

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 Ramucirumab (New Therapeutic Indication: Hepatocellular Carcinoma)

of 20 February 2020

At its session on 20 February 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on 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 ramucirumab in accordance with the resolution of 20 October 2016:**

Ramucirumab

Resolution of: 20 February 2020
Entry into force on: 20 February 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 1 August 2019):

Cyramza monotherapy is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have a serum alpha fetoprotein (AFP) of ≥ 400 ng/ml and who have been previously treated with sorafenib.

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

Adult patients with advanced or unresectable hepatocellular carcinoma without curative therapy intent and for whom locoregional therapy is not an option who have a serum alpha fetoprotein (AFP) of ≥ 400 ng/ml and who have been previously treated with sorafenib.

Appropriate comparator therapy:

- Best supportive care
- or
- Cabozantinib

Extent and probability of the additional benefit of ramucirumab compared with best supportive care:

Proof of a minor additional benefit

Study results according to endpoints:¹

Adult patients with advanced or unresectable hepatocellular carcinoma without curative therapy intent and for whom locoregional therapy is not an option who have a serum alpha fetoprotein (AFP) of ≥ 400 ng/ml and who have been previously treated with sorafenib.

REACH study: Ramucirumab + BSC vs placebo + BSC (observation of the sub-population of patients with AFP ≥ 400 ng/ml)

REACH-2 study: Ramucirumab + BSC vs placebo + BSC

Total: pooled data of the sub-population of patients with AFP ≥ 400 ng/ml from the REACH study and patients from the REACH 2 study

Mortality

Endpoint	Ramucirumab + BSC		Placebo + BSC		Ramucirumab + BSC vs placebo + BSC
	N	Median survival time in months [95% CI] <i>Patients with event n (%)</i>	N	Median survival time in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value ^a Absolute difference (AD) ^b
Overall survival					
REACH	119	7.82 [5.82; 9.33] 99 (83.2)	131	4.21 [3.68; 4.76] 116 (88.5)	0.67 [0.51; 0.90]; 0.006 ^c + 3.6 months
REACH-2	197	8.51 [7.00; 10.58] 147 (74.6)	95	7.29 [5.42; 9.07] 74 (77.9)	0.71 [0.53; 0.95]; 0.020 ^c + 1.2 months
Total ^d	316	8.08 [6.87; 9.30] 246 (77.8)	226	5.03 [4.34; 6.08] 190 (84.1)	0.69 [0.57; 0.84]; < 0.001 + 3.1 months

¹ Data from the dossier evaluation of the IQWiG (A19-73) and the addendum (A20-03) unless otherwise indicated.

Morbidity

Endpoint	Ramucirumab + BSC		Placebo + BSC		Ramucirumab + BSC vs placebo + BSC
	N	Median survival time in months [95% CI] <i>Patients with event n (%)</i>	N	Median survival time in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value ^a Absolute difference (AD) ^b
Progression-free survival (PFS)^e					
REACH	119	2.7 [1.5; 2.8] 106 (89.1)	131	1.5 [1.4; 2.1] 122 (93.1)	0.70 [0.53; 0.92] 0.0106 ^c +1.2 months
REACH-2	197	2.83 [2.76; 4.11] 172 (87.3)	95	1.61 [1.45; 2.69] 86 (90.5)	0.45 [0.34; 0.60] < 0.0001 ^c +1.2 months
Total ^d	316	2.79 [2.73; 2.83] 278 (88.0)	226	1.54 [1.45; 2.00] 209 (92.5)	0.57 [0.47; 0.69] < 0.0001 +1.3 months
Symptomatology					
REACH					
FHSI-8 (total score) MID ≥ 5 points ^f	119	7.13 [4.17; 21.65] 32 (26.9)	131	2.83 [1.84; 9.03] 46 (35.1)	0.57 [0.36; 0.90] 0.014
REACH-2					
FHSI-8 (total score) MID ≥ 5 points ^f	197	6.97 [4.67; 9.76] 72 (36.5)	95	3.02 [2.79; 6.93] 31 (32.6)	0.65 [0.42; 1.01] 0.056
Total^d					
FHSI-8 (total score) MID ≥ 5 points ^f					0.61 [0.45; 0.84] 0.002
Health status					
REACH					
EQ-5D VAS MID ≥ 7 mm	119	1.87 [1.51; 2.96] 64 (53.8)	131	1.48 [1.45; 1.68] 69 (52.7)	0.810 [0.547; 1.143] 0.2179
EQ-5D VAS MID ≥ 10 mm	119	1.91 [1.51; 2.96] 63 (52.9)	131	1.58 [1.48; 1.84] 66 (50.4)	0.846 [0.596; 1.200] 0.3276

