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: Hepatocellular Carcinoma)

of 20 February 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 1 August 2019, 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 28 August 2019, 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 ramucirumab with the new therapeutic indication (treatment of adult patients with advanced or unresectable hepatocellular carcinoma).

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 2 December 2019, 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, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General 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 monotherapy is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have a serum alpha fetoprotein (AFP) of ≥ 400 ng/ml and who have been previously treated with sorafenib.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with advanced or unresectable hepatocellular carcinoma without curative therapy intent and for whom locoregional therapy is not an option who have a serum alpha fetoprotein (AFP) of ≥ 400 ng/ml and who have been previously treated with sorafenib.

- Best supportive care

  or

- Cabozantinib

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.

[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.

3. As comparator therapy, medicinal products 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 accordance with the authorisation status, the active ingredients cabozantinib, mitomycin, sorafenib, and regorafenib are available. Regorafenib is currently not sold in Germany.

On 2. Non-medicinal treatment is not considered an appropriate comparator therapy. It is assumed that both curative treatment (corresponding to BCLC stage 0 and A) and locoregional therapy in BCLC stage B, in particular transarterial (chemo)embolisation (TACE or TAE), are out of the question in the present therapeutic indication.

On 3. For the therapeutic indication, the following G-BA resolutions or guidelines are available for medicinal or non-medicinal treatments:

- Quality assurance measures for proton therapy of inoperable hepatocellular carcinoma; resolution of 16 July 2009, 27 November 2015, and 27 July 2017
- Assessment according to Section 137h SGB V Ultrasound-guided highly intensive focused ultrasound for the treatment of hepatocellular carcinoma; resolution of 16 March 2017
- Cabozantinib: Resolution on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V dated 6 June 2019

On 4. Overall, the treatment options are limited in the present therapeutic indication. According to current guidelines, patients with advanced hepatocellular carcinoma in Child-Pugh A stage after progress should be treated with sorafenib therapy either alone with the best possible supportive therapy with the aim of alleviating disease symptoms and improving quality of life or in addition to the best possible supportive therapy with cabozantinib.

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 is assessed as follows:

Proof of a minor additional benefit.

Justification:

The present benefit assessment included a sub-population of the REACH study and the entire REACH-2 study in the form of a meta-analysis. Both studies are randomised, placebo-controlled, double-blind, multi-centre studies in which one treatment with ramucirumab + BSC was compared with a treatment with placebo + BSC. To be included in the studies, patients with advanced or inoperable hepatocellular carcinoma must have already received sorafenib therapy. According to the study protocols, only patients with an ECOG performance status of 0 or 1 and with only slightly reduced liver function (Child-Pugh stage A) could be included in the studies.

The REACH study was a negative study; the goal of an overall survival extension was not achieved. However, subsequent analysis of sub-groups showed a significant benefit for ramucirumab in patients with an AFP value ≥ 400 ng/ml. This result was considered hypothesis generating and was the basis for REACH-2. Only patients with an AFP value ≥ 400 ng/ml were included in REACH-2. In the present benefit assessment, a meta-analytical evaluation of the data from the sub-population of patients with AFP ≥ 400 ng/ml from the REACH study (119 patients in the ramucirumab + BSC arm and 131 patients in the placebo + BSC arm) and all patients from the REACH 2 study is performed (randomisation of 292 patients in a 2:1 ratio; 197 patients in the ramucirumab + BSC arm and 95 patients in the placebo + BSC arm).

In the REACH study, the randomisation of patients was stratified according to geographical region and aetiology of the disease at the start of study. In the REACH-2 study, randomisation was stratified according to geographical region, macrovascular invasion, and ECOG-PS.

In both studies, treatment with ramucirumab was performed according to the product information. In the REACH study, 29 (24.4%) and 18 (14.1%) patients in the ramucirumab + BSC arm and placebo + BSC arm, respectively, experienced adverse events that led to a dose adjustment. In the REACH-2 study, such a dose adjustment was necessary because of AEs in 67 (34.0%) and 12 (12.6%) patients in the ramucirumab + BSC arm and placebo + BSC arm, respectively. In both studies, patients should receive supportive therapy to alleviate symptoms and complications in the sense of BSC.

