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 Dacomitinib

of 17 October 2019

At its session on 17 October 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, 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. Annex XII shall be amended in alphabetical order to include the active ingredient dacomitinib as follows:

Dacomitinib

Resolution of: 17 October 2019
Entry into force on: 17 October 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 2 April 2019):

Vizimpro, as monotherapy, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations.

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

a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with the activating EGFR mutations L858R[1] or del 19[2]:

Appropriate comparator therapy:

Afatinib or gefitinib or erlotinib or osimertinib

Extent and probability of the additional benefit of dacomitinib compared with gefitinib:

An additional benefit is not proven.

a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19:

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).

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

Extent and probability of the additional benefit of dacomitinib compared with the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:

a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19:

ARCHER 1050 study: dacomitinib vs gefitinib[3,4]

Study design: randomised, open, two-armed

Mortality

Endpoint	Dacomitinib		Gefitinib		Dacomitinib vs gefitinib
	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					
	227	34.1 [29.5; 37.7] 103 (45.5)	225	26.8 [23.7; 32.1] 117 (52.0)	0.76 [0.58; 0.99] 0.044 7.3 months

Morbidity

Endpoint	Dacomitinib		Gefitinib		Dacomitinib vs gefitinib
	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]					
	227	14.7 [11.1; 16.6] 136 (59.9)	225	9.2 [9.1; 11.0] 179 (79.6)	0.59 [0.47; 0.74] p < 0.0001 5.5 months
Disease symptoms – time until once confirmed deterioration[c]					

[3] Data from the dossier evaluation of the IQWiG (A19-39) unless otherwise indicated.
[4] data cut-off 17 February 2017

Endpoint	Dacomitinib		Gefitinib		Dacomitinib vs gefitinib
	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]
Symptom scales of the EORTC QLQ-C30					
Fatigue	226	29.0 [15.0; n.c.] 92 (40.7)	222	n.a. [20.8; n.c.] 75 (33.8)	1.30 [0.95; 1.76] 0.090
Nausea and vomiting	226	n.a. 50 (22.1)	222	n.a. 35 (15.8)	1.44 [0.93; 2.22] 0.099
Pain	226	33.7 [17.7; n.c.] 87 (38.5)	222	n.a. [24.9; n.c.] 68 (30.6)	1.40 [1.02; 1.93] 0.036
Dyspnoea	226	n.a. 50 (22.1)	222	n.a. 44 (19.8)	1.03 [0.68; 1.55] 0.897
Insomnia	226	n.a. 51 (22.6)	222	n.a. 46 (20.7)	1.09 [0.73; 1.63] 0.662
Loss of appetite	226	n.a. [17.7; n.c.] 87 (38.5)	222	n.a. 60 (27.0)	1.61 [1.16; 2.24] 0.004
Constipation	226	n.a. [39.4; n.c.] 35 (15.5)	222	n.a. 38 (17.1)	0.82 [0.51; 1.30] 0.393
Diarrhoea	226	0.5 [0.3; 0.5] 179 (79.2)	222	40.2 [12.1; 40.2] 93 (41.9)	3.45 [2.65; 4.49] < 0.001 39.7 months
Symptom scales of the EORTC QLQ-LC13					
Dyspnoea	226	40.2 [40.2; n.c.] 75 (33.2)	222	n.a. [20.8; n.c.] 74 (33.3)	0.99 [0.72; 1.37] 0.957
Coughing	226	n.a. 30 (13.3)	222	n.a. 33 (14.9)	0.86 [0.52; 1.41] 0.538
Haemoptysis	226	n.a. 13 (5.8)	222	n.a. 16 (7.2)	0.77 [0.37; 1.61] 0.485
Sore mouth	226	0.5 [0.5; 1.0] 155 (68.6)	222	n.a. 73 (32.9)	3.27 [2.45; 4.35] < 0.001