Endpoint	Ramucirumab + BSC		Placebo + BSC		Ramucirumab + BSC vs placebo + BSC
	N	Median survival time in months [95% CI] <i>Patients with event n (%)</i>	N	Median survival time in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value ^a Absolute difference (AD) ^b
REACH-2					
EQ-5D VAS MID ≥ 7 mm	197	2.96 [2.79; 4.67] 96 (48.7)	95	1.87 [1.54; 2.79] 42 (44.2)	0.723 [0.498; 1.049] 0.0851
EQ-5D VAS MID ≥ 10 mm	197	2.96 [2.79; 4.67] 96 (48.7)	95	1.87 [1.54; 2.79] 42 (44.2)	0.715 [0.493; 1.037] 0.0753
Total					
EQ-5D VAS MID ≥ 7 mm	316	2.83 [2.33; 3.25] 160 (50.6)	226	1.64 [1.48; 1.87] 111 (49.1)	0.769 [0.596; 0.991] 0.0388
EQ-5D VAS MID ≥ 10 mm	316	2.86 [2.33; 3.29] 159 (50.3)	226	1.64 [1.51; 1.94] 108 (47.8)	0.782 [0.605; 1.011] 0.0550

Health-related quality of life

Endpoint not recorded

Side effects⁹

Endpoint	Ramucirumab + BSC		Placebo + BSC		Ramucirumab + BSC vs Placebo + BSC
	N	Median in months [95% CI] <i>Patients with event n (%)</i>	N	Median in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value ^a Absolute difference (AD) ^b
Total adverse events (presented additionally)					
REACH	119	0.23 [0.10; 0.39] 115 (96.6)	128	0.43 [0.30; 0.49] 124 (96.9)	-
REACH-2	197	0.33 [0.20; 0.39] 191 (97.0)	95	0.46 [0.26; 0.56] 82 (86.3)	-

Endpoint	Ramucirumab + BSC		Placebo + BSC		Ramucirumab + BSC vs Placebo + BSC
	N	Median in months [95% CI] <i>Patients with event n (%)</i>	N	Median in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value ^a Absolute difference (AD) ^b
Serious adverse events (SAE)					
REACH	119	14.49 [5.85; n.c.] 43 (36.1)	128	6.74 [3.09; n.c.] 47 (36.7)	0.94 [0.62; 1.42]; 0.75
REACH-2	197	16.39 [7.62; n.c.] 66 (33.5)	95	6.14 [3.94; 9.86] 27 (28.4)	0.81 [0.51; 1.29] 0.38
Total ^d	316	14.49 [7.62; n.c.] 109 (34.5)	223	6.74 [3.94; 18.07] 74 (33.2)	0.88 [0.64; 1.20]; 0.41
Severe adverse events (CTCAE grade 3 or 4)					
REACH	119	3.25 [2.00; 7.13] 65 (54.6)	128	2.33 [1.87; 3.42] 74 (57.8)	0.89 [0.64; 1.25]; 0.48
REACH-2	197	3.65 [2.60; 5.16] 116 (58.9)	95	5.06 [2.79; 6.14] 42 (44.2)	1.04 [0.73; 1.49]; 0.84
Total ^d	316	3.61 [2.63; 4.67] 181 (57.3)	223	3.09 [2.33; 3.91] 116 (52.0)	0.96 [0.75; 1.22]; 0.71
Therapy discontinuation because of adverse events					
REACH	119	24.18 [14.62; 24.18] 17 (14.3)	128	n.a. [7,56; n.c.] 13 (10.2)	1.09 [0.52; 2.27]; 0.827
REACH-2	197	19.55 [13.37; n.c.] 35 (17.8)	95	n.a. 10 (10.5)	1.07 [0.51; 2.22]; 0.87
Total ^d	316	19.55 [14.62; n.c.] 52 (16.5)	223	n.a. 23 (10.3)	1.08 [0.64; 1.81]; 0.78
Specific adverse events					
Peripheral oedema (PT, AE)					
REACH	119	7.85 [5.52; n.c.] 42 (35.3)	128	n.a. [6,11; n.c.] 25 (19.5)	1.83 [1.11; 3.01] 0.016
REACH-2	197	16.59 [8.80; n.c.] 50 (25.4)	95	n.a. 13 (13.7)	1.58 [0.85; 2.93] 0.142

Endpoint	Ramucirumab + BSC		Placebo + BSC		Ramucirumab + BSC vs Placebo + BSC
	N	Median in months [95% CI] <i>Patients with event n (%)</i>	N	Median in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value ^a Absolute difference (AD) ^b
Total ^d	316	16.59 [8.77; n.c.] 92 (29.1)	223	n.a. 38 (17.0)	1.73 [1.17; 2.55] 0.005
Reproductive system and breast disorders (SOC, AE)					
REACH	119	no data available 4 (3.3) ^h	128	no data available 0 (0) ^h	n.c. ⁱ ; no data available
REACH-2	197	n.a. [13.57; n.c.] 11 (5.6)	95	n.a. 0 (0)	n.c. ⁱ ; 0.111
Total ^d	316	n.a. 15 (4.7)	223	n.a. 0 (0)	n.c. ⁱ ; 0.022
Renal and urinary disorders (SOC, AE)					
REACH	119	n.a. [7.95; n.c.] 25 (21.0)	128	n.a. [6.74; n.c.] 17 (13.3)	1.35 [0.72; 2.51] 0.35
REACH-2	197	n.a. [9.26; n.c.] 49 (24.9)	95	n.a. [6.44; n.c.] 8 (8.4)	2.27 [1.06; 4.87]; 0.030
Total ^d	316	n.a. [9.26; n.c.] 74 (23.4)	223	n.a. [6.74; n.c.] 25 (11.2)	1.69 [1.05; 2.70]; 0.028
Headache (PT, AE)					
REACH	119	n.a. 25 (21.0)	128	n.a. [7.52; n.c.] 9 (7.0)	3.16 [1.48; 6.78]; 0.002
REACH-2	197	no data available 28 (14.2)	95	no data available 5 (5.3)	2.69 [1.03; 6.97] no data available
Total ^d	316	n.a. 53 (16.8)	223	n.a. 14 (6.3)	2.97 [1.63; 5.41]; < 0.001
Injury, poisoning, and procedural complications (SOC, AE)					
REACH	119	n.a. 11 (9.2)	128	n.a. 5 (3.9)	2.12 [0.73; 6.14]; 0.156
REACH-2	197	22.47 [13.34; 22.47] 26 (13.2)	95	n.a. 4 (4.2)	2.40 [0.83; 7.00]; 0.098

Endpoint	Ramucirumab + BSC		Placebo + BSC		Ramucirumab + BSC vs Placebo + BSC
	N	Median in months [95% CI] <i>Patients with event n (%)</i>	N	Median in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value ^a Absolute difference (AD) ^b
Total ^d	316	22.47 [n.c.] 31 (11.7)	223	n.a. 9 (4.0)	2.26 [1.07; 4.79]; 0.029
Gastrointestinal disorders (SOC, CTCAE grade ≥ 3)					
REACH	119	13.54 [10.15; n.c.] 17 (14.3)	128	18.07 [4.24; n.c.] 27 (21.1)	0.56 [0.30; 1.04]; 0.061
REACH-2	197	n.a. 20 (10.2)	95	9.86 [n.c.] 9 (9.5)	0.74 [0.33; 1.65]; 0.457
Total ^d	316	n.a. [15.41; n.c.] 37 (11.7)	223	18.07 [9.86; n.c.] 36 (16.1)	0.62 [0.38; 1.004]; 0.0499
Hypertension (PT, CTCAE grade ≥ 3)					
REACH	119	n.a. 14 (11.8)	128	n.a. 3 (2.3)	4.60 [1.32; 16.09]; 0.009
REACH-2	197	n.a. 24 (12.2)	95	n.a. 5 (5.3)	1.98 [0.75; 5.23]; 0.161
Total ^d	316	n.a. 38 (12.0)	223	n.a. 8 (3.6)	2.87 [1.32; 6.24]; 0.006
Hyperbilirubinaemia (PT, CTCAE grade ≥ 3)					
REACH	119	n.a. 3 (2.5)	128	15.87 [15.87; n.c.] 12 (9.4)	0.22 [0.06; 0.78] 0.010 n.c.
REACH-2	197	n.a. 0 (0)	95	n.a. 0 (0)	n.c.
Total ^d	316	n.a. 3 (0.9)	223	15.87 [15.87; n.c.] 12 (5.4)	0.22 [0.06; 0.78]; 0.010
Investigations (SOC, CTCAE grade ≥ 3)					
REACH	119	n.a. 16 (13.4)	128	n.a. [6.44; n.c.] 29 (22.7)	0.52 [0.28; 0.96]; 0.034

