Gemeinsamer Bundesausschuss

Justification

of 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 Cabozantinib (New Therapeutic Indication: Renal cell carcinoma, first-line treatment, combination with cabozantinib)

of 21 October 2021

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 studies 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 benefits,
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. Costs of therapy for the statutory health insurance,
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 cabozantinib (Cabometyx) was listed for the first time on 1 August 2014 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 26 March 2021, Cabometyx received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the commission of 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, 12.12.2008, p. 7).

On 26 April 2021, the pharmaceutical company has 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 (first-line therapy of advanced renal cell carcinoma, combination with nivolumab) 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 2 August 2021, 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 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 cabozantinib.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of cabozantinib (Cabometyx) in accordance with the product information

Cabometyx, in combination with nivolumab, is indicated for the first-line treatment of advanced renal cell carcinoma in adults

Therapeutic indication of the resolution (resolution from 21.10.2021):

- see therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)

Appropriate comparator therapy:

- Pembrolizumab in combination with axitinib

b) Adult patients with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3)

1 General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Appropriate comparator therapy:

- Avelumab in combination with axitinib (only for patients with a poor-risk profile)

or

- Nivolumab in combination with ipilimumab

or

- Pembrolizumab in combination with axitinib

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 products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In terms of authorisation status, the active ingredients aldesleukin, avelumab in combination with axitinib, bevacizumab in combination with interferon alfa-2a, cabozantinib, interferon alfa-2a, ipilimumab in combination with nivolumab, nivolumab in combination with ipilimumab, pazopanib, pembrolizumab in combination with axitinib, sunitinib, temsirolimus and tivozanib are available for the treatment of advanced renal cell carcinoma in previously untreated adults.

on 2. For patients in the present therapeutic indication, it is assumed that surgery and/or radiotherapy with curative objectives are not (or no longer) an option at the time of the treatment decision and that the treatment is palliative. Therefore, a non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication. The use of resection and/or radiotherapy as a palliative patient-individual therapy option for symptom control depending on the localisation and symptomatology of the metastases remains unaffected.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Avelumab in combination with axitinib: Resolution of 14 May 2020
- Pembrolizumab in combination with axitinib: Resolution of 14 May 2020
- Ipilimumab in combination with nivolumab: Resolution of 15 August 2019
- Nivolumab in combination with ipilimumab: Resolution of 15 August 2019
- Cabozantinib: Resolution of 6 December 2018
- Tivozanib: Resolution of 19 April 2018

Annex VI - Prescribability of approved medicinal products in non-approved therapeutic indications; Part B: Active ingredients that are not prescribable in off-label uses:

- Inhaled interleukin-2 (Proleukin®) for the treatment of renal cell carcinoma - resolution of 8 June 2016

on 4. The general state of medical knowledge in the present therapeutic indication was represented by a systematic search for guidelines and reviews of clinical studies. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

For first-line treatment of advanced renal cell carcinoma, current guidelines unanimously recommend immune checkpoint inhibitor-based combination therapies.

For these immune checkpoint inhibitor-based combination therapies, results from benefit assessment procedures are also available.

Accordingly, the G-BA identified an indication of a considerable additional benefit compared with sunitinib for the combination therapy of nivolumab and ipilimumab in adult patients with previously untreated advanced renal cell carcinoma with an intermediate risk profile (IMDC score[2] 1-2) and poor-risk profile (IMDC score ≥ 3) by resolution of 15 August 2019.

For pembrolizumab in combination with axitinib, the resolution dated 14 May 2020 identified a hint for a considerable additional benefit over sunitinib for adult patients with previously untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0-2). For adults with a poor-risk profile (IMDC score ≥ 3), there was an indication of a considerable additional benefit over sunitinib.

According to the resolution of 14 May 2020, there is no additional benefit for avelumab in combination with axitinib over sunitinib for adult patients with previously untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0-2). For adults with a poor-risk profile (IMDC score ≥ 3), a hint for a considerable additional benefit over sunitinib was identified.

[2] International Metastatic Renal-Cell Carcinoma Database Consortium

In the guidelines and the written statements of the scientific-medical societies, a distinction is made between patients with a favourable, intermediate and poor-risk profile on the basis of risk scores (IMDC score), and therapy recommendations are made separately according to IMDC risk profile.

