Resolution
by the Federal Joint Committee
on an amendment to the Pharmaceutical Directive (AM-RL):
Appendix XII – Resolutions on the benefit assessment of pharmaceuticals with new active ingredients, in accordance with the German Social Code, Book Five (SGB V), section 35a
Cabozantinib

From 22 January 2015

In its session on 22 January 2015, the Federal Joint Committee resolved to amend the Pharmaceutical Directive (AM-RL), version published 18 December 2008/22 January 2009 (Federal Gazette, number 49a of 31 March 2009), last amended on 19 March 2015 (Federal Gazette, AT 20 April 2015 B3) as follows:

I.

Appendix XII shall be amended in alphabetical order to include the active ingredient cabozantinib:

Cabozantinib

Therapeutic indication:

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

For patients in whom rearranged during transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision.

1. Extent of additional benefit of the pharmaceutical

Cabozantinib is authorized as a pharmaceutical for the treatment of a rare disease in accordance with EC regulation number 141/2000 of the European Parliament and Council of 16 December 1999 on orphan drugs. In accordance with SGB V section 35a, paragraph 1, sentence 10, the additional medical benefit has been proved through market authorization.

In accordance with the rules of procedure of the Federal Joint Committee, chapter 5, section 12, paragraph 1, number 1, sentence 2, the Federal Joint Committee determines the extent of the additional benefit for the number of patients and patient groups for whom a therapeutically significant additional benefit exists. This quantification of the additional benefit has been conducted in accordance with the criteria laid out in the rules of procedure, chapter 5, section 5, paragraph 7, numbers 1 to 4.

Extent of additional benefit:

minor

Study results according to endpoints[1]:

Endpoint	Intervention arm (cabozantinib)		Control arm (placebo)		Intervention vs. control
Mortality					
Overall survival (OS)	N	Events n (%) Weeks (median) [95% CI]	N	Events n (%) Weeks (median) [95% CI]	HR [95% CI] p-value AD[2]
1. Interim analysis					
Overall population	219	66 (30.1%) 91.9 [72.1; 124.0]	111	30 (27.0%) n. c. 62.3; n. c.]	0.98 [0.63; 1.52] p = 0.93
2. Interim analysis[3]					
Overall population	219	103 (47.0%) 113.1 [99.6; 133.6]	111	59 (53.2%) 88.4 [71.3; 116.0]	0.83 [0.60; 1.14] p = 0.24

[1] Data for target population of the authorization study XL184-301 from the G-BA benefit assessment and the pharmaceutical company dossier. If not otherwise indicated, the results at data cut-off on 15 June 2011 are shown.

[2] Information on absolute difference (AD) shown only for statistically significant results ($p < 0.05$).

[3] Data cut-off: 15 June 2012, post hoc analysis (information in weeks).

