Resolution

Gemeinsamer Bundesausschuss

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: NSCLC, First- Line, EGFR Mutation, Combination with Erlotinib)

of 20 August 2020

At its session on 20 August 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 February 2020:

Ramucirumab

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

New therapeutic indication (according to the marketing authorisation of 23 January 2020):

Cyramza in combination with erlotinib is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations

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

a) Adult patients with metastatic NSCLC with the activating EGFR mutations L858R[1] or del 19[2]; first-line therapy:

Appropriate comparator therapy:

Afatinib or gefitinib or erlotinib or osimertinib

Extent and probability of the additional benefit of ramucirumab in combination with erlotinib compared with erlotinib:

An additional benefit is not proven.

b) Adult patients with metastatic NSCLC with activating EGFR mutations other than L858R[1] or del 19[2]; first-line therapy:

Appropriate comparator therapy:

A patient-individual therapy depending on the activating EGFR mutation with selection of:

- Afatinib, gefitinib, erlotinib, osimertinib
- Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)
- Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed; *cf* Annex VI to Section K of the Pharmaceuticals Directive)
- Carboplatin in combination with nab-paclitaxel

and

- Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment).

Extent and probability of the additional benefit of ramucirumab in combination with erlotinib compared with the appropriate comparator therapy:

[1] Exon 21 substitution mutation
[2] Exon 19 deletion

An additional benefit is not proven.

Study results according to endpoints:

a) Adult patients with metastatic NSCLC with the activating EGFR mutations L858R or del 19; first-line therapy:

RELAY study: Ramucirumab + erlotinib **vs** placebo + erlotinib[3,4]

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

Mortality

Endpoint	**Ramucirumab + erlotinib**		**Erlotinib**		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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	224	n.a. 37 (16.5)	225	n.a. 42 (18.7)	0.83 [0.53; 1.30] 0.421

Morbidity

Endpoint	**Ramucirumab + erlotinib**		**Erlotinib**		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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS)[b]					
	224	19.4 [15.38; 21.55] 122 (54.5)	225	12.4 [10.97; 13.50] 158 (70.2)	0.59 [0.46; 0.76] < 0.0001 7.0 months
Disease symptomatology					
LCSS ASBI (time to first deterioration)[c]					
≥ 15 mm	224	28.1 [24.6; n.c.] 75 (33.5)	225	n.a. [16.7; n.c.] 72 (32.0)	0.96 [0.68; 1.34] 0.786

[3] Data from the dossier assessment of the IQWiG (A20-13) unless otherwise indicated.
[4] Data cut-off 23 January 2019

Health status					
EQ-5D VAS (time to first deterioration)[d]					
≥ 7 mm	224	7.2 [3.8; 15.0] 122 (54.5)	225	5.3 [3.3; 8.8] 126 (56.0)	0.93 [0.72; 1.21] 0.594
≥ 10 mm	224	7.4 [4.2; 15.0] 121 (54.0)	225	5.4 [3.3; 10.6] 124 (55.1)	0.95 [0.74; 1.23] 0.704

Endpoint	**Ramucirumab + erlotinib**			**Erlotinib**			Intervention vs control
	N[e]	Values at start of study MV (SD)	Mean Change via the Follow-up surveys MV (SE)	N[e]	Values at start of study MV (SD)	Mean Change via the Follow-up surveys MV (SE)	MD [95% CI] p value
Disease symptomatology							
LCSS ASBI[f]							
	216	21.1 (15.2)	−4.6 (0.7)	216	18.3 (14.6)	−5.2 (0.7)	0.58 [−1.43; 2.59] 0.572
Health status							
EQ-5D VAS[g]							
	218	75.1 (17.1)	2.6 (0.9)	219	77.6 (16.7)	1.6 (0.9)	1.00 [−1.37; 3.38] 0.408

