Resolution
by the Federal Joint Committee
on an amendment to the Pharmaceutical Directive (AM-RL):
Appendix XII – Resolutions on the benefit assessment of pharmaceuticals with new active ingredients, in accordance with the German Social Code, Book Five (SGB V), section 35a
Afatinib

From 8 May 2014

In its session on 8 May 2014, the Federal Joint Committee resolved to amend the Pharmaceutical Directive (AM-RL), version published 18 December 2008/22 January 2009 (Federal Gazette, number 49a of 31 March 2009), last amended on 29 April 2014 (Federal Gazette, AT 20 May 2014 B2) as follows:

I.

Appendix XII shall be amended in alphabetical order to include the active ingredient afatinib:

Afatinib

Therapeutic indication

Giotrif® as a monotherapy is indicated for the treatment of adult EGFR-TKI-naïve patients with locally advanced and/or metastatic non-small-cell lung cancer (NSCLC) with epidermal-growth-factor-receptor (EGFR) mutation(s).

1. Additional benefit of the pharmaceutical over appropriate comparator

1) Treatment-naïve patients with ECOG performance status 0 or 1:

Appropriate comparator:

- Gefitinib or erlotinib or
- Cisplatin in combination with a third-generation cytotoxic agent (vinorelbine, gemcitabine, docetaxel, paclitaxel, pemetrexed), following the respective authorized therapeutic indication

Extent and probability of additional benefit over ciclosporin in combination with pemetrexed:

a) Patient group with EGFR mutation Del19:

Indication of a considerable additional benefit

b) Patient group with EGFR mutation L858R:

Hint of minor additional benefit

c) Patient group with other EGFR mutations:

Indication of a minor additional benefit

Study results according to endpoints[1, 2, 3, 4]:

Endpoint	Intervention arm (afatinib)	Control arm (cisplatin +pemetrexed)	Intervention vs. control
Mortality			
Overall survival (OS)	Months (median) [95% CI]	Months (median) [95% CI]	HR [95% CI] p-value AD[5]
Subgroup: EGFR mutation Del19	N = 113	N = 57	
1st data cut-off (9 February 2012)	n. c. [n. c.; n. c.]	n. c. [18.79; n. c.]	0.58 [0.31; 1.07] p = 0.075
2nd data cut-off (21 January 2013)	31.57 [n/a]	21.13 [n/a]	0.55 [0.36; 0.85] p = 0.006 AD: 10.44 months

Endpoint	Intervention arm (afatinib)	Control arm (cisplatin + pemetrexed)	Intervention vs. control
Subgroup: EGFR mutation L858R	N = 91	N = 47	
1st data cut-off (9 February 2012)	n. c. [17.71; n. c.]	n. c. [21.2; n. c.]	1.77 [0.84; 3.76] p = 0.130
2nd data cut-off (21 January 2013)	27.17 [n/a]	n. c. [n/a]	1.30 [0.76; 2.23] p = 0.332
Subgroup: other EGFR mutations	N = 26	N = 11	
1st data cut-off (9 February 2012)	15.41 [7.49; 24.90]	19.65 [6.77; n. c.]	1.99 [0.66; 6.01] p = 0.213
2nd data cut-off (21 January 2013)	15.93 [n/a]	n. c. [n/a]	3.08 [1.04; 9.15] p = 0.034

