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 (new therapeutic indication)

From 5 March 2015

In its session on 5 March 2015, 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 24 February 2015 (Federal Gazette, AT 27 March 2015 B2), as follows:

I.

In appendix XII, the following information shall be added after number 4 to the details of the benefit assessment of aflibercept in the therapeutic indication "treatment of visual impairment due to macular oedema secondary to retinal vein occlusion" in accordance with the resolution of 20 March 2014:

Aflibercept

Therapeutic indication:

Eylea® is indicated for adults for the treatment of visual impairment due to diabetic macular oedema (DME).

1. Additional benefit of the pharmaceutical over appropriate comparator

Appropriate comparator for patients with visual impairment due to diabetic macular oedema[1]:

Ranibizumab

Extent and probability of additional benefit over ranibizumab:

An additional benefit has not been proved.

Study results according to endpoints[2]:

Endpoint	Intervention		Control		Group difference
Comparison	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p-value
Mortality					
Aflibercept vs. laser					
VISTA	152	0 (0%)	154	1 (0.6%)	0.34 [0.01; 8.23] n.i.
VIVID	135	4 (3.0%)	133	1 (0.8%)	3.94 [0.45; 34.80] n.i.
Meta-analysis (VISTA, VIVID)					1.54 [0.15; 15.99] p = 0.72
Ranibizumab vs. laser					
RESTORE	115	2 (1.7%)	110	2 (1.8%)	0.96 [0.14; 6.67] n.i.

[1] It is assumed that the fovea centralis is also affected in patients with visual impairment due to diabetic macular oedema.

[2] Data from the benefit assessment conducted by the Institute for Quality and Efficiency in Health Care (IQWiG) if not otherwise indicated.

Endpoint	Intervention		Control		Group difference
REVEAL	133	1 (0.8%)	131	0 (0%)	2.96 [0.12; 71.89] n.c.
Meta-analysis (RESTORE, REVEAL)					1.30 [0.25; 6.82] p = 0.758
Indirect comparison[3, 4]					
Aflibercept vs. ranibizumab (with REVEAL)					1.18 [0.07; 20.70] p = 0.909
Aflibercept vs. ranibizumab (without REVEAL)					1.61 [0.08; 33.70] n.i.
Morbidity					
Improvement in visual acuity ≥ 10 ETDRS letters					
Aflibercept vs. laser					
VISTA	151	88 (58.3%)	154	30 (19.5%)	2.99 [2.11; 4.24] p < 0.001
VIVID	135	72 (53.3%)	132	34 (25.8%)	2.07 [1.49; 2.88] p < 0.001
Meta-analysis (VISTA, VIVID)					2.48 [1.73; 3.56] p < 0.001
Ranibizumab vs. laser					
RESTORE	115	43 (37.4%)	110	17 (15.5%)	2.42 [1.47; 3.98] p < 0.001
REVEAL	133	45 (33.8%)	128	17 (13.3%)	2.55 [1.54; 4.21] n.i.
Meta-analysis (RESTORE, REVEAL)					2.48 [1.74; 3.53] p < 0.001
Indirect comparison[3, 4]					
Aflibercept vs. ranibizumab (with REVEAL)					1.00 [0.60; 1.65] n.i.
Aflibercept vs. ranibizumab (without REVEAL)					1.02 [0.55; 1.89] n.i.

[3] Adjusted indirect comparison according to Bucher.

[4] Due to limited data on the REVEAL, information is shown for the entire study pool and for the sensitivity analysis (without REVEAL).

