Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
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 nivolumab)

of 21 October 2021

At its session on 21 October 2021, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No 49a of 31 March 2009), as last amended by the publication of the resolution of DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of cabozantinib in accordance with the resolution of 06 June 2019:

Cabozantinib

Resolution of: 21 October 2021
Entry into force on: 21 October 2021
BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 26 March 2021):

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 of 21 October 2021):

- see therapeutic indication according to marketing authorisation

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

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

Extent and probability of the additional benefit of cabozantinib in combination with nivolumab compared to the appropriate comparator therapy:

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)

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

Extent and probability of the additional benefit of cabozantinib in combination with nivolumab compared to pembrolizumab in combination with axitinib:

An additional benefit is not proven.

Study results according to endpoints: [1]

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

No data are available to allow an assessment of the additional benefit.

Summary of results for relevant clinical endpoints[1]

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	∅	No data available.
Side effects	↔	No relevant difference for the benefit assessment.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

[1] Data from the dossier assessment of the IQWiG (A24-49) and from the addendum (A21-119), unless otherwise indicated.

Adjusted Bucher indirect comparison of cabozantinib + nivolumab vs pembrolizumab + axitinib via the bridge comparator sunitinib

CheckMate 9ER study: cabozantinib + nivolumab vs sunitinib

KEYNOTE-426 study: pembrolizumab + axitinib vs sunitinib

Relevant sub-populations of the CheckMate 9ER or KEYNOTE-426 study: patients with an intermediate or poor-risk profile (IMDC score 1 to 6)

Mortality

Endpoint	**Cabozantinib + nivolumab or Pembrolizumab + axitinib**		**Sunitinib (Bridge comparator)**		**Group Difference**
	N	Median survival time in months [95%-CI] *Patients with event n (%)*	N	Median survival time in months [95%-CI] *Patients with event n (%)*	Hazard ratio [95%-CI] p-value Absolute difference (AD)[a]
Overall survival					
cabozantinib + nivolumab vs sunitinib					
Data cut-off of 10.09.2020	249	n.a. 71 (28.5)	256	29.47 [23.82; n.c.] 101 (39.5)	0.62 [0.45; 0.84] 0.002
pembrolizumab + axitinib vs sunitinib					
Data cut-off of 06.01.2020	294	n. d. 116 (39.5)	298	n. d. 154 (51.7)	0.63 [0.50; 0.81] < 0.001
Adjusted indirect comparison Cabozantinib + nivolumab vs pembrolizumab + axitinib					0.98 [0.66; 1.46]

Morbidity

Symptomatology (FKSI-DRS)
No usable data available
Symptomatology (EORTC-QLQ-C30)
Only collected in KEYNOTE-426 study
Health status (EQ-5D VAS)
No usable data available

Health-related quality of life

health-related quality of life (EORTC-QLQ-C30)
Only collected in KEYNOTE-426 study

Side effects

Endpoint	Cabozantinib + nivolumab or Pembrolizumab + axitinib		Sunitinib (Bridge comparator)		Group Difference
	N	Median time to event in months [95%-CI] *Patients with event n (%)*	N	Median time to event in months [95%-CI] *Patients with event n (%)*	Hazard ratio [95%-CI] p-value Absolute difference (AD)[a]
Total adverse events (presented additionally) [b]					
cabozantinib + nivolumab vs sunitinib					
Data cut-off of 10.09.2020	246	0.46 [0.43; 0.49] 245 (99.6)	249	0.36 [0.33; 0.43] 246 (98.8)	-
pembrolizumab + axitinib vs sunitinib					
Data cut-off of 02.01.2019	292	n. d. 286 (97.9)	295	n. d. 295 (100)	-
Serious adverse events (SAE) [b]					
cabozantinib + nivolumab vs sunitinib					
Data cut-off of 10.09.2020	246	16.82 [12.22; 23.66] 124 (50.4)	249	19.25 [11.20; n. a.] 110 (44.2)	0.89 [0.69; 1.16] 0.401
pembrolizumab + axitinib vs sunitinib					
Data cut-off of 02.01.2019	292	n. d. 136 (46.6)	295	n. d. 116 (39.3)	1.08 [0.84; 1.39] n. d.
Adjusted indirect comparison Cabozantinib + nivolumab vs pembrolizumab + axitinib					0.82 [0.57; 1.18]
Severe adverse events (CTCAE grade ≥ 3) [b]					
cabozantinib + nivolumab vs sunitinib					
Data cut-off of 10.09.2020	246	4.37 [2.79; 5.78] 190 (77.2)	249	2.76 [2.10; 4.40] 176 (70.7)	0.86 [0.70; 1.06] 0.177
pembrolizumab + axitinib vs sunitinib					
Data cut-off of 02.01.2019	292	n. d. 228 (78.1)	295	n. d. 220 (74.6)	0.90 [0.75; 1.08] n. d.
Adjusted indirect comparison Cabozantinib + nivolumab vs pembrolizumab + axitinib					0.96 [0.72; 1.26]