Health-related quality of life

Endpoint not surveyed

Side effects

Endpoint	Ramucirumab + erlotinib		Erlotinib		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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Adverse events (AE) (presented additionally)					
	221	0.2 [0.1; 0.2] 221 (100)	225	0.2 [0.1; 0.2] 225 (100)	-
Serious adverse events (SAE)					
	221	n.a. [25.8; n.c.] 65 (29.4)	225	n.a. 47 (20.9)	1.40 [0.96; 2.03] 0.081
Severe adverse events (CTCAE grade ≥ 3)					
	221	3.9 [2.5; 4.3] 159 (71.9)	225	12.0 [6.2; 20.9] 121 (53.8)	1.58 [1.25; 2.00] < 0.001 8.1 months
Discontinuation because of AE					
	221	n.a. 28 (12.7)	225	n.a. 24 (10.7)	1.13 [0.66; 1.96] 0.650
Specific adverse events					
Peripheral oedema (PT, AE)	221	33.1 [33.1; n.c.] 50 (22.6)	225	n.a. 10 (4.4)	5.24 [2.65; no data available[h]] < 0.001
Diarrhoea (PT, severe AE with CTCAE grade ≥ 3)	221	n.a. 16 (7.2)	225	n.a. 3 (1.3)	5.36 [1.56; no data available[h]] 0.003
Hypertension (PT, severe AE with CTCAE grade ≥ 3)	221	n.a. 52 (23.5)	225	n.a. 12 (5.3)	4.56 [2.43; 8.54] < 0.001
Infections and infestations (SOC, severe AE) with CTCAE grade ≥ 3)	221	33.4 [33.4; n.c.] 38 (17.2)	225	n.a. 15 (6.7)	2.52 [1.39; 4.59] 0.002

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation

[b] Data from: dossier on ramucirumab Module 4A from 14 February 2020, data cut-off of 23 January 2019
[c] Time to first deterioration; defined as an increase of the score by ≥ 15 mm compared with baseline
[d] Time to first deterioration; defined as a decrease of the score by ≥ 7 or ≥ 10 mm compared with baseline
[e] Number of patients included in the evaluation to calculate the effect estimate; values at the start of study may be based on other patient numbers.
[f] Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for intervention
[g] Higher (increasing) values indicate better health status; positive effects (intervention minus control) indicate an advantage for intervention
[h] According to the pharmaceutical company > 9.99

Abbreviations used:
AD = absolute difference; ASBI = Average Symptom Burden Index; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D = European Quality of Life Questionnaire – 5 Dimensions; HR = hazard ratio; CI = confidence interval; LCSS = Lung Cancer Symptom Scale; MD = mean difference; MMRM = mixed model with repeated measurements; MV = mean value; N = number of patients assessed; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT: preferred term; SD = standard deviation; SE = standard error; SOC = 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	↔	No difference relevant for the benefit assessment
Morbidity	↔	No differences relevant for the benefit assessment
Health-related quality of life	∅	No data available.
Side effects	↓↓	Disadvantage in the endpoint severe AE (CTCAE grade ≥ 3) as well as in detail for specific 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

b) Adult patients with metastatic NSCLC with activating EGFR mutations other than L858R or del 19; first-line therapy:

There is no data that would allow for the assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

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

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

a) Adult patients with metastatic NSCLC with the activating EGFR mutations L858R or del 19; first-line therapy:

approx. 690 to 1,560 patients

b) Adult patients with metastatic NSCLC with activating EGFR mutations other than L858R or del 19; first-line therapy:

approx. 90 to 250 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: 7 May 2020):

https://www.ema.europa.eu/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 internal medicine and pneumology, specialists in pulmonary medicine, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with non-small cell lung cancer.

If the use of ramucirumab is considered, the EGFR mutation status must be determined by a validated test procedure.

