Resolution

Gemeinsamer Bundesausschuss

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 06 June 2019

At its meeting on 06 June 2019, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive) in the version dated 18 December 2008/22 January 2009 (BAnz. No. 49a of 31 March 2009), as last amended onTT. Monat JJJJ (BAnz AT TT.MM.JJJJ BX), as follows:

I. In Annex XII, the following information is to be added after number 4 to the information on the benefit assessment of cabozantinib in accordance with the resolution of 6 December 2018:

Cabozantinib

Resolution from: 06 June 2019
Entry into force on: 06 June 2019
BAnz AT TT. MM JJJJ Bx

New therapeutic indication (according to the marketing authorisation of 12 November 2018):

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

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

Adult patients with hepatocellular carcinoma without curative therapy intent and for whom locoregional therapy is out of the question who have previously received sorafenib

Appropriate comparator therapy:

Best supportive care

Extent and probability of the additional benefit of Cabozantinib compared to the appropriate comparator therapy:

Hint for a minor additional benefit

Study results according to endpoints[1]:

Adult patients with hepatocellular carcinoma without curative therapy intent and for whom locoregional therapy is out of the question who have previously received sorafenib

CELESTIAL study:

Cabozantinib + best supportive care **vs** placebo + best supportive care, third data cut-off

Mortality

Endpoint	**Cabozantinib + Best supportive care**		**Placebo + Best supportive care**		Intervention vs control
	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[a] Absolute difference (AD)[b]
Overall survival					
	512	10.3 [9.1; 11.6] *381 (74.4[c])*	261	8.2 [6.9; 9.6] *197 (75.5[c])*	0.78 [0.66; 0.93] 0.006 + 2.1 months

[1] Data from the dossier evaluation of the Institute for Quality and Efficiency in Health Care (IQWiG) (A18-85) unless otherwise indicated.

Morbidity

Endpoint	Cabozantinib + Best supportive care			Placebo + Best supportive care			Intervention vs control
	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[a] Absolute difference (AD)[b]
Progression-free survival[d]							
	512	4.9 [3.8; 5.5] *414 (81)*		261	1.9 [1.9; 2.0] *241 (92)*		0.45 [0.38; 0.54] < 0.0001 + 3.0 months
	N[e]	Values at start of study MV (SD)	Change at end of study MV (SE)[f]	N[e]	Values at start of study MV (SD)	Change at end of study MV (SE)[f]	MD [95% CI] p value[f]
Health status (EQ-5D VAS)							
Mean change at end of study compared to start of study[g]	447	No data available[h]	−7.35 (1.37)	242	No data available[h]	−2.77 (1.52)	−4.59 [no data available] < 0.001 Hedges' g[i]: −0.26 [−0.41; −0.10]

Health-related quality of life

Endpoint
Not collected

Side effects

Endpoint	Cabozantinib + Best supportive care		Placebo + Best supportive care		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)[k,l]					
	509	8.0 [7.0; 9.0] *505 (99)*	261	15.0 [14.0; 16.0] *250 (96)*	2.23 [1.88; 2.63]