For patients with a favourable risk profile (IMDC score 0), combination therapy of pembrolizumab and axitinib is recommended. In addition, the combination of avelumab and axitinib (with a weaker recommendation grade) is also recommended.

For patients with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3), pembrolizumab in combination with axitinib and nivolumab in combination with ipilimumab are preferred. In addition, the combination of avelumab and axitinib is also recommended, with a weaker level of recommendation.

Patients with favourable, intermediate, and poor-risk profiles have different prognoses and responses to therapy, which translates into considerable differences in overall survival.

Against this background and taking into account the existing therapy recommendations separated according to risk profile (favourable; intermediate/poor) as well as the authorisation status of the medicinal products under consideration, the G-BA considers it appropriate to consider the patient populations with the favourable risk profile and intermediate/poor-risk profile separately, despite partially overlapping therapy recommendations.

Therefore, in the overall assessment of the available evidence, pembrolizumab in combination with axitinib represents the appropriate comparator therapy for a) patients with previously untreated, advanced renal cell carcinoma with a favourable risk profile (IMDC score 0).

For b) patients with previously untreated advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3), multiple treatment options with comparable evidence are available with pembrolizumab in combination with axitinib, nivolumab in combination with ipilimumab and avelumab in combination with axitinib (only for patients with poor-risk profile) and are determined to be equally appropriate comparators.

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 in combination with nivolumab is assessed as follows:

a) <u>Adult patients with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)</u>

An additional benefit is not proven.

b) Adult patients with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3)

An additional benefit is not proven.

Justification:

In the absence of direct comparative studies of cabozantinib in combination with nivolumab versus the appropriate comparator therapy for patient groups a) and b), the pharmaceutical company uses an adjusted indirect comparison according to the method of Bucher et al. for the proof of an additional benefit. For these indirect comparisons using the bridge comparator sunitinib, the pharmaceutical company includes for both patient population a) and b) the CheckMate 9ER study with cabozantinib in combination with nivolumab (vs sunitinib) and the KEYNOTE-426 study with pembrolizumab in combination with axitinib (vs sunitinib).

The studies are randomised open-label, controlled, multicentre Phase III studies.

CheckMate 9ER

The study included adults with advanced or metastatic renal cell carcinoma (stage IV according to the AJCC classification[3]) with a clear cell component regardless of their risk profile. A total of 651 patients were randomly assigned in a 1:1 ratio to treatment with either cabozantinib in combination with nivolumab (intervention arm; N = 323) or sunitinib (comparator arm; N = 328). Randomisation was stratified by IMDC risk profile (favourable vs intermediate vs poor), region (the United States/ Canada/ Western Europe/ Northern Europe vs rest of the World), and programmed death-ligand 1 (PD-L1) status (≥ 1% vs < 1% or indeterminate).

The treatments with cabozantinib in combination with nivolumab and sunitinib were carried out according to the requirements in the product information. Patients were treated until disease progression, the occurrence of unacceptable persistent toxicity, or discontinuation of therapy at the discretion of the doctor or study participant. After discontinuation of the study medication, there were no limitations with regard to subsequent therapies.

The study, which is still ongoing, will assess overall survival as well as endpoints on symptomatology, health status and adverse events, among other things.

The IMDC score[4] was collected in the study as a disease characteristic start of the study, allowing patients to be differentiated by risk profile according to the IMDC score.

For the CheckMate 9ER study, results regarding two data cut-offs were submitted by the pharmaceutical company in the dossier for the benefit assessment. For the present benefit assessment, the results of the second data cut-off of 10.09.2020 are used. As part of the written statement procedure, the pharmaceutical company also submitted evaluations of a further data cut-off of 24.06.2021. However, with regard to this data cut-off, it remains unclear what the specific reason was for conducting this data cut-off and whether this is the prespecified third data cut-off of the CheckMate 9ER study. Due to these uncertainties, the data cut-off of 24.06.2021 is not used for the benefit assessment.