In both the REACH and REACH-2 studies, patients were treated until disease progression, unacceptable toxicity, or withdrawal of consent.

After discontinuation of the study medication, in the REACH study 36.1% and 24.4% and in the REACH-2 study 26.9% and 28.4% of the patients in the test and control arm, respectively received systemic, non-radiological tumour therapy.

For the total population of the REACH study, the final analysis was planned after 438 deaths and was conducted in March 2015. In the REACH-2 study, the final analysis was planned after 221 deaths and took place with the data cut-off in March 2018.

Extent and probability of the additional benefit

Mortality

For overall survival there is a statistically significant difference in favour of ramucirumab + BSC compared with placebo + BSC (hazard ratio (HR): 0.69 [95% confidence interval (CI): 0.57; 0.84]; p value < 0.001). The median overall survival in the intervention arm was 3.05 months longer than in the control arm (8.08 vs 5.03 months). This is assessed as a small increase in overall survival.
There is, therefore, a minor additional benefit for this endpoint.

Morbidity

Progression-free survival (PFS)

In both REACH studies, PFS was defined as the time from randomisation to disease progression or death by any cause, whichever occurred earlier. Progression was assessed using imaging techniques based on the RECIST criteria.

The event-time analysis for PFS in the pooled patient population (patients of the sub-population AFP ≥ 400 ng/ml from the REACH study and all patients from the REACH-2 study) showed a statistically significant difference in favour of ramucirumab + BSC compared with placebo + BSC (stratified HR: 0.572; [95% CI: 0.472; 0.694]; p value < 0.0001). The PFS was extended by 1.3 months (median) for patients in the ramucirumab + BSC arm (2.8 months) compared with patients in the placebo + BSC arm (1.5 months).

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 collected as an independent endpoint via the endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively by means of imaging procedures (according to RECIST 1.1). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The overall statement on the extent of the additional benefit remains unaffected.

Health status (surveyed using EQ-5D VAS)

In the REACH and REACH-2 studies, the health status was assessed via the EQ-5D using the visual analogue scale (VAS).
For the benefit assessment, the pharmaceutical company presented responder analyses for the period up to the first deterioration from the baseline. As *minimal important difference* (MID) the pharmaceutical company defines a change of 7 mm or 10 mm as sensitivity analysis and refers in this respect to the study by Pickard *et al.*, 2007.

This responder analysis was not used in the IQWiG dossier evaluation because the study underlying the derivation of the MID (Pickard *et al.*, 2007) of the IQWiG was classified as unsuitable to validate the MID. This is justified on one hand 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. In addition, the IQWiG does not consider the ECOG-PS and FACT-G anchors used in the study to be suitable for the derivation of MID. Against the background that responder analyses based on a MID have general advantages for a clinical evaluation of effects compared with an analysis of standardised mean differences and taking into account that the validation study in question has already been used in earlier evaluations, the G-BA nevertheless uses the responder analyses in the present assessment to assess the effects on symptomatology.

Based on an MID of 7 mm, the responder analyses of the pooled evaluations show a statistically significant but small difference in extent between the treatment arms in favour of ramucirumab + BSC compared with placebo + BSC; based on an MID of 10 mm, there is no statistically significant difference. These results are not considered sufficient to deduce an added benefit for the health status endpoint with the necessary certainty.

In addition to the event time analyses for the REACH-2 study, the pharmaceutical company submitted evaluations based on mean value differences. However, these evaluations are not usable because of the high proportion of missing values and strongly decreasing return rates with partly relevant differences between the therapy arms.

Symptomatology (surveyed using FHSI-8)

For the benefit assessment, the pharmaceutical company presented responder analyses with different response criteria: Deterioration by ≥ 3 points (sensitivity analyses for ≥ 2 and ≥ 4 points) and a responder analysis submitted in the written statement procedure with a response criterion of ≥ 5 points Although no validation is available for these response criteria, the

response criterion of ≥ 5 points is used for the present assessment against the background of the current scientific discussion on the requirements for response criteria. For the response criterion of ≥ 5 points, there is a statistically significant difference in favour of ramucirumab + BSC compared with placebo + BSC.

Quality of life

In the REACH and REACH-2 studies, data on health-related quality of life were not collected with the appropriate tools.

Side effects

Because of the different lengths of observation times in the treatment arms, event time analyses are used.