4. Treatment costs

Annual treatment costs:

a) Adult patients with metastatic NSCLC with the activating EGFR mutations L858R or del 19; first-line therapy:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ramucirumab	€ 82,971.64
Erlotinib	€ 15,087.40
Total:	€ 98,059.04
Appropriate comparator therapy:	
Afatinib	€ 30,105.59
Erlotinib	€ 15,087.40
Gefitinib	€ 9,952.09
Osimertinib	€ 68,749.82

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

b) Adult patients with metastatic NSCLC with activating EGFR mutations other than L858R or del 19; first-line therapy:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ramucirumab	€ 82,971.64
Erlotinib	€ 15,087.40
Total:	€ 98,059.04
Appropriate comparator therapy: a patient-individual therapy depending on the activating EGFR mutation with selection of:	
Afatinib, gefitinib, erlotinib, osimertinib	
Afatinib	€ 30,105.59
Erlotinib	€ 15,087.40
Gefitinib	€ 9,952.09

Designation of the therapy	Annual treatment costs/patient
Osimertinib	€ 68,749.82
Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)	
Cisplatin plus docetaxel	
Cisplatin	€ 1,953.32
Docetaxel	€ 20,617.61
Total:	€ 22,570.93
Additionally required SHI services:	€ 319.71 – 410.31
Cisplatin plus gemcitabine	
Cisplatin	€ 1,953.32 – 2,419.30
Gemcitabine	€ 7,973.38
Total:	€ 9,926.70 – 10,392.68
Additionally required SHI services:	€ 319.71 – 410.31
Cisplatin plus paclitaxel	
Cisplatin	€ 2,209.97
Paclitaxel	€ 19,915.34
Total:	€ 22,125.31
Additionally required SHI services:	€ 543.93 – 634.53
Cisplatin plus pemetrexed	
Cisplatin	€ 1,953.32
Pemetrexed	€ 67,146.25
Total:	€ 69,099.57
Additionally required SHI services:	€ 442.51 – 578.80
Cisplatin plus vinorelbine	
Cisplatin	€ 1,953.32 – 2,419.30
Vinorelbine	€ 4,592.00 – 5,535.57
Total:	€ 6,545.32 – 7,954.87
Additionally required SHI services:	€ 319.71 – 410.31
Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)	
Carboplatin plus docetaxel	
Carboplatin	€ 8,484.94
Docetaxel	€ 20,617.61
Total:	€ 29,102.55

Designation of the therapy	Annual treatment costs/patient
Carboplatin plus gemcitabine	
Carboplatin	€ 8,484.94
Gemcitabine	€ 7,973.38
Total:	€ 16,458.32
Carboplatin plus paclitaxel	
Carboplatin	€ 8,484.94
Paclitaxel	€ 19,915.34
Total:	€ 28,400.28
Additionally required SHI services:	€ 224.22
Carboplatin plus pemetrexed	
Carboplatin	€ 8,484.94
Pemetrexed	€ 67,146.25
Total:	€ 75,631.19
Additionally required SHI services:	€ 122.80 – 168.50
Carboplatin plus vinorelbine	
Carboplatin	€ 8,484.94
Vinorelbine	€ 4,592.00 – 5,535.57
Total:	€ 13,076.94 – € 14,020.51
Carboplatin plus nab-paclitaxel	
Carboplatin	€ 8,484.94
nab-paclitaxel	€ 37,958.80
Total:	€ 46,443.74
Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment).	
Gemcitabine	€ 6,966.18
Vinorelbine	€ 6,874.80 – € 8,287.44

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

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs per unit	Number per cycle	Number per patient per year[5]	Costs per patient per year
Medicinal product to be assessed:					
Ramucirumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
Appropriate comparator therapy:					
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Vinorelbine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	34.8	€ 2,818.80
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	34.8	€ 2,818.80
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
nab-paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	52.2	€ 4,228.20
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Gemcitabine (monotherapy)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	39	€ 3,159.00

[5] Calculated and standardised for one year

Designation of the therapy	Type of service	Costs per unit	Number per cycle	Number per patient per year[5]	Costs per patient per year
Vinorelbin (monotherapy)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	52.1	€ 4,220.10

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 20 August 2020.

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

Berlin, 20 August 2020

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

Prof. Hecken