Endpoint	Intervention arm (cabozantinib)		Control arm (placebo)		Intervention vs. control
Subgroup: ECOG PS = 0[4]	123	46 (37.4%) 124.0 [106.1; n. c.]	56	19 (33.9%) 171.6 [106.4; n. c.]	1.27 [0.74; 2.17] p = 0.3836
Subgroup: ECOG PS = 1 or 2[4]	95	56 (58.9%) 77.7 [58.4; 129.7]	55	40 (72.7%) 56.7 [33.4; 77.1]	0.63 [0.42; 0.95] p = 0.0245 AD: 5.3 months[5]
Subgroup: RET mutation = positive[6]	107	47 (43.9%) 124.0 [100.9; n. c.]	62	33 (53.2%) 91.7 [75.7; n. c.]	0.79 [0.51; 1.24] p = 0.3120
Subgroup: RET mutation = negative[6]	35	20 (57.1%) 76.3 [59.1; n. c.]	11	8 (72.7%) 68.9 [10.6; 171.6]	0.92 [0.39; 2.17] p = 0.8450
Subgroup: RET mutation = unknown[6]	77	36 (46.8%) 108.6 [73.9; n. c.]	38	18 (47.4%) 87.9 [45.1; n. c.]	0.83 [0.47; 1.46] p = 0.5126
Subgroup: RET M918T = positive[7]	81	31 (38.3%) 146.7 [112.1; n. c.]	45	27 (60.0%) 81.6 [62.3; n. c.]	0.57 [0.34; 0.96] p = 0.0306 AD: 16.3 months[5]
Subgroup: RET M918T = negative[7]	75	44 (58.7%) 99.6 [64.6; 122.4]	32	18 (56.3%) 107.6 [48.6; n. c.]	1.23 [0.7; 2.16] p = 0.4641
Subgroup: RET M918T = unknown[7]	63	28 (44.4%) 108.6 [74.3; n. c.]	34	14 (41.2%) 106.4 [50.0; n. c.]	0.96 [0.50; 1.82] p = 0.8905
Final analysis[8]					
Overall population	219	141 (64.4%) 26.6 [23.2; 31.6]	111	77 (69.4%) 21.1 [16.4; 32.4]	0.85 [0.64; 1.12] p = 0.2409
Subgroup: ECOG PS = 0[9]	123	72 (58.5%) 31.9 [26.6; 46.3]	56	33 (58.9%) 39.5 [32.4; 55.2]	1.07 [0.71; 1.62] p = 0.7471
Subgroup: ECOG PS = 1 or 2[9]	95	68 (71.6%) 20.0 [13.7; 26.4]	55	44 (80.0%) 12.2 [9.5; 16.4]	0.68 [0.46; 0.99] p = 0.0437 AD: 7.8 months
Subgroup: RET mutation = positive[10]	107	64 (59.8%) 31.6 [25.8; 47.9]	62	42 (67.7%) 24.8 [17.4; 36.7]	0.79 [0.54; 1.17] p = 0.2397
Subgroup: RET mutation = negative[10]	35	25 (71.4%) 17.5 [13.6; 30.6]	11	11 (100.0%) 15.8 [11.5; 34.3]	0.68 [0.33; 1.38] p = 0.2825
Subgroup: RET mutation = unknown[10]	77	52 (67.5%) 25.0 [17.1; 31.9]	38	24 (63.2%) 24.5 [10.4; 38.1]	0.91 [0.56; 1.48] p = 0.7100
Subgroup: RET M918T = positive[11]	81	44 (54.3%) 44.3 [29.3; 56.4]	45	32 (71.1%) 18.9 [14.2; 35.3]	0.60 [0.38; 0.94] p = 0.0255 AD: 25.4 months
Subgroup: RET M918T = negative[11]	75	56 (74.7%) 20.2 [14.9; 26.6]	32	24 (75.0%) 21.5 [11.5; 38.1]	1.12 [0.70; 1.82] p = 0.6308
Subgroup: RET M918T = unknown[11]	63	41 (65.1%) 26.2 [19.7; 42.3]	34	21 (61.8%) 31.4 [12.1; 44.0]	0.92 [0.54; 1.56] p = 0.7577
Morbidity					
Progress-free survival (PFS)[12]	N	Events n (%) Weeks (median) [95% CI]	N	Events n (%) Weeks (median) [95% CI]	HR [95% CI] p-value AD[2]
Overall population	219	79 (36.1%) 48.6 [40.1; 59.7]	111	60 (54.1%) 17.4 [12.9; 23.6]	0.28 [0.19; 0.40] p < 0.0001 AD: 31.2 weeks

[4] Subgroup analysis according to ECOG PS (ascertained for 329 patients); interaction test: p = 0.035.
[5] Own, approximate conversion of AD into months, calculated by dividing the AD in weeks by 4.
[6] Subgroup analysis according to RET mutation status; interaction test: p = 0.974.
[7] Subgroup analysis according to RET M918 mutation status; interaction test: p = 0.144.
[8] Data cut-off: 28 August 2014; submission of final analysis of overall survival (in months) during hearing procedure.
[9] Subgroup analysis according to ECOG PS (ascertained for 329 patients); interaction test: p = 0.078.
[10] Subgroup analysis according to RET mutation status; interaction test: p = 0.744.
[11] Subgroup analysis according to RET M918 mutation status; interaction test: p = 0.153.
[12] Data cut-off: 6 April 2011; a priori planned final analysis of PFS.

