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
Aflibercept

from 15 August 2013

In its session on 15 August 2013, 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 20 June 2013 (Federal Gazette, AT 6 September 2013 B3), as follows:

I.

In appendix XII, in the details of the benefit assessment of aflibercept in the indication "for adults for the treatment of neovascular (wet) age-related macular degeneration" in accordance with the resolution of 6 June 2013, the following shall be added after number 4:

Aflibercept

Therapeutic indication from 1 February 2013:

Zaltrap® in combination with a chemotherapy consisting of irinotecan/5-fluorouracil/folinic acid (FOLFIRI) is used for the treatment of metastatic colorectal cancer (MCRC) that has progressed under or following a regime containing oxaliplatin.

1. Additional benefit of the pharmaceutical over appropriate comparator

Appropriate comparator:

The appropriate comparator for the treatment of patients with metastatic colorectal cancer who have been previously treated with a regime containing oxaliplatin is combination chemotherapy with 5-fluorouracil, folinic acid, and irinotecan.

Extent and probability of additional benefit over combination chemotherapy with 5-fluorouracil, folinic acid, and irinotecan:

Indication of a minor additional benefit.

Study results according to endpoints[1]

Mortality

	Aflibercept+FOLFIRI N = 612	FOLFIRI N = 614	Aflibercept+FOLFIRI vs. FOLFIRI	
Endpoint	Median overall survival [95% CI]		Absolute difference[2]	HR [95% CI] p-value
Overall survival	13.5 months [12.52; 14.95]	12.1 months [11.07; 13.08]	+1.4 months	HR 0.82 [0.71; 0.93] 0.003

Morbidity

No applicable data available

Health-related quality of life

No data on health-related quality of life were collected in the study submitted.

[1] Data from the dossier assessment conducted by the Institute for Quality and Efficiency in Health Care (IQWiG) (A13-08).
[2] Figures shown for significant differences only.

Side effects

Endpoint		Aflibercept+FOLFIRI N = 611	FOLFIRI N = 605	Aflibercept+FOLFIRI vs. FOLFIRI	
		Incident rate		Absolute difference[2]	RR [95% CI] p-value
AEs overall[3]		99.2%	97.9%		
SAEs[4]	Age < 65 years	42.6%	33.6%	+9%	RR 1.27 [1.06; 1.52] 0.010
	Age ≥ 65 years	59.0%	31.3%	+27.7%	RR 1.88 [1.51; 2.35] <0.001
Severe AEs (CTCAE grade 3 and 4)		83.5%	62.5%	+21%	RR 1.34 [1.24; 1.43] <0.001
Termination of treatment due to AEs		26.8%	12.1%	+14.7%	RR 2.22 [1.73; 2.86] <0.001

Abbreviations used: AD = absolute difference; CTCAE = common terminology criteria for adverse events; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; RR = relative risk; AE = adverse event; SAE = serious adverse event

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

   Number: 3,500 to 10,400 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 Zaltrap® (active ingredient: aflibercept) at the following public link (last accessed: 8 July 2013):

   http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002532/WC500139484.pdf

   Treatment with Zaltrap® of patients with metastatic colorectal cancer shall be initiated and monitored by an experienced specialist physician (internist specialized in haematology and oncology, as well as other physicians from other fields of specialty participating in the oncology agreement), or prescribed based on a recommendation by a cross-disciplinary tumor conference.

   The VELOUR study upon which the benefit assessment is based includes only those patients who have a histologically or cytologically confirmed diagnosis of metastatic adenocarcinoma of the large intestine or rectum. No data to assess therapy with aflibercept for non-adenocarcinoma of the large intestine or rectum are available.

   No sufficient data to assess therapy with aflibercept for patients who have been previously treated in combination with an anti-EGFR active ingredient (cetuximab, panitumumab) are available.

4. Costs of treatment

   Duration of treatment:

Description of therapy	Mode of treatment	Number of cycles per patient per year[5]	Duration per treatment per cycle (days)	Number of treatment days per patient per year
Pharmaceutical evaluated: Aflibercept+FOLFIRI				
Aflibercept	In cycles: 1 cycle = 14 days Day 1 = 1 x daily	26	1	26
FOLFIRI	In cycles: 1 cycle = 14 days			
Irinotecan	Day 1 = 1 x daily	26	1	26
Folinic acid	Day 1 = 1 x daily	26	1	26

[3] No effect estimate is given due to the high incident rate in both groups.
[4] Divided by age group due to proven effect modification.
[5] Standardized calculation for one year.

