Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients in Accordance with Section 35a SGB V – Cabozantinib (New Therapeutic Indication: Hepatocellular Carcinoma)

From 6 June 2019

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. Medicinal benefit,
3. Additional medicinal 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. Therapy costs for statutory health insurance funds,
6. Requirements for 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 shall pass a resolution 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 cabozantinib was listed for the first time on 18 August 2014 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 12 November 2018, CABOMETYX, which is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib, received marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2 number 2a to Regulation (EC) number 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 10 December 2018, 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 cabozantinib with the new therapeutic indication 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 the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 March 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 cabozantinib 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 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 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 cabozantinib.

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 cabozantinib (Cabometyx®) in accordance with the product information

CABOMETYX is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib.

2.1.2 Appropriate comparator therapy

In adult patients without curative therapy intent for whom locoregional therapy is out of the question and who previously received sorafenib, the appropriate comparator therapy for cabozantinib as a monotherapy for the treatment of hepatocellular carcinoma (HCC) is:

- Best supportive care

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 comparative therapy, medicinal products or non-drug treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee (G-BA) shall be preferred.

[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.

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 approval status, the active ingredients mitomycin, sorafenib, and regorafenib are available. Regorafenib is currently not sold in Germany.

On 2. Non-drug 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 planned therapeutic indication, the following G-BA resolutions or guidelines are available for medicinal or non-medicinal therapies:

- 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

For the therapeutic indication concerned, there are no resolutions on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V.

On 4. Overall, the treatment options are limited in the present therapeutic indication. According to the currently accepted state of medical knowledge, there is no specific standard therapy available for patients whose advanced liver cell carcinoma at Child-Pugh A stage was initially treated with sorafenib. Following progress under sorafenib therapy, current guidelines recommend the best possible supportive therapy with the aim of alleviating symptoms of disease and improving quality of life. Accordingly, best supportive care represents the appropriate comparator therapy in the therapeutic indication at hand.

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

2.1.3 Extent and probability of the additional benefit

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

In adults with hepatocellular carcinoma (HCC) who have previously been treated with sorafenib there is evidence of a minor additional benefit for treatment with cabozantinib as a monotherapy.

Justification:

The present benefit assessment is based on the results of the third data cut-off of the CELESTIAL study. This randomised, double-blind study compares cabozantinib + best supportive care with placebo + best supportive care. The study, conducted in 94 centres in 19 countries, is still ongoing. To be included in the study, patients must have histologically or cytologically confirmed HCC as well as prior therapy with sorafenib. In addition, the trial only included patients for whom a curative approach such as liver transplantation, resection and radiofrequency ablation had been ruled out. According to the study protocol, only patients with ECOG performance status 0 or 1 and with Child-Pugh Stage A, which corresponds to a slightly impaired liver function, were eligible for the study.

A total of 773 patients were randomised at a ratio of 2:1 to the verum (N = 512) or placebo arm (N = 261). These had a median age of 64 years; 80% were male. Approximately 71% of the patients had previously been treated with one and approximately 28% with two systemic, non-radiological cancer therapy regimens. Stratification was performed according to disease aetiology at baseline (hepatitis B virus [HBV] with or without hepatitis C virus [HCV], HCV [without HBV], others), geographic region (Asia, others) and extrahepatic disease dissemination and/or macrovascular invasion at baseline (yes, no).

In accordance with the study protocol, the study medication was reduced from 60 mg to 40 mg or from 40 mg to 20 mg in the case of unacceptable toxicity. This was done in 326 patients (64%) in the cabozantinib arm and in 34 patients (13%) in the placebo arm. In both arms, patients were to receive supportive therapy to alleviate symptoms and complications, including pain therapy, measures for liver decompensation, treatment of infections, nutritional support, psychological support, and treatment of anaemia.

Even beyond disease progression, treatment could have been continued until the treating doctor considered there was no longer any clinical benefit or until unacceptable side effects occurred, the patient decided to terminate treatment, or other systemic or local cancer therapy was required.