Endpoint	Difference after 12 weeks (cabozantinib vs. placebo)		Difference after 24 weeks (cabozantinib vs. placebo)	
MDASI-THY: Symptoms[13]	N	Difference[14] [95% CI] p-value AD[2]	N	Difference[14] [95% CI] p-value AD[2]
Pain	231	0.18 [–0.11; 0.46] p = 0.2288	151	–0.01 [–0.43; 0.41] p = 0.9636
Fatigue	231	0.04 [–0.22; 0.30] p = 0.7748	150	–0.06 [–0.47; 0.35] p = 0.7729
Nausea	230	0.78 [0.38; 1.17] p = 0.0001 AD: 0,78[14]	150	0.64 [0.10; 1.18] p = 0.0206 AD: 0,64[14]
Sleep disturbance	229	–0.16 [–0.46; 0.15] p = 0.3087	152	–0.12 [–0.51; 0.27] p = 0.5491
Feeling of distress and despair	231	0.07 [–0.22; 0.37] p = 0.6230	150	–0.15 [–0.56; 0.26] p = 0.4663
Shortness of breath	227	–0.32 [–0.58; –0.06] p = 0.0166 AD: –0.32[14]	151	–0.63 [–0.98; –0.28] p = 0.0005 AD: –0.63[14]
Forgetfulness	230	0.36 [0.09; 0.63] p = 0.0086 AD: 0,36[14]	150	0.16 [–0.37; 0.69] p = 0.5449
Loss of appetite	232	0.79 [0.46; 1.12] p <0.0001 AD: 0,79[14]	151	0.45 [–0.04; 0.95] p = 0.0738
Drowsiness	229	0.15 [–0.14; 0.44] p = 0.3165	151	0.14 [–0.31; 0.59] p = 0.5468
Dry mouth	230	0.61 [0.32; 0.91] p <0.0001 AD: 0,61[14]	151	0.43 [0.05; 0.80] p = 0.0255 AD: 0,43[14]
Feeling of sadness	232	0.05 [–0.27; 0.38] p = 0.7489	152	–0.03 [–0.48; 0.42] p = 0.8893
Vomiting	232	0.27 [–0.10; 0.64] p = 0.1552	152	0.05 [–0.41; 0.51] p = 0.8185
Numbness or tingling sensation	232	0.08 [–0.23; 0.39] p = 0.6050	151	–0.01 [–0.42; 0.40] p = 0.9670
Hoarseness	226	0.11 [–0.18; 0.39] p = 0.4638	149	–0.04 [–0.44; 0.36] p = 0.8446
Problems due to sensation of heat	224	–0.33 [–0.62; –0.04] p = 0.0272 AD: –0.33[14]	149	–0.32 [–0.74; 0.10] p = 0.1385
Rapid heartbeat	225	–0.48 [–0.78; –0.17] p = 0.0023 AD: –0.48[14]	149	–0.37 [–0.77; 0.02] p = 0.0657
Problems due to shivering	227	0.56 [0.21; 0.91] p = 0.0019 AD: 0,56[14]	148	0.82 [0.33; 1.31] p = 0.0012 AD: 0,82[14]
Problems swallowing	227	0.12 [–0.13; 0.37] p = 0.3352	150	–0.02 [–0.37; 0.33] p = 0.9075
Diarrhoea	226	0.20 [–0.12; 0.52] p = 0.2248	149	0.42 [–0.04; 0.88] p = 0.0721

[13] Assessment of each question on a scale of 0 (no impairment) to 10 (total impairment).

[14] Effect estimates of difference between intervention arm and control arm; difference < 0: advantage of cabozantinib; difference 0: disadvantage of cabozantinib.

Endpoint	Difference after 12 weeks (cabozantinib vs. placebo)		Difference after 24 weeks (cabozantinib vs. placebo)	
Quality of life				
MDASI-THY: Quality of life[13]	N	Difference[14] [95% CI] p-value AD[2]	N	Difference[14] [95% CI] p-value AD[2]
General activity	224	0.12 [–0.17; 0.42] p = 0.4139	148	–0.06 [–0.47; 0.35] p = 0.7894
Mood	225	0.01 [–0.27; 0.30] p = 0.9249	149	–0.22 [–0.62; 0.17] p = 0.2677
Work (including housework)	225	–0.13 [–0.42; 0.15] p = 0.3547	150	–0.22 [–0.62; 0.17] p = 0.2698
Relationships to other persons	222	0.37 [0.05; 0.69] p = 0.0222 AD: 0,37[14]	149	–0.16 [–0.61; 0.28] p = 0.4735
Walking	226	0.15 [–0.13; 0.43] p = 0.2888	148	0.02 [–0.35; 0.40] p = 0.8988
Vitality	227	–0.03 [–0.32; 0.25] p = 0.8317	150	0.05 [–0.35; 0.45] p = 0.8178

