the inclusion of continuous analyses or responder analyses.

In the recent past, the IQWiG has not used the responder analyses because the study on which the derivation of the minimal important difference MID is based (Pickard et al., 2007) is no longer considered suitable by the IQWiG to prove the validity of the MID. This is justified by the fact that the work mentioned does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion on deriving a valid MID.

Instead of responder analyses, the IQWiG used analyses of mean differences.

Because responder analyses based on a MID have general advantages for a clinical evaluation of effects compared with analysis of standardised mean differences and because the validation study in question has already been used in earlier assessments, the G-BA has decided to draw on responder analyses in the current assessment to determine the effects on health status.

No statistically significant differences between the study arms were found in either analysis variant.

Quality of life

Data on health-related quality of life were not surveyed in the RELAY study.

Side effects

Adverse events (AE)

AE were surveyed up to 30 days after the end of treatment.

In the RELAY study, an adverse event occurred in 100% of the patients in both the intervention and comparator arm.

Serious adverse events (SAE)

SAE were surveyed up to 30 days after the end of treatment.

For the serious adverse events, there was no statistically significant difference between the study arms.

Severe AE (CTCAE grade ≥ 3)

With regard to severe adverse events with CTCAE grade ≥ 3, there was a statistically significant disadvantage of ramucirumab in combination with erlotinib compared with erlotinib

Discontinuation because of AE

For the endpoint “therapy discontinuation because of an AE”, there was no statistically significant difference between the study arms.

Specific AE

Ramucirumab in combination with erlotinib was found to have a statistically significant disadvantage compared with erlotinib in terms of the specific AE peripheral oedema (PT) as well as the specific severe AE (CTCAE grade ≥ 3), diarrhoea (PT), hypertension (PT), and infections and infestations (SOC).

Overall assessment

To assess the additional benefit of ramucirumab in combination with erlotinib compared with erlotinib, results on mortality (overall survival), morbidity (symptomatology and health status), and side effects are available from the double-blind, randomised, controlled RELAY study.

In the endpoint category mortality, the results for the endpoint overall survival show no statistically significant difference between the study arms. Median survival had not yet been achieved because of the low number of events; final analyses on the endpoint overall survival are pending. No additional benefit is identified for the overall survival endpoint.

In the morbidity category, there are no statistically significant differences between the study arms in terms of either symptomatology (surveyed using the LCSS ASBI) or the endpoint general health status (surveyed using the EQ-5D VAS).
For the endpoint "time to diagnosis of CNS metastases", no additional benefit is determined on the basis of the data available against the background of relevant uncertainties regarding the interpretation and reliability of data, particularly in view of the very low number of events.

Data on health-related quality of life were not surveyed in the RELAY study.

For the side effects, there is no statistically significant difference between the study arms with regard to the endpoints serious AE and discontinuation because of AE. For severe adverse events (CTCAE grade ≥ 3), there is a moderate disadvantage of ramucirumab in combination with erlotinib compared with erlotinib. In detail, negative effects of ramucirumab in combination with erlotinib are observed in the area of specific AE.
Taking into account the clinical relevance, the disadvantage in side effects does not reach a level that would justify a lower benefit in the overall assessment given that moderate disadvantages were shown only for the endpoint severe AE (CTCAE grade ≥ 3) as well as in detail for the specific AE.

Overall, the G-BA concludes that an additional benefit of ramucirumab in combination with erlotinib compared with erlotinib in the first-line treatment of metastatic NSCLC with the activating EGFR mutations L858R or del 19 is not proven.

a) Adult patients with metastatic NSCLC with activating EGFR mutations other than L858R or del 19; first-line therapy:

For the treatment of adult patients with first-line treatment of metastatic NSCLC with activating EGFR mutations other than L858R or del 19, an additional benefit is not proven.

Justification:

For adult patients with first-line treatment of metastatic NSCLC with activating EGFR mutations other than L858R or del 19, no data were provided to assess the additional benefit of ramucirumab in combination with erlotinib compared with the appropriate comparator therapy. In the RELAY study presented, only patients with the activating EGFR mutations L858R or del 19 were examined.

2.1.4 Summary of the assessment

This assessment refers to the benefit assessment of a new therapeutic indication for the active ingredient ramucirumab. The therapeutic indication assessed here is as follows: "Cyramza in combination with erlotinib is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations."