3 American-Joint-Committee-on-Cancer
4 International-Metastatic-Renal-Cell-Carcinoma-Database-Consortium

KEYNOTE-426

The study included adults with advanced or metastatic clear cell renal cell carcinoma (stage IV according to the AJCC classification). A total of 861 patients were randomly assigned in a 1:1 ratio to treatment with either pembrolizumab in combination with axitinib (intervention arm; N = 432) or sunitinib (comparator arm; N = 429). Randomisation was stratified by region (North America vs Western Europe vs Rest of the World) and risk profile according to IMDC score (favourable vs intermediate vs poor) at the start of the study.

The treatments with pembrolizumab in combination with axitinib and sunitinib were carried out according to the requirements in the product information. Patients were treated until disease progression, the occurrence of unacceptable persistent toxicity, or discontinuation of therapy at the discretion of the doctor or study participant. After discontinuation of the study medication, there were no limitations with regard to subsequent therapies.

The study, which is still ongoing, will assess overall survival as well as endpoints on symptomatology, health status, health-related quality of life and adverse events, among other things.

For this benefit assessment, the third data cut-off of 06.01.2020 is used for the endpoint overall survival, and the second data cut-off of 02.01.2019 is used for the endpoints concerning side effects. The IMDC score was collected in the study as a disease characteristic start of the study, allowing patients to be differentiated by risk profile according to the IMDC score.

a) Adult patients with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)

Relevant for the evaluation of patient population a) is the sub-population of patients with a favourable risk profile (IMDC score 0). With regard to the CheckMate 9ER study, there are 74 patients in the intervention arm and 72 patients in the comparator arm of the study. For the KEYNOTE-426 study, this is 138 patients in the intervention arm and 131 patients in the comparator arm.

As a prerequisite for the consideration of the adjusted indirect comparison to patient group a), a broad similarity can be observed with regard to the design of the studies and the bridge comparator sunitinib, according to the above explanations.

However, uncertainties relevant to the evaluation arise with regard to the similarity of the relevant sub-populations of the CheckMate 9ER and KEYNOTE-426 studies as a further prerequisite for consideration of the adjusted indirect comparison to patient population a). The reasons for this are as follows. Both the CheckMate 9ER and KEYNOTE-426 studies included patients regardless of their risk profile. The sub-population of patients with a favourable risk profile (IMDC score 0), which is relevant for the assessment of the additional benefit, accounts for only a small percentage of the total population in both studies with 22% (CheckMate 9ER) and 31% (KEYNOTE-426). Information on the patient characteristics of the relevant sub-populations of the two studies is only available for the CheckMate 9ER study. Corresponding data are missing for the study KEYNOTE-426. Since, in contrast to the CheckMate 9ER study, no data on the sub-population with an intermediate or poor-risk profile (patient group b) are available for the KEYNOTE-426 study, it cannot be indirectly inferred with

sufficient certainty that the sub-population of the KEYNOTE-426 study is sufficiently similar to that of the CheckMate 9ER study.

Thus, no appropriate data are available to evaluate the additional benefit of cabozantinib in combination with nivolumab in patient group a). An additional benefit of cabozantinib in combination with nivolumab versus the appropriate comparator therapy is therefore not proven.

b) Adult patients with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3)

Relevant for the evaluation of patient population b) is the sub-population of patients with an intermediate or poor-risk profile (IMDC score 1 to 6). With regard to the CheckMate 9ER study, there are 249 patients in the intervention arm and 256 patients in the comparator arm of the study. For the KEYNOTE-426 study, there are 294 patients in the intervention arm and 298 patients in the comparator arm.

As already described for patient group a), as a prerequisite for consideration of the adjusted indirect comparison to patient group b), a broad similarity can be observed with regard to the design of the studies and the bridge comparator sunitinib.

Also, with regard to the similarity of the relevant sub-populations of the studies CheckMate 9ER and KEYNOTE-426, in contrast to patient group a), a sufficient prerequisite for the consideration of the adjusted indirect comparison can be assumed. The reasons for this are as follows. Although no data are available for the relevant sub-population of patients with an intermediate or poor-risk profile (IMDC score 1 to 6) in the KEYNOTE-426 study, the majority of patients in the overall study population have an intermediate or poor-risk profile: approx. 80% in the CheckMate 9ER study and approx. 70% in the KEYNOTE-426 study. In view of this high percentage and taking into account the largely identical study design, it is possible to assume sufficient similarity on the basis of the overall populations to consider the adjusted indirect comparison to patient group b).