Endpoint	Intervention arm (afatinib)		Control arm (cisplatin + pemetrexed)		Intervention vs. control
Morbidity					
Progress-free survival (PFS)					
PFS	N	Months (median) [95% CI] Patients with events n (%)	N	Months (median) [95% CI] Patients with events n (%)	HR [95% CI] p-value AD[5]
Subgroup: EGFR mutation Del19	113	13.70 [n/a] 67 (59.3%)	57	5.55 [n/a] 35 (61.4%)	0.28 [0.18; 0.44] p < 0.0001 AD: 8.15 months
Subgroup: EGFR mutation L858R	91	10.84 [n/a] 63 (69.2%)	47	8.11 [n/a] 26 (55.3%)	0.73 [0.46; 1.17] p = 0.1871
Subgroup: other EGFR mutations	26	2.76 [n/a] 22 (84.6%)	11	9.92 [n/a] 8 (72.7%)	1.89 [0.84; 4.28] p = 0.1198
Improvement in symptoms: EORTC QLQ-LC13					
Improvement in symptoms (EORTC QLQ-LC13)	N	Patients with events[6] n (%)	N	Patients with events n (%)	RR [95% CI][7] p-value AD[5]
Dyspnoea					
Subgroup: EGFR mutation Del19 or L858R	195	83 (42.6%)	96	21 (21.9%)	0.51 [0.34; 0.78] p = 0.002 AD: 20.7%
Subgroup: other EGFR mutations	23	6 (26.1%)	11	5 (45.5%)	1.75 [0.68; 4.55] p = 0.249
Haemoptysis	218	24 (11.0%)	107	11 (10.3%)	0.93 [0.48; 1.82] p = 0.842
Cough	218	121 (55.5%)	105	38 (36.2%)	0.65 [0.49; 0.86] p = 0.003 AD: 19.3%
Pain (arm/shoulder)	218	66 (30.3%)	107	19 (17.8%)	0.59 [0.37; 0.93] p = 0.022 AD: 12.5%
Pain (chest)	218	91 (41.7%)	107	36 (33.6%)	0.81 [0.59; 1.10] p = 0.171
Pain (other)	207	66 (31.9%)	98	30 (30.6%)	0.96 [0.67; 1.37] p = 0.824
Hair loss	218	20 (9.2%)	107	6 (5.6%)	0.61 [0.25; 1.47] p = 0.274
Pain in the mouth	216	16 (7.4%)	106	9 (8.5%)	1.15 [0.52; 2.50] p = 0.733
Peripheral neuropathy	218	22 (10.1%)	107	9 (8.4%)	0.83 [0.40; 1.75] p = 0.630

Endpoint	Intervention arm (afatinib)		Control arm (cisplatin + pemetrexed)		Intervention vs. control
Problems swallowing	218	17 (7.8%)	107	12 (11.2%)	1.43 [0.71; 2.94] p = 0.310
Improvement in symptoms: EORTC QLQ-C30					
Improvement in symptoms (EORTC QLQ-C30)	N	Patients with events[6] n (%)	N	Patients with events n (%)	RR [95% CI][7] p-value AD[5]
Dyspnoea					
Subgroup: EGFR mutation Del19 or L858R	195	89 (45.6%)	96	26 (27.1%)	0.59 [0.41; 0.85] p = 0.005 AD: 18.5%
Subgroup: other EGFR mutations	23	5 (21.7%)	11	5 (45.5%)	2.08 [0.76; 5.88] p = 0.152
Fatigue	218	77 (35.3%)	107	27 (25.2%)	0.71 [0.49; 1.04] p = 0.077
Insomnia	218	100 (45.9%)	106	40 (37.7%)	0.82 [0.62; 1.09] p = 0.178
pain	218	74 (33.9%)	107	30 (28.0%)	0.83 [0.58; 1.18] p = 0.292
Loss of appetite	218	64 (29.4%)	107	27 (25.2%)	0.86 [0.58; 1.27] p = 0.442
Diarrhoea	218	11 (5.0%)	107	16 (15.0%)	2.94 [1.43; 6.25] p = 0.004 AD: –10%
Nausea and vomiting	218	48 (22.0%)	107	9 (8.4%)	0.38 [0.19; 0.75] p = 0.005 AD: 13.6%
Constipation	218	69 (31.7%)	106	25 (23.6%)	0.75 [0.50; 1.11] p = 0.144
Time until worsening of symptoms: EORTC QLQ-LC13					
Time until worsening of symptoms (EORTC QLQ-LC13)	N	Months[8] median [95% CI] Patients with events n (%)	N	Months (median) [95% CI] Patients with events n (%)	RR [95% CI][9] p-value AD[5]
Dyspnoea					
Subgroup: EGFR mutation Del19 or L858R	204	96 (47.1%)	104	61 (58.7%)	0.55 [0.40; 0.77] p < 0.001 AD: –11.6%
Subgroup: other EGFR mutations	26	22 (84.6%)	11	6 (54.5%)	2.37 [0.96; 5.85] p = 0.055
Haemoptysis	230	n. c. 45 (19.6%)	115	n. c. 11 (9.6%)	1.75 [0.89; 3.43] p = 0.101
Cough	230	n. c. [15.2;n.c.] 78 (33.9%)	115	8.0 [4.44; n. c.] 44 (38.3%)	0.60 [0.41; 0.87] p = 0.007 AD: –4.4%
Pain (arm/shoulder)	230	10.4 [n/a] 109 (47.4%)	115	n. c. 43 (37.4%)	0.94 [0.65; 1.34] p = 0.721
Pain (chest)	230	n. c. 79 (34.3%)	115	8.3 [n/a] 45 (39.1%)	0.65 [0.44; 0.94] p = 0.023 AD: –4.8%
Pain (other)	230	4.9 [n/a] 129 (56.1%)	115	6.2 [n/a] 49 (42.6%)	1.09 [0.78; 1.52] p = 0.621
Hair loss	230	3.5 [n/a] 154 (67%)	115	1.7 [n/a] 77 (67%)	0.61 [0.46; 0.81] p < 0.001 AD: 1.8 months