In the therapeutic indication to be considered, the following patient groups were distinguished:

a) Adult patients with metastatic NSCLC with the activating EGFR mutations L858R or del 19; first-line therapy

a) Adult patients with metastatic NSCLC with activating EGFR mutations other than L858R or del 19; first-line therapy:

About patient group a)

The appropriate comparator therapy was determined by the G-BA as follows:

Afatinib or gefitinib or erlotinib or osimertinib

For this patient group, the pharmaceutical company presents results from the double-blind, randomised, controlled RELAY study in which ramucirumab in combination with erlotinib is compared with erlotinib. The RELAY study included adult patients without previous treatment for metastatic NSCLC with the EGFR mutations L858R or del 19.

In the endpoint category mortality, for the endpoint overall survival, there was no statistically significant difference between the study arms. Final analyses on the endpoint of overall survival are pending. No additional benefit is identified for the overall survival endpoint.

For the endpoints in the morbidity category (symptomatology and general health status), there was no statistically significant difference between the study arms.

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

For the side effects, there was no statistically significant difference between the study arms with regard to the endpoints serious AE and discontinuation because of AE. For severe adverse events (CTCAE grade ≥ 3), there was a moderate disadvantage of ramucirumab in combination with erlotinib. In detail, negative effects of ramucirumab in combination with erlotinib were observed in the area of specific AE.
Taking into account the clinical relevance, the disadvantage in side effects does not reach a level that would justify a lower benefit in the overall assessment given that moderate disadvantages were shown only for the endpoint severe AE (CTCAE grade ≥ 3) as well as in detail for the specific AE.

Overall, the G-BA concludes that an additional benefit of ramucirumab in combination with erlotinib compared with erlotinib in the first-line treatment of metastatic NSCLC with the activating EGFR mutations L858R or del 19 is not proven.

About patient group b)

The appropriate comparator therapy was determined by the G-BA as follows:

A patient-individual therapy depending on the activating EGFR mutation with selection of:

- Afatinib, gefitinib, erlotinib, osimertinib
- Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)
- Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed; *cf* Annex VI to Section K of the Pharmaceuticals Directive)
- Carboplatin in combination with nab-paclitaxel

and

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

For patients with activating EGFR mutations other than L858R or del 19, no data were provided to assess the additional benefit of ramucirumab in combination with erlotinib compared with the appropriate comparator therapy. In the RELAY study presented, only patients with the activating EGFR mutations L858R or del 19 were examined.
For the treatment of adult patients with first-line treatment of metastatic NSCLC with activating EGFR mutations other than L858R or del 19, an additional benefit is not proven.

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

In order to enable a consistent consideration of the patient numbers taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication (dacomitinib: 17 October 2019, pembrolizumab: 19 September 2019; osimertinib: 17 January 2019, atezolizumab, 16 March 2018, pembrolizumab: 3 August 2017), the G-BA uses the following derivation of patient numbers:

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 incidence for 2020 (62 380 patients)[6] is used as the basis for the calculations.

This patient group is limited to the target population via 7 calculation steps:

1. The proportion of lung cancer patients with NSCLC is approx. 80.3–82%.[7]

2. Of these, 49.2% are Stage IV patients.[8]

3. First-line therapy is performed in 76.9 to 78.5% of cases.[8]

4. The proportion of activating EGFR mutations is approx. 4.9–10.3%.[7]

5. Patient group a: Adult patients with locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19: Sum of the proportions of L858R (23.7–27.3%) and del 19 (61.3–61.9%) = approx. 86–89% [9]

6. Patient group b: Adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19 = 11–14%

7. Number of SHI patients: 85.9% [10]

For

- Patient group a: Adult patients with locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19:

  690 to 1,560 patients

- Patient group b: Adult patients with locally advanced or metastatic NSCLC with rare activating EGFR mutations:

  90 to 250 patients

[6] Robert Koch Institute. Cancer in Germany 2015/2016; 12th edition. 2019
[7] Resolution on osimertinib of 17 January 2019
[8] Resolution on pembrolizumab of 3 August 2017
[9] Resolution on dacomitinib of 17 October 2019
[10] Resolution on pembrolizumab of 19 September 2019

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 Cyramza® (active ingredient: ramucirumab) at the following publicly accessible link (last access: 7 May 2020):

https://www.ema.europa.eu/documents/product-information/cyramza-epar-product-information_de.pdf

Treatment with ramucirumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and pneumology, specialists in pulmonary medicine, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with non-small cell lung cancer.

If the use of ramucirumab is considered, the EGFR mutation status must be determined by a validated test procedure.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 July 2020).