Endpoint	Cabozantinib + nivolumab or Pembrolizumab + axitinib		Sunitinib (Bridge comparator)		Group Difference
	N	Median time to event in months [95%-CI] *Patients with event n (%)*	N	Median time to event in months [95%-CI] *Patients with event n (%)*	Hazard ratio [95%-CI] p-value Absolute difference (AD)[a]
Therapy discontinuations due to adverse events[b]					
cabozantinib + nivolumab vs sunitinib					
Data cut-off of 10.09.2020	246	n.a. 74 (30.1)	249	n.a. 41 (16.5)	1.46 [0.99; 2.15] 0.054
pembrolizumab + axitinib vs sunitinib					
Data cut-off of 02.01.2019	292	n. d. 87 (29.8)	295	n. d. 44 (14.9)	1.82 [1.26; 2.63] n. d.
Adjusted indirect comparison Cabozantinib + nivolumab vs pembrolizumab + axitinib					-
Immune-mediated SAEs					
No usable data available					
Immune-mediated severe AEs					
No usable data available					

[a] Absolute difference (AD) is given only in the case of a statistically significant difference; own calculation
[b] without detection of progression of the underlying disease

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; n.d. = no data available; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; vs = versus

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 400 – 760 patients

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

approx. 2390 – 3420 patients

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.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Cabozantinib in combination with nivolumab	
Cabozantinib	€ 65,515.31
Nivolumab	€ 79,308.84 - € 79,613.87
Total	€ 144,824.15 - 145,129.18
Appropriate comparator therapy:	
Pembrolizumab in combination with axitinib	
Pembrolizumab	€ 99,706.18
Axitinib	€ 46,868.22
Total	€ 146,574.39

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 October 2021)

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Nivolumab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	13.0	€ 923
				26.1	€ 1,853.10
Pembrolizumab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	8.7	€ 617.70
				17.4	€ 1,235.40

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Cabozantinib in combination with nivolumab	
Cabozantinib	€ 65,515.31
Nivolumab	€ 79,308.84 - € 79,613.87
Total	€ 144,824.15 - 145,129.18
Appropriate comparator therapy:	
Avelumab in combination with axitinib (only for patients with a poor-risk profile)	
Avelumab	€ 82,182.64
Axitinib	€ 46,868.22
Total	€ 129,050.85
Nivolumab in combination with ipilimumab	
Initial treatment	
Nivolumab	€ 12,201.36
Ipilimumab	€ 29,046.08
Total initial treatment	€ 41,247.44
Follow-up treatment	
Nivolumab	€ 56,736.32 - € 61,311.83
Initial treatment + total follow-up treatment	€ 97,983.76 - € 102,559.27
Pembrolizumab in combination with axitinib	
Pembrolizumab	€ 99,706.18
Axitinib	€ 46,868.22
Total	€ 146,574.39

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1st October 2021)

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Nivolumab (in combination with cabozantinib)	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	13.0	€ 923
				26.1	€ 1,853.10
Pembrolizumab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	8.7	€ 617.70
				17.4	€ 1,235.40
Avelumab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
Nivolumab in combination with ipilimumab					
Nivolumab (follow-up treatment with nivolumab in a 14-day cycle)	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	24.1	€ 1,711.10
Nivolumab (follow-up treatment with nivolumab in a 28-day cycle)	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	13.3	€ 944.30
Ipilimumab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	4	€ 284.00
Total					€ 1,228.30 - € 1,995.10

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 21 October 2021.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 21 October 2021

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

Prof. Hecken