After the study medication was discontinued, 28% and 33% of the patients in the cabozantinib or placebo arm received systemic, non-radiological cancer therapy, and 3.7% and 5.4%, respectively, received local, liver-directed, non-radiological cancer therapy.

For this benefit assessment, the third data cut-off of 1 December 2017 was used. This is an additional analysis, which was not pre-specified in comparison to the first and second data cut-off. However, the study protocol stipulated that an open-label phase with crossover to the cabozantinib arm could be initiated, if at the first or second data cut there was a statistically significant improvement in overall survival. The required significance was attained on 1 June 2017 for the second data cut off, and the open-label phase started on 1 December 2017. The third data cut off from 1 December 2017 thus represents the last data cut off before unblinding and crossover, and also the longest possible observation period. In addition, at the time of the previous data cut-off, randomisation had not yet been completed.

Extent and probability of the additional benefit

Mortality

In terms of overall survival, there is a statistically significant difference in favour of cabozantinib + BSC compared with placebo + BSC. In patients with cabozantinib, the event occurred 2.1 months (median) later (hazard ratio (HR): 0.78; [95% confidence interval (CI): 0.66; 0.93]; p value = 0.006). This is classified as a small extension of lifetime.

There is, therefore, a minor additional benefit for this endpoint.

Morbidity

Progression-free survival (PFS)

In the CELESTIAL study, PFS was defined as the time between randomisation and disease progression or death by any cause. Progression was assessed using imaging techniques based on the RECIST criteria.

There is a statistically significant difference in favour of cabozantinib (HR: 0.45; [95% CI: 0.38; 0.54]; p value < 0.0001). The median PFS was 4.9 months in patients in the cabozantinib arm and 1.9 months in patients in the placebo arm.

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 into account the aforementioned aspects, there are different views within the G-BA regarding how relevant the PFS endpoint is for patients. The overall statement on the extent of the additional benefit remains unaffected.

EQ-5D VAS

In this study, health status is measured using the visual analogue scale (VAS) of EQ-5D. In the dossier, the pharmaceutical company presented both *a priori* planned MMRM evaluations and event time analyses in the event of deterioration by ≥ 7 and ≥ 10 points respectively.

However, it is uncertain whether event time analyses are based on a one-off or a permanent deterioration. Furthermore, the return rate in relation to the entire study population decreased very rapidly and diverged increasingly between the cabozantinib and placebo arms. Therefore, in contrast to previous benefit assessments, MMRM evaluations are used instead of responder analyses.

These reveal a statistically significant disadvantage in the cabozantinib arm; however, the 95% confidence interval of the standardised mean difference is not entirely outside the irrelevance range of -0.2 to 0.2.

Overall, there are no relevant differences for this endpoint.

Quality of life

Data on quality of life are not collected in the CELESTIAL study.

Side effects

Adverse events (AE) in total

The results for the endpoint “total adverse events” are only presented on a supplementary basis. Within the framework of the written statement procedure, the pharmaceutical company submitted data on the overall rate of adverse events without recording the progression of the underlying disease. In this operationalisation, almost every patient suffered an adverse event in both arms (cabozantinib arm: 99%; placebo arm: 96%).

Serious AE

There is a statistically significant difference unfavourable to cabozantinib (HR: 1.31; [95% CI: 1.02; 1.69]; p = 0.035).

Severe AEs (CTCAE grade ≥ 3)

With regard to the endpoint severe AEs (CTCAE grade ≥ 3), there is a statistically significant difference unfavourable to cabozantinib (HR: 2.60; [95% CI: 2.13; 3.18]; p < 0.001). Patients in the test arm were affected by this event 3.1 (median) months earlier.

Withdrawal because of adverse events

There is a statistically significant difference between the two treatment arms to the detriment of cabozantinib (HR: 1.64; [95% CI: 1.18; 2.28]; p = 0.003). Most of the withdrawals because of AEs are due to severe AEs (CTCAE grade ≥ 3).