According to the product information (Cisplatin Accord (last revised: April/2015) cisplatin is dosed differently depending on the combination partner. According to the product information of the combination partners, the single dose of cisplatin in combination with vinorelbine or gemcitabine is 75–100 mg/m^2, in combination with docetaxel or pemetrexed, 75 mg/m^2, and in combination with paclitaxel, 80 mg/m^2.

Carboplatin is based on a cycle duration of 3 weeks. For the use of carboplatin in the off-label indication “combination therapy for advanced NSCLC”, the dosage specified in Annex VI of the Pharmaceuticals Directive is up to 500 mg/m² or AUC 6.0 (Area Under the Curve). For the use of carboplatin in combination with nab-paclitaxel, the dosage of AUC 6.0 is also used according to the product information.

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”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Ramucirumab	continuously, 1 × per 14-day cycle	26.1	1	26.1

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Erlotinib	continuously, 1 × daily	365	1	365
Appropriate comparator therapy				
a) Adult patients with metastatic NSCLC with the activating EGFR mutations L858R or del 19; first-line therapy:				
Afatinib	1 × daily	365	1	365
Erlotinib	1 × daily	365	1	365
Gefitinib	1 × daily	365	1	365
Osimertinib	1 × daily	365	1	365
a) Adult patients with metastatic NSCLC with activating EGFR mutations other than L858R or del 19; first-line therapy:				
Afatinib, gefitinib, erlotinib, osimertinib				
Afatinib	1 × daily	365	1	365
Erlotinib	1 × daily	365	1	365
Gefitinib	1 × daily	365	1	365
Osimertinib	1 × daily	365	1	365
Cisplatin or carboplatin in combination with a third generation cytostatic agent				
Cisplatin	1 × per 21-day cycle	17.4 cycles	1	17.4
Carboplatin	1 × per 21-day cycle	17.4 cycles	1	17.4
+ vinorelbine	2 × per 21-day cycle	17.4 cycles	2	34.8
+ gemcitabine	2 × per 21-day cycle	17.4 cycles	2	34.8
+ docetaxel	1 × per 21-day cycle	17.4 cycles	1	17.4
+ paclitaxel	1 × per 21-day cycle	17.4 cycles	1	17.4
+ pemetrexed	1 × per 21-day cycle	17.4 cycles	1	17.4

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Carboplatin in combination with nab-paclitaxel				
Carboplatin	1 × per 21-day cycle	17.4 cycles	1	17.4
+ nab-paclitaxel	3 × per 21-day cycle	17.4 cycles	3	52.2
Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment)				
Gemcitabine	3 × per 28-day cycle	13 cycles	3	39
Vinorelbine	1 × per 7-day cycle	52.1 cycles	1	52.1

Usage and consumption:

The body surface calculated using the Du Bois formula using an average body weight of 77.0 kg and an average body height of 1.72 m (according to the 2017 microcensus) = 1.90 m² (calculated to 2 decimal places). Differences between women and men were not to be considered because of the therapeutic indication. [11]

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					
Ramucirumab	10 mg/kg = 770 mg	770 mg	1 × 500 mg + 3 × 100 mg	26.1	26.1 × 500 mg + 78.3 × 100 mg
Erlotinib	150 mg	150 mg	1 × 150 mg	365	365 × 150 mg
Appropriate comparator therapy					
a) Adult patients with metastatic NSCLC with the activating EGFR mutations L858R or del 19; first-line therapy:					