Adverse events (AE) in total

The total rate of AEs is presented only as a supplement because the operationalisation of side effects also includes events that are not patient-relevant.

Serious AE, severe AE (CTCAE grade ≥ 3), discontinuation because of adverse events

For the benefit assessment, event time analyses are available for the endpoints serious AEs, severe AEs (CTCAE grade ≥ 3), and discontinuation because of AEs.

For the designated endpoints, the meta-analysis shows no statistically significant difference between the treatment groups. In each case, there is no hint for a higher or lower harm from ramucirumab + BSC compared with placebo + BSC. An additional benefit is thus not proven.

Specific adverse events

Regarding specific AE, the respective event rates and Kaplan-Meier curves for the specific AE "gastrointestinal disorders", "hyperbilirubinemia", and "examinations" show that these AEs occur less frequently and later in the ramucirumab + BSC arm than in the placebo + BSC arm. In each case there is an indication that ramucirumab + BSC is less harmful than placebo + BSC. On the other hand, the specific AE "peripheral oedema", "headache", and "hypertension" occur more frequently and earlier in the ramucirumab + BSC arm than in the placebo + BSC arm. In each case, this gives an indication of a greater harm from ramucirumab + BSC compared with placebo + BSC.

In the overall view of the results on side effects, there are statistically significant differences in the specific adverse events. They show positive and negative effects of ramucirumab + BSC compared with placebo + BSC. In the overall consideration of all endpoints, neither an advantage nor a disadvantage of ramucirumab + BSC compared with placebo + BSC was found in the side effects category.

Overall assessment

For the assessment of the additional benefit of ramucirumab for the treatment of patients with advanced or inoperable hepatocellular carcinoma who have serum alpha-fetoprotein (AFP) of ≥ 400 ng/ml and who have been previously treated with sorafenib, results on mortality, morbidity and side effects are available from the meta-analysis (includes sub-population of patients with AFP ≥ 400 ng/ml from the REACH study and patients from the REACH 2 study).

In terms of overall survival, ramucirumab + BSC has a minor advantage compared with placebo + BSC.

In the morbidity category, a statistically significant effect in favour of ramucirumab + BSC was shown for the endpoint symptomatology (measured via FHSI-8), which was assessed as clinically relevant.

No suitable data on health-related quality of life are available from the REACH and REACH-2 studies. Thus, it cannot be assessed to what extent therapy with ramucirumab + BSC compared with placebo + BSC affects the quality of life of the patients. Statements on quality of life are given high priority, especially in the present advanced palliative therapy situation.

In the overall view of the results on side effects, there are statistically significant differences in the specific adverse events. They show positive and negative effects of ramucirumab + BSC compared with placebo + BSC. In the overall consideration of all endpoints neither an advantage nor a disadvantage of ramucirumab + BSC compared with placebo + BSC was found in the side effects category.

In the overall assessment the G-BA concluded that there is a minor additional benefit for ramucirumab + BSC compared with placebo + BSC in the treatment of patients with advanced or inoperable hepatocellular carcinoma who have a serum alpha-fetoprotein (AFP) of ≥ 400 ng/ml and who have previously been treated with sorafenib.

Reliability of data (probability of additional benefit)

In the REACH and REACH-2 studies, the additional benefit is assessed based on two randomised, double-blind, and directly comparative Phase III studies. From the REACH study, only the sub-population of patients with serum AFP levels ≥ 400 ng/ml was relevant for the benefit assessment. The risk of bias at the study level is classified as low.

The risk of bias for the results on the overall survival endpoint is also classified as low.

The risk of bias for the endpoint symptomatology as well as for the endpoints on side effects (SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation because of AEs, and specific AEs) is considered high. However, a downgrading of the reliability of data for the overall assessment is not justified.

The reliability of data supporting the finding of an additional benefit must therefore be classified as “proof”.

2.1.4 Summary of the assessment

For the assessment of the additional benefit of ramucirumab for the treatment of patients with advanced or inoperable hepatocellular carcinoma who have serum alpha-fetoprotein (AFP) of ≥ 400 ng/ml and who have been previously treated with sorafenib, results on mortality, morbidity, and side effects are available.

For overall survival, the meta-analysis shows a slight advantage of ramucirumab + BSC compared with placebo + BSC.