Endpoint	Intervention		Control		Group difference
Worsening of visual acuity ≥ 10 ETDRS letters					
Aflibercept vs. laser					
VISTA	151	2 (1.3%)	154	26 (16.9%)	0.08 [0.02; 0.32] n.i.
VIVID	135	3 (2.2%)	132	21 (15.9%)	0.14 [0.04; 0.46] n.i.
Meta-analysis (VISTA, VIVID)					0.11 [0.04; 0.27] p < 0.001
Ranibizumab vs. laser					
RESTORE	115	4 (3.5%)	110	14 (12.7%)	0.27 [0.09; 0.80] n.i.
REVEAL	133	4 (3.0%)	128	8 (6.3%)	0.48 [0.15; 1.56] n.i.
Meta-analysis (RESTORE, REVEAL)					0.35 [0.16; 0.78] p < 0.01
Indirect comparison[3, 4]					
Aflibercept vs. ranibizumab (with REVEAL)					0.31 [0.09; 1.04] n.i.
Aflibercept vs. ranibizumab (without REVEAL)					0.40 [0.10; 1.66] n.i.
Improvement in visual acuity ≥ 15 ETDRS letters					
Aflibercept vs. laser					
VISTA	151	47 (31.1%)	154	12 (7.8%)	3.99 [2.21; 7.23] n.i.
VIVID	135	45 (33.3%)	132	12 (9.1%)	3.67 [2.03; 6.61] n.i.
Meta-analysis (VISTA, VIVID)					3.83 [2.52; 5.81] p < 0.001
Ranibizumab vs. laser					
RESTORE	115	26 (22.6%)	110	9 (8.2%)	2.76 [1.36; 5.63] p < 0.001
REVEAL	133	25 (18.8%)	128	10 (7.8%)	2.41 [1.20; 4.81] n.i.

Endpoint	Intervention		Control		Group difference
Meta-analysis (RESTORE, REVEAL)					2.57 [1.57; 4.23] p < 0.001
Indirect comparison[3, 4]					
Aflibercept vs. ranibizumab (with REVEAL)					1.49 [0.78; 2.84] n.i.
Aflibercept vs. ranibizumab (without REVEAL)					1.38 [0.61; 3.16] n.i.
Worsening of visual acuity ≥ 15 ETDRS letters					
Aflibercept vs. laser					
VISTA	151	1 (0.7%)	154	14 (9.1%)	0.07 [0.01; 0.55] n.i.
VIVID	135	0 (0%)	132	14 (10.6%)	0.03 [0.00; 0.56] n.i.
Meta-analysis (VISTA, VIVID)					0.06 [0.01; 0.29] p < 0.001
Ranibizumab vs. laser					
RESTORE	115	1 (0.9%)	110	9 (8.2%)	0.11 [0.01; 0.83] n.i.
REVEAL	133	2 (1.5%)	128	5 (3.9%)	0.38 [0.08; 1.95] n.i.
Meta-analysis (RESTORE, REVEAL)					0.23 [0.07; 0.84] p = 0.03
Indirect comparison[3, 4]					
Aflibercept vs. ranibizumab (with REVEAL)					0.24 [0.03; 1.90] n.i.
Aflibercept vs. ranibizumab (without REVEAL)					0.53 [0.04; 7.27] n.i.

Comparison study	N[5]	MV at study begin (SD)	Change in MV (SD)	N[5]	MV at study begin (SD)	Change in MV (SD)	DM [95% CI] p-value
Mean change in BCVA after 52 weeks over initial value (ETDRS letters) Aflibercept vs. Laser							
VISTA	151	59.4 (10.9)	10.7 (8.21)	154	59.7 (11.0)	0.2 (12.53)	10.5 [8.12; 12.88] p < 0.001
VIVID	135	58.8 (11.2)	10.7 (9.32)	132	60.8 (10.6)	1.2 (10.65)	9.5 [7.10; 11.90] p < 0.001

[5] Number of patients in the calculation of the effect estimates; the values at study begin can be based on different numbers of patients