Accordingly, the demographic and clinical characteristics of the included patients are comparable between the study arms of both the CheckMate 9ER and KEYNOTE-426 studies. Patients in both studies averaged 60 to 61 years of age and were 80% of white ancestry. The sex ratio is similar in both studies, with about a quarter of patients being female. Patient characteristics describing disease severity are largely balanced between patients in terms of Karnofsky Performance Status (KPS) and metastasis location. In the case of the sarcomatoid characteristics, the assessment cannot be conclusive since, for more than 30%, no data are available in the KEYNOTE-426 study.

With regard to any prior treatment, patients in both studies were allowed to have received adjuvant or neoadjuvant therapy. However, no data are available on how many patients actually received adjuvant therapy. In terms of advanced or metastatic stage, all patients were not pretreated. The percentage of patients submitted to a previous nephrectomy was slightly lower in the CheckMate 9ER study, at about 70% than in the KEYNOTE-426 study, at just over 80%. Radiotherapy had been received by about 14% in the CheckMate 9ER study and slightly less than 10% in the KEYNOTE-426 study.

In the CheckMate 9ER study, 34% of patients in the comparator arm received systemic therapy as subsequent therapy. This involved mainly immunotherapy consisting of PD 1/PD-L1 inhibitors and/or CTLA-4 inhibitors. The percentage with subsequent systemic therapy was higher in the KEYNOTE-426 study and was 56% of patients in the comparator arm. Equal

percentages of patients received PD1/PD-L1 inhibitors and/or VEGF/VEGFR inhibitors in the further course of the disease. However, the available data on subsequent therapies do not indicate which therapy the patients received as the first subsequent therapy in each case.

Overall, despite remaining uncertainties based on the total populations, sufficient similarity can be assumed for the consideration of the adjusted indirect comparison regarding patient population b).

Extent and probability of the additional benefit

Mortality

For the endpoint overall survival, the adjusted indirect comparison shows no statistically significant difference between the treatment groups.

With regard to overall survival, an additional benefit of cabozantinib in combination with nivolumab is therefore not proven.

Morbidity

FKSI-DRS and EQ-5D VAS

In the CheckMate 9ER study, cabozantinib was administered continuously, and nivolumab was administered every two weeks in the intervention arm. Patient-reported endpoints on symptomatology (using FKSI-DRS) and health status (using EQ-5D VAS) were collected every two weeks in this arm, i.e. each time before nivolumab was administered. In the comparator arm, sunitinib was administered continuously for four weeks of a 6-week cycle, followed by a 2-week treatment break. Patient-reported endpoints were collected every six weeks in the comparator arm, i.e. before each 4-week treatment phase.

Thus, data on patient-reported endpoints were collected at different time points in each of the study arms in the CheckMate 9ER study. In the dossier, the pharmaceutical company only evaluates the results at the joint survey time points of both arms (i.e. every six weeks). The evaluated survey time point (every 6 weeks) for the patients in both study arms was before the administration or at two-week intervals after the administration of a potentially burdensome therapy. Therefore, it can be assumed that the burden of treatment over the course of the cycle was mapped comparably in both study arms at the time of the assessment.

In the KEYNOTE-426 study, pembrolizumab was administered once at the start of a 3-week cycle and axitinib continuously in the intervention arm. Patient-reported endpoints on symptomatology (using FKSI-DRS) and health status (using EQ-5D VAS) were collected on day one of each cycle for the first 24 weeks of the study, corresponding to once every three weeks. In the comparator arm, sunitinib was administered continuously for four weeks of a 6-week cycle, followed by a 2-week treatment break. Patient-reported endpoints were collected at day one of each cycle for the first 24 weeks of the study and additionally at day 29 of each cycle after four weeks. After week 24, patient-reported endpoints were collected in parallel every six weeks at the start of a new cycle in both study arms (or at the start of every second cycle in the intervention arm).

Due to the resulting time-shifted collection of patient-reported endpoints in the KEYNOTE-426 study during the first 24 weeks of the study, the burden of treatment over the course of the cycle is unequally reflected in the study arms.