Serious adverse events (SAE)[l]					
	509	10.8 [6.9; 13.3] *230 (45.2[c])*	261	10.5 [6.9; 27.9] *86 (33.0[c])*	1.31 [1.02; 1.69] 0.035 −0.3 months
Severe adverse events (CTCAE grade ≥ 3)[l]					
	509	1.0 [1.0; 1.1] *428 (84.1[c])*	261	4.1 [3.7; 5.6] *132 (50.6[c])*	2.60 [2.13; 3.18] < 0.001 −3.1 months
Withdrawal because of adverse events[l]					
	509	19.7 [13.5; n.c.] *176 (34.6[c])*	261	n.a. [12.6; n.c.] *46 (17.6[c])*	1.64 [1.18; 2.28] 0.003
Specific adverse events					
Nervous system disorders (SOC, CTCAE grade ≥ 3)					
	509	n.a. *46 (9.0)*	261	n.a. *5 (1.9)*	4.10 [1.62; 10.37] 0.001
Reduced appetite (PT, CTCAE grade ≥ 3)					
	509	n.a. *29 (5.7)*	261	n.a. *2 (0.8)*	5.75 [1.36; 24.27] 0.007
Diarrhoea (PT, CTCAE grade ≥ 3)					
	509	n.a. *49 (9.6)*	261	n.a. [15.4; n.c.] *4 (1.5)*	5.34 [1.92; 14.86] < 0.001
Fatigue (PT, CTCAE grade ≥ 3)					
	509	n.a. *56 (11.0[c])*	261	n.a. *10 (3.8)*	2.66 [1.35; 5.24] 0.003
Hypertension (PT, CTCAE grade ≥ 3)					
	509	n.a. [21.9; n.c.] *81 (15.9[c])*	261	n.a. *5 (1.9)*	8.31 [3.36; 20.54] < 0.001
Palmar-plantar erythrodysaesthesia (PT, CTCAE grade ≥ 3)					
	509	n.a. *85 (16.7[c])*	261	n.a. *0 (0)*	n.c.[m] < 0.001
Mucosa inflammation (PT, AEs)					
	509	n.a. *70 (13.8[c])*	261	n.a. *5 (1.9)*	7.40 [2.98; 18.35] < 0.001

Stomatitis (PT, AEs)					
	509	n.a. *70 (13.8 [c])*	261	n.a. *5 (1.9)*	7.34 [2.96; 18.21] < 0.001

[a] HR, CI: stratified Cox regression model; p value: stratified log-rank test; stratification factors: Aetiology of the disease (HBV [with or without HCV], HCV [without HBV], Other), geographical region (Asia, other), and extrahepatic spread of the disease and/or macrovascular invasion (yes, no)
[b] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[c] Calculation of the IQWiG
[d] Data from the dossier of the pharmaceutical company
[e] Number of patients included in the evaluation to calculate the effect estimation.
[f] MMRM stratified according to the following factors: Aetiology of the disease (HBV [with or without HCV], HCV [without HBV], Other), geographical region (Asia, other), and extrahepatic spread of the disease and/or macrovascular invasion (yes, no)
[g] Negative values mean a deterioration of the state of health
[h] At the time of the second data cut-off of 1 June 2017, the following values from the start of the study were available for the patients randomised up to this point in time: 73.53 (18.9) in the cabozantinib arm and 76.15 (16.22) in the comparator arm.
[i] Effect estimation for Hedges' g: Quotient of the mean difference and the pooled standard deviation of both treatment arms from the initial value.
[k] Data from the statement of the pharmaceutical company
[l] Without progress of the underlying disease
[m] HR calculations not possible; relative risk (RR) with reverse effect direction: 0.01; [95% CI]: 0.00; 0.18), calculation of the IQWiG

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life – 5 Dimensions; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HR = hazard ratio; CI = confidence interval; MD = mean value difference; MMRM = mixed model with repeated measurements; MV = mean value; N = number of patients evaluated; n = number of patients with event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; SD = standard deviation; SE = standard error; SOC = system organ class; AE = adverse event; VAS = visual analogue scale; vs = versus

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

Adult patients with hepatocellular carcinoma without curative therapy intent and for whom locoregional therapy is out of the question who have previously received sorafenib

Approx. 1,280–4,900 patients

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.

4. Treatment costs

Annual treatment costs:

Adult patients with hepatocellular carcinoma without curative therapy intent and for whom locoregional therapy is out of the question who have previously received sorafenib

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Cabozantinib	€ 71,938.82
Best supportive care	Different for each individual patient
Appropriate comparator therapy:	
Best supportive care	Different for each individual patient

Cost after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 May 2019)

Costs for additional SHI services required: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 06 June 2019.

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

Berlin, 06 June 2019

Federal Joint Committee
in accordance with Section 91 SGB V
Chair

Prof Hecken