Endpoint	Intervention arm (afatinib)		Control arm (cisplatin + pemetrexed)		Intervention vs. control
Pain in the mouth	230	0.8 [n/a] 194 (84.3%)	115	2.9 [n/a] 68 (59.1%)	2.47 [1.86; 3.28] p < 0.001 AD: –2.1 months AD: 25.2%
Peripheral neuropathy	230	2.9 [n/a] 155 (67.4%)	115	5.1 [n/a] 64 (55.7%)	1.24 [0.92; 1.67] p = 0.156
Problems swallowing	230	2.8 [n/a] 142 (61.7%)	115	10.4 [n/a] 43 (37.4%)	1.85 [1.31; 2.61] p < 0.001 AD: –7.6 months AD: 24.3%
Time until worsening of symptoms: EORTC QLQ-C30					
Time until worsening of symptoms (EORTC QLQ-C30)	N	Months[8] median [95% CI] Patients with events n (%)	N	Months median [95% CI] Patients with events n (%)	RR [95% CI][9] p-value AD[5]
Dyspnoea					
Subgroup: EGFR mutation Del19 or L858R	204	68 (33.3%)	104	52 (50.0%)	0.39 [0.27; 0.56] p < 0.001 AD: –16.7%
Subgroup: other EGFR mutations	26	15 (57.7%)	11	3 (27.3%)	2.84 [0.82; 9.83] p = 0.086
Fatigue					
Subgroup: EGFR mutation Del19	113	72 (63.7%)	57	45 (78.9%)	0.55 [0.37; 0.80] p = 0.002 AD: –15.2%
Subgroup: EGFR mutation L858R	91	52 (57.1%)	47	27 (57.4%)	0.69 [0.43; 1.11] p = 0.122
Subgroup: other EGFR mutations	26	22 (84.6%)	11	8 (72.7%)	1.56 [0.69; 3.51] p = 0.282
Insomnia	230	9.7 [n/a] 114 (49.6%)	115	20.5 [n/a] 45 (39.1%)	1.00 [0.70; 1.43] p = 0.993
Pain	230	4.2 [2.79; 5.59] 144 (62.6%)	115	3.09 [2.17; 3.98] 72 (62.6%)	0.82 [0.62; 1.10] p = 0.191
Loss of appetite	230	3.8 [n/a] 136 (59.1%)	115	2.8 [n/a] 69 (60.0%)	0.84 [0.62; 1.13] p = 0.241
Diarrhoea	230	0.8 [n/a] 208 (90.4%)	115	13.7 [n/a] 30 (26.1%)	7.74 [5.15; 11.63] p < 0.001 AD: –12.9 months AD: 64.3%
Nausea and vomiting	230	7.4 [n/a] 123 (53.5%)	115	2.1 [n/a] 74 (64.3%)	0.55 [0.40; 0.74] p < 0.001 AD: 5.3 months AD: –10.8%
Constipation	230	14.1 [n/a] 102 (44.3%)	115	7.6 [n/a] 48 (41.7%)	0.73 [0.51; 1.04] p = 0.077