Endpoint	Intervention arm (cabozantinib) N = 214	Control arm (placebo) N = 109	Intervention vs. control
Patients with at least one event	n (%)	n (%)	RR [95% CI] p-value
Side effects			
AE	214 (100%)	103 (94.5%)	1.06 [1.01; 1.11] p = 0.0143
SAE	90 (42.1%)	25 (22.9%)	1.83 [1.26; 2.68] p = 0.0017
AE CTCAE grade 3 or 4	163 (76.2%)	41 (37.6%)	2.02 [1.57; 2.61] p = 0.0001
Withdrawal due to AE	33 (15.4%)	9 (8.3%)	1.87 [0.93; 3.76] p = 0.0803
Frequent AE/AE of particular interest (all severities)			
Diarrhoea	135 (63.1%)	36 (33.0%)	1.91 [1.44; 2.6][15] p = 0.01[15]
PPE syndrome	107 (50.0%)	2 (1.8%)	27.25 [7.07; 158.79][15] p = 0.01[15]
Weight loss	102 (47.7%)	11 (10.1%)	4.72 [2.65; 9.01][15] p = 0.01[15]
Decrease in appetite	98 (45.8%)	17 (15.6%)	2.94 [1.85; 4.88][15] p = 0.01[15]
Nausea	92 (43.0%)	23 (21.1%)	2.04 [1.37; 3.14][15] p = 0.01[15]
Fatigue	87 (40.7%)	31 (28.4%)	1.43 [1.01; 2.07][15] p = 0.04[15]

Abbreviations used: AD = absolute difference; ECOG PS = Eastern Cooperative Oncology Group Performance Status; CI = confidence interval; MDASI-THY = MD Anderson Symptom Inventory Thyroid Module; n = number of patients with event; N = total number of patients with data on relevant endpoint; n. c. = not calculable; OR = odds ratio; PPE syndrome = palmoplantar erythrodysesthesia (hand-foot syndrome); RR = relative risk; (S)AE = (serious) adverse event

[15] Own calculation.

2. Number of patients and criteria for defining patients groups eligible for treatment

   Target population: approx. 60 to 500 patients

3. Requirements for quality-assured administration

   The specifications outlined in the product information are to be followed. The European Medicines Agency (EMA), the European regulatory authority, provides the contents of the product information for cabozantinib (Cometriq®) at the following publicly accessible link (last accessed: 1 December 2014):

   http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002640/WC500163703.pdf

   Initiation and monitoring of treatment with cabozantinib must be conducted by a specialist for internal medicine, haematology, oncology, endocrinology, or other specialist physician participating in the oncology agreement and experienced in the treatment of patients with medullary thyroid cancer.

   The pharmaceutical has been authorized under a so-called "conditional approval" scheme. That means that additional proof of benefit is expected for this pharmaceutical. The European Medicines Agency will assess new information on this pharmaceutical at least annually and update the product information as needed.

4. Costs of treatment

   Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient	Duration per treatment (days)	Number of treatment days per patient per year
Cabozantinib	1 x daily	ongoing	365	365

   Consumption:

Description of therapy	Dosage per patient per treatment day	Consumption per treatment day	Average annual consumption according to strength
Cabozantinib	140 mg	1 x 80 mg + 3 × 20 mg	365 tablets with 80 mg + 1,095 tablets with 20 mg

   Costs:

   Cost of pharmaceutical:

Description of therapy	Cost per pack[16] (pharmacy retail price)	Cost after legally mandated rebates
Cabozantinib	€7,656.66	€7,220.89 [€1.77[17]; €434.00[18]]

   "Lauer-Taxe", effective: 1 January 2015

   Costs for additional, necessary SHI benefits:

   not applicable

   Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Cabozantinib	€94,129.46

II.

Validity

1. This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 22 January 2015.
2. This resolution remains valid until 1 June 2018.

The justification for this resolution will be published on the websites of the Federal Joint Committee at www.g-ba.de.

Berlin, 22 January 2015

The Federal Joint Committee
in accordance with SGB V,
section 91

The Chair
Hecken

[16] COMETRIQ 20/80 mg 140 mg/day dosage for 28 days (112 hard capsules).
[17] Rebate in accordance with SGB V, section 130.
[18] Rebate in accordance with SGB V, section 130a.