Endpoint	Intervention			Control			Group difference
Meta-analysis (VISTA, VIVID)							10.00 [8.31; 11.69] n.i.
Ranibizumab vs. laser							
RESTORE	115	64.7 (10.1)	6.8 (8.3)	110	62.6 (11.0)	0.9 (11.4)	5.9 [3.30; 8.50] p < 0.001
REVEAL	133	n.i.	6.6 (7.68)	128	n.i.	1.8 (8.27)	4.8 [2.86; 6.74] n.i.
Meta-analysis (RESTORE, REVEAL)							5.19 [3.64; 6.74] n.i.
Indirect comparison[3, 4]							
Aflibercept vs. ranibizumab (with REVEAL)							4.81 [2.52; 7.11] n.i. Hedges'g[6]: 0.37 [0.12; 0.62]
Aflibercept vs. ranibizumab (without REVEAL)							4.10 [1.00; 7.20] n.i.
Mean change in BCVA from week 4 to week 52 over initial value (ETDRS letters)							
Aflibercept vs. laser[7]							
VISTA	151	59.4 (10.9)	9.4 (0.52)	154	59.7 (10.9)	1.3 (0.83)	8.1 [6.3; 10.0] p < 0.0001
VIVID	135	58.8 (11.2)	8.2 (0.64)	132	60.8 (10.6)	1.1 (0.79)	7.1 [5.3; 8.9] p < 0.0001
Meta-analysis (VISTA, VIVID)							7.7 [6.4; 9.1] p < 0.0001
Ranibizumab vs. laser[7]							
RESTORE	115	n.i.	6.1 (6.4)	110	n.i.	0.8 (8.6)	5.4 [3.5; 7.4] p < 0.0001
REVEAL	133	n.i.	5.9 (6.0)	128	n.i.	1.4 (6.5)	n.i.
Meta-analysis (RESTORE, REVEAL)							4.8 [3.6; 6.0] p < 0.0001
Indirect comparison[3, 4, 9]							

[6] The relevance assessment using Hedges'g is based on a threshold of 0.2.

[7] Data from the dossier submitted by the pharmaceutical company.

[9] Data from the dossier submitted by the pharmaceutical company; Hedges'g figures according to the calculation shown in the IQWiG benefit assessment addendum.

Endpoint	Intervention			Control			Group difference
Aflibercept vs. ranibizumab (with REVEAL)							2.95 [1.16; 4.73] n.i. Hedges'g[6]: 0.19 [–0.06; 0.44]
Aflibercept vs. ranibizumab (without REVEAL)							2.44 [0.07; 4.81] n.i.
Medical condition (EQ-5D-VAS)							
Aflibercept vs. laser							
VISTA	151	74.3 (17.1)	–0.3 (17.9)	154	73.5 (18.2)	–2.4 (17.6)	2.1 [–1.88; 6.08] n.i.
VIVID	135	68.0 (19.4)	4.3 (16.7)	132	71.3 (19.4)	2.8 (17.2)	1.5 [–2.57; 5.57] n.i.
Meta-analysis (VISTA, VIVID)							1.81 [–1.04; 4.65] n.i.
Ranibizumab vs. laser							
RESTORE	115	n.i.	2.6 [n.i.]	110	n.i.	2.4 [n.i.]	n.i.
REVEAL	129	n.i.	–1.1 (12.7)	125	n.i.	1.0 (13.9)	–2.1 [–5.4; 1.2] n.i.
Indirect comparison[3]							
Aflibercept vs. ranibizumab (without RESTORE)[10]							3.91 [–0.43; 8.25] n.i.
Quality of life							
NEI VFQ-25 overall score							
Aflibercept vs. Laser							
VISTA	147	70.5 (17.10)	6.8 (11.92)	151	68.7 (18.06)	4.8 (14.13)	2.0 [–0.97; 4.97] n.i.
VIVID	134	71.2 (17.84)	5.3 (10.87)	120	77.4 (15.16)	2.3 (10.06)	3.0 [0.41; 5.59] n.i.
Meta-analysis (VISTA, VIVID)							2.57 [0.62; 4.52] n.i.
Ranibizumab vs. laser							
RESTORE	114	72.8 (16.9)	5.0 (13.0)	108	73.5 (18.2)	0.6 (12.6)	4.4 [1.0; 7.8] 0.014
REVEAL	n.i.						
Indirect comparison[3]							
Aflibercept vs. ranibizumab (without REVEAL)							–1.83 [–5.73; 2.06] n.i.

[10] The RESTORE was not used for the indirect comparison because information on variance was missing.