Endpoint	Dacomitinib		Gefitinib		Dacomitinib vs gefitinib
	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]
Dysphagia	226	n.a. 69 (30.5)	222	n.a. 32 (14.4)	2.47 [1.62; 3.77] < 0.001
Peripheral neuropathy	226	6.3 [4.6; 12.3] 120 (53.1)	222	n.a. 56 (25.2)	2.84 [2.06; 3.92] < 0.001
Alopecia	226	5.6 [4.2; 10.4] 115 (50.9)	222	n.a. [31.7; n.c.] 80 (36.0)	1.68 [1.26; 2.24] < 0.001
Chest pains	226	n.a. 33 (14.6)	222	n.a. 38 (17.1)	0.81 [0.51; 1.30] 0.375
Pain in the arm or shoulder	226	n.a. [34.6; n.c.] 45 (19.9)	222	n.a. 46 (20.7)	0.90 [0.59; 1.36] 0.612
Other pains	226	n.a. 70 (31.0)	222	n.a. 45 (20.3)	1.61 [1.11; 2.35] 0.012
Health status					
EQ-5D VAS (time until once confirmed deterioration by ≥ 10 points)[c]					
	224	27.2 [9.4; n.c.] 99 (44.2)	221	n.a. [21.5; n.c.] 70 (31.7)	1.58 [1.16; 2.15] 0.003

(Continuation)

Endpoint	Dacomitinib			Gefitinib			Dacomitinib vs gefitinib
	N	Values at start of study MV (SD)	Change at the end of study MV (SE)	N	Values at start of study MV (SD)	Change at the end of study MV (SE)	MD [95% CI] p value
Health status							
EQ-5D VAS							
	224	73.05 (19.62)	0.31 (1.38)	221	74.71 (17.62)	1.19 (2.17)	−0.88 [−5.94; 4.18] 0.733

(Continuation)

Health-related quality of life

Endpoint	Dacomitinib		Gefitinib		Dacomitinib vs gefitinib
	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]
Health-related quality of life – time until permanent deterioration[d]					
Global health status and functional scales of the EORTC QLQ-C30					
Global health status	226	26.3 [17.7; n.c.] 92 (40.7)	222	n.a. 52 (23.4)	1.99 [1.41; 2.81] < 0.001
Physical function	226	n.a. 60 (26.5)	222	n.a. [27.0; n.c.] 45 (20.3)	1.38 [0.94; 2.04] 0.099
Role function	226	n.a. [19.5; n.c.] 87 (38.5)	222	n.a. [24.9; n.c.] 64 (28.8)	1.48 [1.07; 2.05] 0.016
Emotional function	226	n.a. 50 (22.1)	222	n.a. 39 (17.6)	1.29 [0.85; 1.96] 0.236
Cognitive function	226	20.5 [13.1; n.c.] 95 (42.0)	222	n.a. [26.3; n.c.] 71 (32.0)	1.40 [1.03; 1.91] 0.031
Social function	226	n.a. [9.4; n.c.] 99 (43.8)	222	n.a. [21.5; n.c.] 75 (33.8)	1.45 [1.07; 1.96] 0.013

(Continuation)

Side effects

Endpoint	Dacomitinib		Gefitinib		Dacomitinib vs gefitinib
	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)					
	227	no data available 226 (99.6)	224	no data available 220 (98.2)	-
Serious adverse events (SAE)					
	227	n.a. [30.4; n.c.] 66 (29.1)	224	n.a. [31.4; n.c.] 52 (23.2)	1.20 [0.84; 1.74] 0.321
Severe adverse events (CTCAE grade 3 or 4)					
	227	5.6 [3.9; 9.2] 146 (64.3)	224	23.5 [13.5; 31.4] 98 (43.8)	1.89 [1.46; 2.45] < 0.001
Therapy discontinuation because of adverse events					
	227	n.a. 41 (18.1)	224	n.a. 29 (12.9)	1.31 [0.81; 2.11] 0.266
Specific adverse events[f]					
Diarrhoea (PT, severe AE (CTCAE grade ≥ 3))	227	n.a. 20 (8.8)	224	n.a. 2 (0.9)	10.22 [2.39; 43.77] < 0.001
Stomatitis (PT, AEs)	227	n.a. [14.6; n.c.] 99 (43.6)	224	n.a. 41 (18.3)	3.40 [2.35; 4.92] < 0.001
Skin and subcutaneous tissue disorders (SOC, severe AEs with CTCAE grade ≥ 3)	227	n.a. 66 (29.1)	224	n.a. 5 (2.2)	14.47 [5.82; 35.94] < 0.001
Includes: Acneiform dermatitis (PT, severe AE (CTCAE grade ≥ 3))	*227*	*n.a.* *31 (13.7)*	*224*	*n.a.* *0 (0.0)*	– [e] *< 0.001*
Dry skin (PT, AEs)	227	n.a. 63 (27.8)	224	n.a. 38 (17.0)	1.74 [1.16; 2.61] 0.007