Endpoint	Intervention arm (afatinib)		Control arm (cisplatin + pemetrexed)		Intervention vs. control
Health-related quality of life					
Improvement in quality of life: EORTC QLQ-C30					
Improvement in quality of life (EORTC QLQ-C30)	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI] p-value AD[5]
Overall health status	218	57 (26.1%)	107	22 (20.6%)	0.79 [0.51; 1.22] p = 0.278
Emotional function	218	77 (35.3%)	107	35 (32.7%)	0.93 [0.67; 1.28] p = 0.644
Cognitive function	218	38 (17.4%)	107	17 (15.9%)	0.91 [0.54; 1.54] p = 0.728
Bodily function					
Subgroup: EGFR mutation Del19	107	29 (27.1%)	56	5 (8.9%)	0.33 [0.13; 0.81] p = 0.015 AD: 18.2%
Subgroup: EGFR mutation L858R	88	20 (22.7%)	40	4 (10.0%)	0.44 [0.16; 1.20] p = 0.110
Subgroup: other EGFR mutations	23	4 (17.4%)	11	3 (27.3%)	1.56 [0.42; 5.88] p = 0.502
Role function	218	65 (29.8%)	107	28 (26.2%)	0.88 [0.60; 1.28] p = 0.498
Social function	217	62 (28.6%)	107	30 (28.0%)	0.98 [0.68; 1.43] p = 0.920
Time until worsening of quality of life: EORTC QLQ-C30					
Time until worsening of quality of life (EORTC QLQ-C30)	N	Months (median) [95% CI] Patients with events n (%)	N	Months (median) [95% CI] Patients with events n (%)	RR [95% CI] p-value AD[5]
Overall health status	230	3.5 [n/a] 142 (61.7%)	115	3.8 [n/a] 65 (56.5%)	1.01 [0.75; 1.37] p = 0.930
Emotional function	230	11.1 [n/a] 112 (48.7%)	115	8.5 [n/a] 45 (39.1%)	0.93 [0.65; 1.32] p = 0.677
Cognitive function	230	4.9 [n/a] 142 (61.7%)	115	3.1 [n/a] 68 (59.1%)	0.77 [0.57; 1.04] p = 0.086
Bodily function					
Subgroup: EGFR mutation Del19	113	57 (50.4%)	57	39 (68.4%)	0.49 [0.32; 0.74] p < 0.001 AD: –18%
Subgroup: EGFR mutation L858R	91	58 (63.7%)	47	25 (53.2%)	0.85 [0.53; 1.36] p = 0.492
Subgroup: other EGFR mutations	26	20 (76.9%)	11	6 (54.5%)	1.98 [0.79; 4.94] p = 0.137
Role function	230	2.9 [n/a] 152 (66.1%)	115	2.4 [n/a] 70 (60.9%)	0.93 [0.70; 1.24] p = 0.617
Social function	230	4.8 [n/a] 133 (57.8%)	115	3.5 [n/a] 62 (53.9%)	0.97 [0.71; 1.31] p = 0.823
EQ-5D					
No evaluable results available. Side effects					

Patients with events	n (%) N = 229	n (%) N = 111	
AE	229 (100%)	109 (98.2%)	