Consequently, no data are available for the indirect comparison, as only the data from the CheckMate 9ER study are usable. Furthermore, both the CheckMate 9ER study and the KEYNOTE-426 study are unblinded studies. This would result in a high risk of bias in the results of the patient-reported endpoints in each of the two studies. Thus, in addition, the requirements for the certainty of results for the performance of an indirect comparison would not be met.

Overall, therefore, no usable data are available for the patient-reported endpoints on symptomatology.

Quality of life

No health-related quality of life data was collected in the CheckMate 9ER study: An adjusted indirect comparison is therefore not possible.

Side effects

Adverse events (AEs) in total

Almost all study participants in the CheckMate 9ER and KEYNOTE-426 studies presented adverse events. The results were only presented additionally.

Serious adverse events (SAEs) and severe AEs (CTCAE grade ≥ 3)

For the endpoints SAEs and severe AEs (CTCAE grade ≥ 3), the adjusted indirect comparison showed no statistically significant differences between cabozantinib in combination with nivolumab versus pembrolizumab in combination with axitinib.

Therapy discontinuation due to AEs

Due to the open study design of the CheckMate 9ER and KEYNOTE-426 studies, the risk of bias in the results for the endpoint therapy discontinuation due to AEs is assessed as high. The results on this endpoint in the context of an indirect comparison are therefore not considered usable.

Immune-mediated SAE and immune-mediated severe AE

From the CheckMate 9ER study, only results on individual immune-mediated AEs are available, but no overall rates on immune-mediated SAEs and immune-mediated severe AEs. There are no results from the KEYNOTE-426 study corresponding to the populations of the questions relevant to the present benefit assessment. Thus, there are no usable data for an indirect comparison.

Overall assessment

For the assessment of the additional benefit of cabozantinib in combination with nivolumab in the first-line treatment of advanced renal cell carcinoma in adults, results are available for the patient group with an intermediate or poor-risk profile (patient population b)) regarding

overall survival and side effects compared with the comparator therapy pembrolizumab in combination with axitinib.

The present assessment is based on an adjusted indirect comparison according to the method of Bucher et al. of the studies CheckMate 9ER (cabozantinib in combination with nivolumab vs sunitinib) and KEYNOTE-426 (pembrolizumab in combination with axitinib vs sunitinib). Cabozantinib in combination with nivolumab was compared to pembrolizumab in combination with axitinib via the bridge comparator sunitinib.

For the endpoint overall survival, the adjusted indirect comparison shows no statistically significant difference between the treatment groups. With regard to overall survival, an additional benefit of cabozantinib in combination with nivolumab is therefore not proven.

For the patient-reported endpoints on symptomatology and health status, there are no usable data for an adjusted indirect comparison.

With regard to health-related quality of life, no data were collected in the CheckMate 9ER study. An adjusted indirect comparison is therefore not possible.

In terms of side effects, there were no statistically significant differences in the endpoints of serious adverse events (SAE) and severe adverse events (CTCAE grade≥ 3) in the adjusted indirect comparison. For other endpoints of the category side effects, no usable data are available.

In the overall assessment, there are neither positive nor negative effects of cabozantinib in combination with nivolumab compared to pembrolizumab in combination with axitinib for patient population b). An additional benefit of cabozantinib in combination with nivolumab compared to pembrolizumab in combination with axitinib is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the medicinal product Cabometyx with the active ingredient cabozantinib.

The therapeutic indication assessed here is as follows: "Cabometyx, in combination with nivolumab, is indicated for the first-line treatment of advanced

renal cell carcinoma in adults. "

In the therapeutic indication to be considered, two patient populations were differentiated:

a) Adult patients with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)

and

b) Adult patients with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3).

Patient population a)

Pembrolizumab in combination with axitinib was determined to be the appropriate comparator therapy.

The pharmaceutical company presents an adjusted indirect comparison of cabozantinib in combination with nivolumab (CheckMate 9ER study) versus pembrolizumab in combination with axitinib (KEYNOTE-426 study) via the bridge comparator sunitinib.

However, it cannot be assessed with sufficient certainty to what extent the sub-populations of the CheckMate 9ER and KEYNOTE-426 studies that are relevant for the assessment of patient population a) are sufficiently similar.

Thus, no appropriate data are available to evaluate the additional benefit of cabozantinib in combination with nivolumab in patient group a). An additional benefit of cabozantinib in combination with nivolumab versus the appropriate comparator therapy is therefore not proven.