Description of therapy	Mode of treatment	Number of cycles per patient per year[5]	Duration per treatment per cycle (days)	Number of treatment days per patient per year
5-fluorouracil (Bolus)	Day 1 = 1 x daily	26	1	26
5-fluorouracil (continuous infusion)	Tag 1 – 2 = 1 x for 46 h	26	1	26
Appropriate comparator: FOLFIRI				
FOLFIRI[6]	In cycles: 1 cycle = 14 days			
Irinotecan	Day 1 = 1 x daily	26	1	26
Folinic acid	Day 1 = 1 x daily	26	1	26
5-fluorouracil (Bolus)	Day 1 = 1 x daily	26	1	26
5-fluorouracil (continuous infusion)	Tag 1 – 2 = 1 x for 46 h	26	1	26

Consumption:

Description of therapy	Strengths (mg)	Dosage	Dosage per patient per treatment day[7]	Consumption according to strength per treatment day	Number of treatment days per patient per year	Average annual consumption according to strength
Aflibercept	100 200	4 mg/kg BW	302.4 mg	2 × 200 mg	26	52 × 200 mg
Irinotecan[8]	40 to 500	180 mg/m^2	340.2 mg	2 × 40 mg 1 × 300 mg	26	52 × 40 mg 26 × 300 mg
Folinic acid[8]	10 to 1,000	400 mg/m^2	756.0 mg	1 × 800 mg	26	26 × 800 mg
5-fluorouracil[8] (Bolus)	200 to 10,000	400 mg/m^2	756.0 mg	1 x 1,000	26	26 x 1,000 mg
5-fluorouracil[8] (continuous infusion)	200 to 10,000	2,400 mg/m^2	4,536.0 mg	1 x 5,000	26	26 x 5,000 mg

Costs:

Cost of pharmaceutical:

Description of therapy	Costs (pharmacy retail price according to pharmaceutical, strength, dosage form and pack size)	Cost after legally mandated rebates
Aflibercept	€528.09 Zaltrap® 25 mg/ml; 100 mg concentrated infusion solution; 4 ml	€460.80 [€1.85[9]; €65.44[10]]
	€1,045.19 Zaltrap® 25 mg/ml; 200 mg concentrated infusion solution; 8 ml	€912.46 [€1.85[9]; €130.88[10]]
Irinotecan	€106.56 Irinotecan Accord 20 mg/ml; 40 mg concentrated infusion solution; 1	€88.07 [€1.85[9]; €16.64[10]]
	€643.77 Irinotecan Accord 20 mg/ml; 300 mg concentrated infusion solution; 1	€561.50 [€1.85[9]; €80.42[10]]
Folinic acid	€304.32[11] 800 mg concentrated infusion solution; 1	€279.27 [€1.85[9]; €23.20[10]]

[6] Due to varying FOLFIRI protocols, the details from the product information for Zaltrap® (aflibercept) are used as an example; effective February 2013.

[7] Dosage calculated for 75.6 kg body weight; 1,89 m² body surface area (BSA).

[8] Identical consumption of aflibercept+FOLFIRI and FOLFIRI.

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

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

[11] Reference price

Description of therapy	Costs (pharmacy retail price according to pharmaceutical, strength, dosage form and pack size)	Cost after legally mandated rebates
5-fluorouracil	€16.34[11] 1,000 mg infusion solution; 1	€14.07 [€1.85[9]; €0.42[10]]
	€33,69[11] 5,000 mg infusion solution; 1	€30.04 [€1.85[9]; €1.80[10]]

"Lauer-Taxe", effective 1 August 2013

Costs for additional, necessary statutory health insurance (SHI) benefits: none

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Pharmaceutical evaluated: Aflibercept+FOLFIRI	
Aflibercept	€47,447.92
Irinotecan	€19,178.64
Folinic acid	€7,261.02
5-fluorouracil	€1,146.86
Appropriate comparator: FOLFIRI	
Irinotecan	€19,178.64
Folinic acid	€7,261.02
5-fluorouracil	€1,146.86

Other SHI expense items:

Description of therapy	Type of benefit	Cost per unit	Number per cycle	Number per patient per year	Costs per patient per year
Aflibercept	Surcharge for the production of a parenteral preparation containing cytostatics	€79	1	26	€2,054

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.

This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 15 August 2013.

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

Berlin, 15 August 2013

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

The Chair
Hecken