Endpoint	Intervention arm (afatinib)	Control arm (cisplatin + pemetrexed)	Intervention vs. control
SAE	66 (28.8%)	25 (22.5%)	
AE CTCAE grade 3 or 4	139 (60.7%)	63 (56.8%)	
Discontinuation of treatment due to AE	32 (14.0%)	17 (15.3%)	
CTCAE grade 3 AEs occurring in ≥ 5% of all patients in one treatment arm			
Diarrhoea	34 (14.8%)	2 (1.8%)	
Rash	30 (13.1%)	0 (0.0%)	
Paronychia	26 (11.4%)	0 (0.0%)	
Fatigue	5 (2.2%)	11 (9.9%)	
Neutropenia	2 (0.9%)	18 (16.2%)	
Leukopaenia	1 (0.4%)	9 (8.1%)	

[1] Data for the target population of the LUX-Lung 3 study from the IQWiG dossier assessment (A13-41), the EPAR, and the dossier submitted by the pharmaceutical company.

[2] The study included treatment-naïve patients with ECOG performance status 0 to 1.

[3] If not otherwise indicated, the results shown are at first data cut-off (9 February 2012).

[4] If not otherwise indicated, the results shown represent the overall population. Subgroups are shown according to EGFR mutation status if one proof of interaction was present for at least one operationalization of the respective endpoint (p-value of interaction test < 0.05).

[5] Information on absolute difference shown only for statistically significant results ($p < 0.05$).

[6] Responder analysis: Percentage of patients who achieved an average score improvement of at least 10 points over the initial score across all days on which they filled out the questionnaire during the time of the study.

[7] Event rate afatinib/chemotherapy; reciprocal values of the effect estimates and CI thresholds to demonstrate the effect direction in comparison to the operationalization "Time until worsening of symptoms"; scores < 1 in favor of afatinib.

[8] No information on median times for subgroups of the overall population.

[9] Time until worsening of score by at least 10 points compared to initial value.

Abbreviations used: CTCAE: common terminology criteria for adverse events; HR: hazard ratio. N: number of evaluated patients. n: number of patients with event. n.c. not calculable. n.i. no information CI: confidence interval. HR: hazard ratio. RR: relative risk. AE: adverse event. SAE: serious adverse event.

Overview (summary)[10]:

Endpoint	Patient group	Benefit/disadvantage of afatinib[11]
Mortality		
Overall survival	Subgroup: EGFR mutation Del19	Benefit
	Subgroup: other EGFR mutations	Disadvantage
Morbidity		
PFS	Subgroup: EGFR mutation Del19	Benefit
Dyspnoea (both questionnaires and both operationalizations for each)	Subgroup: EGFR mutation Del19 or L858R	Benefit
Cough (both operationalizations)	Overall population	Benefit
Pain in arm/shoulder (improvement)	Overall population	Benefit
Pain in chest (Time until worsening)	Overall population	Benefit
Hair loss (Time until worsening)	Overall population	Benefit
Fatigue (Time until worsening)	Subgroup: EGFR mutation Del19	Benefit
Nausea and vomiting (both operationalizations)	Overall population	Benefit
Pain in the mouth (Time until worsening)	Overall population	Disadvantage

Endpoint	Patient group	Benefit/disadvantage of afatinib[11]
Problems swallowing (Time until worsening)	Overall population	Disadvantage
Diarrhoea (both operationalizations)	Overall population	Disadvantage
Health-related quality of life		
Bodily function (both operationalizations)	Subgroup: EGFR mutation Del19	Benefit

[10] The endpoints of the LUX-Lung 3 study in which there were statistically significant differences between the treatment arms are shown.

[11] Comparison with cisplatin in combination with pemetrexed.

2) Treatment-naïve patients with ECOG performance status 2:

Appropriate comparator:

– Gefitinib or erlotinib or

– Gemcitabine

Extent and probability of additional benefit:

An additional benefit has not been proved.

3) Patients previously treated with one or more chemotherapeutic regimen(s):

Appropriate comparator:

Gefitinib or erlotinib

Extent and probability of additional benefit:

An additional benefit has not been proved.