Patient population b)

The appropriate comparator therapy was determined to be:

- Avelumab in combination with axitinib (only for patients with a poor-risk profile)

or

- Nivolumab in combination with ipilimumab

or

- Pembrolizumab in combination with axitinib

.

The pharmaceutical company presents an adjusted indirect comparison of cabozantinib in combination with nivolumab (CheckMate 9ER study) versus pembrolizumab in combination with axitinib (KEYNOTE-426 study) via the bridge comparator sunitinib. Despite remaining uncertainties based on the total populations, sufficient similarity can be assumed for the consideration of the adjusted indirect comparison regarding patient population b).

For the endpoint overall survival, the adjusted indirect comparison shows no statistically significant difference between the treatment groups.

For the patient-reported endpoints on symptomatology and health status, there are no usable data for an adjusted indirect comparison.

With regard to health-related quality of life, no data were collected in the CheckMate 9ER study. An adjusted indirect comparison is therefore not possible.

In terms of side effects, there were no statistically significant differences in the endpoints of serious adverse events (SAE) and severe adverse events (CTCAE grade≥ 3) in the adjusted indirect comparison. For other endpoints of the category side effects, no usable data are available.

In the overall assessment, there are neither positive nor negative effects of cabozantinib in combination with nivolumab compared to pembrolizumab in combination with axitinib for patient group b). An additional benefit of cabozantinib in combination with nivolumab compared to pembrolizumab in combination with axitinib is therefore not proven.

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).

The G-BA bases its resolution on the patient numbers from the statements submitted by the pharmaceutical company. The procedure of the pharmaceutical company is mathematically and methodologically comprehensible. Uncertainties arise only from the fact that the calculation performed by the pharmaceutical company assumes that the percentage of patients with an initial diagnosis in stage IV, which is determined exclusively via the cases with a known stage, also occurs in the cases without allocation to a specific stage.

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 Cabometyx (active ingredient: cabozantinib) at the following publicly accessible link (last access: 15 September 2021):

https://www.ema.europa.eu/en/documents/product-information/cabometyx-epar-product-information_en-0.pdf

Treatment with cabozantinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, as well as specialists in nephrology and specialists participating in the Oncology Agreement experienced in the treatment of patients with renal cell carcinoma.

In the CheckMate 9ER study, only patients with renal cell carcinoma with clear cell histology were examined. No data are available for patients with non-clear cell renal cell carcinoma.

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 October 2021).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed: Cabozantinib in combination with nivolumab				
Cabozantinib	1 x daily	365	1	365
Nivolumab	1 x per 14 day cycle	26.1	1	26.1
	or			
	1 x per 28 day cycle	13.0	1	13.0
Appropriate comparator therapy				
a) Adult patients with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)				
Pembrolizumab in combination with axitinib				
Pembrolizumab	1 x per 21 day cycle	17.4	1	17.4
	or			
	1 x per 42 day cycle	8.7	1	8.7
Axitinib	2 x daily	365	1	365
b) Adult patients with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3)				
Avelumab in combination with axitinib (only for patients with a poor-risk profile)				
Avelumab	1 x per 14 day cycle	26.1	1	26.1
Axitinib	2 x daily	365	1	365
Nivolumab in combination with ipilimumab				
Initial treatment				
Nivolumab	1 x per 21 day cycle	4.0	1	4.0
Ipilimumab	1 x per 21 day cycle	4.0	1	4.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Follow-up treatment				
Nivolumab	1 x per 14 day cycle (3 weeks after last dose of initial treatment)	20.1	1	20.1
	or			
	1 x per 28 day cycle (6 weeks after last dose of initial treatment)	9.3	1	9.3
Pembrolizumab in combination with axitinib				
Pembrolizumab	1 x per 21 day cycle	17.4	1	17.4
	or			
	1 x per 42 day cycle	8.7	1	8.7
Axitinib	2 x daily	365	1	365

Consumption:

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg) [5].