11 https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Afatinib or gefitinib or erlotinib or osimertinib					
Afatinib	40 mg	40 mg	1 × 40 mg	365	365 × 40 mg
Erlotinib	150 mg	150 mg	1 × 150 mg	365	365 × 150 mg
Gefitinib	250 mg	250 mg	1 × 250 mg	365	365 × 250 mg
Osimertinib	80 mg	80 mg	1 × 80 mg	365	365 × 80 mg
a) Adult patients with metastatic NSCLC with activating EGFR mutations other than L858R or del 19; first-line therapy:					
Afatinib, gefitinib, erlotinib, osimertinib					
Afatinib	40 mg	40 mg	1 × 40 mg or	365	365 × 40 mg
Erlotinib	150 mg	150 mg	1 × 150 mg	365	365 × 150 mg
Gefitinib	250 mg	250 mg	1 × 250 mg	365	365 × 250 mg
Osimertinib	80 mg	80 mg	1 × 80 mg	365	365 × 80 mg
Cisplatin or carboplatin in combination with a third generation cytostatic agent					
Cisplatin	75 mg/m^2 = 142.5 mg	142.5 mg	1 × 100 mg + 1 × 50 mg	17.4	17.4 × 100 mg + 17.4 × 50 mg
	80 mg/m^2 = 152 mg	152 mg	1 × 100 mg + 1 × 50 mg + 1 × 10 mg	17.4	17.4 × 100 mg + 17.4 × 50 mg + 17.4 × 10 mg
	100 mg/m^2 = 190 mg	190 mg	2 × 100 mg	17.4	34.8 × 100 mg
Carboplatin	500 mg/m^2 =	950 mg	1 × 600 mg + 1 × 450 mg	17.4	17.4 × 600 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
	950 mg				17.4 × 450 mg
+ vinorelbine	25 mg/m² = 47.5 mg	47.5 mg	1 × 50 mg	34.8	34.8 × 50 mg
	30 mg/m² = 57 mg	57 mg	1 × 50 mg + 1 × 10 mg	34.8	34.8 × 50 mg + 34.8 × 10 mg
+ gemcitabine	1250 mg/m² = 2375 mg	2375 mg	1 × 2,000 mg + 2 × 200 mg	34.8	34.8 × 2,000 mg + 69.6 × 200 mg
+ docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 × 160 mg	17.4	17.4 × 160 mg
+ paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 × 100 mg + 1 × 150 mg	17.4	34.8 × 100 mg + 17.4 × 150 mg
+ pemetrexed	500 mg/m² = 950 mg	950 mg	2 × 500 mg	17.4	34.8 × 500 mg
Carboplatin in combination with nab-paclitaxel					
Carboplatin	500 mg/m² = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	17.4	17.4 × 600 mg + 17.4 × 450 mg
+ nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 × 100 mg	52.2	104.4 × 100 mg
Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment)					
Gemcitabine	1000 mg/m² = 1900 mg	1900 mg	1 × 2000 mg	39	39 × 2000 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	25 mg/m² = 47.5 mg	47.5 mg	1 × 50 mg	52.1	52.1 × 50 mg –
	30 mg/m² = 57 mg	57 mg	1 × 50 mg + 1 × 10 mg	52.1	52.1 × 50 mg + 52.1 × 10 mg

Costs:

Costs of the medicinal product:

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 Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Designation of the therapy	Package 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					
Ramucirumab 500 mg	1 CIS	€ 2,087.10	€ 1.77	€ 119.00	€ 1,966.33
Ramucirumab 100 mg	1 CIS	€ 429.79	€ 1.77	€ 23.80	€ 404.22
Erlotinib 150 mg	30 FCT	€ 1,304.83	€ 1.77	€ 63.00	€ 1,240.06
Appropriate comparator therapy					
Afatinib 40 mg	28 FCT	€ 2,451.59	€ 1.77	€ 140.35	€ 2,309.47
Carboplatin 600 mg	1 CIS	€ 292.99	€ 1.77	€ 13.74	€ 277.48
Carboplatin 450 mg	1 CIS	€ 222.22	€ 1.77	€ 10.29	€ 210.16
Cisplatin 100 mg	1 CIS	€ 74.39	€ 1.77	€ 3.10	€ 69.52
Cisplatin 50 mg	1 CIS	€ 46.24	€ 1.77	€ 1.73	€ 42.74
Cisplatin 10 mg	1 CIS	€ 16.82	€ 1.77	€ 0.30	€ 14.75
Docetaxel 160 mg	1 CIS	€ 1,362.13	€ 1.77	€ 175.44	€ 1,184.92

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Erlotinib 150 mg	30 FCT	€ 1,304.83	€ 1.77	€ 63.00	€ 1,240.06
Gefitinib 250 mg	30 FCT	€ 861.15	€ 1.77	€ 41.40	€ 817.98
Gemcitabine 2,000 mg	1 CIS	€ 189.07	€ 1.77	€ 8.68	€ 178.62
Gemcitabine 200 mg	1 CIS	€ 27.85	€ 1.77	€ 0.83	€ 25.25
nab-paclitaxel	1 PIS	€ 418.27	€ 1.77	€ 52.91	€ 363.59
Osimertinib	30 FCT	€ 6,000.73	€ 1.77	€ 348.29	€ 5,650.67
Paclitaxel 100 mg	1 CIS	€ 346.28	€ 1.77	€ 16.33	€ 328.18
Paclitaxel 150 mg	1 CIS	€ 514.49	€ 1.77	€ 24.52	€ 488.20
Pemetrexed	1 PIC	€ 2,469.43	€ 1.77	€ 538.17	€ 1,929.49
Vinorelbine 50 mg	10 CIS	€ 1,388.38	€ 1.77	€ 67.07	€ 1,319.54
Vinorelbine 10 mg	10 CIS	€ 286.33	€ 1.77	€ 13.42	€ 271.14
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; PIC = powder for the preparation of an infusion solution concentrate; PIS = powder for the preparation of an infusion suspension					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 July 2020

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 assessed 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 standard expenditure in the course of the treatment are not shown.