2. Number of patients and criteria for defining patients eligible for treatment

1) Treatment-naïve patients with ECOG performance status 0 or 1:

Number: approx. 530 – 3,630 patients, of which:

a) Patients with EGFR mutation Del19:

Number: approx. 320 – 2,180 patients

b) Patients with EGFR mutation L858R:

Number: approx. 120 – 830 patients

c) Patient group with other EGFR mutations:

Number: approx. 90 – 620 patients

2) Treatment-naïve patients with ECOG performance status 2:

Number: approx. 70 – 1,180 patients

3) Patients previously treated with one or more chemotherapeutic regimen(s):

Number: approx. 40 – 170 patients

3. Requirements for quality-assured administration

The specifications outlined in the product information are to be followed. The European Medicines Agency (EMA), the European regulatory authority, provides the product information for Giotrif® (active ingredient: afatinib) at the following public link (last accessed: 1 March 2014):
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002280/WC500152392.pdf

Treatment with enzalutamide may be initiated and monitored only by a specialist for internal medicine and haematology, oncology, pneumology, or other specialist physicians participating in the oncology agreement and experienced in the treatment of patients with non-small-cell lung cancer.

An EGFR mutation status must be present before starting treatment with afatinib. The EGFR mutation status must be determined in a quality-assured laboratory facility with a validated and robust procedure to prevent false negative or false positive results.

4. Costs of treatment

Summary for patient groups 1), 2) and 3)[12]:

Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient	Duration per treatment (days)	Number of treatment days per patient per year
Pharmaceutical evaluated				
Afatinib	1 x daily	ongoing	365	365
Appropriate comparator[12]				
Gefitinib	1 x daily	ongoing	365	365
Erlotinib	1 x daily	ongoing	365	365
Gemcitabine (monotherapy)	3 x per 28-day cycle	13 cycles	3	39
Cisplatin in combination with a third-generation cytotoxic agent				
Cisplatin	1 x per 21-day cycle	17 cycles	1	17
Vinorelbine	2 x per 21-day cycle	17 cycles	2	34
Gemcitabine	2 x per 21-day cycle	17 cycles	2	34
Docetaxel	1 x per 21-day cycle	17 cycles	1	17
Paclitaxel	1 x per 21-day cycle	17 cycles	1	17
Pemetrexed	1 x per 21-day cycle	17 cycles	1	17

[12] The appropriate comparator as determined for the respective patient group.

Consumption:

Description of therapy	Dosage	Dose per patient per treatment day[13](mg)	Consumption per treatment day according to strength	Average annual consumption according to strength
Pharmaceutical evaluated				
Afatinib	40 mg	40 mg	1 × 40 mg	365 tablets with 40 mg
Appropriate comparator[12]				
Gefitinib	250 mg	250 mg	1 × 250 mg	365 tablets with 250 mg
Erlotinib	150 mg	150 mg	1 × 150 mg	365 tablets with 150 mg
Gemcitabine (monotherapy)	1,000 mg/m^{2}BSA	1,890 mg	2 x 1,000 mg	78 vials with 1,000 mg
Cisplatin in combination with a third-generation cytotoxic agent				
Cisplatin (range)	75 – 100 mg/m^2 BSA	141.75 – 189 mg	1 x 100 mg + 1 x 50 mg to 2 × 100 mg	17 vials with 100 mg + 17 vials with 50 mg to 34 vials with 100 mg
Vinorelbine	25 – 30 mg/m^2 BSA	47.25 – 56.7 mg	1 × 50 mg to 1 x 50 mg + 1 × 10 mg	34 vials with 50 mg to 34 vials with 50 mg + 34 vials with 10 mg

Description of therapy	Dosage	Dose per patient per treatment day[13](mg)	Consumption per treatment day according to strength	Average annual consumption according to strength
Gemcitabine	1,250 mg/m² BSA	2,362.5 mg	2 x 1,000 mg + 2 × 200 mg	68 vials with 1,000 mg + 68 vials with 200 mg
Docetaxel	75 mg/m² BSA	141.75 mg	1 × 160 mg	17 vials with 160 mg
Paclitaxel	175 mg/m² BSA	330.75 mg	1 x 300 mg + 2 × 30 mg	17 vials with 300 mg + 34 vials with 30 mg
Pemetrexed	500 mg/m² BSA	945 mg	2 × 500 mg	34 vials with 500 mg

[13] Dosage calculated with a body surface area (BSA) of 1.89 m².