Endpoint	Dacomitinib		Gefitinib		Dacomitinib vs gefitinib
	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]
Alopecia (PT, AEs)	227	n.a. 53 (23.3)	224	n.a. 28 (12.8)	2.02 [1.28; 3.20] 0.002
Chest pain (PT, AEs)	227	n.a. 24 (10.6)	224	n.a. 34 (15.2)	0.57 [0.33; 0.96] 0.032
Paronychia (PT, severe AE (CTCAE grade ≥ 3))	227	n.a. 17 (7.5)	224	n.a. 3 (1.3)	5.82 [1.70; 19.87] 0.001
Conjunctivitis (PT, AEs)	227	n.a. 43 (18.9)	224	n.a. 10 (4.5)	4.87 [2.44; 9.72] < 0.001
Respiratory, thoracic, and mediastinal disorders (SOC, AEs)	227	10.2 [6.7; 15.9] 124 (54.6)	224	16.3 [11.1; n.c.] 98 (43.8)	1.33 [1.02; 1.74] 0.035
Metabolism and nutrition disorders (SOC, AEs)	227	15.9 [9.2; 23.9] 110 (48.5)	224	25.8 [16.8; n.c.] 81 (36.2)	1.45 [1.09; 1.93] 0.011
Back pains (PT, AEs)	227	n.a. 18 (7.9)	224	n.a. 37 (16.5)	0.41 [0.23; 0.72] 0.002
Eye diseases (SOC, AEs)	227	n.a. 44 (19.4)	224	n.a. 22 (9.8)	2.03 [1.21; 3.39] 0.006
Investigations (SOC, severe AE (CTCAE grade ≥ 3))	227	n.a. 19 (8.4)	224	n.a. 37 (16.5)	0.44 [0.25; 0.77] 0.003
Includes: Alanine transaminase increased (PT, severe AE (CTCAE grade ≥ 3))	*227*	*n.a.* *2 (0.9)*	*224*	*n.a.* *20 (8.9)*	*0.09* *[0.02; 0.40]* *< 0.001*

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

Endpoint	Dacomitinib		Gefitinib		Dacomitinib vs gefitinib
	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]

[b] Data from: dossier on dacomitinib Module 4A from 26 April 2019, data cut-off of 29 July 2016
[c] A once confirmed deterioration is considered to be an increase in score of at least 10 points compared with the baseline measured on at least 2 consecutive rounds.
[d] A once confirmed deterioration is considered to be a decrease in score of at least 10 points compared with the baseline measured on at least 2 consecutive rounds.
[e] Order of magnitude of HR not interpretable (0 events in gefitinib arm)
[f] Selection in accordance with IQWiG methodology; selection based on those identified in the study Events based on frequency and differences between treatment arms and taking into account patient relevance.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; EORTC QLQ-LC13: lung cancer-specific add-on module to the EORTC QLQ-C30; HR = hazard ratio; CI = confidence interval; 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; RCT: randomised controlled trial; SOC: system organ class; vs = versus

a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19:

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

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

a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19:

Approx. 790 to 1910 patients

b) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19:

Approx. 100 to 300 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 Vizimpro® (active ingredient: dacomitinib) at the following publicly accessible link (last access: 26 August 2019):

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

Treatment with dacomitinib 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 carcinoma.