Another advantage of ramucirumab compared with best supportive care is the improvement of symptomatology.

No suitable data on health-related quality of life are available. Thus it cannot be assessed to what extent therapy with ramucirumab + BSC compared with placebo + BSC affects the quality of life of the patients.

In the overall consideration of all endpoints neither an advantage nor a disadvantage of ramucirumab + BSC compared with placebo + BSC was found in the side effects category.

In the overall view there is proof of a minor additional benefit for ramucirumab + BSC compared with placebo + BSC in the treatment of patients with advanced or inoperable hepatocellular carcinoma who have serum alpha-fetoprotein (AFP) of ≥ 400 ng/ml and who have been previously treated with sorafenib.

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).

Patient numbers for this resolution are calculated using the patient numbers from the resolution on cabozantinib dated 6 June 2019 (1,280–4,900 patients). These are adult patients with hepatocellular carcinoma without curative therapy intent and for whom locoregional therapy is out of the question and who have previously received sorafenib. There is great uncertainty regarding the calculation of the proportion of patients who have an AFP value ≥ 400 ng/ml. This is based on two publications (Ganten 2017 and Hennenfent 2017) from which a range of 37.61–45.1% results.

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: 28 October 2019):

https://www.ema.europa.eu/en/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 gastroenterology, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with hepatocellular carcinoma.

The study only included patients who had a Child-Pugh stage A disease.

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 February 2020).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

Costs of the appropriate comparator therapy

The treatment costs for best supportive care are different for each individual patient.

Because best supportive care has been determined as an independent appropriate comparator therapy, best supportive care is also reflected in the medicinal product to be evaluated as well as in the further appropriate comparator therapy.

The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

Treatment duration:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration varies from patient to patient and/or is shorter on average.

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, every 14 days	26.1	1	26.1
+ best supportive care	different for each individual patient			
Appropriate comparator therapy				
Best supportive care				
Best supportive care	different for each individual patient			
Cabozantinib				
Cabozantinib	continuously, 1 × daily	365	1	365
+ best supportive care	different for each individual patient			

Usage and consumption:

For the calculation of the dosages as a function of body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average body weight): 77.0 kg).[2]

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					

German Federal Office For Statistics, 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
Ramucirumab	8 mg/kg BW	616 mg	1 × 500 mg + 2 × 100 mg	26.1	26.1 × 500 mg + 52.2 × 100 mg
+ best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care					
Best supportive care	different for each individual patient				
Cabozantinib					
Cabozantinib	60 mg	60 mg	1 × 60 mg	365.0	365 × 60 mg
+ best supportive care	different for each individual patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated bothon 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.

Costs of the medicinal product:

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	€ 2,141.07	€ 1.77	€ 119.00	€ 2,020.30

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
Ramucirumab 100 mg	1 CIS	€ 440.91	€ 1.77	€ 23.80	€ 415.34
+ best supportive care[3]	different for each individual patient				
Appropriate comparator therapy					
Best supportive care					
Best supportive care	different for each individual patient				
Cabozantinib					
Cabozantinib 60 mg	30 FCT	€ 5,709.38	€ 1.77	€ 322.79	€ 5,384.82
+ best supportive care[3]	different for each individual patient				
Abbreviations: CIS = Concentrate for the preparation of an infusion solution; FCT = film-coated tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 February 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 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 standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

Other services covered by SHI funds:

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

[3] The costs for best supportive care are also shown here, as best supportive care also represents an independent appropriate comparator therapy.

[Hilfstaxe”] (last revised: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. 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

On 28 August 2019, 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 1, sentence 3 VerfO.

By letter dated 29 August 2019 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 28 November 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 2 December 2019. The deadline for submitting written statements was 23 December 2019.

The oral hearing was held on 6 January 2020.

By letter dated 6 January 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 31 January 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 11 February 2020, and the proposed resolution was approved.

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

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	27 August 2019	Determination of the appropriate comparator therapy
Subcommittee Medicinal Products	6 January 2020	Information on written statements received; preparation of the oral hearing Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	14 January 2020 21 January 2020 4 February 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	11 February 2020	Concluding discussion of the draft resolution
Plenum	20 February 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 February 2020

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

Prof. Hecken