Endpoint	Intervention		Control		Group difference
Comparison study	N	Patients with at least one event n (%)	N	Patients with at least one event n (%)	RR [95% CI] p-value
Side effects AE					
Aflibercept vs. laser					
VISTA	152	139 (91.4%)	154	146 (94.8%)	n.i.
VIVID	135	119 (88.1%)	133	112 (84.2%)	n.i.
Ranibizumab vs. laser					
RESTORE	n.i.				
REVEAL	n.i.				
SAE					
Aflibercept vs. laser[11]					
VISTA	152	42 (27.6%)	154	54 (35.1%)	0.79 [0.56; 1.10] p = 0.210
VIVID	135	30 (22.2%)	133	24 (18.0%)	1.23 [0.76; 1.99] p = 0.498
Ranibizumab vs. laser					
RESTORE	115	26 (22.6%)	110	17 (15.5%)	1.46 [0.84; 2.54] n.c.
REVEAL	133	21 (15.8%)	128	19 (14.8%)	1.06 [0.60; 1.88] n.i.
Meta-analysis (RESTORE, REVEAL)					1.25 [0.84; 1.87] p = 0.264
Indirect comparison[3, 4, 11]					
Aflibercept vs. ranibizumab (with REVEAL)					
VISTA vs. RESTORE and REVEAL					0.63 [0.37; 1.07] p = 0.088
VIVID vs. RESTORE and REVEAL					0.98 [0.53; 1.84] p = 0.949
Aflibercept vs. ranibizumab (without REVEAL)					
VISTA vs. RESTORE					0.54 [0.28; 1.03] p = 0.064
VIVID vs. RESTORE					0.84 [0.40; 1.75] p = 0.643
Withdrawal due to AE					

[11] Because there was a significant heterogeneity of the VISTA and VIVID studies for the endpoint SAE (Q = 2.24; df = 1; p = 0.134; I^2 = 55%), the two studies were not consolidated into a meta-analysis. They are compared separately to the ranibizumab studies in the indirect comparison.

Endpoint	Intervention		Control		Group difference
Aflibercept vs. laser					
VISTA	152	3 (2.0%)	154	4 (2.6%)	0.76 [0.17; 3.34] n.i.
VIVID	135	4 (3.0%)	133	8 (6.0%)	0.49 [0.15; 1.60] n.c.
Meta-analysis (VISTA, VIVID)					0.58 [0.23; 1.46] p = 0.250
Ranibizumab vs. laser					
RESTORE	115	7 (6.1%)	110	6 (5.5%)	1.12 [0.39; 3.22] p = 0.860
REVEAL	n.i.				
Indirect comparison[3]					
Aflibercept vs. ranibizumab (without REVEAL)					0.52 [0.13; 2.11] p = 0.358
Ocular AE Aflibercept					
vs. laser					
VISTA	152	87 (57.2%)	154	103 (66.9%)	0.86 [0.72; 1.02] n.i.
VIVID	135	80 (59.3%)	133	82 (61.7%)	0.96 [0.79; 1.17] n.i.
Meta-analysis (VISTA, VIVID)					0.90 [0.79; 1.03] p = 0.12
Ranibizumab vs. laser					
RESTORE	115	49 (42.6%)	110	43 (39.1%)	1.09 [0.80; 1.49]; n.i.
REVEAL	n.i.				
Indirect comparison[3]					
Aflibercept vs. ranibizumab (without REVEAL)					0.83 [0.59; 1.16] n.i.
Ocular SAE					
Aflibercept vs. laser					
VISTA	152	2 (1.3%)	154	6 (3.9%)	0.34 [0.07; 1.65] n.i.
VIVID	135	3 (2.2%)	133	6 (4.5%)	0.49 [0.13; 1.93] n.i.
Meta-analysis (VISTA, VIVID)					0.42 [0.15; 1.18] p = 0.10

Endpoint	Intervention		Control		Group difference
Ranibizumab vs. laser					
RESTORE	115	0 (0%)	110	2 (1.8%)	0.19 [0.01; 3.94] n.i.
REVEAL	n.i.				
Indirect comparison[3]					
Aflibercept vs. ranibizumab (without REVEAL)					2.19 [0.09; 53.62] n.i.
Withdrawal due to ocular AE					
Aflibercept vs. laser					
VISTA	152	0 (0%)	154	0 (0%)	n.i.
VIVID	135	0 (0%)	133	4 (3.0%)	0.11 [0.01; 2.01] p = 0.044
Ranibizumab vs. laser					
RESTORE	115	0 (0%)	110	3 (2.7%)	0.14 [0.01; 2.62] p = 0.079
REVEAL	n.i.				
Indirect comparison[3]					
Aflibercept vs. ranibizumab (without REVEAL)					0.79 [0.02; 36.73] p = 0.902