Specific adverse events

There are statistically significant differences to the detriment of cabozantinib with regard to the SOC "Nervous system disorders" (CTCAE degree ≥ 3) as well as the PTs (preferred term) "Reduced appetite" (CTCAE degree ≥ 3), "Diarrhoea" (CTCAE grade ≥ 3), "Fatigue" (CTCAE grade ≥ 3), "Hypertension" (CTCAE grade ≥ 3), "Palmar-plantar erythrodysaesthesia" (CTCAE grade ≥ 3), "Mucositis" (AEs), and "Stomatitis" (AEs).

In summary, with regards to side effects, cabozantinib was exclusively detrimental compared to BSC. These are particularly evident in the case of severe AEs and withdrawal because of AEs.

Overall assessment

The assessment of the additional benefit of cabozantinib in treating patients with hepatocellular carcinoma who had previously been treated with sorafenib is based on the results of the CELESTIAL study on mortality, morbidity and side effects.

In terms of overall survival, cabozantinib + BSC has a minor advantage over placebo + BSC.

For the endpoint "morbidity", only data collected by EQ-5D VAS are available. The MMRM analyses show a statistically significant disadvantage to the detriment of cabozantinib. However, it cannot be concluded that this effect is relevant. Overall, no disadvantage has been identified.

The patients' quality of life was not collected in the study. An assessment of the additional benefit in terms of quality of life is therefore not possible. In the present palliative, late-stage therapeutic situation, patient reports on quality of life and morbidity are especially important.

With regards to endpoint category adverse events, cabozantinib + BSC was exclusively detrimental compared to placebo + BSC. This shows an increase in severe and serious adverse events as well as an increased rate of withdrawals because of adverse events; these are considered to be a relevant overall disadvantage, which is why this assessment finds there is less benefit in the adverse events category.

In the overall assessment, the G-BA has come to the conclusion that, although there is a relevant disadvantage with regard to the endpoint adverse events, this does not entirely call into question the advantage with regard to overall survival. Cabozantinib thus has a minor additional benefit compared with best supportive care in treating adult patients with hepatocellular carcinoma without curative therapy intent and for whom locoregional therapy is out of the question who have previously received sorafenib.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of a randomised, double-blind, placebo-controlled comparison with the appropriate comparator therapy. At the study level, the risk of bias is classified as low.

For the endpoints overall survival and withdrawal because of AEs, the risk of bias is also estimated to be low. For the endpoint health status collected using EQ-5D VAS, the risk of bias is considered to be high. More than 10% of the patients were not included in the evaluation. In addition, the return rate, which was based solely on patients receiving treatment and not on all the patients in the study, fell sharply early on and diverged increasingly in both treatment arms.

In the present indication – palliative care of patients suffering from late-stage cancer with limited survival time – data on morbidity and quality of life are generally given high priority in benefit assessment. In the present assessment in which a moderate prolongation of survival time is offset by a significant increase in side effects, some of which are severe, the lack of data on the quality of life of patients is of great concern. Furthermore, morbidity data are limited to the data collected by EQ 5D-VAS. In the statements submitted in the present benefit assessment procedure, clinical experts also emphasised that, for the therapeutic situation under consideration, a full assessment would require corresponding data on patient-reported endpoints.

Under consideration of relevant uncertainties described above, a hint of an additional benefit can be derived for cabozantinib.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment for the active ingredient cabozantinib in a new therapeutic indication:

“CABOMETYX is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib”.

Best supportive care (BSC) was determined as an appropriate comparator therapy by the G-BA.

For the assessment, the pharmaceutical company submitted data from the ongoing, randomised, blinded CELESTIAL study. Cabozantinib + BSC is compared with placebo + BSC.

With respect to mortality, cabozantinib results in a minor increase in lifetime compared with BSC.

With respect to morbidity as measured by health status data obtained by EQ-5D VAS, no relevant difference between cabozantinib and BSC has been demonstrated.

