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 (reassessment after the deadline: thyroid carcinoma.)

of 16 December 2021

At its session on 16 December 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. Annex XII is amended as follows:

1. The information on Cabozantinib in the version of the resolution of 22 January 2015 (BAnz AT 30.04.2015 B2), last modified on 1 October 2020, is repealed.

2. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Cabozantinib in the version of the resolution of 21 October 2021:

Cabozantinib

Resolution of: 16 December 2021
Entry into force on: 16 December 2021
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 24 March 2014):

Cometriq is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

Therapeutic indication of the resolution (resolution of 16 December 2021):

see therapeutic indication according to marketing authorisation

1. Extent of the additional benefit and significance of the evidence

Cabozantinib is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

<u>Adult patients with progressive, unresectable, locally advanced or metastatic medullary thyroid carcinoma</u>

Extent of the additional benefit and significance of the evidence of Cabozantinib:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival only with positive RET- M918T mutational status; no relevant differences for the benefit assessment in the case of negative or unknown RET M918T mutational status
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	n.a.	The data are not assessable.
Side effects	↓	Disadvantages in the endpoints of serious AEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs
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		

EXAM study: cabozantinib vs placebo

Study design: randomised, double-blind, two-armed

Final data cut-off: 28 August 2014

[1] Data from the dossier assessment of the G-BA (published on 1. Oktober 2021), and from the amendment to the dossier assessment (published on 16 December 2021), unless otherwise indicated.

Endpoint	Cabozantinib		Placebo		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 (%)*	HR [95% CI] p-value AD[a]
Mortality					
Overall survival	219	26.6 [23.20; 31.61] *141 (64.4)*	111	21.1 [16.39; 32.36] *77 (69.4)*	0.85 [0.64; 1.12] 0.241
Subgroup analysis for RET-M918T mutational status (presented additionally)					
Positive	81	44.3 [29.34; 56.44] *44 (54.3)*	45	18.9 [14.19; 35.29] *32 (71.1)*	0.60 [0.38; 0.94] 0.026 AD= +25.4 months
Negative	75	20.2 [14.92; 26.61] *56 (74.7)*	32	21.5 [11.47; 38.08] *24 (75.0)*	1.12 [0.70; 1.82] 0.631
Unknown	63	26.2 [19.75; 42.35] *41 (65.1)*	34	31.4 [12.06; 43.99] *21 (61.8)*	0.92 [0.54; 1.56] 0.758

Endpoint	Cabozantinib		Placebo		Group difference
	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	HR [95% CI] p-value AD[a]
Morbidity					
Progression-free survival (PFS)[b]	219	48.6 [40.1; 59.7] *79 (36.1)*	111	17.4 [12.9; 23.6] *60 (54.1)*	0.28 [0.19; 0.40] p < 0.0001 AD=+31.2 weeks
Symptomatology (MDASI)	No usable data available.				
Health-related quality of life					
MDASI – THY	No usable data available.				

Endpoint	Cabozantinib		Placebo		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	HR [95% CI]; p-value
Side effects					
Total, without detection of progression of the underlying disease					
AE	214	214 (100)	109	104 (95.4)	-
SAE	214	189 (88.3)	109	45 (41.3)	2.75 [1.97; 3.83]; < 0.0001
Severe AEs (CTCAE grade ≥ 3)	214	114 (53.3)	109	24 (22.0)	1.87 [1.19; 2.95]; 0.006
Discontinuation due to AEs	214	50 (23.4)	109	10 (9.2)	2.71 [1.37; 5.35]; 0.002
Adverse events according to SOC					
Ear and labyrinth disorders	214	25 (11.7)	109	2 (1.8)	4.50 [1.05; 19.26] 0.027
Gastrointestinal disorders	214	203 (94.9)	109	67 (61.5)	2.99 [2.25; 3.97] < 0.0001
General disorders and administration site conditions	214	178 (83.2)	109	66 (60.6)	1.78 [1.34; 2.37] < 0.0001
Infections and infestations	214	134 (62.6)	109	37 (33.9)	1.67 [1.16; 2.41] 0.0057
Metabolic and nutrition disorders	214	143 (66.8)	109	34 (31.2)	2.53 [1.74; 3.68] < 0.0001

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	214	7 (3.3)	109	11 (10.1)	0.20 [0.07; 0.54] 0.001
Nervous system disorders	214	148 (69.2)	109	35 (32.1)	2.55 [1.76; 3.70] < 0.0001
Renal and urinary disorders	214	44 (20.6)	109	4 (3.7)	3.69 [1.30; 10.43] 0.008
Reproductive system and breast disorders	214	31 (14.5)	109	5 (4.6)	2.51 [0.97; 6.52] 0.050
Respiratory, thoracic and mediastinal disorders	214	144 (67.3)	109	48 (44.0)	1.63 [1.17; 2.26] 0.003
Skin and subcutaneous tissue disorders	214	186 (86.9)	109	46 (42.2)	3.91 [2.81; 5.44] < 0.0001
Vascular disorders	214	114 (53.3)	109	16 (14.7)	3.55 [2.09; 6.02] < 0.0001
Serious adverse events according to SOC					
Gastrointestinal disorders	214	34 (15.9)	109	4 (3.7)	3.36 [1.18; 9.56] 0.016
Metabolism and nutrition disorders	214	17 (7.9)	109	1 (0.9)	6.90 [0.91; 52.38] 0.030
Severe adverse events (CTCAE grade ≥3) according to SOC					
Gastrointestinal disorders	214	86 (40.2)	109	6 (5.5)	6.28 [2.73; 14.42] < 0.0001

Endpoint	Cabozantinib		Placebo		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	HR [95% CI]; p-value
General disorders and administration site conditions	214	54 (25.2)	109	11 (10.1)	1.99 [1.03; 3.85] 0.037
Metabolic and nutrition disorders	214	52 (24.3)	109	9 (8.3)	2.16 [1.05; 4.43] 0.031
Nervous system disorders	214	23 (10.7)	109	1 (0.9)	10.30 [1.39; 76.47] 0.005
Vascular disorders	214	27 (12.6)	109	2 (1.8)	6.11 [1.44; 25.83] 0.005

a Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b Data from the dossier of the pharmaceutical company Module 4 A, last revised 30.06.2021

Abbreviations used:
AD: Absolute difference: CTCAE: Common Terminology Criteria for Adverse Events; HR: Hazard Ratio; CI: Confidence Interval; N: Number of patients evaluated; n: Number of patients with (at least 1) event; n.c.: not calculable; n.a.: not achieved; RCT: Randomised Controlled Trial; SAE: Serious Adverse Event; AE: Adverse Event; n.d.: no data available

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

approx. 50 – 670 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 Cometriq (active ingredient: cabozantinib) at the following publicly accessible link (last access: 6 October 2021):

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

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

4. Treatment costs

Annual treatment costs:

Adult patients with progressive, unresectable, locally advanced or metastatic medullary thyroid carcinoma

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Cabozantinib	€ 70,025.64

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

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 December 2021.

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

Berlin, 16 December 2021

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

Prof. Hecken