Costs:

Cost of pharmaceutical

Description of therapy	Cost (pharmacy retail price)[14]	Cost after legally mandated rebates
Pharmaceutical evaluated		
Afatinib	€3,231.89	€3,048.79 [€1.80[15]; €181.30[16]]
Appropriate comparator[12]		
Gefitinib	€3,458.64	€3,262.59 [€1.80[15]; €194.25[16]]
Erlotinib	€2,887.67	€2,663.71 [€1.80[15]; €222.16[16]]
Gemcitabine (monotherapy)	€74.21	€69.41 [€1.80[15]; €3.00[16]]
Cisplatin in combination with a third-generation cytotoxic agent		
Cisplatin	€83.74 (100 mg) €47.37 (50 mg)	€72.73 [€1.80[15]; €9.21[16]] €43.84 [€1.80[15]; €1.73[16]]
Vinorelbine	€152.31 (50 mg) €39.25 (10 mg)	€143.80 [€1.80[15]; €6.71[16]] €36.11 [€1.80[15]; €1.34[16]]
Gemcitabine	€74.21 (1,000 mg) €28.68 (200 mg)	€69.41 [€1.80[15]; €3.00[16]] €26.04 [€1.80[15]; €0.84[16]]
Docetaxel	€1,554.98	€1,357.68 [€1.80[15]; €195.50[16]]
Paclitaxel	€1,281.62 (300 mg) €138.05 (30 mg)	€1,219.52 [€1.80[15]; €60.30[16]] €130.22 [€1.80[15]; €6.30[16]]
Pemetrexed	€2,533.24	€2,077.28 [€1.80[15]; €454.16[16]]

[14] "Lauer-Taxe", effective: 1 April 2014.

[15] Rebate in accordance with SGB V, section 130.

[16] Rebate in accordance with SGB V, section 130a.

Costs for additional, necessary statutory health insurance (SHI) benefits:

therapy	Type of benefit	Costs per pack[17]	Treatment days per year	Annual costs per patient
Cisplatin in combination with a third-generation cytotoxic agent				
Cisplatin	Forced diuresis: mannitol 10% inf. sol., 375 ml/day[18] hydration: sodium chloride 0.9% inf. sol., 3 – 4.4 l/day[19]	€93.10 €34.48 or €22.51	17 17	€158.27 €175.85 – €272.70
Paclitaxel	Premedication Dexamethasone 40 mg/day, oral[20] Diphenhydramine 50 mg/day, i. v.[21] Ranitidine 50 mg/day, i. v.[22]	 €112.40 €55.41 €13.03	 17 17 17	 €95.54 €28.26 €44.30
Pemetrexed	Premedication Dexamethasone 8 mg/day, oral[23] Folate 350 – 1,000 µg/day, oral[24] Vitamin B12 1,000 µg/day, i. m.[25]	 €72.01 €12.00 €36.11	 51 365 6	 €73.45 €43.80 – €109.50 €2.17

[17] Cost after legally mandated rebates (SGB V, sections 130 and 130a).

[18] Pharmacy retail price: €102.36, 10 x 500 ml (“Lauer-Taxe”, effective: 15 April 2014); Average annual consumption: 17 bottles.

[19] Pharmacy retail price: €39.88, 10 x 1,000 ml or €25.92, 10 x 500 ml (“Lauer-Taxe”, effective: 15 April 2014); Average annual consumption: 51 – 85 bottles.

[20] Pharmacy retail price: €123.05 €, 8 mg splittable (“Lauer-Taxe”, effective: 15 April 2014); Average annual consumption: 85 tablets.