Non-prescription medicinal products are subject to the regulations on the prescribability of non-prescription medicinal products (OTC medicinal products) at the expense of statutory health insurance. These medicinal products are not subject to the current medicinal product price regulation but rather, in accordance with Section 129, paragraph 5a of the German Social Code, Book V, (SGB V) when a non-prescription medicinal product is sold and invoiced in accordance with Section 300 SGB V, for the insured person, a pharmaceutical selling price in the amount of the selling price of the pharmaceutical company – plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the 31 December 2003 version – shall apply.

Cost per package	Costs after deduction of statutory rebates[12]	Costs per service[13]	Treatment days per year	Costs per patient per year
Cisplatin				
Anti-emetic treatment				
In clinical practice, appropriate anti-emetic treatment is established before and/or after cisplatin administration. The product information of cisplatin does not contain any concrete information on this, which is why the necessary costs cannot be quantified.				
Forced diuresis with mannitol 10% infusion solution, 37.5 g/day				
10 × 500 ml: € 103.54	€ 88.55 (€ 5.18; € 9.81)	€ 8.86	17.4	€ 154.08
Hydration: sodium chloride 0.9% infusion solution, 3–4.4 l/day				
10 × 1,000 ml: € 34.58 10 × 500 ml: € 22.14	€ 31.73 (€ 1.73; € 1.12) € 20.34 (€ 1.11; € 0.69)	€ 9.52 – 14.73	17.4	€ 165.63 – 256.23
Pemetrexed				
Pre-medication: Dexamethasone 2 × 4 mg/day, oral				
100 × 4 mg: € 77.27 (FB)	€ 70.10 (€ 1.77; € 5.40)	€ 1.40	52.2	€ 73.18
Folic acid: 350 – 1,000 µg/day[14], oral				
100 × 400 µg: € 15.56	€ 12.52 (€ 0.78; € 2.26)	€ 0.13 – 0.25	365	€ 45.70 – 91.40
Vitamin B12: 1,000 µg/day, i.m.				
10 × 1,000 µg: € 7.22 (FB)	€ 6.53 (€ 0.36; € 0.33)	€ 0.65	6	€ 3.92
Paclitaxel				
Pre-medication: Dexamethasone 2 × 20 mg/day, oral				
50 × 20 mg: € 115.62 (FB)	€ 113.85 (€ 1.77; €0.00)	€ 4.55	17.4	€ 79.24
Antihistamine: Dimetindene 1 mg per 10 kg BW, i.v.				
5 × 4 mg: € 18.15	€ 14.46 (€1.77; € 1.92)	€ 5.78[15]	17.4	€ 100.64
Ranitidine: 50 mg/day, i.v.				
5 × 50 mg: € 14.70	€ 12.74 (€1.77; € 0.19)	€ 2.55	17.4	€ 44.34

Other services covered by SHI funds:

12 Section 130 SGB V and Section 130a SGB V

13 Proportionate costs of costs per package for consumption per treatment day. Rounded interim result.

14 The cost of folic acid is calculated on the basis of the single dose of 400 µg of the non-divisible tablets available for cost calculation, based on a dose range of 400–800 µg per day, even if a dose range of 350–1000 µg is specified in the product information.

15 For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average height: 1.72 m, average body weight: 77 kg).
Source: German Federal Office For Statistics, Wiesbaden 2018:
https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 11. Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating 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 ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

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 26 June 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 28 January 2020.

On 14 February 2020, the pharmaceutical company submitted a dossier for the benefit assessment of ramucirumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 17 February 2020 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 ramucirumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 May 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 May 2020. The deadline for submitting written statements was 5 June 2020.

The oral hearing was held on 22 June 2020.

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 were discussed at the session of the subcommittee on 28 July 2020, and the proposed resolution was approved.

At its session on 20 August 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	26 June 2018	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	28 January 2020	Redefinition of the appropriate comparator therapy
Working group Section 35a	17 June 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	22 June 2020	Conduct of the oral hearing
Working group Section 35a	1 July 2020 14 July 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	28 July 2020	Concluding discussion of the draft resolution
Plenum	20 August 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 August 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken