Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee 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 Encorafenib (New Therapeutic Indication: Metastatic Colorectal Cancer with a BRAF V600E Mutation after Prior Systemic Therapy; in Combination with Cetuximab)

of 17 December 2020

At its session on 17 December 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 encorafenib in accordance with the resolution of 22 March 2019:

Encorafenib

Resolution of: 17 December 2020
Entry into force on: 17 December 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 2 June 2020):

Encorafenib is indicated in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.

Therapeutic indication of the resolution (resolution of 17 December 2020):

See new therapeutic indication according to marketing authorisation

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

Adult patients with metastatic colorectal cancer with a BRAF V600E mutation, who have received prior systemic therapy

Appropriate comparator therapy for encorafenib in combination with cetuximab:

- A patient-individual therapy with the selection of
  - 5-fluorouracil + folinic acid + oxaliplatin ± bevacizumab
  - Capecitabine + oxaliplatin ± bevacizumab
  - 5-fluorouracil + folinic acid + irinotecan ± aflibercept or ramucirumab or bevacizumab or cetuximab or panitumumab
  - Irinotecan ± cetuximab or panitumumab
  - Trifluridine/tipiracil
  - 5-fluorouracil ± bevacizumab
  - Capecitabine ± bevacizumab
- taking into consideration the general condition and the type and number of previous therapies.

Extent and probability of the additional benefit of encorafenib in combination with cetuximab compared with irinotecan + cetuximab and FOLIRI + cetuximab:

Hint for a considerable additional benefit

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
Morbidity	↑	Advantage in the endpoint diarrhoea
Health-related quality of life	↔	No statistically significant or relevant difference
Side effects	↑	Advantages for severe and serious AEs and discontinuation because of AE
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 (A20-56) unless otherwise indicated.

BEACON CRC study (unblinded RCT): Encorafenib + cetuximab **vs** irinotecan + cetuximab or FOLFIRI + cetuximab

Endpoint	Encorafenib + cetuximab		Irinotecan + cetuximab or FOLFIRI + cetuximab		Encorafenib + cetuximab **vs** Irinotecan + cetuximab or FOLFIRI + cetuximab
	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 Absolute difference (AD)[b]
Mortality					
Overall survival					
	220	9.3 [8.0; 11.3] 128 (58.2)	221	5.9 [5.1; 7.1] 157 (71.0)	0.61 [0.48; 0.77] < 0.001[a] AD: 3.4 months
Morbidity					
Progression-free survival (PFS)[c]					
PFS (BICR)	220	4.3 [4.1; 5.5] 167 (75.9)	221	1.5 [1.5; 1.9] 147(66.5)	0.44 [0.35; 0.55]; < 0.0001 [a] AD: 2.8 months

a. HR [95% CI] from stratified Cox regression model, p value based on stratified log rank test; stratified by ECOG-PS (0 vs 1), previous treatment with irinotecan (yes vs no), and cetuximab source (US marketing authorisation vs EU marketing authorisation).
b. Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
c. Data from the dossier of the pharmaceutical company.

BICR: blinded independent review committee; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; CI: confidence interval; N: number of patients evaluated; n: number of patients with (at least one) event; RCT: randomised controlled trial; vs: versus

Endpoint	Encorafenib + cetuximab			Irinotecan + cetuximab or FOLFIRI + cetuximab			Encorafenib + cetuximab **vs** Irinotecan + cetuximab or FOLFIRI + cetuximab
	N	Values at the start of study MV (SD)	Mean change during the course of the study MW[a] [95% CI]	N	Values at the start of study MV (SD)	Mean change during the course of the study MV[a] [95% CI]	MD [95% CI][b] p value Hedges' g [95% CI]
Morbidity							
Symptomatology							
Health status (EQ-5D VAS)[d, e]	194	67.5 (19.0)	0.90 [−1.00; 2.80]	166	68.7 (18.6)	−2.35 [−5.15; 0.45]	3.25 [−0.13; 6.62]; 0.059
Symptomatology (EORTC QLQ−C30)[f, e]							
Fatigue	190	39.8 (25.3)	1.90 [−0.34; 4.27]	167	38.5 (24.9)	4.61 [1.16; 8.05]	−2.64 [−6.77; 1.50]; 0.209
Nausea and vomiting	189	8.4 (16.4)	−0.27 [−2.02; 1.48]	167	11.5 (20.7)	4.35 [1.75; 6.94]	−4.62 [−7.75; −1.48] 0.004 Hedges' g [95% CI] −0.31 [−0.52; −0.11]
Pain	191	33.3 (30.1)	−1.03 [−3.57; 1.51]	167	33.2 (30.3)	1.70 [−2.27; 5.67]	−2.73 [−7.44; 1.97]; 0.254
Dyspnoea	189	16.6 (25.9)	2.05 [−0.36; 4.47]	167	16.6 (24.0)	6.27 [2.78; 9.76]	−4.22 [−8.46; 0.02]; 0.051
Insomnia	190	27.5 (31.0)	3.00 [0.12; 5.89]	167	33.1 (30.9)	−0.81 [−5.26; 3.65]	3.81 [−1.50; 9.12]; 0.158
Loss of appetite	189	24.7 (30.4)	−1.57 [−4.43; 1.29]	167	25.2 (30.1)	5.15 [0.63; 9.68]	−6.72 [−12.07; −1.38]; 0.014 Hedges' g [95% CI] −0.27 [−0.48; −0.06]
Constipation	190	17.0 (27.4)	−1.56 [−4.00; 0.88]	166	18.5 (29.0)	4.12 [0.46; 7.78]	−5.68 [−10.08; −1.28]; 0.012 Hedges' g

							[95% CI] −0.28 [−0.48; −0.07]
Diarrhoea	189	17.6 (24.0)	−5.24 [−7.93; −2.55]	167	16.0 (21.3)	7.37 [2.99; 11.76]	−12.61 [−17.75; −7.47]; < 0.001 Hedges' g [95% CI] −0.53 [−0.74; −0.31]
Health-related quality of life							
EORTC QLQ−C30[d]							
Global health status	193	61.7 (20.8)	0.29 [−1.70; 2.29]	166	62.3 (21.8)	−3.62 [−6.69; −0.55]	3.92 [0.26; 7.57]; 0.036 Hedges' g [95% CI] 0.23 [0.02; 0.44]
Physical functioning	189	74.1 (20.6)	−2.59 [−4.85; −0.33]	167	75.5 (20.2)	−5.46 [−8.80; −2.12]	2.86 [−1.16; 6.89]; 0.162
Role functioning	191	69.1 (29.9)	−2.42 [−5.13; 0.29]	167	72.5 (28.3)	−6.35 [−10.50; −2.19]	3.92 [−1.03; 8.88]; 0.120
Emotional functioning	190	74.1 (21.9)	2.75 [0.61; 4.89]	167	74.3 (22.2)	0.46 [−2.68; 3.60]	2.28 [−1.51; 6.08]; 0.237
Cognitive functioning	190	84.4 (19.7)	−1.93 [−4.05; 0.19]	167	83.2 (19.1)	−2.54 [−5.64; 0.55]	0.61 [−3.14; 4.36]; 0.748
Social functioning	190	71.5 (26.9)	−0.29 [−2.84; 2.26]	167	74.9 (24.3)	−2.95 [−6.56; 0.67]	2.66 [−1.77; 7.08]; 0.238
FACT-C[d]							
FACT-G total score	191	75.0 (14.9)	−0.09 [−1.67; 1.49]	165	76.0 (16.5)	−3.87 [−6.09; −1.64]	3.78 [1.05; 6.50]; 0.007 Hedges' g [95% CI] 0.29 [0.09; 0.50]
Physical well-being	193	20.5 (5.5)	−0.02 [−0.55; 0.51]	166	20.9 (5.3)	−1.64 [−2.40; −0.89]	1.62 [0.70; 2.54]; < 0.001 Hedges' g [95% CI] 0.37 [0.16; 0.58]

Social/familiar well-being	193	22.0 (5.2)	−0.72 [−1.25; −0.20]	167	22.3 (5.3)	−1.42 [−2.15; −0.69]	0.69 [−0.20; 1.59]; 0.129
Emotional well-being	191	16.3 (4.3)	1.19 [0.77; 1.60]	166	16.0 (5.0)	0.95 [0.34; 1.56]	0.24 [−0.50; 0.97]; 0.527
Functional well-being	191	16.2 (5.9)	−0.70 [−1.32; −0.08]	167	17.0 (6.1)	−1.47 [−2.38; −0.56]	0.77 [−0.33; 1.87]; 0.169

a. Estimated per MMRM analysis
b. MMRM analysis adjusted for time (continuous), treatment time and value at the start of study with change from the start of study as dependent variable and unstructured covariance matrix. Values from the end-of-treatment survey and the 30-day follow-up are not included in the analysis.
c. Standardised adjusted mean difference; shown only if the adjusted mean difference from the MMRM analysis is statistically significant
d. Higher (increasing) values mean better quality of life/better health status; if the calculated effects (intervention minus control) are positive, this means an advantage for the intervention.
e. Time to permanent deterioration.
f. Lower (decreasing) values mean a lower burden of symptoms; if the calculated effects (intervention minus control) are negative, this means an advantage for the intervention.

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: European Quality of Life 5 Dimensions; FACT-C: Functional Assessment of Cancer Therapy – Colon Cancer; FACT-G: Functional Assessment of Cancer Therapy – General; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; CI: confidence interval; MD: mean difference; MMRM: mixed model with repeated measurements; MV: mean value; N: number of patients evaluated; SD: standard deviation; SMD: standardised mean difference; VAS: visual analogue scale

Endpoint	Encorafenib + cetuximab		Irinotecan + cetuximab or FOLFIRI + cetuximab		Encorafenib + cetuximab **vs** Irinotecan + cetuximab or FOLFIRI + cetuximab
	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[b]
Side effects[a]					
Adverse events in total					
	216	0.1 [0.0; 0.1] 212 (98.1)	193	0.1 [0.1; 0.1] 190 (98.4)	
Serious adverse events (SAE)					
	216	12.0 [6.9; n.c.] 86 (39.8)	193	5.2 [3.2; n.c.] 77 (39.9)	0.65 [0.47; 0.89]; 0.008
Severe adverse events (CTCAE grade 3 or 4)					
	216	4.7 [3.9; 6.4] 124 (57.4)	193	1.4 [1.1; 2.1] 124 (64.2)	0.47 [0.36; 0.62]; < 0.001
Therapy discontinuations because of adverse events[c]					
	216	n.a. [17.5; n.c.] 26 (12.0)	193	n.a. [8.1; n.c.] 33 (17.1)	0.36 [0.21; 0.63]; < 0.001
Specific adverse events					
Skin and subcutaneous tissue disorders (SOC)					
AEs	216	0.9 [0.7; 1.2] 164 (75.9)	193	0.5 [0.4; 0.6] 141 (73.1)	0.71 [0.57; 0.90]; 0.005
Severe AEs (CTCAE grade ≥ 3)	216	n.a. 7 (3.2)	193	n.a. 12 (6.2)	0.37 [0.14; 0.96]; 0.035

a. Results are based on the safety population (i.e. all patients who received at least one dose of study medication);
b. HR [95% CI] from unstratified Cox regression model; p value from unstratified log rank test.
c. Discontinuation of at least 1 of the components

CTCAE: Common Terminology Criteria for Adverse Events; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; CI: confidence interval; N: number of patients evaluated; n: number of patients with (at least one) event; N: number of patients evaluated; n.c.: not calculable; n.a.:not achieved; SOC: system organ class; SAE: serious adverse event; AE: adverse event; vs: versus

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

approx. 525–1,235 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 Braftovi (active ingredient: encorafenib) at the following publicly accessible link (last access: 10 December 2020):
https://www.ema.europa.eu/documents/product-information/braftovi-epar-product-information_de.pdf

Treatment with encorafenib in combination with cetuximab should be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and gastroenterology, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with metastatic colorectal cancer.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Encorafenib	€ 55,445.06
Cetuximab	€ 72,253.26
Total:	€ 127,698.32
Appropriate comparator therapy:	
FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) ± bevacizumab	
FOLFOX 4	
Oxaliplatin	€ 4,425.72
Folinic acid	€ 4,197.56
5-fluorouracil	€ 481.18
Total:	€ 9,104.46
Bevacizumab	€ 37,237.13 – 74,474.26
FOLFOX 4 + bevacizumab	€ 46,341.59 – 83,578.72
FOLFOX 6	
Oxaliplatin	€ 4,425.72
Folinic acid	€ 3,226.72
5-fluorouracil	€ 481.18

Designation of the therapy	Annual treatment costs/patient
Total:	€ 8,133.62
CAPOX (capecitabine + oxaliplatin) ± bevacizumab	
CAPOX	
Oxaliplatin	€ 5,860.64
Capecitabine	€ 1,021.48
Total:	€ 6,882.12
Bevacizumab	€ 37,478.73
CAPOX + bevacizumab	€ 44,360.85
FOLFIRI (5-fluorouracil, folinic acid, irinotecan) ± aflibercept or ramucirumab or bevacizumab or cetuximab or panitumumab	
FOLFIRI	
Irinotecan	€ 16,448.48
Folinic acid	€ 7,003.31
5-fluorouracil	€ 1,014.77
Total:	€ 24,466.56
Aflibercept	€ 39,069.61
FOLFIRI + aflibercept	€ 63,536.17
Ramucirumab	€ 72,421.50
FOLFIRI + ramucirumab	€ 96,888.06
Bevacizumab	€ 37,237.13
FOLFIRI + bevacizumab	€ 61,703.69
Cetuximab	€ 72,253.26
FOLFIRI + cetuximab	€ 96,719.82
Panitumumab	€ 77,263.57
FOLFIRI + panitumumab	€ 101,730.13
Irinotecan ± cetuximab or panitumumab	
Irinotecan monotherapy	€ 21,429.32
Irinotecan + cetuximab or panitumumab	
Irinotecan	€ 12,690.60
Cetuximab	€ 72,253.26
Irinotecan + cetuximab	€ 84,943.86
Irinotecan	€ 12,690.60
Panitumumab	€ 77,263.57
Irinotecan + panitumumab	€ 89,954.17
Trifluridine/tipiracil	
Trifluridine/tipiracil	€ 42,876.08
5-fluorouracil ± bevacizumab	

Designation of the therapy	Annual treatment costs/patient
5-fluorouracil	€ 1,014.77
Folinic acid	€ 9,032.01
Bevacizumab	€ 37,237.13
5-fluorouracil + folinic acid + bevacizumab	€ 47,283.91
Capecitabine ± bevacizumab	
Capecitabine	€ 2,700.71
Bevacizumab	€ 37,478.73
Capecitabine + bevacizumab	€ 40,179.44

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

Costs for additionally required SHI services: None

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Cetuximab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	52.1	€ 3,699.10
Appropriate comparator therapy:					
FOLFOX 4					
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	12	€ 972
Folinic acid	Surcharge for the preparation of a parenteral calcium folinate solution	€ 39	2	24	€ 936
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	24	€ 1,944
FOLFOX 6					
Oxaliplatin	Surcharge for production of a	€ 81	1	12	€ 972

	parenteral preparation containing cytostatic agents				
Folinic acid	Surcharge for the preparation of a parenteral calcium folinate solution	€ 39	1	12	€ 468
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	12	€ 972
CAPOX					
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	8	€ 648
FOLFIRI					
Irinotecan	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
Folinic acid	Surcharge for the preparation of a parenteral calcium folinate solution	€ 39	1	26.1	€ 1,017.90
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
5-fluorouracil (de Gramont)					
Folinic acid	Surcharge for the preparation of a parenteral calcium folinate solution	€ 39	2	52.2	€ 2,035.80
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	52.2	€ 4,228.20
Combination and monotherapies					
Bevacizumab (14-day cycle)	Surcharge for the preparation of	€ 71	1	26.1	€ 1,853.10

	parenteral solutions with monoclonal antibodies				
Bevacizumab (21-day cycle)	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	17.4	€ 1,235.40
Ramucirumab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
Aflibercept	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
Irinotecan	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Irinotecan (in combination with cetuximab or panitumumab)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
Cetuximab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	52.1	€ 3,699.10
Panitumumab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	26.1	€ 1,853.10

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 17 December 2020.

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

Berlin, 17 December 2020

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

Prof. Hecken