[21] Pharmacy retail price: €59.92, 100 x 2 ml (“Lauer-Taxe”, effective: 15 April 2014); Average annual consumption: 51 ampoules.

[22] Pharmacy retail price: €15.02, 5 x 5 ml (“Lauer-Taxe”, effective: 15 April 2014); Average annual consumption: 17 ampoules.

[23] Pharmacy retail price: €79.18 €, 4 mg (“Lauer-Taxe”, effective: 15 April 2014); Average annual consumption: 102 tablets.

[24] Pharmacy retail price: €13.90 €, 0.4 mg (“Lauer-Taxe”, effective: 15 April 2014); Average annual consumption: 365 – 912.5 tablets.

[25] Pharmacy retail price: €41.77, 100 x 1 ml (“Lauer-Taxe”, effective: 15 April 2014); Average annual consumption: 6 ampoules.

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Pharmaceutical evaluated	
Afatinib	€39,743.16
Appropriate comparator[12]	
Gefitinib	€39,694.85
Erlotinib	€32,408.47
Gemcitabine (monotherapy)	€5,413.98
Cisplatin in combination with a third-generation cytotoxic agent	
Cisplatin (range) Additional necessary SHI expense items	€1,981.69 – €2,472.82 €334.12 – €430.97
Vinorelbine	€4,889.20 – €6,116.94
Gemcitabine	€6,490.60
Docetaxel	€23,080.56
Paclitaxel Additional necessary SHI expense items	€25,159.32 €168.10
Pemetrexed Additional necessary SHI expense items	€70,627.52 €119.42 – €185.12

Other SHI expense items:

Description of therapy	Type of benefit	Cost per unit	Number per cycle	Number per patient per year	Cost per patient per year
Gemcitabine (monotherapy)	Surcharge for the production of a parenteral preparation containing cytostatics	€79	3	39	€3,081

Description of therapy	Type of benefit	Cost per unit	Number per cycle	Number per patient per year	Cost per patient per year
Cisplatin in combination with a third-generation cytotoxic agent					
Cisplatin	Surcharge for the production of a parenteral preparation containing cytostatics	€79	1	17	€1,343
Vinorelbine	Surcharge for the production of a parenteral preparation containing cytostatics	€79	2	34	€2,686
Gemcitabine	Surcharge for the production of a parenteral preparation containing cytostatics	€79	2	34	€2,686
Docetaxel	Surcharge for the production of a parenteral preparation containing cytostatics	€79	1	17	€1,343
Paclitaxel	Surcharge for the production of a parenteral preparation containing cytostatics	€79	1	17	€1,343
Pemetrexed	Surcharge for the production of a parenteral preparation containing cytostatics	€79	1	17	€1,343

The "Hilfstaxe" (a pricing contract for substances and formulations made with substances) has not been used in its entirety to calculate the costs because it (1) is negotiated flexibly, (2) is not representative for the provision of care due to the large number of invoicing modes for cytostatics, largely non-public contracts, which are not bound by the "Hilfstaxe and (3) may not include all relevant substances at any one time, and for these reasons is unsuitable for a standardized cost overview. In contrast, the publicly accessible pharmacy retail price shown in the "Lauer-Taxe" is a suitable basis for a standardized calculation.

According to the "Hilfstaxe" (effective: 2nd supplementary agreement on the pricing contract for substances and formulations made with substances, from 29 February 2012), surcharges of maximum €79 apply per application-ready preparation to parenteral preparations containing cytostatics. This amount can be lowered in contracts. These additional extra costs are not added to the pharmacy retail price; they follow the calculation regulations set forth in the "Hilfstaxe". The costs shown are based on the pharmacy retail price and the maximum surcharge, and thus only approximate the actual treatment costs.

II.

Validity

1. This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 8 May 2014.
2. This resolution remains valid until 15 May 2015.

The justification for this resolution will be published on the websites of the Federal Joint Committee at www.g-ba.de.

Berlin, 8 May 2014

The Federal Joint Committee in
accordance with SGB V,
section 91

The Chair
Hecken