Abbreviations used: BCVA: best corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; EQ-5D-VAS: Euro-Qol-5D visual analog scale; n.i.: no information; CI: confidence interval; MV: mean value, DM: difference of means; N. number of evaluated patients; n: number of patients with at least one event; n.c. not calculated; NEI VFQ-25: National Eye Institute 25-item Visual Function Questionnaire; RR: relative risk; SD: standard deviation; (S)AE: (serious adverse) event

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

   Number (patients with visual impairment due to diabetic macular oedema): 128,350 – 132,360 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 contents of the product information for Eylea® (active ingredient: aflibercept) at the following public link (last accessed: 21 January 2015):

   http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002392/WC500135815.pdf

   Eylea® may be administered only by a qualified ophthalmologist experienced in the administration and follow-up care of intravitreal injections.

   The administering physicians must consider the information provided by the pharmaceutical company as required in the EPAR (see EPAR, p. 77 ff. at the following link: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002392/WC500172846.pdf).

4. Costs of treatment

Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient per year	Duration per treatment (days)	Number of treatme days per patient per year
Aflibercept first year	5 injections (one per month), afterwards every 2 months	8	1	8
Aflibercept following years	Injection intervals increased depending on disease progression	0[12] – 6	1	0 – 6
Ranibizumab first year	Monthly injections until maximum visual acuity is achieved and/or no signs of disease activity; continued treatment based on disease activity as measured by visual acuity and/or morphological criteria	3 – 12	1	3 – 12
Ranibizumab following years	Continued treatment based on disease activity as measured by visual acuity and/or morphological criteria	0[12] – 12	1	0 – 12

Consumption:

Description of therapy	Strength (mg)	Number per pack (mg)	Average annual consumption (packs)
Aflibercept	2	4	First year: 8 Following years:
Ranibizumab	0.5	2.3	First year: 3 – 12 Following years: 0 – 12

Costs:

Cost of pharmaceutical:

Description of therapy	Cost (pharmacy retail price)	Cost after legally mandated rebates
Aflibercept	€1,101.77	€1,039.61 [€1.77[13]; €60.39[14]]
Ranibizumab	€1,262.96	€1,191.87 [€1.77[13]; €69.32[14]]

"Lauer-Taxe", effective: 15 January 2015

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

Description of therapy	Type of benefit	Costs per unit[15]	Number per patient per year	Cost per patient per year
Aflibercept	Intravitreal injection and follow-up examinations	Not quantifiable[16, 17, 18, 19]	First year: 8 Following years: 0 – 6	not quantifiable
Ranibizumab	Intravitreal injection and follow-up examinations	Not quantifiable[16, 17, 19]	First year: 3 – 12 Following years: 0 – 12	not quantifiable

[12] If progression findings are stable for 12 months after the previous treatment year, no further injections are administered in the following year.

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

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

[15] In accordance with the German Uniform Value Scale (EBM). Reference value for 2015: 10.2718 euro cents.

[16] EBM codes for the intravitreal injection: either GOP 31371/36371 (right eye) or GOP 31372/36372 (left eye) or GOP 31373/36373 (both eyes).

[17] No EBM codes are available for part of the post-operative check-ups.

[18] The aflibercept product information recommends basing treatment intervals after 12 months on functional and morphological progress (effective: August 2014). Check-up intervals should be determined by the attending physician; they may be more frequent than injection intervals. Costs for morphological examinations, e.g. optical coherence tomography OCT, cannot be quantified at the time of resolution, as they are not reflected in the EBM.

[19] Vision check-ups included in basic price.

Annual treatment costs:

Description of therapy	Annual treatment costs per patient[20]
Aflibercept	First year: €8,316.88 Following years: €0 – €6,237.66
Ranibizumab	First year: €3,575.61 – €14,302.44 Following years: €0 – €14,302.44

II.

This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 5 March 2015.

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

Berlin, 5 March 2015

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

The Chair
Prof. Hecken

[20] Costs for additional SHI expenses not quantifiable.