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient / year	Average annual consumption by potency
Medicinal product to be assessed: Cabozantinib in combination with nivolumab					
Cabozantinib	40 mg	40 mg	1 x 40 mg	365	365 x 40 mg

[5] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient / year	Average annual consumption by potency
Nivolumab	240 mg	240 mg	2 x 100 mg + 1 x 40 mg	26.1	52.2 x 100 mg + 26.1 x 40 mg
	or				
	480 mg	480 mg	4 x 100 mg + 2 x 40 mg	13.0	52.0 x 100 mg 26.0 x 40 mg
Appropriate comparator therapy					
a) Adult patients with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)					
Pembrolizumab in combination with axitinib					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
Axitinib	5 mg	10 mg	2 x 5 mg	365	730 x 5 mg
b) Adult patients with previously untreated, advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor-risk profile (IMDC score ≥ 3)					
Avelumab in combination with axitinib (only for patients with a poor-risk profile)					
Avelumab	800 mg	800 mg	4 x 200 mg	26.1	104.4 x 200 mg
Axitinib	5 mg	10 mg	2 x 5 mg	365	730 x 5 mg
Nivolumab in combination with ipilimumab					
Initial treatment					
Nivolumab	3 mg/kg KG	231 mg	2 x 100 mg 1 x 40 mg	4	8 x 100 mg + 4 x 40 mg
Ipilimumab	1 mg/kg KG	77 mg	2 x 50 mg	4	8 x 50 mg
Follow-up treatment					
Nivolumab	240 mg	240 mg	2 x 100 mg 1 x 40 mg	20.1	40.2 x 100 mg + 20.1 x 40 mg
	or				

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient / year	Average annual consumption by potency
	480 mg	480 mg	4 x 100 mg 2 x 40 mg	9.3	37.2 x 100 mg + 18.6 x 40 mg
Pembrolizumab in combination with axitinib					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
Axitinib	5 mg	10 mg	2x 5 mg	365	730 x 5 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Cabozantinib 40 mg	30 HC	€ 5,709.38	€ 1.77	€ 322.79	€ 5,384.82
Nivolumab 100 mg	1 CIS	€ 1,344.24	€ 1.77	€ 73.81	€ 1,268.66
Nivolumab 40 mg	1 CIS	€ 544.32	€ 1.77	€ 29.53	€ 513.02
Appropriate comparator therapy					
Avelumab 200 mg	1 CIS	€ 834.55	€ 1.77	€ 45.59	€ 787.19
Axitinib 5 mg	56 FCT	€ 3,597.14	€ 1.77	€ 0.00	€ 3,595.37

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Ipilimumab 50 mg	1 CIS	€ 3,849.07	€ 1.77	€ 216.54	€ 3,630.76
Nivolumab 100 mg	1 CIS	€ 1,344.24	€ 1.77	€ 73.81	€ 1,268.66
Nivolumab 40 mg	1 CIS	€ 544.32	€ 1.77	€ 29.53	€ 513.02
Pembrolizumab 100 mg	1 CIS	€ 3,037.06	€ 1.77	€ 170.17	€ 2,865.12
Abbreviations: FCT = film-coated tablets, CIS = concentrate for the preparation of an infusion solution.					

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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.

According to the avelumab product information, patients are required to be premedicated with an antihistamine and paracetamol prior to the first 4 infusions of avelumab. The product information does not provide any specific information why the necessary costs cannot be quantified.

Other SHI services:

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

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but instead follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy sales price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 22 December 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 26 April 2021, 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 29 April 2021 in conjunction with the resolution of the G-BA of 1st 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 29 July 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 2nd August 2021. The deadline for submitting written statements was 23 August 2021.

The oral hearing was held on 6 September 2021.

By letter dated 7 September 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addenda prepared by the IQWiG was submitted to the G-BA on 30 September 2021 and 1st October 2021.

On 1st October 2021, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1, dated 1st October 2021, replaces version 1.0 of the dossier assessment dated 29 July 2021. The evaluation result was not affected by the changes in version 1.1 compared to version 1.0.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 12 October 2021, and the proposed resolution was approved.

At its session on 21 October 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	22 December 2020	Determination of the appropriate comparator therapy

Working group Section 35a	1 September 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	6 September 2021 7 September 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 September 2021 22 September 2021 6 October 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	12 October 2021	Concluding discussion of the draft resolution
Plenum	21 October 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 21 October 2021

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

Prof. Hecken