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

4. Treatment costs

Annual treatment costs:

a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Dacomitinib	€ 55,302.98
Appropriate comparator therapy:	
Afatinib	€ 30,931.27
Erlotinib	€ 33,145.16
Gefitinib	€ 18,381.52
Osimertinib	€ 70,637.23

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 October 2019

b) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Dacomitinib	€ 55,302.98
Appropriate comparator therapy: a patient-individual therapy depending on the activating EGFR mutation with selection of:	
afatinib, gefitinib, erlotinib, osimertinib	
Afatinib	€ 30,931.27
Erlotinib	€ 33,145.16
Gefitinib	€ 18,381.52

Designation of the therapy	Annual treatment costs/patient
Osimertinib	€ 70,637.23
Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)	
Cisplatin plus docetaxel	
Cisplatin	€ 1,959.42
Docetaxel	€ 20,741.53
Total:	€ 22,700.95
Additionally required SHI services:	€ 321.03 – € 411.93
Cisplatin plus gemcitabine	
Cisplatin	€ 1,959.42–2,427.26
Gemcitabine	€ 7,999.18
Total:	€ 9,958.60–10,426.44
Additionally required SHI services:	€ 321.03 – € 411.93
Cisplatin plus paclitaxel	
Cisplatin	€ 2,216.63
Paclitaxel	€ 20,269.78
Total:	€ 22,486.41
Additionally required SHI services:	€ 554.57 – € 645.47
Cisplatin plus pemetrexed	
Cisplatin	€ 1,959.42
Pemetrexed	€ 67,076.22
Total:	€ 69,035.64
Additionally required SHI services:	€ 444.63 – € 581.63
Cisplatin plus vinorelbine	
Cisplatin	€ 1,959.42–2,427.26
Vinorelbine	€ 4,608.33 – € 5,555.19
Total:	€ 6,567.75 – € 7,982.45
Additionally required SHI services:	€ 321.03 – € 411.93
Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)	
Carboplatin plus docetaxel	
Carboplatin	€ 8,514.45
Docetaxel	€ 20,741.53
Total:	€ 29,255.98

Designation of the therapy	Annual treatment costs/patient
Carboplatin plus gemcitabine	
Carboplatin	€ 8,514.45
Gemcitabine	€ 7,999.18
Total:	€ 16,513.63
Carboplatin plus paclitaxel	
Carboplatin	€ 8,514.45
Paclitaxel	€ 20,269.78
Total:	€ 28,784.23
Additionally required SHI services:	€ 233.55
Carboplatin plus pemtrexed	
Carboplatin	€ 8,514.45
Pemetrexed	€ 67,076.22
Total:	€ 75,590.67
Additionally required SHI services:	€ 123.61–169.71
Carboplatin plus vinorelbine	
Carboplatin	€ 8,514.45
Vinorelbine	€ 4,608.33 – € 5,555.19
Total:	€ 13,122.78 – € 14,069.64
Carboplatin plus nab-paclitaxel	
Carboplatin	€ 8,514.45
nab-paclitaxel	€ 41,219.22
Total:	€ 49,733.67
Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment).	
Gemcitabine	€ 7,154.55
Vinorelbine	€ 7,048.03 – € 8,496.18

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 October 2019

Other services covered by SHI funds:

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient per year[5]	Cost per patient per year
Medicinal product to be assessed:					
not applicable					
Appropriate comparator therapy:					
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Vinorelbine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	34	€ 2,754
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	34	€ 2,754
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
nab-paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	51	€ 4,131
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Gemcitabine (Monotherapy)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	39	€ 3,159
Vinorelbine (Monotherapy)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	52	€ 4,212

5 calculated and standardised for one year

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 17 October 2019.

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

Berlin, 17 October 2019

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The chair

Prof Hecken