Data on quality of life are not collected in the CELESTIAL study. In the present therapeutic situation, however, this data, as well as more extensive data on morbidity, is crucial.

With respect to side effects, cabozantinib is only associated with disadvantages.

In the overall assessment, the G-BA concludes that, although a relevant disadvantage with regard to side effects exists, this does not entirely call into question the advantage with regard to overall survival.

Thus a minor additional benefit is determined. A number of relevant uncertainties, including the lack of data on quality of life and only limited data on morbidity, limit the reliability of data. Therefore, the probability of the additional benefit is classified in the category “hint”.

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).

This resolution is based on the number of patients specified in the pharmaceutical company's dossier. Although the figures presented are generally associated with uncertainties, they are nevertheless plausible. In particular, there is great uncertainty regarding how the percentage of patients judged to be eligible for further systemic therapy after treatment with sorafenib was arrived at. This is based on an expert estimate with no recourse to epidemiological data (Frenette *et al.* 2016)[2], which results in a very wide range of 50–100%.

2.3 Requirements for 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 Cabometyx® (active ingredient: Cabozantinib) at the following publicly available link (last access: 7 March 2019):

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

Treatment with Cabozantinib should only be initiated and monitored by specialists in internal medicine, haematology, and, 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 summary of product characteristics and the information listed in the LAUER-TAXE® (last revised: 15 May 2019).

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

Treatment duration:

If no maximum therapy duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual therapy 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				
Cabozantinib	continuous, 1 × daily	365	1	365

[2] Frenette CT, Lencioni R, Finn RS. Novel second-line treatments for hepatocellular carcinoma: discussion. Clin Adv Hematol Oncol 2016; 14 (Suppl 12): 1–16.

Best supportive care	Different for each individual patient
Appropriate comparator therapy	
Best supportive care	Different for each individual patient

Usage and consumption:

Designation of the therapy	Dosage	Dosage /patient /treatment days	Consumption based on medication potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Cabozantinib	60 mg	60 mg	1 × 60 mg	365	365 × 60 mg
Best supportive care	Different for each individual patient				
Appropriate comparator therapy					
Best supportive care	Different for each individual patient				

Costs:

To facilitate comparability, the pharmaceutical costs were approximated both on the basis of the pharmacy sales price level and also the price less statutory rebates in accordance with Section 130 and Section 130a German Social Code, Book Five (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 pharmaceutical costs were then calculated on the basis of the costs per pack less the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Cabozantinib	30 FTA	€ 6,269.32	€ 1.77	€ 354.77	€ 5,912.78
Best supportive care	Different for each individual patient				
Appropriate comparator therapy					
Best supportive care	Different for each individual patient				
Abbreviations: FCT = film-coated tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 May 2019

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.

Since there are no 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, no costs for additionally required SHI services had to be taken into account.

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its meeting on 07 August 2018.

On 10 December 2018, the pharmaceutical company submitted a dossier for the benefit assessment of cabozantinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 11 December 2018 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 cabozantinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 March 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 15 March 2019. The deadline for submitting written statements was 05 April 2019.

The oral hearing was held on 24 April 2019.

By letter dated 24 April 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addenda created by the IQWiG was submitted to the G-BA on 15 May 2019.

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 meetings.

The evaluation of the statements received and the oral hearing were discussed at the meeting of the subcommittee on 28. Mai 2019, and the proposed resolution was approved.

At its meeting on 06 June 2019 , the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Time course of consultation

Meeting	Date	Subject of consultation
Subcommittee Medicinal products	7 August 2018	Determination of the appropriate comparator therapy
Working group Section 35a	16 April 2019	Information on written statements received; Preparation of the oral hearing
Subcommittee Medicinal products	24 April 2019	Conduct of the oral hearing; Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	29 April 2019 14 May 2019 21 May 2019	Consultation on the dossier evaluation of the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	28 May 2019	Concluding discussion of the proposed resolution
Plenum	6 June 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 June 2019

Federal Joint Committee
in accordance with Section 91 SGB V
Chair

Prof Hecken