Endpoint	Ramucirumab + BSC		Placebo + BSC		Ramucirumab + BSC vs Placebo + BSC
	N	Median in months [95% CI] <i>Patients with event n (%)</i>	N	Median in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value ^a Absolute difference (AD) ^b
REACH-2	197	17.51 [11.99; n.c.] 28 (14.2)	95	n.a. 11 (11.6)	0.68 [0.32; 1.42]; 0.295
Total ^d	316	n.a. [13.83; n.c.] 44 (13.9)	223	n.a. [8.25; n.c.] 40 (17.9)	0.58 [0.36; 0.92]; 0.020
Bleedings/haemorrhages (pre-specified set of PTs)					
REACH	119	13.37 [5.55; n.c.] 31 (26.1)	128	16.62 [4.24; n.c.] 28 (21.9)	1.10 [0.66; 1.85]; 0.717
REACH-2	197	19.55 [11.99; n.c.] 48 (24.4)	95	9.86 [n.c.] 12 (12.6)	1.46 [0.77; 2.78]; 0.242
Total ^d	316	13.83 [11.99; n.c.] 79 (25.0)	223	16.62 [9.86; n.c.] 40 (17.9)	1.24 [0.83; 1.84]; 0.296
Hepatic encephalopathy (PT, SAE)					
REACH	119	n.a. 3 (2.5)	128	n.a. 0 (0)	n.c. ⁱ ; 0.071
REACH-2	197	n.a. 3 (1.5)	95	n.a. 0 (0)	n.c. ⁱ ; 0.431
Total ^d	316	n.a. 6 (1.9)	223	n.a. 0 (0)	n.c. ⁱ ; 0.053
<p>^a Unless otherwise stated, HR and CI: unstratified Cox proportional hazards model; p value: unstratified log-rank test; for pooled analysis stratified by study</p> <p>^b Absolute difference (AD) given only in the case of a statistically significant difference; own calculation</p> <p>^c Analysis stratified by the randomisation strategies of the respective study</p> <p>^d IPD meta-analysis</p> <p>^e Data from the dossier of the pharmaceutical company</p> <p>^f Time to first deterioration; defined as a decrease of the score by ≥ 5 points compared with baseline</p> <p>^g Events that are attributable to the progression of the underlying disease are also recorded as AEs.</p> <p>^h Calculation of the IQWiG</p> <p>ⁱ Because no event occurred in at least 1 treatment arm, the HR cannot be estimated.</p> <p>^k Contains the PTs increased aspartate aminotransferase and increased bilirubin in the blood.</p> <p>Abbreviations used: AD = absolute difference; BSC = best supportive care; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life – 5 Dimensions; FHSI-8 = FACT Hepatobiliary Symptom Index-8; HR = hazard ratio; IPD = individual patient data; CI = confidence interval; MID = minimal important difference; mm = millimetre; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = Preferred Term; SOC</p>					

= system organ class; SAE = serious adverse event; AE: adverse event; VAS = visual analogue scale; vs = versus

Summary of results for relevant clinical endpoints

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

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

Adult patients with advanced or unresectable hepatocellular carcinoma without curative therapy intent and for whom locoregional therapy is not an option who have a serum alpha fetoprotein (AFP) of ≥ 400 ng/ml and who have been previously treated with sorafenib.

approx. 500 to 2,200 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 Cyramza® (active ingredient: ramucirumab) at the following publicly accessible link (last access: 28 October 2019):

https://www.ema.europa.eu/en/documents/product-information/cyramza-epar-product-information_de.pdf

Treatment with ramucirumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, 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 advanced or unresectable hepatocellular carcinoma without curative therapy intent and for whom locoregional therapy is not an option who have a serum alpha fetoprotein (AFP) of ≥ 400 ng/ml and who have been previously treated with sorafenib.

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ramucirumab	€ 74,410.58
+ best supportive care ²	different for each individual patient
Appropriate comparator therapy:	
Best supportive care	
Best supportive care	different for each individual patient
Cabozantinib	
Cabozantinib	€ 65,515.31
+ best supportive care ²	different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2020

Costs for additionally required SHI services: not applicable

² The costs for best supportive care are also shown here, as best supportive care also represents an independent appropriate comparator therapy.

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Ramucirumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.1

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 20 February 2020.

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

Berlin, 20 February 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken